

THIS WEEK

ANALYSIS

COVER STORY

1 **Alas, porphyria**

Treatment of acute porphyrias has long relied on hemin infusions, but the therapy has many drawbacks. A team led by Alnylam has created an siRNA therapeutic that reduces disease symptoms in mice. The company still needs a strategy to reduce misdiagnosis of the rare disorder.

TRANSLATIONAL NOTES

4 **Go west, FDA**

The FDA's first two centers for regulatory sciences were focused on modernizing methods and building bridges to academia. The agency now is at earlier drug development and has partnered with Stanford and UCSF to create a center focused on quantitative pharmacology that will give the FDA a foothold on the West Coast.

6 **Sanford-Burnham goes fourth**

The Sanford-Burnham Medical Research Institute has been seeking broader industrial partnerships that tap both its basic research and drug discovery expertise. Its new deal with Daiichi is the most expansive of its four recent industry partnerships.

TARGETS & MECHANISMS

8 **De-stressing glaucoma**

Glucocorticoids are standard care for a host of allergic and inflammatory eye conditions, but they can elevate intraocular pressure and result in secondary open-angle glaucoma. A chemical chaperone called sodium phenylbutyrate could eliminate that side effect, according to new research from the University of Iowa.

THE DISTILLERY

10 **This week in therapeutics**

Inhibiting BET bromodomain proteins to treat AML with chromosome 7q deletions; blocking HDACs in ECFCs *ex vivo* to promote post-transplant revascularization in ischemic tissue; antagonizing TGFB to increase bone strength in osteoporosis; and more...

17 **This week in techniques**

Inducible ablation of hypothalamic orexin neurons in mice to model narcolepsy; expansion of CD19-specific CAR T memory stem cells to improve adoptive T cell therapy; *in vitro* condensation of human MSCs to aid *in vivo* formation of functional cartilage; and more...

INDEXES

20 **Company and institution index**

20 **Target and compound index**

Alas, porphyria

By Amy Donner, Senior Editor

For over two decades, treatment of acute porphyrias has relied on hemin infusions that restore heme levels, but the therapy is slow to work, has side effects and is expensive. Now, a team led by **Alnylam Pharmaceuticals Inc.** has created an siRNA therapeutic that reduces disease symptoms in mice.¹

However, to really improve patient care, the company will also need a strategy to raise awareness and combat misdiagnosis of these rare disorders.

Alnylam is completing IND-enabling toxicity studies. The company expects to submit an IND in 2014 and start clinical trials in 2015.

Acute hepatic porphyrias are orphan diseases caused by enzyme deficiencies that disrupt heme biosynthesis and ultimately result in misregulation of aminolevulinic synthase-1 (ALAS-1), the first enzyme in the heme biosynthetic pathway. These inherited disorders are characterized by life-threatening acute attacks that include severe abdominal pain, muscle weakness, seizures and paralysis.

According to Karl Anderson, the prevalence of acute porphyrias is unknown. "It is estimated at about 5 per 100,000. We usually see only those who are sick and not the many others who have not yet developed symptoms," he said.

Anderson is director of the Porphyria Laboratory & Center and a professor in the Department of Preventative Medicine and Community Health at **The University of Texas Medical Branch**.

There are three known triggers of acute attacks: drugs that induce heme-dependent cytochrome P450 enzyme activity in the liver, hormonal changes, and starvation or extreme dieting.

Robert Desnick told *SciBX* that during an acute attack, patients often experience a prodromal period with brain fog and fatigue. Then, he said, "All hell breaks loose. They get excruciating abdominal pain that takes them to the emergency room."

However, the disease is often undiagnosed or misdiagnosed in the emergency room and mistaken for appendicitis because of the severe abdominal pain and a general lack of awareness about the condition.

Desnick is dean of genetic and genomic medicine and a professor and chair emeritus of genetics and genomic sciences at the **Icahn School of Medicine at Mount Sinai**.

Standard therapy for the attacks is i.v. infusion of hemin to restore heme levels. But patients often take a few days to respond, and because hemin cannot be stored in pharmacies, timely availability can be a problem.

In addition, transfusions are expensive, sometimes require an indwelling port and can damage veins because of the low solubility of hemin.

Recordati S.p.A. markets Normosang human hemin for treatment of hepatic porphyria. **uniQure N.V.** has the gene therapy AMT-021 in

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Phase I/II testing for porphyria. The therapy restores porphobilinogen deaminase, the enzyme most commonly disrupted by mutations that cause porphyria.

"Hemin has been a great drug, and we are grateful for it," said Desiree Lyon, executive director of the **American Porphyria Foundation (APF)**. But, she noted, a new therapy would be welcome.

Hemin has been the mainstay of porphyria therapy because it provides exogenous heme that can restore feedback control over *ALAS-1* expression. Overexpression of *ALAS-1* during acute attacks causes accumulation of the metabolites 5-aminolevulinic acid (ALA) and porphobilinogen (PBG). Research over the last few years has shown ALA to be the primary mediator of the disease's neurotoxicity.

"Because all patients have a similar chemical presentation despite different genetic mutations, it was tough to figure out which metabolite was causing the trouble or whether heme deficiency itself was the culprit. We are more and more confident that the toxic molecule is ALA," said Montgomery Bissell, director of the Porphyria Center and a professor of gastroenterology at the **University of California, San Francisco**.

Thus, Desnick and his colleague Makiko Yasuda joined forces with Alnylam to test whether directly targeting the overexpression of *ALAS-1* could prevent accumulation of ALA and PBG or restore normal metabolite levels and potentially provide a better therapy than hemin.

Yasuda is an assistant professor of genetics and genomic sciences at the Icahn School of Medicine.

Running interference

The team tested 45 siRNAs to find the most potent repressor of *Alas-1* mRNA expression in cultured mouse hepatocytes. The researchers

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then formulated the optimal siRNA, dubbed *Alas1*-siRNA1, in lipid nanoparticles to enable i.v. delivery to the liver.

In a mouse model of acute intermittent porphyria, prophylactic *Alas1*-siRNA1 prevented upregulation of *Alas-1* mRNA and accumulation of ALA and PBG in urine and plasma, whereas control siRNA did not. Protection against the acute attacks persisted for at least two weeks.

Next, the team compared how fast *Alas1*-siRNA1 and hemin produced their effects in a therapeutic setting. In the same mouse model, but after an attack was triggered, the siRNA reduced plasma and urine levels of ALA and PBG within 8 hours, whereas metabolite levels were stably elevated for at least 16 hours after hemin treatment.

Finally, the researchers looked at therapeutic and safety properties of *Alas1*-siRNA1. In the mice, the compound protected against neuromotor decline induced by repeated acute attacks and caused no change in liver alanine aminotransferase (Alt) and aspartate aminotransferase (Ast) levels, which are markers of liver function.

Furthermore, *Alas1*-siRNA1 did not lead to hepatic heme deficiency or affect the activity of the heme-dependent protein Cyp2e1 (cytochrome P450 family 2E1).

Bissell told *SciBX* that the demonstration that the siRNA does not deplete heme pools is particularly important. “You need to maintain heme production at a certain level to maintain function of heme proteins in the liver. Heme proteins turn over rapidly, and

there is a lot of heme cycling. You don’t want to alter ALA production so much that you disrupt this.”

The study was published in the *Proceedings of the National Academy of Sciences*.

“This paper provides preclinical proof of concept for our acute porphyria program,” said Alnylam CEO John Maraganore. Alnylam is developing ALN-AS1, an *N*-acetylgalactosamine (GalNAc)-siRNA conjugate targeting *ALAS-1* that can be delivered subcutaneously for the treatment of the acute hepatic porphyrias.

Rapid response

According to Bissell and the study’s authors, one key benefit of the siRNA is its fast kinetics versus hemin.

Desnick and Yasuda said that although the siRNA reduced ALA and PBG levels faster than hemin, exactly why needs additional study. “Exogenous heme works primarily by decreasing *ALAS-1* RNA production and by preventing the *ALAS-1* protein from maturing. To the best of my knowledge, there are no studies characterizing how long each of these processes take to become fully functional and what the durability of each is *in vivo*,” said Yasuda.

For hemin, Bissell said, “it takes about three days before there is a clear biochemical response, and by day three or four, there is a rapid clinical response.”

He added that there is often a lag in starting treatment because of delays in diagnosis. “When we’re talking about evaluating people in the emergency room, the key diagnostic test is urine PBG. But this is not available as an urgent test,” said Bissell, and it can take up to a week to get the results. “People can sit for days without a diagnosis.”

As with all orphan diseases, the low prevalence of porphyrias could present challenges in enlisting enough patients for clinical trials. In both the U.S. and Europe, networks of clinical centers focused on porphyria help recruit patients and manage trials for the disease. In the U.S., the Porphyrias Consortium

is one of the NIH’s Rare Disease Clinical Research Networks. The consortium includes five clinical centers in the U.S. and the APF. In Europe, the European Porphyria Network consists of 33 clinical centers in 21 countries and, like the APF, it aims to improve the diagnosis and treatment of porphyria.

Maraganore said that Alnylam plans to leverage the U.S. and European networks for its clinical trials of ALN-AS1.

Bissell also noted that Alnylam’s subcutaneous formulation of the siRNA offers a significant treatment advantage over i.v. hemin as it would move treatment out of an infusion center and into the home, thus saving money and bypassing complications associated with the infusion itself. “This would be a major step forward,” he said.

“If patients get access to a therapeutic that can head off these attacks at home, it would change the dynamic of the disease,” said Desnick.

Alnylam and the Icahn School of Medicine have filed patents related to the findings. Alnylam has additional patents associated with its ALN-AS1 program. Method of use patents held by Mount Sinai are exclusively licensed to Alnylam.

