

## THIS WEEK

### ANALYSIS

#### COVER STORY

##### 1 **Personalizing cystic fibrosis *in vitro***

A team at University Medical Center Utrecht has developed a rapid and quantitative *in vitro* intestinal cell-based assay for function of cystic fibrosis transmembrane conductance regulator that could help identify prospective responders to targeted cystic fibrosis therapies. The researchers are now planning to test how well the approach can predict drug responses in the clinic.

#### TRANSLATIONAL NOTES

##### 4 **Uprooting CEEDD**

Although GlaxoSmithKline has quietly shuttered its Center of Excellence for External Drug Discovery, the pharma maintains it is not deprioritizing early program partnerships. Rather, GSK has shifted the establishment of early partnerships to its R&D scientists.

#### TARGETS & MECHANISMS

##### 6 **PNAG: broadening infection protection**

A multi-institutional team has added more than 20 pathogens to the list of known bacteria that express the capsule polysaccharide poly-*N*-acetylglucosamine. The findings open up new indications for Alopexx Vaccine and Alopexx Pharmaceuticals, which are developing a vaccine and an antibody for passive immunization, respectively.

##### 8 **Shrinking old hearts**

Boston researchers have discovered a blood-borne protein called growth differentiation factor 11 that can reverse age-related cardiac hypertrophy in mice. The protein could be used as a therapeutic agent once its long-term effects are understood.

#### THE DISTILLERY

##### 10 **This week in therapeutics**

Mitigating chemotherapy-induced infertility by blocking PI3K-PTEN-AKT signaling; treating osteoarthritis by disrupting TGF $\beta$ 1 signaling; alleviating neuropathic pain by inhibiting GRIN2B; and more...

##### 17 **This week in techniques**

Screening platform for detecting RAF dimerization in cells; phage display system for rapid mammalian expression of library hits; database of human phosphatase-substrate interactions; and more...

#### INDEXES

##### 18 **Company and institution index**

##### 18 **Target and compound index**

## Personalizing cystic fibrosis *in vitro*

By *Chris Cain, Senior Writer*

A team at **University Medical Center Utrecht** has developed a rapid and quantitative *in vitro* intestinal cell-based assay for CFTR function that could help prospectively identify responders to targeted cystic fibrosis therapies.<sup>1</sup> The researchers are now planning to test how well the approach can predict drug responses in the clinic.

Cystic fibrosis is caused by inherited mutations that reduce the function of the cystic fibrosis transmembrane conductance regulator (CFTR), an anion channel that helps keep the lung and intestinal epithelium hydrated and prevents the mucus buildup that leads to airway obstruction and infection.

The only marketed disease-modifying treatment for CF is Kalydeco ivacaftor, a small molecule CFTR potentiator from **Vertex Pharmaceuticals Inc.** that increases chloride transport through the channel. The drug was approved last year and is indicated to treat only the 4% of patients with CF carrying the G551D CFTR mutation.

Additional compounds from Vertex are in late-stage development to treat patients carrying  $\Delta$ F508 CFTR, the dominant disease-associated mutation, carried by about two-thirds of patients. These include VX-809 and VX-661, which are related compounds that act directly on mutant CFTR to correct its structure.

This year, VX-809 in combination with Kalydeco entered Phase III testing to treat patients carrying the  $\Delta$ F508 CFTR mutation. VX-661 is in Phase II testing with Kalydeco in the same population.

Despite these recent clinical advances, a significant fraction of patients with CF are not eligible for existing treatments because they carry rare mutations in which the efficacy of CFTR-targeted compounds has not been confirmed.

Even for those patient populations addressed by existing treatments, multiple academic teams and companies are seeking to develop additional compounds and combination therapies that will further improve CFTR function.<sup>2</sup>

The development and testing of CFTR-targeted compounds has been hampered by a lack of robust *in vitro* assays to quantify their activity. The gold standard for preclinical testing relies on cultured bronchial lung epithelial cells taken from lung explants.<sup>3</sup> However, access to these bronchial cells is limited because it requires sampling of patient tissue obtained after a lung transplant or biopsy, and their replicative potential is limited.

