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Agonizing switch in prostate cancer

By Amy Donner, Senior Editor

Aragon Pharmaceuticals Inc. researchers have uncovered how a specific androgen receptor mutation results in turning second-generation antagonists for prostate cancer into agonists.¹ The results could allow the company, which is being acquired by **Johnson & Johnson**, to develop third-generation molecules that overcome the resistance mechanism.

Antiandrogen drugs were the first targeted therapy approved for prostate cancer and have substantially improved survival rates for patients. However, many castration-resistant prostate cancers (CRPCs) become resistant to antiandrogens because of elevated androgen receptor expression or mutation.²

Second-generation antiandrogens are effective against prostate cancers resistant to first-generation drugs because they antagonize both the overexpressed and the mutated receptors. These include marketed drug Xtandi enzalutamide, from **Astellas Pharma Inc.** and **Medivation Inc.**, and Aragon's ARN-509, which is in Phase II testing.

Like with first-generation molecules, the duration of the therapeutic response to Xtandi or ARN-509 is limited because patients develop resistance to these compounds.

"With the selective pressure from therapeutics in cancer treatment, drug resistance seems inevitable. We need to determine whether we can anticipate and deal with drug resistance preemptively in the drug design and development process, instead of waiting to react," said Yang Shen, a research assistant professor at the **Toyota Technological Institute at Chicago**.

In a paper published in *eLife* earlier this year, Shen and collaborators at the **Memorial Sloan-Kettering Cancer Center** and **The University of Chicago** ran a prospective study to predict androgen receptor mutations that confer resistance to Xtandi and ARN-509.³

A mutagenesis-based screening approach in prostate cancer cell lines identified the F876L mutation as one that confers resistance to Xtandi and ARN-509. The mutation was validated in cell culture and xenograft models.

Now, an Aragon team led by James Joseph and Jeffrey Hager has gone a step further and showed the clinical relevance of the F876L mutation. In short, the mutation arises spontaneously in patients receiving ARN-509 and turns the antagonistic effect of the drug into an agonistic one, thereby stripping the drug of its antitumor effect.

Joseph is a principal scientist at the company, and Hager is senior director of biology.

The group generated prostate cancer cell lines resistant to ARN-509

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and Xtandi via prolonged *in vitro* selection in the presence of drug. DNA sequencing analyses showed that the F876L mutation emerged in three independent, resistant lines.

In the mutated cell lines, the drugs actually stimulated expression of androgen receptor-dependent genes and cell proliferation, suggesting the compounds agonized the mutant version of the androgen receptor. The conversion of an antagonistic to an agonistic effect by mutation was reminiscent of the effect of androgen receptor mutations acquired in response to treatment with first-generation antiandrogens.²

The group showed that the F876L mutation was responsible for reversing the response of prostate cancer cell lines to drugs in cell lines expressing the androgen receptor mutant and in castrated, xenograft male mouse models for prostate cancer.

The Aragon team then evaluated circulating tumor DNA isolated from plasma samples from patients enrolled in a Phase I trial of ARN-509. The F876L mutation occurred in 3 of 29 ARN-509-treated patients. Two of those three patients had progressive disease.

Importantly, the mutation was not detected in pretreatment samples, which suggests the mutation is acquired during the course of treatment.

Results were published in *Cancer Discovery*.

According to Nigel Brooks, senior project director with AstraZeneca plc's Oncology Innovative Medicines Unit, "It is very important that the mutation has been identified independently in two separate laboratories, strengthening the notion that this is a true adaptive response to these particular antihormonal therapies."

Third time is a charm

According to Hager, the findings "set the stage for co-development of next-generation agents coupled with a blood-based companion diagnostic to guide treatment decisions."

Aragon would not comment on whether it is developing such agents or a diagnostic.

Brooks said AstraZeneca is trying to target the androgen receptor in a way that affects all mutations as well as full-length androgen receptor and splice variant forms of androgen receptor.

"The description of this specific mutation as well as other changes to the androgen receptor, such as alternate splicing, guides the development of further androgen receptor-targeted therapies that may overcome all these resistance mechanisms. The discovery of the mutation in human plasma DNA may provide a way to develop a blood-based diagnostic approach to guide treatment decisions," said Brooks.

"Once a full antagonist of F876L androgen receptor is in hand, patients with rising PSA [prostate-specific antigen] levels or progressive disease should be screened while on second-generation antiandrogen therapy, and those acquiring the mutation should receive the next-generation therapy," said Hager.

"We need to determine whether we can anticipate and deal with drug resistance preemptively in the drug design and development process, instead of waiting to react."

— Yang Shen,
Toyota Technological Institute
at Chicago

“The discovery of the mutation in human plasma DNA may provide a way to develop a blood-based diagnostic approach to guide treatment decisions.”

**—Nigel Brooks,
AstraZeneca plc**

used as a predictive marker for response to other antiandrogen agents,” said Brooks.

Aragon did not disclose whether determining the frequency of androgen receptor mutations is part of the Phase II trial design for ARN-509.

MSKCC is developing a third-generation antiandrogen. In the *eLife* paper, one of the center’s compounds, dubbed DR103, inhibited growth of prostate cancer cell lines expressing the F876L mutant androgen receptor, whereas Xtandi or vehicle did not. MSKCC is testing the compound in mouse xenograft models for prostate cancer.⁴

MSKCC has filed patent applications covering DR103 and other

Because of the small sample size in the clinical portion of the *Cancer Discovery* report, there is not yet a reliable estimate of the frequency of F876L in patients who develop progressive disease while taking second-generation antiandrogens.

“We need further information on the prevalence of this mutation and if it can be

chemical entities disclosed in its paper as well as the F876L mutation. Aragon also has filed a patent application on the F876L mutation.

Medivation did not respond to requests for comment.

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Medivation Inc. (NASDAQ:MDVN), San Francisco, Calif.
Memorial Sloan-Kettering Cancer Center, New York, N.Y.
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NCATS's nine lives

By Michael J. Haas, Senior Writer

The NIH's National Center for Advancing Translational Sciences (NCATS) has awarded a total of \$12.7 million to 9 academic research groups to repurpose compounds from 5 pharma partners in the center's Discovering New Therapeutic Uses for Existing Molecules program.

According to Christine Colvis, director of the program, the 9 projects were selected from about 160 applicants through an NIH peer review process, and the awards for the first year range from about \$500,000 to \$3 million (see Table 1, "NCATS's first repurposing round"). Colvis said that the academic partners would own any new IP generated by the partnership, and the pharmas would have options to license that IP.

Last year, NCATS disclosed details about the first library of therapeutics in the program. Eight pharmas provided the library with

a total of 58 compounds that had completed at least Phase I testing but did not reach registration for their original indications.¹

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National Center for Advancing Translational Sciences,
Bethesda, Md.