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uniQure N.V. (NASDAQ:QURE) Amsterdam, the Netherlands
University of California, San Francisco, Calif.
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“If patients get access to a therapeutic that can head off these attacks at home, it would change the dynamic of the disease.”

**—Robert Desnick,
Icahn School of Medicine
at Mount Sinai**

“This paper provides preclinical proof of concept for our acute porphyria program.”

**—John Maraganore,
Alnylam Pharmaceuticals Inc.**

Go west, FDA

By C. Simone Fishburn, Senior Editor

Whereas the FDA's first two centers for regulatory sciences were focused on modernizing methods for evaluating drugs and devices and on building bridges with local academia, the agency now is looking at early drug development.

To do so, the FDA partnered with **Stanford University** and the **University of California, San Francisco (UCSF)** to create a new center focused on quantitative pharmacology that will give it a foothold on the West Coast.

But the FDA has not moved its attention away from later stage activities; it also announced a new center at **The Johns Hopkins University** that will work on improvements in clinical evaluation, social and behavioral science and food safety.

When the FDA laid out its strategy for advancing regulatory science in 2011, a core goal was to tap into academia to access fresh thinking about regulatory processes and deliver training opportunities for agency scientists. The strategic plan's overall aims were to develop new tools, standards and approaches for assessing safety, efficacy, quality and performance of products regulated by the FDA.¹

As part of the plan, the agency launched its first two Centers of Excellence in Regulatory Science and Innovation (CERSIs) at the **University of Maryland, College Park** and **Georgetown University**. The former focuses on improving the review and evaluation of drugs and medical devices. The latter focuses on new methods for decision making, such as sharing research data and using bioinformatics.

The FDA's acting chief scientist Stephen Ostroff told *SciBX* that the first two CERSIs were pilot initiatives created close to home in order to facilitate direct interactions of FDA staff with academic scientists.

Now, the agency has included early drug development in its scope for innovation. In this second round, he said, the FDA solicited applications covering topics across the spectrum of drug development activities from better evaluation of early stage compounds to postmarketing surveillance. The result was the two new CERSIs at Johns Hopkins and Stanford-UCSF, which were awarded about \$750,000 and \$3.3 million by the FDA, respectively.

The Johns Hopkins CERSI's strategy for improving clinical studies and evaluation will involve collaborative training projects between scientists from the FDA and Johns Hopkins centers including the Center for Clinical Trials, the United States Cochrane Center, the Evidence-Based Practice Center and the Center for Drug Safety and Effectiveness.

The UCSF-Stanford center is the first in the CERSI network to be tasked with developing training programs and recommendations for improving preclinical safety and efficacy tests. In addition, the UCSF-Stanford CERSI will work on strategies for improving clinical trials and evaluation and on ways of harnessing diverse data sets through information sciences to accelerate new drug development.

Ostroff told *SciBX* that a key component of the CERSIs is the training of both FDA and academic scientists. One of the agency's priorities, he

said, is to get on the map as a career destination for graduate students, who often know little about the FDA. In addition, the agency wants to raise awareness of regulatory processes among scientists who will go on to work in the biotech industry.

"We want to work with academic centers around the country to generate a pipeline of individuals who will get excited about the work at the FDA," he said. "We also want to educate future industry employees on how the FDA operates."

"We want to work with academic centers around the country to generate a pipeline of individuals who will get excited about the work at the FDA. We also want to educate future industry employees on how the FDA operates."

—Stephen Ostroff,
Food and Drug Administration

Kathleen Giacomini, one of the heads of the Stanford-UCSF CERSI, told *SciBX* that "the FDA doesn't really have a presence [in the Bay Area], but the climate of innovation is here—so they don't have a sense of what's going on here. We need an FDA face on the West Coast."

Giacomini is chair of bioengineering and therapeutic sciences at the **University of California, San Francisco School of Pharmacy** and cochair of the UCSF Center for Quantitative Pharmacology.

Russ Altman, a professor of bioengineering, genetics and medicine and director of the

Biomedical Informatics Training Program at the **Stanford University School of Medicine**, will be the other head of the CERSI.

Informatics for innovation

The Stanford-UCSF CERSI will use informatics and data-driven computer models to develop predictions about drug metabolism, toxicity and effectiveness in different disease models and diverse populations.

Ostroff told *SciBX* that the new CERSI "sits in an area with very sophisticated computational capacity and strong modeling and clinical capacity."

UCSF said in a press release that the partnership will combine its School of Pharmacy's expertise in pharmacology and therapeutics with Stanford's strength in bioinformatics.

Giacomini said that the industry is "using old tools for early toxicology and drug safety." She added, "The FDA talks about 'modernizing the toolkit', so we need to ask how we can use biomarkers, SNPs and so on in the regulatory framework to give us more reliable safety signals."

Giacomini said that one starting point will be to develop tools that can improve the transition to the clinic, for example, by creating better predictions of the starting dose for first-in-human studies. That will require collecting data from the literature and making evidence-based recommendations on which biomarkers to follow or which endpoints to employ, she told *SciBX*.

Giacomini said that the CERSI would also like to address complex scenarios—such as progressive diseases for which information from diverse sources needs to be integrated. For example, she said, "how do you evaluate a multiple sclerosis therapeutic when the data come from numerous sources such as imaging and blood samples and the disease is progressing?"

Giacomini added that the Stanford group will mine available databases of electronic medical records and the FDA Adverse Event Reporting System to connect adverse events with biological signals that could be used in predictive modeling.

Ostroff noted that use of animal data from packages submitted to the FDA would require a separate agreement to be negotiated with the submitting party.

Giacomini said that the center also will focus on questions related to the slow timelines of drug development, such as how to develop three drugs that work together without it taking three times as long.

The CERSI's specific goals and metrics will be defined through a series of meetings between the FDA, Stanford and UCSF, Ostroff said. He does not expect the center's output to result directly in new FDA guidelines for preclinical safety and efficacy evaluation. Instead, he expects the work will build an information base to support the use of alternative methodologies in regulatory decisions.

In addition, Ostroff emphasized that the training component is a key aspect of what the CERSI will deliver. Giacomini said that the training could involve student exchanges and joint research projects between the FDA and the CERSI scientists from UCSF and Stanford.

Giacomini said that the **California Institute for Quantitative Biosciences** will also support the training provided by the CERSI. She added that the hope is that the center can help local biotechs develop better data packages for regulators by providing courses in regulatory sciences that would use FDA materials supplemented by Stanford and

UCSF coursework. In addition, she said, visiting scientists from the FDA could help educate academics and entrepreneurs about regulatory sciences.

"We envision a rich exchange program between the FDA and UCSF and Stanford scientists, as well as a broad curriculum in regulatory sciences including drugs, biologics, devices and diagnostics," she said.

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California Institute for Qualitative Biosciences,
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Food and Drug Administration, Silver Spring, Md.

Georgetown University, Washington, D.C.

The Johns Hopkins University, Baltimore, Md.

Stanford University, Stanford, Calif.

Stanford University School of Medicine, Stanford, Calif.

University of California, San Francisco, Calif.

University of California, San Francisco School of Pharmacy,
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Sanford-Burnham goes fourth

By Michael J. Haas, Senior Writer

Sanford-Burnham Medical Research Institute's outreach to industry has resulted historically in deals focused either on a narrow range of projects or the work of individual investigators, but the institute also has been seeking broader partnerships that tap both its basic research and drug discovery expertise. Its new deal with **Daiichi Sankyo Co. Ltd.** is its most expansive to date in terms of the range of projects and number of faculty members it will encompass.

Sanford-Burnham's expanding approach to industry partnerships contrasts with that of **The Scripps Research Institute**, which has moved away from the institute-wide agreements it had previously maintained with pharma.^{1,2}

Under the three-year deal, Sanford-Burnham will conduct preclinical studies to identify and validate new cardiovascular and metabolic disease targets. Researchers from the institute and Daiichi Sankyo's Cardiovascular-Metabolics Research Laboratories will perform screening to identify new compounds against those targets.

"We are escalating our pharma partnering efforts as part of our new 10-year plan" to speed the development and licensing of preclinical therapies, said Leslie Molony, the institute's senior director of business development.

The plan was announced this year and involves closer collaborations with existing partners, the formation of disease-focused teams to expand the internal cross talk between labs and clinics, and using the institute's small molecule drug discovery platform to validate preclinical candidates that could be licensed to pharmas.³

Indeed, Sanford-Burnham approached Daiichi and introduced it to the institute's resources and capabilities in March 2013, Molony said.

The pharma's decision to enter a collaboration "was based on a combination of several factors, including the number of key opinion leaders we have in cardiovascular and metabolic diseases and the capacity of the institute's Conrad Prebys Center for Chemical Genomics to conduct screening and drug discovery," she said.

Another factor influencing Daiichi's decision is the existing partnerships that Sanford-Burnham's Lake Nona campus in Orlando, Fla., has with **Florida Hospital** and **The Translational Research Institute for Metabolism and Diabetes** (TRI). Those deals, said Molony, could enable future translational research by giving Daiichi access to clinical resources.

TRI is a 2009 joint venture between Sanford-Burnham and Florida Hospital that gives the institute access to patients in the clinic and fosters cross talk between clinical and preclinical researchers.⁴

Sanford-Burnham and Daiichi have selected an undisclosed subset of cardiovascular and metabolic diseases to study, and a joint steering committee will choose specific projects. Molony said that all Sanford-Burnham researchers working in cardiovascular and/or metabolic diseases are free to propose their projects as candidates to the joint steering committee. Although not the institute's first pharma collaboration that is open to all comers, "this partnership with Daiichi Sankyo engages both our high-impact biomedical research and drug discovery capabilities and integrates the two in ways we have not been able to do in the past," she said.