Instead of primary cells, many phenotypic screens rely on cell lines engineered to express CFTR mutants. But these cell lines are less physiologically relevant than patients' bronchial cells. Indeed, Jeffrey Beekman,

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SciBX is produced by BioCentury Publications, Inc. and Nature Publishing Group Joint Steering Committee: Karen Bernstein, Ph.D., Chairman & Editor-in-Chief, BioCentury; David Flores, President & CEO, BioCentury; Bennet Weintraub, Finance Director, BioCentury; Steven Inchoombe, Managing Director, Nature Publishing Group; Peter Collins, Ph.D., Publishing Director, NPG; Christoph Hesselmann, Ph.D., Chief Financial Officer, NPG.

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principal investigator of pediatric pulmonology at UMC Utrecht, told SciBX the lack of more accessible primary cell models has hindered the development and testing of CF treatments.

“A big issue for drug screening is to have a relevant cell model, and the field has generally agreed that it is important to move to primary cells as quickly as possible,” he said. “False positives are commonly identified in cell line-based screening approaches. Up to 90% of hits in these cells could not be validated in primary cells, and there may be false negatives that are simply missed.”

Thus, Beekman teamed up with Hans Clevers, professor of molecular genetics at the **Hubrecht Institute** and president of the **Royal Netherlands Academy of Arts and Sciences**, to develop a more accessible primary cell culture model for CFTR function.

The starting point for the model was a recent culture technique developed in Clevers’s lab that enabled intestinal stem cells to be grown into organoids that recapitulate the phenotype of *in vivo* intestinal tissue architecture.<sup>4,5</sup> “These primary adult stem cell cultures can be cultured for long times *in vitro* without genetic modifications and can be bio-banked,” said Beekman. To measure CFTR function in these organoids, the team treated them with forskolin, a commonly used pharmacological tool that activates the transporter by raising intracellular cyclic AMP (cAMP) levels.

By activating CFTR, forskolin induces fluid transport across the organoid’s intestinal epithelial barrier. The results were immediate and striking. “In organoids derived from mice, after 40

minutes some just pop because

they have so much fluid and tension in them due to the amount of fluid transport. We were amazed by the quantity and the speed of the response and the complete dependency on CFTR,” Beekman said.

Because the effect is dependent on CFTR function, organoids expressing defective CFTR should have less forskolin-induced swelling than those expressing normal CFTR. Compounds or conditions that improve CFTR function should restore the normal swelling response.

Indeed, in organoids derived from mouse intestinal cells, treatment with CFTR inhibitors or use of cells lacking *Cftr* or carrying  $\Delta F508$  *Cftr* reduced the forskolin-induced swelling compared with vehicle or wild-type controls. In  $\Delta F508$  *Cftr* organoids, corrector compounds increased forskolin-induced swelling compared with vehicle.

Beekman said the results were highly quantitative and provided a large signal-to-noise ratio that allowed the relative effects of different compounds to be measured.

“We plate 30–70 organoids per well, in triplicate, at several time points. More than 90% of the organoids in a single well respond quickly by swelling, allowing a uniform and accurate measurement between the three wells. The measurements are quantified by fluorescently labeling the organoids, and their relative increase is measured by confocal microscopy and quantified by image analysis of a series of images within a time frame of typically 60 minutes for human structures,” he said. “This quantification method is straightforward and fully compatible with high throughput screens.”

Having optimized the approach, the team next applied it to patient samples to determine its clinical relevance. In organoids derived from

**“This quantification method is straightforward and fully compatible with high throughput screens.”**

—Jeffrey Beekman,  
University Medical Center Utrecht

rectal biopsy tissue from patients with CF, those carrying *CFTR* mutations associated with mild defects in *CFTR* function had mild reductions in forskolin-induced swelling compared with healthy controls. Organoids from patients with mutations associated with severe defects in *CFTR* function, such as those homozygous for  $\Delta F508$  *CFTR*, had highly reduced swelling.