National Institutes of Health, Bethesda, Md.

Table 1. NCATS's first repurposing round.

Source (unless otherwise noted): BCIQ: BioCentury Online Intelligence; National Center for Advancing Translational Science (NCATS).

Company	Academic partner(s)	Compound ^A	Mechanism ^A	New indication	Original indication(s) ^B
AstraZeneca plc (LSE:AZN; NYSE:AZN)	University of Virginia	Zibotentan (ZD4054)	Endothelin A receptor antagonist	Peripheral artery disease (PAD)	Phase III to treat castration-resistant prostate cancer (CRPC); Phase II to treat non-small cell lung cancer (NSCLC) and ovarian cancer; Phase I to treat solid tumors
	Baylor College of Medicine Yale University	Saracatinib (AZD0530)	Src inhibitor	Lymphangioliomyomatosis (LAM) Alzheimer's disease (AD)	Phase IIb to treat ovarian, breast, prostate and renal cancer
Eli Lilly and Co. (NYSE:LLY)	Indiana University	LY500307	Estrogen receptor- β agonist	Schizophrenia	Phase II to treat lower urinary tract symptoms (LUTS) in benign prostatic hyperplasia (BPH)
Johnson & Johnson (NYSE:JNJ)	Virginia Commonwealth University; University of Pittsburgh	JNJ-39393406 ²	Nicotinic acetylcholine receptor α_7 (CHRNA7) agonist ²	Smoking addiction	Phase I to treat AD and cognitive impairment in schizophrenia
Pfizer Inc. (NYSE:PFE)	The University of Rhode Island, Kingston	PF-05190457 (PF-5190457)	Ghrelin receptor (GHSR) antagonist	Alcohol addiction	Phase I to treat type 2 diabetes
	Yale University	PF-03463275	Glycine transporter type 1 (GlyT1; SLC6A9) inhibitor	Cognitive impairment in schizophrenia	Phase II to treat negative symptoms in schizophrenia
Sanofi (Euronext:SAN; NYSE:SNY)	Kennedy Krieger Institute; University of Washington Mayo Clinic	SAR115740 ³⁻⁷	Transient receptor potential vanilloid 1 (TRPV1; VR1) antagonist ³⁻⁷	Duchenne muscular dystrophy (DMD) ³⁻⁵ Aortic stenosis ^{6,7}	Phase I to treat acute and chronic pain

^ANCATS did not disclose compounds and/or mechanisms for all projects; in those instances, the cited reference by the academic partner and other research groups reports a potential therapeutic target in the new indication that corresponds to the mechanism of a compound the pharma originally provided to the NCATS program, from which one can infer the identity of the compound in the project receiving the NCATS award. ^BDenotes the disease indication in which the company has already tested the compound in the clinic; in most cases, the company discontinued development of the compound because of lack of efficacy, failure to meet trial endpoints or for undisclosed reasons.

Finding drugs for the faint of heart

By Kai-Jye Lou, Senior Writer

Harvard University researchers have developed an organ on a chip that recapitulates genetic, morphological and functional markers of failing myocardium.¹ The system could help identify therapeutic candidates that slow or reverse heart failure with better reliability than current *in vitro* culture systems.

Traditional *in vitro* models of heart failure involve exposing cultured cardiomyocytes to chemical or mechanical stimuli that induce pathological gene expression, hypertrophy and remodeling.²⁻⁴

A Harvard team led by Kevin Kit Parker has been developing heart-on-a-chip systems that also recapitulate contractile function, which is considered a better proxy of cardiac output than changes in gene expression and electrophysiological properties. Parker is a professor of bioengineering and applied physics at Harvard and core member of the **Wyss Institute for Biologically Inspired Engineering at Harvard University**.

Parker's team previously used neonatal rat ventricular myocytes and its own muscular, thin-film technology to engineer an organ-on-a-chip microsystem that recapitulates the healthy myocardium.⁵ The system could be used to screen compounds for cardiotoxicity but not for the ability to correct a disease phenotype.

Now, the same group has engineered a microsystem that recapitulates the failing myocardium. The new chip consists of neonatal rat ventricular myocytes seeded on a fibronectin-patterned flexible silicone membrane. The chip further incorporates a custom-built multiwell system that allows the user to subject the engineered myocardium to uniaxial and cyclical stretch.

Cyclic stretching of myocardium recreated pathological heart failure-associated changes to myocyte shape, sarcomere alignment, calcium cycling and gene expression. Importantly, the stretched myocardium showed lower contractile functionality than unstretched myocardium.

Results were published in the *Proceedings of the National Academy of Sciences*.

"The results in the current study are exciting for heart failure because until now, there has not been a way to scale down a system that replicates the major parameters of the failing myocardium to one that could be easily used by bench scientists at pharmaceutical companies," said Paul August, director and U.S. head of the Early to Candidate Unit at **Sanofi**. "This system could help move the relevant disease models more upstream in the drug discovery process and could improve our ability to interrogate the effects of compounds before we reach animal models."

"What the Parker group has achieved in the current study is an extension of their earlier heart-on-a-chip system," said David Giegel, founder and president of **TissueNetix Inc.** "This new system will now allow scientists to set up specific assays to test compounds for their ability to ameliorate the disease phenotype."

TissueNetix is developing a cardiac cell conduction array to assess compounds for potential cardiotoxicity during the drug discovery process. The assay consists of normal human cardiomyocytes that are electrically coupled and beat in a manner similar to the heart. Giegel said TissueNetix's assay should be more reliable at detecting cardiotoxicity than cellular assays currently used in industry.

Looking at more with less

The new system's ability to recapitulate more aspects of heart failure than conventional cellular models should yield more reliable and sensitive detection of compounds that affect disease phenotype.

"When cells are taken out of the body and grown in culture, they usually won't behave as they would in the body," which decreases the reliability of the observed results, said Shuichi Takayama, a professor in the Department of Biomedical Engineering at the **University of Michigan**.

"The special format system developed by this group allows cultured cardiomyocytes to behave as they would in the body. The hope is that such a system will have better correlation to the disease and allow users to more reliably link their observations to disease mechanisms."

"One of the compelling advantages of the described model is that this system permits quantitative analysis of the contractility of engineered cardiac muscle *in vitro* during electrical and pharmacological simulation,"

added Dongeun Huh, an assistant professor in the Department of Bioengineering at the **University of Pennsylvania**.

"The fact that this system allows for concurrent measurements of genetic, structural and functional phenotypes in a single device in an array format makes this microengineered disease model a unique, robust platform for quantitative analysis of integrated cardiac responses to various external stimuli such as therapeutic agents, pathogens, chemicals, environmental toxins and cosmetics," added Huh.