Ownership of any new IP generated by the collaborators would be assigned to whichever party invents it, she said. The collaboration will focus on projects only as far as lead optimization. If Daiichi Sankyo wants to continue developing a project beyond that stage, it would do so in-house. Financial details of the partnership are undisclosed.

Daiichi markets or co-markets at least 12 therapies to treat cardiovascular or metabolic indications and is developing or co-developing at least 6 other clinical-stage therapies between the 2 disease areas (*see* Table 1, "Daiichi Sankyo's cardiovascular and endocrine/metabolic disease pipelines").

Table 1. Daiichi Sankyo's cardiovascular and endocrine/metabolic disease pipelines. The therapies that **Daiichi Sankyo Co. Ltd.** (Tokyo:4568) has in its pipelines to treat cardiovascular or endocrine/metabolic diseases may hint at the indications for which the pharma seeks to identify new targets and small molecule therapies through its partnership with the **Sanford-Burnham Medical Research Institute**.

Source: *BCIQ: BioCentury Online Intelligence*

Product	Description	Status	Partners
Cardiovascular disease pipeline			
Benicar/Olmec olmesartan	Angiotensin II type 1 receptor (AGTR1) antagonist	Marketed for hypertension	Pfizer Inc. (NYSE:PFE)
Azor/Sevikar olmesartan/amlodipine	Fixed-dose combination of olmesartan and amlodipine, a dihydropyridine calcium channel blocker	Marketed for hypertension	Not applicable
Benicar HCT olmesartan/hydrochlorothiazide	Fixed-dose combination of olmesartan and hydrochlorothiazide, a diuretic	Marketed for hypertension	Not applicable
Tribenzor/Sevikar HCT olmesartan/amlodipine/hydrochlorothiazide	Fixed-dose combination of olmesartan, amlodipine and hydrochlorothiazide	Marketed for hypertension	Not applicable
Effient prasugrel	Purinergic receptor P2Y G protein-coupled 12 (P2RY12; P2Y12) antagonist	Marketed for acute coronary syndrome; approved for ischemia/reperfusion injury	Eli Lilly and Co. (NYSE:LLY)
Lixiana edoxaban	Oral factor Xa inhibitor	Marketed for venous thromboembolism; in registration for fibrillation	Not applicable

(Continues on p. 7)

Table 1. Daiichi Sankyo's cardiovascular and endocrine/metabolic disease pipelines. (continued)

Product	Description	Status	Partners
Collatgene beperminogene perplasmid (AMG0001; HGF gene therapy)	Plasmid encoding human <i>hepatocyte growth factor/scatter factor (HGF/SF)</i>	Phase III for ischemia/reperfusion injury	Vical Inc. (NASDAQ:VICL); AnGes MG Inc. (Tokyo:4563)
		Phase III for peripheral vascular disease	Vical; AnGes MG; Mitsubishi Tanabe Pharma Corp. (Tokyo:4508)
CS-3150 (XL550)	Small molecule antagonist of the mineralocorticoid receptor	Phase II for hypertension	Exelixis Inc. (NASDAQ:EXEL)
Endocrine/metabolic disease pipeline			
Sapropterin hydrochloride (Biopten Granules 10%)	Chemically synthesized form of natural tetrahydrobiopterin (THB; BH4)	Marketed for phenylketonuria	Not applicable
Kuvan sapropterin hydrochloride	Small molecule formulation of tetrahydrobiopterin	Marketed for phenylketonuria	BioMarin Pharmaceutical Inc. (NASDAQ:BMRN); Merck KGaA (Xetra:MRK)
Tenelia teneligliptin	Dipeptidyl peptidase-4 (DPP-4; CD26) inhibitor	Marketed for type 2 diabetes	Mitsubishi Tanabe Pharma; Handok Inc. (KSE:002390)
Invokana canagliflozin	Sodium-glucose cotransporter 2 (SGLT2) inhibitor	Marketed for type 2 diabetes	Mitsubishi Tanabe Pharma; Johnson & Johnson (NYSE:JNJ)
Fastic/Starlix nateglinide	D-Phenylalanine amino acid derivative that blocks ATP-dependent potassium channel (KATP)	Marketed to prevent or treat type 2 diabetes	Novartis AG (NYSE:NVS; SIX:NOVN); Ajinomoto Co. Inc. (Tokyo:2802); Astellas Pharma Inc. (Tokyo:4503)
Cholestagel/Welchol colesvelam	Nonabsorbed bile acid sequestrant	Marketed for type 2 diabetes	Sanofi (Euronext:SAN; NYSE:SNY)
		Marketed for hypercholesterolemia	Sanofi; Valeant Pharmaceuticals International Inc. (TXS:VRX; NYSE:VRX)
Benicar/Olmeac olmesartan	AGTR1 antagonist	Phase III for diabetes	Not applicable
DS-1150	Solute carrier family 2 facilitated glucose transporter member 4 (SLC2A4; GLUT4) translocation enhancer	Phase I for diabetes	Not applicable
DS-1442	Cholesteryl ester transfer protein (CETP) inhibitor	Phase I for dyslipidemia	Not applicable
DS-7309	Glucokinase (GCK; GK) activator	Phase I for diabetes	Not applicable
DS-8500	G protein-coupled receptor 119 (GPR119) agonist	Phase I for diabetes	Not applicable

Four now

Daiichi Sankyo is the institute's fourth pharma partner in as many years.

In 2010, Sanford-Burnham and TRI partnered with **Takeda Pharmaceutical Co. Ltd.** to support the clinical development of an undisclosed obesity compound from the pharma.⁴ The two institutes renewed the deal with Takeda last year.⁵

In 2011, Sanford-Burnham signed two pharma deals: a three-year partnership with the Ortho-McNeill-Janssen Pharmaceutical Inc. unit of **Johnson & Johnson** to develop therapeutics against new targets in Alzheimer's disease (AD) and other neuropsychiatric indications,⁶ and a partnership with **Pfizer Inc.** to discover mechanisms and therapies for undisclosed diseases under the pharma's Global Centers for Therapeutic Innovation initiative.⁷ According to Molony, the 2011 partnership with Pfizer was the institute's first that was open to all comers.

In 2013, Sanford-Burnham entered into a separate partnership with Pfizer to identify and validate targets to prevent and treat insulin resistance and organ damage in obesity-related diabetes. Under the three-year deal, the pharma is using the institute's Conrad Prebys Center for Chemical Genomics to conduct high throughput screening for new targets using investigational compounds from Pfizer and a compound library from the NIH.⁵

In January, Sanford-Burnham announced that it had received an anonymous \$275 million gift to fund its 10-year drug development plan.

The institute expects to raise another \$225 million for the plan from philanthropists, investors and other sources over the next decade.³

Daiichi Sankyo did not respond to requests for comment.

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COMPANIES AND INSTITUTIONS MENTIONED

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The Translational Research Institute for Metabolism and Diabetes, Winter Park, Fla.

De-stressing glaucoma

By Benjamin Boettner, Associate Editor

Glucocorticoids are standard of care for a host of allergic and inflammatory eye conditions, but they elevate intraocular pressure about a third of the time and can result in secondary open-angle glaucoma. A chemical chaperone called sodium phenylbutyrate could eliminate that side effect, according to new research from **The University of Iowa**.¹

The findings may hand a new indication to two companies—one Swedish, one Canadian—that market oral versions of phenylbutyrate (PBA) for other diseases.

Glaucomas develop when aqueous fluid that enters the eye via the ciliary body is not effectively drained through structures including the trabecular meshwork. This leads to elevated intraocular pressure (IOP) and causes progressive degeneration of retinal ganglion cells and damage to the optic nerve. The ultimate result is visual field loss and blindness.

Primary open-angle glaucoma is the most common type and results from progressive increases in intraocular pressure that damage the optic nerve.² Primary glaucoma typically is treated with latanoprost, a generic prostaglandin F receptor (PTGFR) agonist.

Other drugs to treat primary open-angle glaucoma include **Allergan Inc.**'s adrenergic receptor α_2 (ADRA2) agonist Alphagan P brimonidine and Latisse bimatoprost, a prostaglandin F analog. **Merck & Co. Inc.** sells the adrenergic receptor β (ADRB) blocker Timoptic timolol.

There are no drugs specifically approved for secondary open-angle glaucoma including glucocorticoid-induced glaucoma. In addition, it is unclear why glucocorticoids cause the condition.

"The clinical standard for treating glucocorticoid-induced glaucoma is to either take patients off steroids or switch them to less potent ones. Being able to specifically lower the steroid-mediated rise in IOP could allow continued glucocorticoid treatments and improve overall therapeutic outcome in many patients," said Val Sheffield, a professor in the Department of Pediatrics at the University of Iowa and a **Howard Hughes Medical Institute** investigator.

Now, Sheffield's group has pinpointed a stress response in the endoplasmic reticulum (ER) as the root of glucocorticoid-induced glaucoma formation. To combat the problem, the researchers used PBA, which they previously showed alleviated ER stress in a mouse model of genetically linked glaucoma.³

The first step was generating a mouse model in which topical ocular administration of the glucocorticoid dexamethasone mimicked the loss of retinal ganglion cells, optic nerve damage and IOP that occur in primary glaucoma.

In cultured human trabecular meshwork cells and in the mice, ER stress markers were reversibly upregulated by dexamethasone. In mice with dexamethasone-triggered IOP, deletion of an ER stress regulator called DNA-damage-inducible transcript 3 (Ddit3; Chop10; Chop; Gadd153) or systemic administration of PBA significantly lowered IOP

and expression of ER stress markers compared with wild-type Chop expression or vehicle administration.

The group was led by Sheffield and Gulab Zode, who now is an assistant professor in the Department of Cell Biology and Immunology at the **University of North Texas Health Science Center**.