Finally, the team examined the effect of *CFTR* potentiators and correctors in the model. In samples homozygous for  $\Delta F508$  *CFTR*, combinations of compounds, including Kalydeco plus VX-809, improved *CFTR* function compared with individual compounds or vehicle controls. Organoids from individual patients showed highly reproducible responses, but responses varied among patient samples, suggesting the assay may be able to predict variation in response to the drug.

Results were published in *Nature Medicine*.

### Clinical correlations

CF researchers and industry scientists agreed the assay could be a powerful tool for compound validation and said it has the potential to guide clinical-trial design if the results are found to correlate with patient response.

Philip Thomas, professor of physiology at **The University of Texas Southwestern Medical Center**, told *SciBX* the new assay will have a key role in validating compounds in different *CFTR* mutant backgrounds. "It was a beautifully executed comprehensive study where they looked at inhibitors, correctors and activators," he said. "In principle it could be used as a primary screen, but the immediate application will be as a secondary assay for compound hits that are identified by screening in cell lines."

He added that the assay will be of particular use for predicting the response of patients with CF carrying rare mutations in *CFTR*. "I would guess that this will open up a whole host of rare genotypes for testing to see if they respond to Kalydeco," said Thomas. "For some of these patients, you have to realize that there might not be primary bronchial epithelial cells available because if you have less severe disease it's unlikely you are going to get a lung transplant."

In his own lab, Thomas, who is also a founder of **Reata Pharmaceuticals Inc.**, is studying *CFTR* folding and the mechanism of action of corrector compounds.

Fred Van Goor, head of biology for Vertex's CF research program, said the key advantage of the approach is its ease of application. "The one advantage that I see is that it is easier to look at specific genotypes of interest. We use cultured airway cells derived from patients with CF, but this approach could extend those studies. We have fairly effectively studied the effect of specific mutations in recombinant cell lines, but this is a nice way to study situations where there are multiple mutations."

Vertex has published preclinical work demonstrating the effect of Kalydeco in human bronchial epithelial cells in patients with other *CFTR* gating mutations besides G551D.<sup>6</sup> Last year, the company began a Phase III trial of Kalydeco in patients carrying the R117H mutation in *CFTR*.

David Weiner, CMO of **Proteostasis Therapeutics Inc.**, agreed the new model could be relevant for patients carrying rare CF mutations. "One of the tremendous potential applications here is if our compounds or other correctors can be developed beyond the  $\Delta F508$  mutant population. It can be difficult to do randomized controlled trials with

such small numbers of patients, so biological surrogate measures for clinical efficacy are particularly important."

Proteostasis President and CSO Peter Reinhart agreed and said the next steps will include validation of the model in additional laboratories and a comparison of results in the *in vitro* assay with *in vivo* patient response. "I think this assay is promising because it provides another way of establishing a set of correlations between preclinical data sets and clinical efficacy," he said.

The company has small molecule proteostasis modulators in lead optimization to treat patients who have  $\Delta F508$  *CFTR*.

Beekman now is using the organoid assay for CF diagnosis and to assess *CFTR* genotypes that are responsive to *CFTR*-restoring drugs such as Kalydeco and VX-809 *in vitro*. "We have the biggest clinical CF center in the Netherlands with about 400 patients with CF, and collaborate tightly with the CF centers in Rotterdam and The Hague. We are trying to see if we can make predictions about CF disease progression and development using this assay, and we are also trying to set up studies to show that drug efficacy *in vitro* also relates to drug efficacy *in vivo*," he said.

He said his lab has easy access to patient samples because it is standard procedure in the centers of Utrecht, Rotterdam and The Hague for patients newly diagnosed with CF to undergo a rectal section biopsy at 12 months old to measure the function of *CFTR* using electrical current *ex vivo*. The rectal biopsies can then be transported and organoid cultures started without affecting the diagnostic procedure.