Megan McCain, a postdoctoral fellow at Harvard and the Wyss Institute and lead author on the paper, added that conventional *in vitro* models miss subtle effects that compounds could have on the heart. She said enabling concurrent assessment of multiple model parameters could improve the consistency and overall quality of data collected from experiments using the chips.

Parker noted that the chips are easier to use and are less costly than animal models and that the manufacturing process is fast and reproducible.

McCain added that the group can create ready-to-use chips in five days.

Adapting for industry use

Parker said the group is trying to build its current failing myocardium-on-a-chip system using human cardiomyocytes derived from induced pluripotent stem (iPS) cells, standardize the fabrication process and adapt the chips for use with high throughput screening systems.

In addition to using human cardiomyocytes, Huh said it would be important to incorporate other cells of the myocardium into the chip system as well to help recapitulate interactions between different cell

(Continues on p. 6)

"This system could help move the relevant disease models more upstream in the drug discovery process and could improve our ability to interrogate the effects of compounds before we reach animal models."

—Paul August, Sanofi

Bilirubin glow

By C. Simone Fishburn, Senior Editor

Bilirubin tests in jaundiced babies are commonplace in maternity wards but involve multiple steps and vary in reliability. **RIKEN Brain Science Institute** researchers have now found that a fluorescent protein identified in eels potently binds bilirubin and might provide a simpler and more reliable diagnostic.¹ Convincing hospitals to invest in a new detection device, however, might turn out to be a bigger challenge than developing the assay.

In searching for the source of the green glow in Japanese unagi eels (*Anguilla japonica*), the RIKEN researchers pinpointed a protein called UnaG. UnaG is the first fluorescent protein identified in a vertebrate—previous ones were found in jellyfish or bacteria.

Because cloned UnaG did not fluoresce on its own in bacteria, the researchers looked for and found a cofactor in the eel's blood that was necessary to trigger fluorescence. That cofactor surprisingly turned out to be bilirubin, a key clinical biomarker of liver function.

When UnaG binds bilirubin it triggers a molecular switch that makes it fluoresce green. The fluorescence intensity was proportional to the concentration of bilirubin from 0–25 mg/dL, which spans the range of

bilirubin levels found in healthy serum to those seen in bilirubinemia.

UnaG is the first example of a ligand-inducible fluorescent protein. All other known fluorogenic compounds are either constantly fluorescent or fluoresce following covalent binding to another molecule.

The team was led by Atsushi Miyawaki, deputy director of the RIKEN Brain Institute, and results were published in *Cell*.

In humans, bilirubin exists in an unconjugated (UC-BR) and a conjugated (C-BR) form. The sum of both components constitutes what is known as total serum bilirubin (TsB). UC-BR is the key parameter used by physicians to determine disease risk and treatment strategy in neonates.

UnaG binds specifically and with high affinity to UC-BR, which is a lipophilic product of heme metabolism that is transported via serum albumin to the liver. In healthy individuals, UC-BR binds glucuronide covalently in the liver, forming water-soluble C-BR that is excreted into bile. In the compromised liver, formation of C-BR can be impaired, which in turn causes buildup of UC-BR in the circulation to toxic levels.

In neonates, excess bilirubin resulting from inefficient breakdown of hemoglobin can lead to a form of brain damage termed kernicterus. Treatment is often simple, most commonly using phototherapy, but early diagnosis is essential.

Bilirubin testing is performed routinely on newborn infants with
(Continues on p. 7)

(Continued from “Finding drugs for the faint of heart,” p. 5)

“The hope is that such a system will have better correlation to the disease and allow users to more reliably link their observations to disease mechanisms.”

—Shuichi Takayama,
University of Michigan

types known to be crucial to the onset and exacerbation of various heart diseases.

“This will eventually lead to more realistic and complete disease models that enable one to probe and understand complex and diverse disease processes in ways that have not been possible using conventional

cell culture and animal models,” Huh told *SciBX*.

McCain said that other research directions pursued by the group include creating chips that use iPS cell–derived cardiomyocytes taken from patients for personalized disease modeling applications and creating chips that could recapitulate interactions between different organs.

Giegel said it would be important for the Harvard researchers to do proof-of-concept studies showing that the system can screen for compounds that correct the disease phenotype.

August wanted to see the Harvard group's chip tested with well-characterized molecules that affect the physiology of the heart.

“Basically, I want to see this technology evaluated against agents that have known effects on cardiovascular function *in vivo*, such as those that modulate cytoskeletal architecture or contractile activity, and see if these chips could recapitulate those effects,” he told *SciBX*.

August added that his group also is working collaboratively with

Parker on another organ-on-a-chip system to model skeletal muscle function in rare diseases.

Takayama added that it would be important to demonstrate cases in which the human myocardium-on-a-chip system accurately predicts the effects of the compound in humans but the traditional human cell culture systems and animal models do not.

Harvard has multiple issued and pending patents covering the myocardium-on-a-chip systems. The technology is available for licensing.

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COMPANIES AND INSTITUTIONS MENTIONED

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University of Michigan, Ann Arbor, Mich.
University of Pennsylvania, Philadelphia, Pa.
Wyss Institute for Biologically Inspired Engineering at Harvard University, Cambridge, Mass.

jaundice and on older children and adults with liver disease, sickle cell disease or other forms of hemolytic anemia.

New assay, old instruments

Miyawaki thinks the direct measurement of UC-BR represents one of the advantages a UnaG-based assay would have over available techniques that employ roundabout methods of quantitation and are variable between laboratories.²

Most marketed bilirubin assays are based on a method first developed in 1916. The most widely used assay measures C-BR and TsB and calculates UC-BR by subtracting C-BR from TsB. The assay employs a reagent that changes color upon binding C-BR.

To provide a measure of TsB, a second compound called an accelerator is added to the reaction, which makes the initial reagent bind to all forms of bilirubin and results in a different measurable color change.

The principal manufacturers of these assays are **Roche's** Roche Diagnostics group, **Danaher Corp.** (previously Beckman Coulter) and **Siemens AG's** Siemens Diagnostics unit.

An alternative method is the Vitros assay from **Johnson & Johnson's** Ortho Clinical Diagnostics division. With this method, TsB and hemoglobin are measured spectrophotometrically. C-BR and UC-BR concentrations are subsequently calculated from those two measurements.

Both techniques are considerably more complex than Miyawaki's assay, which can determine UC-BR levels by direct measurement and works with high sensitivity in both blood and serum.

Stanley Lo, an associate professor at **Medical College of Wisconsin** and associate director of clinical laboratories at **Children's Hospital of Wisconsin**, told *SciBX* that "something specific for unconjugated bilirubin would be very attractive for the newborn population."