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

"The finding that suppression of ER stress by PBA, an existing drug, can prevent the glaucoma response to steroids is important and presents an unexplored avenue," said Joel Schuman, director of the **University of Pittsburgh Medical Center's** Eye Center and a professor of clinical and translational sciences at the **University of Pittsburgh School of Medicine**.

Formulating PBA

Sheffield said that his group is going to collaborate with the Department of Ophthalmology at the University of Iowa to test whether PBA can prevent IOP elevation in patients treated with glucocorticoids. "Our plan is to formulate a PBA eye drop, but the details are not in place at this time," he said.

PBA is marketed by **Swedish Orphan Biovitrum AB** as Ammonaps sodium phenylbutyrate in an oral formulation to treat urea cycle disorder. **Valeant Pharmaceuticals International Inc.** sells an orally available desalted glycerol derivative called HPN-100 for the indication. Neither company returned calls for comment.

Schuman and Robert Weinreb both said that a new formulation of PBA—preferably for local delivery to the eye—is needed for the new ophthalmic indication.

"This could minimize systemic side effects. Local administration of PBA via eye drop or, alternatively, long-acting intracameral injection—if safe—does seem reasonable," said Weinreb, a distinguished professor and director of the Shiley Eye Center at the **University of California, San Diego**.

Weinreb and Jonathan Lin, an associate professor in the Department of Pathology and Department of Ophthalmology at the **University of California, San Diego School of Medicine**, wanted to see a more refined picture of what happens when glucocorticoids upregulate ER stress.

"Studies of aqueous dynamics to sort out whether the increased pressure is solely related to increased outflow resistance in the trabecular meshwork or also changes in the ciliary body would be of interest," said Weinreb.

Lin said that it would be "interesting to find out if misfolded proteins indeed accumulate on the anatomical level and how glucocorticoids and other triggers exactly cause the ER stress. Investigating the response in knockout situations for other ER stress genes could provide a way to test for specific requirements and work out which parts of the ER stress response confer the pathogenic effects."

Lin is investigating how the unfolded protein response senses ER stress in diseases involving retinal degeneration.

Schuman said that one approach could be to manipulate human primary trabecular meshwork cells and human organ cultures in which

"The finding that suppression of ER stress by PBA, an existing drug, can prevent the glaucoma response to steroids is important and presents an unexplored avenue."

— Joel Schuman,
University of Pittsburgh
Medical Center

“We believe that ER stress is not limited to glucocorticoid glaucoma. Currently, we are studying the involvement of ER stress in general primary glaucoma.”

—Val Sheffield,
The University of Iowa

eukaryotic translation initiation factor 2 α kinase 3 (EIF2AK3; PERK), which functions upstream of Chop activation. He suggested that local application of PERK inhibitors to the eye could circumvent the side effects of systemic versions.

Marciniak is a senior clinical research fellow at the **Medical Research Council** based at the **Cambridge Institute for Medical Research**. He studies the unfolded protein response in pulmonary and other diseases.

Playing chaperone

In the longer term, Sheffield's group wants to use PBA more broadly in primary glaucoma.

“If steroids promote increased flux of proteins through the secretory pathway to cause ER stress, and this would be more common in glaucoma, then ER stress-directed treatments might have broader benefits in this condition,” said Marciniak.

Sheffield said, “We believe that ER stress is not limited to glucocorticoid glaucoma. Currently, we are studying the involvement of ER stress in general primary glaucoma. We are also planning to conduct a clinical study on primary open-angle glaucoma-associated

eyes obtained from cadavers are perfused and treated with molecules that induce or manipulate the ER stress response.

Stefan Marciniak said that given the benefits of *Chop* gene deletion in the mouse model of glaucoma, it would make sense to attempt to target

ER stress-causing mutations to test whether PBA can reduce elevated IOP in these patients.”

The findings have not been patented.

Boettner, B. *SciBX* 7(22); doi:10.1038/scibx.2014.634
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Allergan Inc. (NYSE:AGN), Irvine, Calif.
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Howard Hughes Medical Institute, Chevy Chase, Md.
Medical Research Council, London, U.K.
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University of North Texas Health Science Center, Fort Worth, Texas
University of Pittsburgh Medical Center, Pittsburgh, Pa.
University of Pittsburgh School of Medicine, Pittsburgh, Pa.
Valeant Pharmaceuticals International Inc. (TSX:VRX; NYSE:VRX), Montreal, Quebec, Canada

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This week in therapeutics

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

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

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cancer				
Acute myelogenous leukemia (AML); myelodysplastic syndrome (MDS)	BET bromodomain proteins; myeloid-lymphoid or mixed-lineage leukemia 3 (MLL3)	<i>In vitro</i> and mouse studies suggest BET inhibition could help treat AML with chromosome 7q deletions. In mouse hematopoietic stem and progenitor cells (HSPCs), shRNA knockdown of <i>Mll3</i> , a tumor suppressor in the chromosome 7q region that often is deleted in AML, resulted in cells that induced a leukemic phenotype when transplanted into mice. The BET inhibitor JQ1 increased survival in the mice compared with vehicle. Next steps include testing BET inhibitors in patients with AML who have 7q deletions and do not respond to current treatments. At least six companies have BET bromodomain inhibitors in Phase I testing to treat various cancers. JQ1 is a research reagent.	Unpatented; licensing status not applicable	Chen, C. <i>et al. Cancer Cell</i> ; published online May 1, 2014; doi:10.1016/j.ccr.2014.03.016 Contact: Scott W. Lowe, Memorial Sloan-Kettering Cancer Center, New York, N.Y. e-mail: lowes@mskcc.org
Brain cancer	Human cytomegalovirus (CMV)	Studies in patients suggest autologous, CMV-specific T cell infusions could help treat glioblastoma multiforme (GBM). CMV is found in GBM tissues, and past studies have suggested the virus could contribute to cancer progression. CMV-specific T cells isolated from patients with GBM were expanded <i>ex vivo</i> . In 11 patients with recurrent GBM receiving standard of care, infusion of autologous, CMV-specific T cells resulted in a median overall survival of about 57 weeks, and 4 patients were progression free for the duration of the study. Next steps include evaluating the therapy in a Phase II trial.	Patented; available for licensing	Schuessler, A. <i>et al. Cancer Res.</i> ; published online May 4, 2014; doi:10.1158/0008-5472.CAN-14-0296 Contact: Rajiv Khanna, Queensland Institute of Medical Research, Herston, Queensland, Australia e-mail: rajivk@qimr.edu.au
Cancer	Fas ligand (TNF superfamily, member 6; FASL); VEGF-A; cyclooxygenase (COX)	Mouse studies suggest inhibiting FASL could improve the efficacy of T cell-based cancer therapies. In multiple mouse models of cancer, an anti-VEGF-A antibody plus a COX inhibitor increased tumor-infiltrating, Cd8 ⁺ T cells and decreased both tumor growth and FasL expression in tumor vasculature compared with no treatment. In tumor-bearing mice, pretreatment with an anti-FasL antibody followed by adoptive tumor-specific T cell transfer therapy led to greater survival and T cell infiltration into the tumor than adoptive T cell transfer alone. Next steps could include testing the combined inhibition of VEGF-A and COX in clinical trials of adoptive T cell therapy or cancer vaccines.	Unpatented; licensing status not applicable	Motz, G.T. <i>et al. Nat. Med.</i> ; published online May 4, 2014; doi:10.1038/nm.3541 Contact: George Coukos, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pa. e-mail: george.coukos@chuv.ch

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cancer	NDC80 homolog kinetochore complex component (NDC80); NIMA-related kinase 2 (NEK2)	SAR studies suggest compounds that block the interaction between NDC80 and NEK2 could help treat cancer. <i>In vitro</i> , a series of 4-aryl-N-arylcarbonyl-2-aminothiazoles selectively blocked the NEK2 binding site on NDC80. In a panel of tumor cell lines, compounds from the series inhibited proliferation with nanomolar IC ₅₀ values. In a mouse xenograft model of breast cancer, the lead compound decreased tumor growth compared with vehicle. Next steps include preclinical development of related compounds for cancer indications. Taivex Therapeutics Corp. has licensed the compounds and has a NEK2-targeted molecule in preclinical development for cancer. SciBX 7(22); doi:10.1038/scibx.2014.638 Published online June 5, 2014	Patented; licensed to Taivex Therapeutics	Lee, Y.-S.E. <i>et al. J. Med. Chem.</i> ; published online April 28, 2014; doi:10.1021/jm401990s Contact: Jiann-Jyh Huang, National Chiayi University, Chiayi City, Taiwan e-mail: lukehuang@mail.ncyu.edu.tw
Cancer	Proteasome subunit- β type 4 (PSMB4); serine hydroxymethyltransferase 2 mitochondrial (SHMT2)	<i>In vitro</i> and mouse studies suggest inhibiting PSMB4 or SHMT2 could help treat cancer. Mapping recurrently amplified regions in 392 primary human cancers and conducting functional RNAi screening identified new potential oncogenic drivers including <i>PSMB4</i> and <i>SHMT2</i> . In cultured fibroblasts, overexpression of PSMB4 increased growth and survival compared with wild-type PSMB4 expression. In multiple human tumor types, expression of <i>PSMB4</i> and <i>SHMT2</i> was higher than that in healthy tissue, with high expression correlating with poor relapse-free survival. Researchers did not disclose next steps, which could include screening for inhibitors of PSMB4 and SHMT2. SciBX 7(22); doi:10.1038/scibx.2014.639 Published online June 5, 2014	Patent and licensing status undisclosed	Lee, G.Y. <i>et al. Cancer Res.</i> ; published online April 22, 2014; doi:10.1158/0008-5472.CAN-13-2683 Contact: Richard M. Neve, Genentech Inc., South San Francisco, Calif. e-mail: never@gene.com
Cancer	Receptor activator of NF- κ B ligand (RANKL; TNFSF11)	<i>In vitro</i> and mouse studies suggest inhibiting RANKL could help promote antitumor immunity. In a mouse model of antigen-expressing melanoma, an anti-RANKL antibody prevented thymic depletion of melanoma-specific T cells, and it increased survival compared with an isotype control. Next steps include measuring the antigen-specific T cell response in patients with cancer treated with an anti-RANKL antibody. Amgen Inc. and Daiichi Sankyo Co. Ltd. market the anti-RANKL mAb Xgeva denosumab to treat bone cancer and osteoporosis. At least two other companies have anti-RANKL antibodies in Phase I testing for the same indications. SciBX 7(22); doi:10.1038/scibx.2014.640 Published online June 5, 2014	Patent application filed; unavailable for licensing	Khan, I.S. <i>et al. J. Exp. Med.</i> ; published online April 21, 2014; doi:10.1084/jem.20131889 Contact: Mark S. Anderson, University of California, San Francisco, Calif. e-mail: manderson@diabetes.ucsf.edu