Beekman also is collaborating with Gergely Lukacs, professor of physiology at **McGill University**, to test new combinations of corrector compounds in the assay.<sup>7</sup>

Clevers and Beekman have filed for patents covering the work, and the IP is available for licensing. Beekman said he is involved with setting up a not-for-profit foundation to handle the licensing of this and other assays using cultured organoids.

Cain, C. *SciBX* 6(23); doi:10.1038/scibx.2013.564

Published online June 13, 2013

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### COMPANIES AND INSTITUTIONS MENTIONED

**Hubrecht Institute**, Utrecht, the Netherlands  
**McGill University**, Montreal, Quebec, Canada  
**Proteostasis Therapeutics Inc.**, Cambridge, Mass.  
**Reata Pharmaceuticals Inc.**, Irving, Texas  
**Royal Netherlands Academy of Arts and Sciences**, Amsterdam, the Netherlands  
**University Medical Center Utrecht**, Utrecht, the Netherlands  
**The University of Texas Southwestern Medical Center**, Dallas, Texas  
**Vertex Pharmaceuticals Inc.** (NASDAQ:VRTX), Cambridge, Mass.

# Uprooting CEEDD

By C. Simone Fishburn, Senior Editor

Although **GlaxoSmithKline plc** has quietly shuttered its Center of Excellence for External Drug Discovery (CEEDD), the pharma maintains it is not deprioritizing early program partnerships. Instead, GSK thinks its R&D scientists have adopted the strategies brought in by CEEDD, and that there is no longer a need for a group dedicated to creating external alliances.

GSK established the CEEDD in 2005 as part of an initiative to build its pipeline by tapping into external talent. The program, which involved approximately 20 GSK scientists, ran through 2012 and brought 16 alliances to the organization. By 2011, however, external alliances were being generated increasingly by non-CEEDD scientists, and CEEDD was no longer the primary driver of external early stage opportunities (*see Figure 1, “Selected deals between GSK and biotechs or academic institutions”*).

The original goal of CEEDD was to establish partnerships for early programs that would share both the risk and the control with the partner. Previously, most of GSK’s early stage deals involved the pharma taking control of the asset. CEEDD deals involved an option-based structure including an up-front payment, sharing of risk up to an option point at Phase II proof of concept (POC) and milestones and royalty payments. At Phase III, optioned programs would be taken over by GSK.

The CEEDD group focused on identifying emerging biotech companies with platforms that could yield multiple products. Most CEEDD alliances involved 4–10 programs and were agnostic to therapeutic area. The program stages ranged from discovery to Phase II.

Partnerships included joint steering committees that set goals and oversaw operations. The intent was for GSK to keep a light touch in the relationship until shortly before the option decision. Research was done by the partners’ scientists, who were able to use GSK facilities to carry out experiments if needed via GSK’s Scinovo group. That group was set up in 2009 as part of the GSK open innovation model, and provides

**Figure 1. Selected deals between GSK and biotechs or academic institutions.** GlaxoSmithKline plc created the Center of Excellence for External Drug Discovery (CEEDD) in 2005 and closed the unit in 2012. During that time, CEEDD formed 16 partnerships with entities that typically had molecules in stages ranging from discovery to Phase II. The graph excludes partnerships outside the scope of CEEDD, including technology, preventative vaccine and diagnostic deals.

Source: BCIQ: BioCentury Online Intelligence; GSK

**“Now external partners are seen as adding something useful rather than intruding on your territory.”**

—Jason Gardner,  
GlaxoSmithKline plc

all GSK partners with access to consultants, the GSK CRO network and facilities for performing studies.

Jason Gardner, who led CEEDD and is now head of GSK’s regenerative medicine Discovery Performance Unit (DPU), described the culture in R&D before 2005 as risk averse, with a pipeline dominated by internal efforts.

For example, he said, one prevailing belief at GSK was that chemokine receptors weren’t druggable.