He added that current assays are complex but do fall within the 10% precision required by the **College of American Pathologists (CAP)** Chemistry Resource Committee.³ CAP, along with the **American Academy of Pediatrics**, issues guidelines for bilirubin testing.

Although Miyawaki's assay for direct, sensitive and reliable measurement of UC-BR could provide a superior test for bilirubin, one

"Something specific for unconjugated bilirubin would be very attractive for the newborn population."

— Stanley Lo,
Medical College of Wisconsin

big hurdle is that few clinical laboratories are equipped with fluorometers.

According to Lo, requiring a new instrument for a single assay could present a significant obstacle to selling it to clinical labs. Hospitals are most open to new assays that do not involve additional investments, so without a wider need for fluorescence detection the

assay is likely to encounter challenges in its adoption, he said.

Nevertheless, Miyawaki is developing a fluorescence detector for use with the assay. He thinks the device will be simple and inexpensive to construct because it only will need single, fixed excitation and emission filters, a photomultiplier tube and an LED.

He also is performing mutagenesis studies on UnaG in search of a derivative that might bind C-BR with high specificity. The separate and precise measurement of C-BR and UC-BR could provide physicians with a better screening tool to help identify the source of a bilirubin-related liver dysfunction.

The products of the research have been patented by the RIKEN Brain Science Institute and are available for licensing. Miyawaki said he is in discussions with undisclosed companies to commercialize the assay.

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COMPANIES AND INSTITUTIONS MENTIONED

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Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
Siemens AG (Euronext:SIE; NYSE:SI), Munich, Germany