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Cancer	SET and MYND domain containing 3 (SMYD3); K-Ras (KRAS); MAP kinase kinase 1 (MAP2K1; MEK1); MAP2K2 (MEK2)	<p>Mouse studies suggest antagonizing SMYD3 could be useful for treating cancers driven by <i>KRAS</i> mutations. In mouse models of <i>Kras</i>-driven pancreatic and lung cancer, <i>Smyd3</i> knockout mice showed less tumor growth and longer survival than wild-type controls. In one of the mouse models, <i>Smyd3</i> deletion increased the potency of the MEK1 and 2 inhibitor Mekinist trametinib, which acts downstream of KRAS. Next steps include identifying and testing SMYD3 inhibitors. GlaxoSmithKline plc markets Mekinist to treat metastatic melanoma with BRAF V600E or V600K mutations. The drug is in Phase II testing to treat patients with non-small cell lung cancer (NSCLC) with <i>KRAS</i> mutations.</p> <p>SciBX 7(22); doi:10.1038/scibx.2014.641 Published online June 5, 2014</p>	Unpatented; licensing status not applicable	<p>Mazur, P.K. <i>et al. Nature</i>; published online May 21, 2014; doi:10.1038/nature13320 Contact: Julien Sage, Stanford University School of Medicine, Stanford, Calif. e-mail: julsage@stanford.edu Contact: Or Gozani, Stanford University, Stanford, Calif. e-mail: ogozani@stanford.edu</p>
Pancreatic cancer	Actin $\alpha 2$ smooth aorta muscle (ACTA2; α -SMA); smoothed (SMO); sonic hedgehog homolog (SHH)	<p>Studies in mice and patients suggest depleting tumor stroma and fibrosis could be deleterious as opposed to helpful in treating pancreatic cancer. Past studies suggested tumor stroma and fibrosis impede drug delivery in patients with pancreatic ductal adenocarcinoma (PDAC). Thus, stroma- and fibrosis-depleting compounds such as hedgehog pathway inhibitors were pursued in the indication as potential complements to chemotherapy. In genetic mouse models of PDAC, depletion of α-Sma⁺ stromal myofibroblasts, knocking out <i>Shh</i> or blocking hedgehog signaling with the SMO inhibitor saridegib all decreased tumor stroma and fibrosis but resulted in the development of a more aggressive disease phenotype and decreased survival compared with what was seen in control mice. In a cohort of 53 patients with PDAC, low levels of the myofibroblast marker α-SMA were associated with decreased overall survival ($p=0.0053$). Next steps include elucidating the role of various stromal cell populations in PDAC and determining whether there are specific scenarios in which stroma- and fibrosis-depleting drugs such as SMO inhibitors could have benefit. Infinity Pharmaceuticals Inc. discontinued saridegib in 2012 after interim data from the Phase II portions of trials in pancreatic cancer, chondrosarcoma and myelofibrosis showed that the compound would not meet its primary endpoint. Roche's Genentech Inc. unit markets the SMO inhibitor Erivedge vismodegib to treat basal cell carcinoma. The drug is being evaluated in multiple investigator-led Phase I and Phase II trials in pancreatic cancer. At least five other companies have SMO inhibitors in Phase III testing or earlier to treat various cancers.</p> <p>SciBX 7(22); doi:10.1038/scibx.2014.642 Published online June 5, 2014</p>	Findings for both studies unpatented; licensing status not applicable	<p>Rhim, A.D. <i>et al. Cancer Cell</i>; published online May 22, 2014; doi:10.1016/j.ccr.2014.04.021 Contact: Ben Z. Stanger, University of Pennsylvania, Philadelphia, Pa. e-mail: bstanger@exchange.upenn.edu Contact: Kenneth P. Olive, Columbia University Medical Center, New York, N.Y. e-mail: kenolive@columbia.edu</p> <p>Özdemir, B.C. <i>et al. Cancer Cell</i>; published online May 22, 2014; doi:10.1016/j.ccr.2014.04.005 Contact: Raghu Kalluri, The University of Texas MD Anderson Cancer Center, Houston, Texas e-mail: rkalluri@mdanderson.org</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Cardiovascular disease				
Arterial thrombosis	S100 calcium binding protein A9 (S100A9; calgranulin B; MRP14)	<p>Studies in mice and patients suggest S100A9 inhibitors could help prevent arterial thrombosis. Patients with acute myocardial infarction (MI) had higher S100A9 levels in arterial thrombi than patients with stable coronary artery disease (CAD). In mouse models of arterial thrombosis, <i>S100a9</i> deficiency decreased thrombin-induced platelet activation and platelet accumulation on arterial walls and increased time to thrombus formation compared with wild-type <i>S100a9</i> expression. In a thrombosis assay using human whole blood, an anti-S100A9 antibody decreased thrombus formation compared with an inactive control antibody. Next steps include investigating the role of S100A9 in venous thrombosis.</p> <p>Active Biotech AB and Teva Pharmaceutical Industries Ltd. have Nerventra laquinimod, an oral quinoline-3-carboxamide immunomodulator that targets S100A9, under EMA review to treat multiple sclerosis (MS). The compound also is in Phase II testing to treat Crohn's disease, lupus and Huntington's disease (HD).</p> <p>Active Biotech and Ipsen Group have tasquinimod (ABR-215050), an oral quinoline-3-carboxamide derivative that binds S100A9, in Phase III testing to treat prostate cancer and in Phase II trials to treat gastric, liver, ovarian and renal cancers.</p> <p>Active Biotech's paquinimod (ABR-215757), a small molecule quinoline-3-carboxamide immunomodulator that targets S100A9, is in Phase II testing to treat lupus.</p> <p>SciBX 7(22); doi:10.1038/scibx.2014.643 Published online June 5, 2014</p>	Patented; unlicensed	<p>Wang, Y. <i>et al. J. Clin. Invest.</i>; published online April 1, 2014; doi:10.1172/JCI70966</p> <p>Contact: Daniel I. Simon, University Hospitals Case Medical Center, Cleveland, Ohio</p> <p>e-mail: daniel.simon@uhhospitals.org</p>
Ischemia/ reperfusion injury	Histone deacetylase (HDAC)	<p>Mouse studies suggest enhancing the revascularization of primary endothelial colony-forming cells (ECFCs) <i>ex vivo</i> with HDAC inhibitors could help treat ischemia. In a mouse model of hind limb ischemia, transplantation of human primary ECFCs pretreated with the HDAC inhibitor trichostatin A improved blood flow recovery and decreased muscle necrosis compared with transplantation of untreated cells. Next steps include evaluating ECFCs pretreated with the pan-deacetylase inhibitor panobinostat in mouse models of vascular repair.</p> <p>Novartis AG's panobinostat is in Phase III testing to treat hematologic malignancies, Hodgkin's disease and multiple myeloma (MM). The compound also is in Phase I trials to treat sickle cell disease.</p> <p>Trichostatin A is a research reagent.</p> <p>SciBX 7(22); doi:10.1038/scibx.2014.644 Published online June 5, 2014</p>	Unpatented; licensing status not applicable	<p>Palii, C.G. <i>et al. Cell Stem Cell</i>; published online May 1, 2014; doi:10.1016/j.stem.2014.03.003</p> <p>Contact: Marjorie Brand, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada</p> <p>e-mail: mbrand@ohri.ca</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Endocrine/metabolic disease				
Obesity	Bacterial bile salt hydrolase (bsh)	<p>Mouse studies suggest bsh-expressing probiotics could help treat obesity. In mice raised under aseptic conditions, expression of bsh from <i>Escherichia coli</i> in the GI tract altered expression of liver and intestinal genes involved in lipid and cholesterol metabolism. In mice fed a normal or high-fat diet, colonization of the GI tract with bsh⁺ <i>E. coli</i> lowered weight gain and resulted in lower serum cholesterol and liver triglyceride levels than colonization with bsh⁻ <i>E. coli</i> and did not cause changes in food intake. Next steps could include testing the effects of bacteria expressing bsh in animal models of obesity.</p> <p>SciBX 7(22); doi:10.1038/scibx.2014.645 Published online June 5, 2014</p>	Patent and licensing status unavailable	<p>Joyce, S.A. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online May 5, 2014; doi:10.1073/pnas.1323599111</p> <p>Contact: Cormac G.M. Gahan, University College Cork, Cork, Ireland e-mail: c.gahan@ucc.ie</p>