Despite that, in 2006 CEEDD investigated—and partnered with—**ChemoCentryx Inc.**, which has a platform of orally administered therapeutics that are highly selective for specific chemokine receptors. In 2009, GSK exercised an option to license exclusive worldwide rights to vercirnon (formerly Traficet-EN), a CC chemokine receptor 9 (CCR9; CDw199) antagonist that showed

positive Phase II data in inflammatory bowel disease (IBD). The molecule now is in four Phase III trials.

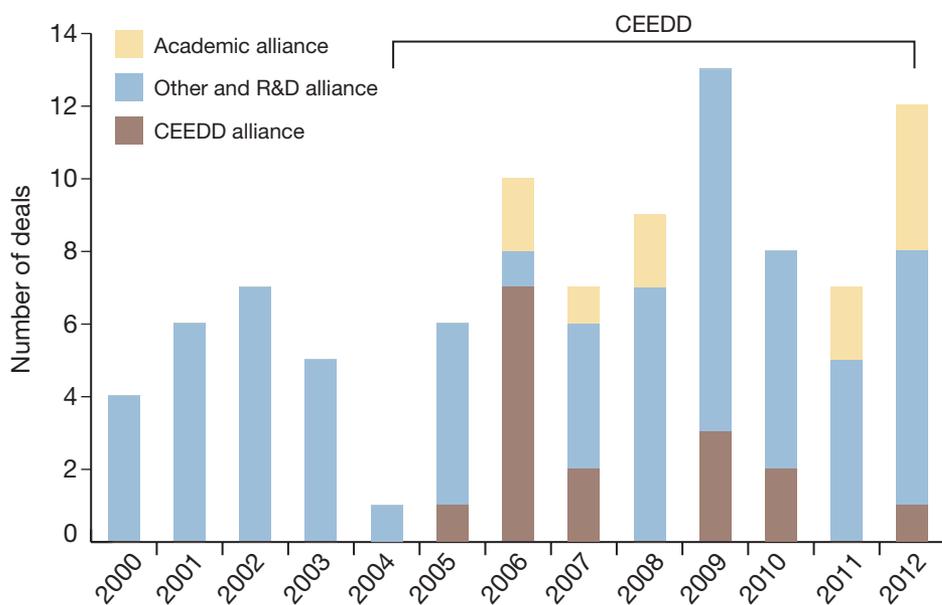
In 2011, GSK exercised an option for exclusive, worldwide rights to CCX354 for rheumatoid arthritis (RA). The CC chemokine receptor 1 (CCR1; CD191) antagonist is in Phase II testing.

CEEDD’s freedom to explore therapeutic areas without restriction led it to expand the activities of GSK. In 2009, the pharma did not have a rare diseases group and had not done any work on Duchenne muscular dystrophy (DMD). That year, CEEDD formed an alliance with **Prosenza B.V.**, which uses exon-skipping antisense technology to create RNA-based compounds for DMD.

GSK obtained exclusive worldwide rights to PRO051 and exclusive options to three other RNA-based compounds for DMD. The deal was expanded in 2010 to include two programs in DMD that target additional disease-related exons.

The lead compound from the alliance, drisapersen (PRO051), now is in Phase III testing with data expected in late 2013.<sup>1</sup>

The deal ultimately led GSK to establish a rare diseases group and enter a new disease space.



**An academic issue**

By late 2010, alliances with early stage biotechs were more common throughout GSK, but deals with academics were still sporadic. To remedy that, GSK established the Discovery Partnerships with Academia (DPAC) group in 2011 to identify discovery opportunities with translational potential in academic organizations.<sup>2</sup>

The push into academia has had clear results. Last year was by far GSK's most productive in terms of forming deals with universities and institutes.

Looking back, Gardner believes CEEDD's legacy was proving to GSK that the company could work productively with external entities and that it changed the overall shape of the pipeline. "Now external partners are seen as adding something useful rather than intruding on your territory," he said.

The number of internal programs at GSK has not changed significantly since 2005, but the number of external ones has grown from a small minority to about 50% of all the company's early stage programs, according to GSK spokesperson Melinda Stubbee.