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				
Cancer	CD47; signal regulatory protein- α (SIRPA)	<p>Cell culture and mouse studies suggest combining tumor-targeting mAbs with an engineered SIRPA variant could help treat cancer. Previous studies have shown that blocking the interaction between SIRPA and CD47 increased the immune response against tumor cells. In cell culture, treatment with an engineered SIRPA variant with high affinity for CD47 antagonized CD47 signaling and increased macrophage-mediated phagocytosis of tumor cells compared with treatment using wild-type SIRPA. In multiple mouse tumor xenograft models, engineered SIRPA increased the efficacy of tumor-targeting mAbs compared with vehicle. Next steps include making an IND submission and testing the engineered SIRPA as an adjunct to mAb therapies for cancer.</p> <p>Radiation Control Technologies Inc. has the CD47 antagonist RCT1938 in preclinical development for various cancers.</p> <p>SciBX 6(25); doi:10.1038/scibx.2013.619 Published online June 27, 2013</p>	Patent pending; available for licensing	<p>Weiskopf, K. <i>et al. Science</i>; published online May 30, 2013; doi:10.1126/science.1238856 Contact: K. Christopher Garcia, Stanford University School of Medicine, Stanford, Calif. e-mail: kcgarcia@stanford.edu</p>
Cancer	Not applicable	<p>Mouse studies suggest a nonvirulent strain of <i>Toxoplasma gondii</i> could help treat cancer. In mouse models for ovarian carcinomas, injection of the nonvirulent <i>T. gondii</i> strain led to decreased tumor volumes and increased survival compared with saline injection. Next steps include evaluating the safety of the <i>T. gondii</i> therapy in animal models and testing it in human tumors.</p> <p>SciBX 6(25); doi:10.1038/scibx.2013.620 Published online June 27, 2013</p>	Covered by issued and filed patents; available for licensing from Dartmouth College Contact: Alla Kan, Dartmouth College, Hanover, N.H. e-mail: alla.kan@dartmouth.edu	<p>Baird, J.R. <i>et al. Cancer Res.</i>; published online May 23, 2013; doi:10.1158/0008-5472.CAN-12-1974 Contact: David J. Bzik, Geisel School of Medicine at Dartmouth, Lebanon, N.H. e-mail: david.j.bzik@dartmouth.edu</p>
Cancer	Platelet derived growth factor receptor B (PDGFRB; PDGFR1; CD140B)	<p>Mouse studies suggest thalidomide could help reduce cardiotoxicity in patients with cancer given Sunitinib. In mice, sunitinib induced cardiotoxicity and microvascular dysfunction. In mice with transverse aortic constriction, sunitinib decreased Pdgfrb expression and pericyte numbers in the microvasculature compared with no treatment. In the same mice, thalidomide decreased sunitinib-induced cardiotoxicity compared with vehicle. Next steps include exploring low-dose thalidomide in combination with various PDGFR inhibitors and understanding the role of pericytes in the heart.</p> <p>Pfizer Inc. markets the receptor tyrosine kinase (RTK) inhibitor Sunitinib to treat gastrointestinal stromal tumors (GISTs) and advanced renal cell carcinoma (RCC). Celgene Corp. markets thalidomide as Thalomid.</p> <p>SciBX 6(25); doi:10.1038/scibx.2013.621 Published online June 27, 2013</p>	Patent and licensing status undisclosed	<p>Chintalgattu, V. <i>et al. Sci. Transl. Med.</i>; published online May 29, 2013; doi:10.1126/scitranslmed.3005066 Contact: Aarif Y. Khakoo, Amgen Inc., South San Francisco, Calif. e-mail: akhakoo@amgen.com Contact: Vishnu Chintalgattu, same affiliation as above e-mail: vishnuc@amgen.com</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Cervical cancer	Histone deacetylase 6 (HDAC6)	<p>Patient sample and cell culture studies suggest inhibiting HDAC6 could help treat cervical cancer. In two human cervical cell lines, small interfering RNA against <i>HDAC6</i> decreased cell proliferation and migration compared with control siRNA. In samples from patients with cervical cancer, expression of HDAC6 and its downstream mediators was higher in cancer cells than in adjacent noncancerous epithelial cells. Next steps could include studying HDAC6 inhibitors in a mouse xenograft model for cervical cancer.</p> <p>Acetylon Pharmaceuticals Inc.'s ACY-1215, an oral selective HDAC6 inhibitor, is in Phase I/II testing for multiple myeloma (MM).</p> <p>At least two other companies have HDAC6 inhibitors in preclinical development to treat various cancers and inflammation.</p> <p>SciBX 6(25); doi:10.1038/scibx.2013.622 Published online June 27, 2013</p>	Patent and licensing status unavailable	<p>Chen, Y.-T. <i>et al. Cancer Res.</i>; published online May 22, 2013; doi:10.1158/0008-5472.CAN-12-4127</p> <p>Contact: Meng-Ru Shen, National Cheng Kung University Hospital, Tainan, Taiwan e-mail: mrschen@mail.ncku.edu.tw</p>
Dermatology				
Alopecia; hair loss	Fibroblast growth factor 9 (FGF9; GAF)	<p>Mouse studies suggest FGF9 could help stimulate hair regrowth. In a mouse model for wound-induced hair neogenesis, transgenic overexpression of <i>Fgf9</i> in the epidermis increased hair follicle formation compared with normal <i>Fgf9</i> expression. In mice deficient in Fgf9-producing $\gamma\delta$ T cells, follicle formation was lower than that in wild-type mice. Next steps include testing the effects of FGF9 on human skin.</p> <p>SciBX 6(25); doi:10.1038/scibx.2013.623 Published online June 27, 2013</p>	Patent application filed; licensed to Follica Inc.; available for licensing	<p>Gay, D. <i>et al. Nat. Med.</i>; published online June 2, 2013; doi:10.1038/nm.3181</p> <p>Contact: George Cotsarelis, University of Pennsylvania, Philadelphia, Pa. e-mail: cotsarel@mail.med.upenn.edu</p>
Dermatology; wounds	Hydroxysteroid 11 β dehydrogenase 1 (HSD11B1; HSD1)	<p>Studies in mice and in human samples suggest inhibiting HSD11B1 could help prevent age-associated skin defects and improve wound healing. Skin samples from aged individuals showed greater HSD11B1 activity than samples from young individuals. In mice, <i>Hsd11b1</i> knockout prevented age-associated dermal atrophy compared with no knockout. In injured mice, a topical HSD11B1 inhibitor accelerated wound healing compared with vehicle. Next steps include studies to determine whether preventing age-induced increases in skin HSD11B1 activity or treating skin with HSD11B1 inhibitors can counteract age-induced impairments in skin function.</p> <p>Eli Lilly and Co.'s LY2523199, an HSD11B1 inhibitor, is in Phase II testing to treat diabetes.</p> <p>At least four other companies have HSD11B1 inhibitors in Phase I testing or earlier to treat diabetes or glaucoma.</p> <p>SciBX 6(25); doi:10.1038/scibx.2013.624 Published online June 27, 2013</p>	Patent and licensing status unavailable	<p>Tiganescu, A. <i>et al. J. Clin. Invest.</i>; published online June 3, 2013; doi:10.1172/JCI64162</p> <p>Contact: Ana Tiganescu, University of California, San Francisco–NCIRE, San Francisco, Calif. e-mail: ana.tiganescu@ncire.org</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Endocrine/metabolic disease				
Creatine transporter deficiency (CTD)	Solute carrier family 6 creatine transporter member 8 (SLC6A8; CRT)	<i>In vitro</i> studies suggest a dodecyl creatine ester could help treat CTD caused by SLC6A8 deficiency. Chemical synthesis and testing in rat brain cells identified a dodecyl creatine fatty ester that was nontoxic to endothelial, glial and neuronal cells. In a rat cell model for the blood brain barrier and in rat cortical neurons, uptake of the compound was greater than that of a control ethyl creatine ester analog. In fibroblasts from patients with CTD caused by SLC6A8 deficiency, the compound increased intracellular creatine levels compared with no treatment. Future studies could include developing a way to deliver the compound that protects it from degradation in plasma. SciBX 6(25); doi:10.1038/scibx.2013.625 Published online June 27, 2013	Patent and licensing status unavailable	Trotier-Faurion, A. <i>et al. J. Med. Chem.</i> ; published online May 22, 2013; doi:10.1021/jm400545n Contact: Aloïse Mabondzo, French Alternative Energies and Atomic Energy Commission, Gif-sur-Yvette, France e-mail: aloise.mabondzo@cea.fr
Diabetes	Toll-like receptor 9 (TLR9); IL-21	<i>In vitro</i> and mouse studies suggest adoptive transfer of TLR9-stimulated pro-B cells could help prevent type 1 diabetes. In nonobese diabetic (NOD) mice, adoptive transfer of bone marrow cells pretreated with a TLR9 agonist delayed disease onset and decreased pancreatic and plasma levels of IL-21 compared with adoptive transfer of cells pretreated with an inactive control oligonucleotide. Ongoing work includes testing adoptive transfer of TLR9-activated pro-B cells in mouse models for other autoimmune diseases. SciBX 6(25); doi:10.1038/scibx.2013.626 Published online June 27, 2013	Unpatented; unlicensed	Montandon, R. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online May 28, 2013; doi:10.1073/pnas.1222446110 Contact: Flora Zavala, University Paris Descartes, Paris, France e-mail: flora.zavala@parisdescartes.fr
Obesity	Serotonin (5-HT _{1B}) receptor; serotonin (5-HT _{2C}) receptor	Mouse studies suggest 5-HT _{1B} receptor agonists could improve the efficacy of 5-HT _{2C} receptor-targeted drugs in treating obesity. In mouse brain slices, co-treatment with 5-HT _{1B} and 5-HT _{2C} receptor agonists increased activation of neurons involved in suppression of food intake compared with either agent alone. The co-treatment also decreased food intake compared with either agent alone or saline. Next steps could include studying the effect of the combined agonists in preclinical obesity models. Arena Pharmaceuticals Inc.'s Belviq lorcaserin (APD356), which Eisai Co. Ltd. markets in the U.S., is a 5-HT _{2C} receptor agonist used to treat obesity. At least two other companies have 5-HT _{2C} receptor agonists in Phase II testing or earlier to treat obesity. At least 14 companies have 5-HT _{1B} receptor agonists on the market or in development for various neurology indications. SciBX 6(25); doi:10.1038/scibx.2013.627 Published online June 27, 2013	Patent and licensing status undisclosed	Doslikova, B. <i>et al. J. Neurosci.</i> ; published online June 5, 2013; doi:10.1523/JNEUROSCI.4326-12.2013 Contact: Lora K. Heisler, The University of Aberdeen, Aberdeen, U.K. e-mail: lora.heisler@abdn.ac.uk Contact: Brian Billups, University of Cambridge, Cambridge, U.K. e-mail: bjb41@cam.ac.uk
Obesity; metabolic syndrome	Potassium channel Kv1.3 (KCNA3)	Mouse studies suggest the KCNA3-inhibiting peptide ShK-186 could help treat obesity or metabolic syndrome. In a mouse model for diet-induced obesity, ShK-186 led to less weight gain than vehicle. In the mouse obesity model, ShK-186 activated metabolism in brown adipose and improved peripheral insulin sensitivity. Next steps include investigating ShK-186 in obesity-related indications in humans. Kineta Inc. has completed Phase Ia testing of ShK-186 in autoimmune diseases. SciBX 6(25); doi:10.1038/scibx.2013.628 Published online June 27, 2013	Patented; licensed to Kineta	Upadhyay, S.K. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online May 31, 2013; doi:10.1073/pnas.1221206110 Contact: K. George Chandy, University of California, Irvine, Calif. e-mail: gchandy@uci.edu