Porphyria	Aminolevulinatase synthase-1 (ALAS-1)	<p>Mouse studies suggest an siRNA targeting <i>ALAS-1</i> could help treat porphyria. In an inducible mouse model of acute intermittent porphyria, prophylactic i.v. infusion of a lipid nanoparticle-encapsulated siRNA targeting <i>Alas-1</i> blocked hepatic <i>Alas-1</i> expression and prevented acute attacks of porphyria, and it decreased the accumulation of neurotoxic porphyrin precursors in urine and plasma compared with i.v. infusion of control siRNA-loaded nanoparticles. In mice with established porphyria, <i>Alas-1</i>-targeting siRNA infusion protected against neuromotor decline and decreased plasma levels of neurotoxic porphyrin precursors with better efficacy than control siRNA or hemin infusion, the current standard of care. Next steps include testing alternative formulations of the siRNA in the mouse and other models.</p> <p>Alnylam Pharmaceuticals Inc. has the <i>ALAS-1</i>-targeting siRNA therapeutic ALN-AS1 in preclinical testing to treat porphyria (<i>see Alas, porphyria, page 1</i>).</p> <p>SciBX 7(22); doi:10.1038/scibx.2014.646 Published online June 5, 2014</p>	Patented by the Icahn School of Medicine at Mount Sinai and Alnylam Pharmaceuticals; exclusively licensed to Alnylam	<p>Yasuda, M. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online May 12, 2014; doi:10.1073/pnas.1406228111</p> <p>Contact: Robert J. Desnick, Icahn School of Medicine at Mount Sinai, New York, N.Y. e-mail: robert.desnick@mssm.edu</p> <p>Contact: Maria I. New, same affiliation as above e-mail: maria.new@mssm.edu</p>
Musculoskeletal disease				
Osteoporosis	Transforming growth factor- β (TGFB; TGF β)	<p>Mouse studies suggest inhibiting TGFB signaling could help treat osteogenesis imperfecta (OI). In a mouse model of recessive OI, a pan-TGFB neutralizing antibody increased bone volume and strength and decreased OI-related lung pathology compared with a nonspecific control antibody. In a mouse model of dominant OI, the antibody increased bone volume compared with the control antibody. Next steps include evaluating an anti-TGFB therapeutic in a Phase I trial.</p> <p>InterMune Inc., Cipla Ltd., GNI Group Ltd., Ildong Pharmaceutical Co. Ltd. and Shionogi & Co. Ltd. market the TGFB inhibitor Pirfenex pirfenidone to treat pulmonary fibrosis. At least 10 other companies have TGFB inhibitors in Phase II or earlier testing in indications other than OI.</p> <p>SciBX 7(22); doi:10.1038/scibx.2014.647 Published online June 5, 2014</p>	Patent application filed; undisclosed company has option to license	<p>Grafe, I. <i>et al. Nat. Med.</i>; published online May 4, 2014; doi:10.1038/nm.3544</p> <p>Contact: Brendan Lee, Baylor College of Medicine, Houston, Texas e-mail: blee@bcm.edu</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Neurology				
Addiction	Adenosine A _{2A} receptor (ADORA _{2A})	<p>Nonhuman primate studies suggest antagonists of presynaptic ADORA_{2A} could help treat cannabis addiction. In cannabinoid-addicted nonhuman primates, an antagonist that selectively inhibits presynaptic ADORA_{2A} decreased self-administration of Δ⁹-tetrahydrocannabinol (THC) and an antagonist selective for postsynaptic ADORA_{2A} increased self-administration compared with vehicle. Next steps include testing presynaptic ADORA_{2A} antagonists in cannabis users.</p> <p>Kyowa Hakko Kirin Co. Ltd. markets the ADORA_{2A} antagonist Nouriasit istradefylline to treat Parkinson's disease (PD).</p> <p>At least seven other companies have ADORA_{2A}-targeted compounds in Phase II or earlier testing to treat various neurological conditions other than addiction.</p> <p>SciBX 7(22); doi:10.1038/scibx.2014.648 Published online June 5, 2014</p>	Unpatented; licensing status not applicable	<p>Justinová, Z. <i>et al. J. Neurosci.</i>; published online May 7, 2014; doi:10.1523/JNEUROSCI.5073-13.2014</p> <p>Contact: Sergi Ferré, National Institutes of Health, Bethesda, Md. e-mail: sferre@mail.nih.gov</p>
Narcolepsy	GABA _B receptor	<p>Mouse studies suggest specific GABA_B receptor agonists could help treat narcolepsy. In multiple mouse models of narcolepsy, the GABA_B receptor agonist <i>R</i>-baclofen normalized non-rapid eye movement sleep and promoted and consolidated sleep during light periods. It also decreased time spent in cataplexy compared with the narcolepsy drug Xyrem sodium oxybate. Next steps could include investigating <i>R</i>-baclofen-based therapeutics for narcolepsy.</p> <p>Jazz Pharmaceuticals plc markets Xyrem. Baclofen is a generic drug used to treat spasticity.</p> <p>SciBX 7(22); doi:10.1038/scibx.2014.649 Published online June 5, 2014</p>	Patent and licensing status unavailable	<p>Black, S.W. <i>et al. J. Neurosci.</i>; published online May 7, 2014; doi:10.1523/JNEUROSCI.0080-14.2014</p> <p>Contact: Thomas S. Kilduff, SRI International, Menlo Park, Calif. e-mail: thomas.kilduff@sri.com</p> <p>Contact: Akihiro Yamanaka, Nagoya University, Nagoya, Japan e-mail: yamank@riem.nagoya-u.ac.jp</p>
Schizophrenia	Not applicable	<p>Mouse studies suggest transplantation of hippocampal γ-aminobutyric acid (GABA)-containing interneurons could help treat schizophrenia. In a mouse model of schizophrenia, grafting live GABAergic interneuron precursors from donor embryos into the hippocampus decreased electrophysiological abnormalities and cognitive deficits compared with grafting killed precursors. Next steps could include testing GABAergic interneuron transplantation in other schizophrenia models and developing pharmacological strategies to increase GABAergic interneuron function.</p> <p>SciBX 7(22); doi:10.1038/scibx.2014.650 Published online June 5, 2014</p>	Unpatented; licensing status not applicable	<p>Gilani, A.I. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online May 2, 2014; doi:10.1073/pnas.1316488111</p> <p>Contact: Holly Moore, Columbia University, New York, N.Y. e-mail: hm2035@columbia.edu</p> <p>Contact: Stewart A. Anderson, Children's Hospital of Philadelphia, Philadelphia, Pa. e-mail: andersons3@emailchop.edu</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Ophthalmic disease				
Glaucoma	Not applicable	<p>Mouse studies suggest decreasing the chemical chaperone sodium 4-phenylbutyrate (PBA) could help prevent glucocorticoid-induced glaucoma. In a mouse model of glucocorticoid-induced glaucoma, PBA in drinking water decreased endoplasmic reticulum stress markers and intraocular pressure compared with water alone. Next steps include designing clinical trials to test PBA eye drop formulations in glucocorticoid-treated patients developing increased intraocular pressure (<i>see De-stressing glaucoma, page 8</i>).</p> <p>SciBX 7(22); doi:10.1038/scibx.2014.651 Published online June 5, 2014</p>	Unpatented; licensing status not applicable	<p>Zode, G.S. <i>et al. J. Clin. Invest.</i>; published online May 1, 2014; doi:10.1172/JCI69774</p> <p>Contact: Val C. Sheffield, The University of Iowa, Iowa City, Iowa e-mail: val-sheffield@uiowa.edu</p> <p>Contact: Gulab S. Zode, University of North Texas Health Science Center, Fort Worth, Texas e-mail: gulab.zode@unthsc.edu</p>
Other				
Other	Plasminogen activator inhibitor 1 (SERPINE1; PAI1)	<p>Mouse studies suggest inhibiting PAI1 could prevent age-related tissue dysfunction. In a mouse model of premature aging, <i>Pai1</i> deletion decreased age-related decline in pulmonary and renal function compared with wild-type expression. Also in the mouse model, a small molecule PAI1 inhibitor or <i>Pai1</i> deletion decreased cellular and serum markers of age-related senescence and increased survival compared with vehicle or normal <i>Pai1</i> expression. Next steps include testing the effects of PAI1 inhibitors in models of normal aging and age-related cardiovascular and neurological diseases.</p> <p>SciBX 7(22); doi:10.1038/scibx.2014.652 Published online June 5, 2014</p>	Patented; available for licensing	<p>Eren, M. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online April 28, 2014; doi:10.1073/pnas.1321942111</p> <p>Contact: Douglas E. Vaughan, Northwestern University Feinberg School of Medicine, Chicago, Ill. e-mail: d-vaughan@northwestern.edu</p>
Progeria	N-acetyltransferase 10 (NAT10)	<p><i>In vitro</i> studies suggest inhibiting NAT10 could help treat Hutchinson-Gilford progeria syndrome (HGPS) and other laminopathies. In a cell-based model of HGPS, a lysine acetyltransferase-inhibiting compound normalized the aberrant nuclear morphology that is a hallmark of progeria. A chemical derivative of the compound called Remodelin was generated and shown to inhibit NAT10. In cells from patients with HGPS, Remodelin decreased multiple disease markers including misshapen nuclei, DNA damage and excess microtubule anchorage compared with no treatment. Next steps include evaluating the potential of Remodelin or other NAT10 inhibitors in <i>in vivo</i> models of HGPS.</p> <p>SciBX 7(22); doi:10.1038/scibx.2014.653 Published online June 5, 2014</p>	Patent application filed covering Remodelin and structural analogs for the treatment of progeria; licensing discussions under way with undisclosed companies	<p>Larrieu, D. <i>et al. Science</i>; published online May 2, 2014; doi:10.1126/science.1252651</p> <p>Contact: Stephen P. Jackson, The Wellcome Trust/Cancer Research UK Gurdon Institute, Cambridge, U.K. e-mail: s.jackson@gurdon.cam.ac.uk</p> <p>Contact: Raphaël Rodriguez, Centre National de la Recherche Scientifique (CNRS), Gif-sur-Yvette, France e-mail: raphael.rodriguez@cns.fr</p>