The majority of CEEDD's scientists have remained with GSK. Successful programs at clinical POC stages have been transferred directly to clinical development groups. For example, the ChemoCentryx CCR9 program is now run by the Immuno-Inflammation Medicines Development Center. Other programs were transitioned during the past year for management by DPUs.

Fishburn, C.S. *SciBX* 6(23); doi:10.1038/scibx.2013.565  
Published online June 13, 2013

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**COMPANIES AND INSTITUTIONS MENTIONED**

**ChemoCentryx Inc.**, Mountain View, Calif.  
**GlaxoSmithKline plc** (LSE:GSK; NYSE:GSK), London, U.K.  
**Prosensa B.V.**, Leiden, the Netherlands



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# PNAG: broadening infection protection

by Michael J. Haas, Senior Writer

A multi-institutional team has added more than 20 pathogens to the list of known bacteria that express poly-*N*-acetylglucosamine, a bacterial capsule polysaccharide that provides a potentially broad-spectrum target for vaccination.<sup>1</sup> The findings open up new indications for **Aloplexx Vaccine LLC** and **Aloplexx Pharmaceuticals LLC**, which are already developing a vaccine and an antibody for passive immunization, respectively.

Over the past two decades, studies by multiple groups have identified poly-*N*-acetylglucosamine (PNAG), a polysaccharide encoded by a conserved four-gene locus, as a component of the surface capsule in at least seven species of bacteria.<sup>2-7</sup>

PNAG is one of many polysaccharides and other carbohydrate polymers found on the outer surface of bacteria that help prevent host macrophages and other cells from engulfing the pathogens.

Anti-PNAG antibodies have been found in circulation in humans and other animals, but these naturally occurring antibodies do not effectively kill PNAG-expressing bacteria or provide adequate immune protection against them, casting doubts on their prophylactic potential.<sup>8-10</sup>

Between 2005 and 2007, teams led by Gerald Pier showed that a deacetylated form of PNAG (dPNAG) elicited bacteria-killing antibodies in mice.<sup>6,11</sup> His teams also developed a human mAb—dubbed F598—that bound to both dPNAG and PNAG and killed bacteria.<sup>12</sup>

Pier is professor of medicine in microbiology and immunology at **Harvard Medical School** and a microbiologist in the department of medicine at **Brigham and Women's Hospital**.

In the current study, Pier's team investigated whether PNAG was expressed on bacteria and other pathogens in which the four-gene PNAG-producing locus has not yet been identified.

**Table 1. Adding pathogens to the PNAG list.** A study in *Proceedings of the National Academy of Sciences*<sup>1</sup> has added 24 more species of Gram-positive bacteria, Gram-negative bacteria, fungi, yeast and parasites to the existing list of pathogens that express the surface antigen poly-*N*-acetylglucosamine (PNAG). There now are about 40 known species of pathogens that express the molecule.