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Inflammation				
Asthma	Serine palmitoyltransferase (SPT)	Mouse studies suggest increasing SPT-mediated sphingolipid synthesis could help treat nonallergic asthma. SPT is a key enzyme that mediates sphingolipid synthesis. In a mouse model for asthma, myriocin inhibited Spt-mediated sphingolipid synthesis and increased airway resistance compared with vehicle. In mice, a deficiency in <i>Spt</i> increased airway resistance and hyperreactivity after asthma induction compared with no deficiency. Next steps could include designing therapies based on sphingolipid supplementation and evaluating them in preclinical models of nonallergic asthma.	Patented by Weill Cornell Medical College; available for licensing	Worgall, T.S. <i>et al. Sci. Transl. Med.</i> ; published online May 22, 2013; doi:10.1126/scitranslmed.3005765 Contact: Stefan Worgall, Weill Cornell Medical College, New York, N.Y. e-mail: stw2006@med.cornell.edu
SciBX 6(25); doi:10.1038/scibx.2013.629 Published online June 27, 2013				
Musculoskeletal disease				
Muscular atrophy	SET and MYND domain containing 3 (SMYD3)	Cell culture and mouse studies suggest inhibiting SMYD3 could help prevent steroid-induced muscular atrophy. In mouse skeletal muscle and myoblast cells, small hairpin RNA against Smyd3 increased myotube size compared with scrambled shRNA. In mice, shRNA knockdown of Smyd3 decreased dexamethasone-induced loss of skeletal muscle compared with no knockdown. Next steps could include screening for inhibitors of SMYD3 and evaluating them in muscular atrophy models.	Patent and licensing status unavailable	Proserpio, V. <i>et al. Genes Dev.</i> ; published online June 1, 2013; doi:10.1101/gad.217240.113 Contact: Giuseppina Caretti, University of Milan, Milan, Italy e-mail: giuseppina.caretti@unimi.it
SciBX 6(25); doi:10.1038/scibx.2013.630 Published online June 27, 2013				
Neurology				
Ataxia	Nemo-like kinase (NLK)	Fly and mouse studies suggest inhibiting NLK could help treat spinocerebellar ataxia type 1 (SCA1). In a fly model for SCA1, an <i>nlk</i> deficiency decreased markers of disease compared with no deficiency. In the fly model, expression of human <i>NLK</i> increased markers of disease compared with expression of a kinase-dead mutant. In a mouse model for SCA1, lower <i>Nlk</i> expression decreased disease-associated behaviors compared with wild-type <i>Nlk</i> expression. Next steps include understanding additional mechanisms downstream of NLK in diseased and normal brain function.	Patent and licensing status undisclosed	Ju, H. <i>et al. J. Neurosci.</i> ; published online May 29, 2013; doi:10.1523/JNEUROSCI.3465-12.2013 Contact: Janghoo Lim, Yale School of Medicine, New Haven, Conn. e-mail: janghoo.lim@yale.edu
SciBX 6(25); doi:10.1038/scibx.2013.631 Published online June 27, 2013				
Ataxia	Ribosomal protein S6 kinase 90 kDa polypeptide 5 (RPS6KA5; MSK1); ataxin 1 (ATXN1)	Fly and mouse studies suggest inhibiting MSK1 could help treat spinocerebellar ataxia type 1 (SCA1), which is caused by a polyglutamine expansion in <i>ATXN1</i> . Fly- and human cell-based screens identified <i>MSK1</i> as a gene in which knockdown leads to decreased levels of mutant ATXN1 and mutant ATXN1-associated toxicity. In mice, small molecule inhibitors of the Mapk pathway or MSK1 decreased Atxn1 levels compared with vehicle. In a mouse model for SCA1, a deficiency in <i>Rps6ka5</i> resulted in less neurodegeneration than no deficiency. Next steps include developing brain-permeable MSK1 inhibitors and conducting additional screens for modifiers of other proteins associated with neurodegenerative disease.	Patent application filed; available for licensing	Park, J. <i>et al. Nature</i> ; published online May 29, 2013; doi:10.1038/nature12204 Contact: Huda Y. Zoghbi, Baylor College of Medicine, Houston, Texas e-mail: hzoghbi@bcm.edu
SciBX 6(25); doi:10.1038/scibx.2013.632 Published online June 27, 2013				

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Schizophrenia	Insulin-like growth factor-2 (IGF-2); insulin-like growth factor-1 receptor (IGF1R; CD221)	A mouse study suggests restoring IGF-2 could help treat schizophrenia. In mice, knockout of <i>DiGeorge syndrome chromosomal region 8 (Dgcr8)</i> , which has been associated with schizophrenia in humans, decreased hippocampal neurogenesis and expression of IGF-2 compared with no knockout. The knockout also impaired responses in behavioral and cognitive tests. In <i>Dgcr^{-/-}</i> mice, intrahippocampal administration of IGF-2 increased neurogenesis and decreased learning deficits compared with vehicle administration. Next steps include developing a system for intravascular administration of IGF-2. SciBX 6(25); doi:10.1038/scibx.2013.633 Published online June 27, 2013	Patent application filed; available for licensing from Chubu University	Ouchi, Y. <i>et al. J. Neurosci.</i> ; published online May 29, 2013; doi:10.1523/JNEUROSCI.2700-12.2013 Contact: Takashi Iwamoto, Chubu University, Kasugai, Japan e-mail: iwamoto@isc.chubu.ac.jp
Other				
Tinnitus	Potassium channel Kv7.2 (KCNQ2); KCNQ3	Mouse and cell culture studies suggest improving the activity of KCNQ2 and KCNQ3 could help prevent tinnitus. In mice, decreased Kcnq2 and Kcnq3 activity was associated with the development of tinnitus-associated hyperactivity in the dorsal cochlear nucleus of the brain. In mice, pretreatment with the nonspecific potassium channel activator Potiga retigabine decreased development of noise exposure-induced tinnitus compared with saline pretreatment. Next steps include developing subtype-selective KCNQ agonists and determining the window for when targeting KCNQ2 and KCNQ3 would be effective in preventing tinnitus. Meda AB, GlaxoSmithKline plc and Valeant Pharmaceuticals International Inc. market Potiga, a potassium channel opener and potentiator of γ -aminobutyric acid (GABA), to treat seizures. The drug also is in Phase II testing to treat pain. SciBX 6(25); doi:10.1038/scibx.2013.634 Published online June 27, 2013	Unpatented; available for partnering	Li, S. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online May 28, 2013; doi:10.1073/pnas.1302770110 Contact: Thanos Tzounopoulos, University of Pittsburgh School of Medicine, Pittsburgh, Pa. e-mail: thanos@pitt.edu
Various				
Anemia; cachexia	Fibroblast activation protein (FAP)	Mouse studies suggest restoring normal levels of FAP expression in healthy tissues could help prevent cancer-associated cachexia and anemia. In mice, depletion of <i>Fap</i> -expressing cells decreased muscle mass and hematopoiesis compared with no depletion. In mouse models for colon cancer and pancreatic ductal adenocarcinoma, compared with in healthy mice, Fap levels were lower in skeletal muscle and bone marrow and correlated with anemia and loss of muscle mass. Next steps could include identifying a strategy to restore FAP expression to healthy tissues during cancer to help prevent cachexia and anemia. SciBX 6(25); doi:10.1038/scibx.2013.635 Published online June 27, 2013	Patent and licensing status undisclosed	Roberts, E.W. <i>et al. J. Exp. Med.</i> ; published online May 27, 2013; doi:10.1084/jem.20122344 Contact: Douglas T. Fearon, University of Cambridge, Cambridge, U.K. e-mail: dtf1000@cam.ac.uk