This week in techniques

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

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

Approach	Summary	Licensing status	Publication and contact information
Assays & screens			
Semiconductor sequencing platform (SSP) for noninvasive diagnosis of incorrect chromosome numbers	<p>A benchtop SSP could help carry out noninvasive prenatal diagnosis of incorrect chromosome numbers using cell-free fetal DNA from maternal plasma. In retrospective karyotyping of 515 pregnant subjects, SSP identified trisomy 21, 18 and 13 with 99.94%–100% sensitivity and 99.46%–100% specificity, and it detected sex chromosome aneuploidies in 15 fetuses. In prospective karyotyping of 1,760 pregnancies, SSP identified 9 cases of trisomy 21, 3 cases each of trisomy 18 and 13, and 1 case of sex chromosome aneuploidy. Next steps include testing SSP on single-gene mutations.</p> <p>The study was performed in partnership with iGenomics Co. Ltd.</p> <p>SciBX 7(22); doi:10.1038/scibx.2014.654 Published online June 5, 2014</p>	Patent and licensing status undisclosed; iGenomics commercializing the technology and diagnostic	<p>Liao, C. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online May 5, 2014; doi:10.1073/pnas.1321997111</p> <p>Contact: Kang Zhang, University of California, San Diego, La Jolla, Calif. e-mail: k5zhang@ucsd.edu</p>
Disease models			
Mouse model of inducible narcolepsy	<p>Mice with inducible ablation of hypothalamic orexin (hypocretin; Hcrt) neurons could be useful models for evaluating narcolepsy therapeutics. Previous mouse models have been unable to replicate patient-specific onset of narcolepsy in adolescence or early adulthood and rarely showed narcolepsy-associated cataplexy. In the new model, induced ablation of the hypothalamic orexin neurons resulted in progressive onset of narcolepsy-associated symptoms, including fragmented sleep-wake cycles, weight gain without increased food intake and frequent episodes of cataplexy. Next steps could include using the model to study disease biology and evaluate therapeutic candidates.</p> <p>SciBX 7(22); doi:10.1038/scibx.2014.655 Published online June 5, 2014</p>	Patent and licensing status unavailable	<p>Tabuchi, S. <i>et al. J. Neurosci.</i>; published online May 7, 2014; doi:10.1523/JNEUROSCI.0073-14.2014</p> <p>Contact: Akihiro Yamanaka, Nagoya University, Nagoya, Japan e-mail: yamank@riem.nagoya-u.ac.jp</p> <p>Contact: Thomas S. Kilduff, SRI International, Menlo Park, Calif. e-mail: thomas.kilduff@sri.com</p>
<i>Recombination activating gene 2 (RAG2)</i> knockout pigs to model immunodeficiency and evaluate transplant-based therapies	<p>Pigs with <i>RAG2</i> knocked out could be useful as models of human immunodeficiencies and for testing transplant-based therapies. <i>In vitro</i>, engineered transcription activator–like effector nucleases (TALENs) were used to knock out <i>RAG2</i> in pig fibroblasts, which were then used in a somatic cell nuclear transfer procedure to generate eight <i>RAG2</i> knockout pigs. The <i>RAG2</i> knockout pigs failed to gain weight and showed a severe combined immunodeficiency phenotype that resulted in death or euthanasia before 29 days. A subsequent cohort of <i>RAG2</i> knockout pigs housed in cleaner conditions remained healthy for eight weeks and rapidly developed teratomas when injected with human induced pluripotent stem (iPS) cells. Next steps could include using the pigs to evaluate transplantation of stem cell–derived tissues.</p> <p>SciBX 7(22); doi:10.1038/scibx.2014.656 Published online June 5, 2014</p>	Unpatented; pigs available from the National Swine Resource and Research Center at the University of Missouri	<p>Lee, K. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online May 5, 2014; doi:10.1073/pnas.1406376111</p> <p>Contact: Jin-Hoi Kim, Konkuk University, Seoul, South Korea e-mail: jhkim541@konkuk.ac.kr</p> <p>Contact: Randall S. Prather, University of Missouri, Columbia, Mo. e-mail: pratherr@missouri.edu</p> <p>Contact: R. Michael Roberts, same affiliation as above e-mail: robertsr@missouri.edu</p>

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Drug delivery			
Fibrin hydrogel for controlled and sustained delivery of recombinant VEGF	<p><i>In vitro</i> and mouse studies suggest a fibrin hydrogel that provides controlled and sustained release of VEGF could help treat ischemia. The fibrin hydrogel contains a fusion protein made up of the N terminus of murine Vegf and an $\alpha 2$ plasmin inhibitor segment that binds fibrin plus a second fusion protein made up of the fibrinolysis inhibitor aprotinin and an $\alpha 2$ plasmin inhibitor segment. In immunodeficient mice, subcutaneous injection of the fusion protein-containing hydrogel resulted in stable release of Vegf over four weeks as it degraded. In two rodent models of hind limb and wound-healing ischemia, intramuscular injection of the fusion protein-containing hydrogel induced stable angiogenesis and increased blood flow to ischemic tissues compared with injection of an empty hydrogel. Next steps include repeating the ischemia experiments in large-animal models. Kuros Biosurgery AG has multiple fibrin hydrogel-based products in Phase II or earlier testing to promote bone repair or wound healing.</p> <p>SciBX 7(22); doi:10.1038/scibx.2014.657 Published online June 5, 2014</p>	Technology for binding growth factors to fibrin patented; licensed to Kuros Biosurgery	<p>Sacchi, V. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online April 28, 2014; doi:10.1073/pnas.1404605111</p> <p>Contact: Andrea Banfi, University of Basel, Basel, Switzerland e-mail: andrea.banfi@usb.ch</p>
Drug platforms			
Adoptive cell therapy using mutation-specific, CD4 ⁺ T cells in epithelial cancer	<p>A single-patient study suggests adoptive cell therapy using tumor mutation-specific, CD4⁺ T cells could help treat epithelial cancer. <i>Ex vivo</i>, patient dendritic cells were transfected with RNAs representing 26 different patient-specific cancer mutations identified via whole-exome sequencing and then cocultured with patient tumor-infiltrating lymphocytes (TILs). Patient CD4⁺ T cells specifically recognized dendritic cells presenting an ErbB2 interacting protein (ERBB2IP) antigen with an E805G mutation. In the patient, adoptive transfer of about 10 billion ERBB2IP^{E805G} mutation-specific, CD4⁺ T cells led to tumor regression that peaked at 7 months and disease stabilization for about 13 months. Next steps include evaluating mutations in additional cancers that would be recognized by T cells and amenable for use in mutation-specific, CD4⁺ T cell therapy.</p> <p>SciBX 7(22); doi:10.1038/scibx.2014.658 Published online June 5, 2014</p>	Patent application filed; licensing status unavailable	<p>Tran, E. <i>et al. Science</i>; published online May 9, 2014; doi:10.1126/science.1251102</p> <p>Contact: Steven A. Rosenberg, National Cancer Institute, Bethesda, Md. e-mail: sar@nih.gov</p>
Expansion of CD19-specific chimeric antigen receptor (CAR) T memory stem cells to improve adoptive T cell therapy	<p>Studies in patient samples and mice suggest increasing the subpopulation of T memory stem cells could help improve the efficacy of CAR-based T cell therapy. In populations of transplanted CD19-specific CAR T cells, a high frequency of cells resembling T memory stem cells correlated with increased expansion and persistence of the CAR T cells. In <i>ex vivo</i>, cultured CAR T cells, IL-7 and IL-15 increased the population of the T memory stem cells compared with IL-2. In tumor-bearing mice, adoptive therapy with IL-7- and IL-15-expanded CAR T cells delayed disease progression and resulted in increased survival compared with therapy using IL-2-expanded CAR T cells. Researchers did not disclose next steps, which could include optimizing CAR T cell culturing conditions to further boost the T memory stem cell subpopulation.</p> <p>SciBX 7(22); doi:10.1038/scibx.2014.659 Published online June 5, 2014</p>	Patent and licensing status undisclosed	<p>Yang, X. <i>et al. Blood</i>; published online April 29, 2014; doi:10.1182/blood-2014-01-552174</p> <p>Contact: Gianpietro Dotti, Baylor College of Medicine, Houston, Texas e-mail: gdotti@bcm.edu</p>

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Expansion of primitive, CD34 ⁺ cord blood cells with histone deacetylase (HDAC) inhibitors	<p>Mouse and <i>ex vivo</i> studies suggest HDAC inhibitors could be used to expand functional cord blood stem cells for transplant. In serum-free cultures of CD34⁺ hematopoietic progenitor cells, the HDAC inhibitor valproic acid (VPA) increased CD34⁺ cell numbers by 4.2-fold and multipotent CD34⁺ and thymus cell antigen 10 (Thy1; CD90)⁺ cell numbers by 144-fold compared with medium alone. In immunodeficient mice, transplanted human CD34⁺ cells treated with VPA and primed with cytokines showed greater engraftment than cells that were only primed with cytokines. Next steps could include assessing the efficacy of the method for replenishing all hematopoietic cell lineages in mice.</p> <p>SciBX 7(22); doi:10.1038/scibx.2014.660 Published online June 5, 2014</p>	Patent and licensing status unavailable	<p>Chaurasia, P. <i>et al. J. Clin. Invest.</i>; published online April 24, 2014; doi:10.1172/JCI70313</p> <p>Contact: Ronald Hoffman, The Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, N.Y. e-mail: ronald.hoffman@mssm.edu</p> <p>Contact: Pratima Chaurasia, same affiliation as above e-mail: pratima.chaurasia@mssm.edu</p>
<i>In vitro</i> condensation of human mesenchymal stem cells (MSCs) to aid <i>in vivo</i> formation of functional cartilage	<p><i>In vitro</i> studies suggest using human MSCs to form structures called condensed mesenchymal cell bodies (CMBs) can generate cartilage that could help promote joint regeneration and bone repair. <i>In vitro</i>, 2.5×10⁵ human MSCs supplemented with transforming growth factor-β3 (TGFB3) formed CMBs within a few days. CMBs layered onto a porous, decellularized bone matrix developed into cartilage that had normal stiffness in five weeks. In an <i>in vitro</i> model of cartilage defect, the fused CMBs filled the defect and integrated with surrounding tissue. Next steps include using CMBs in animal models to generate cartilage and bone grafts and initiating pre-IND discussions with the FDA.</p> <p>SciBX 7(22); doi:10.1038/scibx.2014.661 Published online June 5, 2014</p>	Covered by pending and filed patents; available for licensing	<p>Bhumiratana, S. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online April 28, 2014; doi:10.1073/pnas.1324050111</p> <p>Contact: Gordana Vunjak-Novakovic, Columbia University, New York, N.Y. e-mail: gv2131@columbia.edu</p>