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			
Quantitative analysis of jumonji C domain-containing histone demethylase (JHDM)-targeting compounds	An assay for quantitative analysis of JHDM inhibitor activity could aid the development of lead compounds that target the class of enzymes. A fluorescent analog of a previously identified selective inhibitor of JHDMs was synthesized and used as a tracer molecule in a fluorescence polarization binding assay. The assay enabled quantitative assessments of the binding affinity and inhibitory activity of multiple JHDM chemical probes. Next steps include developing a panel of fluorescence polarization assays for additional JHDMs and using them to determine the specificity of additional JHDM probes. SciBX 6(25); doi:10.1038/scibx.2013.636 Published online June 27, 2013	Unpatented; licensing status not applicable	Xu, W. <i>et al. J. Med. Chem.</i> ; published online May 30, 2013; doi:10.1021/jm3018628 Contact: Xiang Wang, University of Colorado at Boulder, Boulder, Colo. e-mail: xiang.wang@colorado.edu
Disease models			
Serine racemase (<i>Srr</i>) knockout mouse model for schizophrenia	<i>Srr</i> knockout mice could be useful for identifying and evaluating therapies to treat schizophrenia. <i>Srr</i> is needed to make the NMDAR coagonist D-serine, which is known to be at low levels in patients with schizophrenia. <i>Srr</i> knockout mice had less brain D-serine than wild-type mice and showed schizophrenia-associated electrophysiological, biochemical and behavioral markers. Peripheral treatment with D-serine increased D-serine levels in the mouse brains compared with vehicle treatment and corrected schizophrenia-like phenotypes. Next steps could include testing other NMDAR modulators in <i>Srr</i> knockout mice. SciBX 6(25); doi:10.1038/scibx.2013.637 Published online June 27, 2013	Patent and licensing status undisclosed	Balu, D.T. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online May 31, 2013; doi:10.1073/pnas.1304308110 Contact: Joseph T. Coyle, Harvard Medical School, Boston, Mass. e-mail: joseph_coyle@hms.harvard.edu
Drug platforms			
Functionalized, methacrylated hyaluronic acid hydrogels for cartilage repair	Methacrylated hyaluronic acid hydrogels functionalized with N-cadherin mimetic peptides could be useful for cartilage repair. An <i>in vitro</i> cartilage formation assay using methacrylated hyaluronic acid hydrogels containing N-cadherin mimetic peptides increased human mesenchymal stem cell (MSC)-mediated chondrogenesis compared with the same hydrogel containing scrambled peptides. In immunodeficient mice, implantation of human MSC-seeded hydrogel disks containing N-cadherin mimetic peptides increased chondrogenesis compared with implantation of hydrogel disks containing scrambled peptides. Next steps include improving the cellular response to the hydrogel and analyzing the system in a large animal model. SciBX 6(25); doi:10.1038/scibx.2013.638 Published online June 27, 2013	Unpatented; licensing status not applicable	Bian, L. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online June 3, 2013; doi:10.1073/pnas.1214100110 Contact: Jason A. Burdick, University of Pennsylvania, Philadelphia, Pa. e-mail: burdick2@seas.upenn.edu
Modulating aryl hydrocarbon receptor (AHR) signaling to expand and differentiate hematopoietic progenitor cells	Modulating AHR signaling could improve the expansion and differentiation of hematopoietic progenitor cells and aid the development of blood products for therapeutic use. In cell culture, human induced pluripotent stem (iPS) cells were differentiated into hematopoietic progenitor cells. During expansion of the progenitor cells, an AHR agonist increased cell yields 600-fold compared with no treatment. In the expanded cell populations, chronic AHR agonism promoted differentiation into erythroid cells, whereas acute AHR antagonism promoted differentiation into megakaryocytes. Next steps include transplantation studies in mice to evaluate the functionality of the derived cells. SciBX 6(25); doi:10.1038/scibx.2013.639 Published online June 27, 2013	Patent pending; licensing details available from Boston University's Office of Technology Development	Smith, B.W. <i>et al. Blood</i> ; published online May 30, 2013; doi:10.1182/blood-2012-11-466722 Contact: George J. Murphy, Boston University School of Medicine, Boston, Mass. e-mail: gimurphy@bu.edu

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Sialic acid binding Ig-like lectin (SIGLEC)-engaging, tolerance-inducing antigenic liposomes (STALs) to suppress antibody response	<p>Mouse studies identified STALs that could help treat autoimmunity and inflammation. In mice, STALs displaying a protein antigen plus a CD22 ligand, which inhibits autoimmunity, decreased the antigen-specific antibody response during an antigen challenge compared with STALs that only displayed the protein antigen. STALs that had a CD22 ligand inhibited the antibody response by inducing B cell apoptosis. In a mouse model for hemophilia, STALs displaying factor VIII plus a CD22 ligand decreased anti-factor VIII antibody production and bleeding compared with CD22-lacking liposomes. Next steps could include testing the STALs in additional disease indications.</p> <p>SciBX 6(25); doi:10.1038/scibx.2013.640 Published online June 27, 2013</p>	Patent and licensing status unavailable	<p>Macauley, M.S. <i>et al. J. Clin. Invest.</i>; published online June 3, 2013; doi:10.1172/JCI69187 Contact: James C. Paulson, The Scripps Research Institute, La Jolla, Calif. e-mail: jpaulson@scripps.edu</p>
Imaging			
Chemical reporter approach using strain-promoted alkyne-azide cycloaddition (SPAAC) to track cellular glycoproteins	<p>A chemical approach to track glycoprotein storage in cells could help identify therapeutics to treat Niemann-Pick type C (NPC). NPC involves impaired cholesterol efflux from cellular vesicles and altered trafficking of glycoproteins. In NPC fibroblasts lacking Niemann-Pick disease type C1 (NPC1) or NPC2, the SPAAC chemical reporter detected accumulated glycoproteins in intracellular vesicles that were distinct from those that accumulated cholesterol. In NPC fibroblasts, a compound that lowered cholesterol accumulation decreased both glycoprotein and cholesterol levels compared with no treatment. Next steps could include using the technology to screen for new therapeutics to treat NPC.</p> <p>SciBX 6(25); doi:10.1038/scibx.2013.641 Published online June 27, 2013</p>	Patent and licensing status unavailable	<p>Mbua, N.E. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online June 3, 2013; doi:10.1073/pnas.1221105110 Contact: Richard Steet, The University of Georgia, Athens, Ga. e-mail: rsteet@ccrc.uga.edu Contact: Geert-Jan Boons, same affiliation as above e-mail: gjboons@ccrc.uga.edu</p>
Simultaneous PET and functional MRI (fMRI)	<p>Nonhuman primate studies suggest simultaneous imaging by PET and fMRI could be useful for correlating drug binding to functional changes in the brain. In nonhuman primates, PET-measured progressive displacement of receptor-bound dopamine by a dopamine receptor antagonist correlated with fMRI-measured increases in cerebral blood volume in the striatum. Changes in receptor occupancy and hemodynamic effects occurred in the same regions of the brain and with corresponding time courses. Next steps include evaluating the combined imaging method for monitoring the effects of various treatments.</p> <p>SciBX 6(25); doi:10.1038/scibx.2013.642 Published online June 27, 2013</p>	Unpatented; unlicensed	<p>Sander, C.Y. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online May 30, 2013; doi:10.1073/pnas.1220512110 Contact: Christin Y. Sander, Massachusetts General Hospital, Charlestown, Mass. e-mail: csander@mit.edu</p>
Markers			
Tumor necrosis factor- α (TNF- α) variants as prognostic markers in cancer	<p><i>In vitro</i>, <i>in vivo</i> and patient sample studies suggest TNF-α expression profiles could help guide cancer treatment. Malignant cells produce the inflammatory cytokine TNF-α, which can be in membrane-tethered or soluble forms. In cultured lung carcinoma cells and in mouse xenograft models, vector-induced expression of soluble TNF-α increased tumor growth, and expression of membrane-tethered TNF-α decreased tumor growth, compared with no TNF-α expression. In biopsies from patients with non-small cell lung cancer (NSCLC), higher expression of membrane-tethered TNF-α relative to soluble TNF-α correlated with increased survival. Next steps include determining how tumors with different ratios of membrane-tethered and soluble TNF-α respond to TNF-α antagonists.</p> <p>SciBX 6(25); doi:10.1038/scibx.2013.643 Published online June 27, 2013</p>	Unpatented; licensing status not applicable	<p>Ardestani, S. <i>et al. Cancer Res.</i>; published online May 23, 2013; doi:10.1158/0008-5472.CAN-13-0002 Contact: Pampee P. Young, Vanderbilt University, Nashville, Tenn. e-mail: pampee.young@vanderbilt.edu</p>

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Danaher Corp.	7	Wyss Institute for Biologically Inspired Engineering at Harvard University	5	Hemoglobin	6	RTK	8
Dartmouth College	8	Y		Histone deacetylase 6	9	S	
E		Yale University	4	HSD1	9	SAR1157403-7	4
Eisai Co. Ltd.	10		HSD11B1	9	Saracatinib	4
Eli Lilly and Co.	4,9	Target and compound index		Hydroxysteroid 11 β dehydrogenase 1	9	Serine palmitoyltransferase	11
F		A		I		Serine racemase	13
Follica Inc.	9	AHR	13	IGF1R	12	Serotonin (5-HT _{1B}) receptor	10
G		Androgen receptor	1	IGF-2	12	Serotonin (5-HT _{2C}) receptor	10
GlaxoSmithKline plc	12	APD356	10	IL-21	10	Serum albumin	6
H		ARN-509	1	Insulin-like growth factor-1 receptor	12	SET and MYND domain containing 3	11
Harvard University	5,6	Aryl hydrocarbon receptor	13	Insulin-like growth factor-2	12	ShK-186	10
I		Ataxin 1	11	J		Sialic acid binding Ig-like lectin	14
Indiana University	4	ATXN1	11	JHDM	13	SIGLEC	14
J		AZD0530	4	JNJ-393934062	4	Signal regulatory protein- α	8
Johnson & Johnson	1,4,7	B		Jumonji C domain-containing histone demethylase	13	SIRPA	8
K		Belviq	10	K		SLC6A8	10
Kennedy Krieger Institute	4	Bilirubin	6	KCNA3	10	SLC6A9	4
Kineta Inc.	10	C		KCNQ2	12	SMYD3	11
M		CD22	14	KCNQ3	12	Solute carrier family 6 creatine transporter member 8	10
Mayo Clinic	4	CD47	8	L		SPT	11
Meda AB	12	CD140B	8	Lorcaserin	10	Srr	13
Medical College of Wisconsin	7	CD221	12	LY500307	4	Sunitinib	8
Medivation Inc.	1	CHRNA7	4	LY2523199	9	Sutent	8
Memorial Sloan-Kettering Cancer Center	1	CRT	10	M		T	
N		c-Src tyrosine kinase	4	Mapk	11	Thalidomide	8
National Center for Advancing Translational Sciences	4	CSK	4	MSK1	11	Thalomid	8
National Institutes of Health	4	D		Myriocin	11	TLR9	10
P		Dexamethasone	11	N		TNF- α	14
Pfizer Inc.	4,8	Dodecyl creatine ester	10	N-Cadherin	13	Toll-like receptor 9	10
R		Dopamine	14	Nemo-like kinase	11	Transient receptor potential vanilloid 1	4
Radiation Control Technologies Inc.	8	DR103	3	Nicotinic acetylcholine receptor α_7	4	TRPV1	4
RIKEN Brain Science Institute	6	E		Niemann-Pick disease type C1	14	Tumor necrosis factor- α	14
Roche	7	Endothelin A receptor	4	NLK	11	U	
S		Enzalutamide	1	NMDAR	13	UnaG	6
Sanofi	4,5	Estrogen receptor- β	4	NPC1	14	V	
Siemens AG	7	Ethyl creatine ester	10	NPC2	14	Vitros	7
		F		P		VR1	4
		Factor VIII	14	PDGFR	8	X	
				PDGFR1	8	Xtandi	1
				PDGFRB	8	Z	
						ZD4054	4
						Zibotentan	4