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Company and institution index**A**

Active Biotech AB	13
Ajinomoto Co. Inc.	7
Allergan Inc.	8
Alnylam Pharmaceuticals Inc.	1,14
American Porphyria Foundation	2
Amgen Inc.	11
AnGes MG Inc.	7
Astellas Pharma Inc.	7

B

BioMarin Pharmaceutical Inc.	7
------------------------------	---

C

California Institute for Quantitative Biosciences	5
Cambridge Institute for Medical Research	9
Cipla Ltd.	14

D

Daiichi Sankyo Co. Ltd.	6,11
-------------------------	------

E

Eli Lilly and Co.	6
Exelixis Inc.	7

F

Florida Hospital Food and Drug Administration	4,19
---	------

G

Genentech Inc.	12
Georgetown University	4
GlaxoSmithKline plc	12
GNI Group Ltd.	14

H

Handok Inc.	7
Howard Hughes Medical Institute	8

I

Icahn School of Medicine at Mount Sinai	1,14
iGenomics Co. Ltd.	17
Ildong Pharmaceutical Co. Ltd.	14
Infinity Pharmaceuticals Inc.	12
InterMune Inc.	14
Ipsen Group	13

J

Jazz Pharmaceuticals plc	15
Johns Hopkins University	4
Johnson & Johnson	7

K

Kuros Biosurgery AG	18
Kyowa Hakko Kirin Co. Ltd.	15

M

Medical Research Council	9
Merck & Co. Inc.	8
Merck KGaA	7
Mitsubishi Tanabe Pharma Corp.	7

N

National Institutes of Health	3,7
National Swine Resource and Research Center at the University of Missouri	17
Novartis AG	7,13

P

Pfizer Inc.	6
-------------	---

R

Recordati S.p.A.	1
Roche	12

S

Sanford-Burnham Medical Research Institute	6
Sanofi	7
Scripps Research Institute	6
Shionogi & Co. Ltd.	14
Stanford University	4
Stanford University School of Medicine	4
Swedish Orphan Biovitrum AB	8

T

Taivex Therapeutics Corp.	11
Takeda Pharmaceutical Co. Ltd.	6
Teva Pharmaceutical Industries Ltd.	13
Translational Research Institute for Metabolism and Diabetes	6

U

uniQure N.V.	1
University of California, San Diego	8
University of California, San Diego School of Medicine	8
University of California, San Francisco	2,4
University of California, San Francisco School of Pharmacy	4
University of Iowa	8
University of Maryland, College Park	4
University of North Texas Health Science Center	8
University of Pittsburgh Medical Center	8
University of Pittsburgh School of Medicine	8
University of Texas Medical Branch	1

V

Valeant Pharmaceuticals International Inc.	7,8
Vical Inc.	7

.....

Target and compound index

4-Aryl- <i>N</i> -arylcarbonyl-2-aminothiazole	11
5-Aminolevulinic acid	2

A

α -SMA	12
α 2 Plasmin	18
ABR-215050	13

ABR-215757	13
ACTA2	12
Actin α 2 smooth aorta muscle	12
Adenosine A_{2A} receptor	15
ADORA _{2A}	15
ADRA2	8
ADRB	8
Adrenergic receptor α_2	8
Adrenergic receptor β	8
AGTR1	6
ALA	2
Alanine aminotransferase	3
ALAS-1	1,14
ALN-AS1	3,14
Alphagan P	8
Alt	3
AMG0001	7
Aminolevulinic synthase-1	1,14
Amlodipine	6
Ammonaps	8
AMT-021	1
Angiotensin II type 1 receptor	6
Aprotinin	18
Aspartate aminotransferase	3
Ast	3
ATP-dependent potassium channel	7
Azor	6

B

Baclofen	15
Bacterial bile salt hydrolase	14
Benicar	6
Benicar HCT	6
Bepermingene perplasmid	7
BET bromodomain proteins	10
BH4	7
Bimatoprost	8
Biopten Granules 10%	7
BRAF	12
Brimonidine	8
Bsh	14

C

Calcium channel	6
Calgranulin B	13
Canagliflozin	7
CD19	18
CD26	7
CD34	19
CD4	18
Cd8	10
CD90	19
CETP	7
Cholestagel	7
Cholesteryl ester transfer protein	7
Chop	8
Chop10	8
CMV	10
Colesevelam	7
Collatogene	7
COX	10
CS-3150	7
Cyclooxygenase	10
Cyp2e1	3
Cytochrome P450	1
Cytochrome P450 family 2E1	3

D

Δ^9 -Tetrahydrocannabinol	15
----------------------------------	----

Ddit3	8
Denosumab	11
Dexamethasone	8
Dipeptidyl peptidase-4	7
DNA-damage-inducible transcript 3	8
DPP-4	7
DS-1150	7
DS-1442	7
DS-7309	7
DS-8500	7

E

Edoxaban	6
Effient	6
EIF2AK3	9
ErbB2 interacting protein	18
ERBB2IP	18
Erivedge	12
Eukaryotic translation initiation factor 2 α kinase 3	9

F

Factor Xa	6
Fas ligand	10
FASL	10
Fastic	7

G

γ -Aminobutyric acid	15
G protein-coupled receptor 119	7
GABA	15
GABA _B receptor	15
Gadd153	8
GalNAc	3
GCK	7
GK	7
Glucokinase	7
GLUT4	7
GPR119	7

H

Hcrt	17
HDAC	13,19
Hemin	1
<i>Hepatocyte growth factor/scatter factor</i>	7
HGF gene therapy	7
HGF/SF	7
Histone deacetylase	13,19
HPN-100	8
Human cytomegalovirus	10
Human hemin	1
Hydrochlorothiazide	6
Hypocretin	17

I

IL-15	18
IL-2	18
IL-7	18
Insulin	7
Invokana	7
Istradefylline	15

J

JQ1	10
-----	----

K

K-Ras	12
KATP	7
KRAS	12

Kuvan	7	Orexin	17	Remodelin	16	Teneligliptin	7
L		P		S		Tetrahydrobiopterin	7
Laquinimod	13	P2RY12	6	S100 calcium binding	6	TGFβ	14
Latanoprost	8	P2Y12	6	protein A9	13	TGFB	14
Latisse	8	PAI1	16	S100A9	13	TGFB3	19
Lixiana	6	Panobinostat	13	Sapropterin hydrochloride	7	THB	7
M		Paquinimod	13	Saridegib	12	THC	15
MAP kinase kinase 1	12	PBA	8	Serine	8	Thy1	19
MAP2K1	12	PBG	2	hydroxymethyltransferase	2	Thymus cell antigen 10	19
MAP2K2	12	PERK	9	2 mitochondrial	11	Timolol	8
MEK1	12	Phenylbutyrate	8	SERPINE1	16	Timoptic	8
MEK2	12	Pirfenex	14	SET and MYND domain	14	TNF superfamily, member 6	10
Mekinin	12	Pirfenidone	14	containing 3	12	TNFSF11	11
Mineralocorticoid receptor	7	Plasminogen activator	6	Sevikar	6	Trametinib	12
MLL3	10	inhibitor 1	16	Sevikar HCT	6	Transcription activator-like	6
MRP14	13	Porphobilinogen	2	SGLT2	7	effector nuclease	17
Myeloid-lymphoid or mixed- lineage leukemia 3	10	Porphobilinogen deaminase	2	SHH	12	Transforming growth	7
N		Prasugrel	6	SHMT2	11	factor-β	14
N-acetylgalactosamine	3	Prostaglandin F	8	SLC2A4	7	Transforming growth	7
N-acetyltransferase 10	16	Prostaglandin F receptor	8	SMO	12	factor-β3	19
NAT10	16	Proteasome subunit-β type 4	11	Smoothened	12	Trichostatin A	13
Nateglinide	7	PSMB4	11	SMYD3	12	V	
NDC80	11	PTGFR	8	Sodium oxybate	15	Valproic acid	19
NDC80 homolog kinetochore complex component	11	Purinergic receptor P2Y G protein-coupled 12	6	Sodium phenylbutyrate	8	VEGF	18
NEK2	11	Q		Sodium-glucose cotransporter 2	7	VEGF-A	10
Nerventra	13	Quinoline-3-carboxamide	13	Solute carrier family 2 facilitated glucose	7	Vismodegib	12
NIMA-related kinase 2	11	R		transporter member 4	12	VPA	19
Normosang	1	R-baclofen	15	Sonic hedgehog homolog	12	W	
Nourias	15	RAG2	17	Starlix	7	Welchol	7
O		RANKL	11	T		X	
Olmeac	6	Receptor activator of NF-κB ligand	11	TALEN	17	Xgeva	11
Olmecartan	6	<i>Recombination activating gene 2</i>	17	Tasquinimod	13	XL550	7
				Tenelia	7	Xyrem	15

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