Pathogen species <sup>A</sup>	Pathogen type	Type of infection or disease <sup>B</sup>	Effect of anti-PNAG antibody <sup>C</sup>	
			<i>in vitro</i>	<i>in vivo</i>
<i>Bacillus subtilis</i>	Gram-positive bacteria	Commensal; food poisoning	Pathogen death	Unknown
<i>Campylobacter jejuni</i>	Gram-negative bacteria	Gastroenteritis	Unknown	Unknown
<i>Citrobacter rodentium</i>	Gram-negative bacteria	Veterinary (only in mice)	Unknown	Unknown
<i>Clostridium difficile</i>	Gram-positive bacteria	Nosocomial infections	Unknown	Unknown
<i>Enterococcus faecalis</i>	Gram-positive bacteria	Nosocomial infections	Pathogen death	Unknown
<i>Haemophilus ducreyi</i>	Gram-negative bacteria	Chancroid (genital ulcers)	Unknown	Unknown
<i>H. influenzae</i>	Gram-negative bacteria	Bacteremia, pneumonia, other infections	Unknown	Unknown
<i>Helicobacter pylori</i>	Gram-negative bacteria	Gastritis; gastric ulcers	Unknown	Unknown
<i>Listeria monocytogenes</i>	Gram-positive bacteria	Listeriosis	Unknown	Pathogen death
<i>Mycobacterium smegmatis</i>	Gram-positive bacteria	None known	Unknown	Unknown
<i>M. tuberculosis</i>	Gram-positive bacteria	Tuberculosis	Unknown	Unknown
<i>Neisseria meningitidis</i>	Gram-negative bacteria	Meningitis	Pathogen death	Pathogen death
<i>N. gonorrhoeae</i>	Gram-negative bacteria	Gonorrhea	Pathogen death	Unknown
<i>Salmonella enterica</i> serovars Typhi and Typhimurium	Gram-negative bacteria	Gastrointestinal infections	Unknown	Unknown
<i>Streptococcus dysgalactiae</i>	Gram-positive bacteria	Veterinary	Unknown	Unknown
<i>S. pneumoniae</i>	Gram-positive bacteria	Pneumonia, otitis media and other infections	Pathogen death	Pathogen death
<i>S. pyogenes</i>	Gram-positive bacteria	Group A streptococcal infections	Pathogen death	Pathogen death
<i>Candida albicans</i>	Yeast	Nosocomial, eye, urinary tract and other infections	Pathogen death	Pathogen death
<i>Aspergillus flavus</i>	Fungus	Aspergillosis	Unknown	Unknown
<i>Fusarium solani</i>	Fungus	Corneal infection	Unknown	Unknown
<i>Cryptococcus neoformans</i>	Fungus	Respiratory	Unknown	Unknown
<i>Plasmodium berghei</i>	Parasite	Malaria (in animal models)	Unknown	Pathogen death
<i>P. falciparum</i>	Parasite	Malaria	Unknown	Unknown
<i>Trichomonas vaginalis</i>	Parasite	Vaginitis and urogenital infections	Unknown	Unknown

<sup>A</sup>Pathogen species listed are the PNAG-expressing pathogens identified in ref. 1. <sup>B</sup>Key illnesses associated with the pathogen. <sup>C</sup>Pathogens that F598 (SAR279356), a human mAb against PNAG and deacetylated PNAG made by **Aloplexx Pharmaceuticals LLC** and **Sanofi**, killed *in vitro* and/or in mice, as reported in ref. 1. Previous studies also reported that F598 killed three additional pathogens *in vitro* and in mice: the *Burkholderia cepacia* complex, including *B. dolosa*, which causes pneumonia in patients with cystic fibrosis (CF);<sup>10</sup> *Escherichia coli*<sup>11</sup> and *S. aureus*,<sup>13</sup> including methicillin-resistant strains (MRSA).

The group used F598 conjugated to a fluorescent agent to detect PNAG on the surfaces of pathogens and found the molecule in 24 pathogens not previously known to express it. Among the new pathogens were

**“Our new study extends the list of PNAG-expressing organisms to most major human pathogens, including 9 of the top 10 causes of nosocomial infections.”**

—Gerald Pier,  
Harvard Medical School

disease-causing bacteria such as *Streptococcus pneumoniae*, *Clostridium difficile* and *Mycobacterium tuberculosis*, as well as the yeast *Candida albicans* and the parasite *Plasmodium falciparum* (see Table 1, “Adding pathogens to the PNAG list”).

In human cell-based bactericidal assays, F598

increased killing of *C. albicans*, *Neisseria meningitidis*, *S. pneumoniae* and other pathogens compared with an inactive control antibody.

Lastly, the team tested the protective effect of the mAb in mice challenged with selected pathogens. In mice exposed to *C. albicans*, *N. meningitidis*, *S. pneumoniae*, *S. pyogenes* or *P. burghei*, pretreatment with the mAb led to decreased symptoms of eye infection, meningitis, lung infection, skin infection or cerebral malaria, respectively, compared with pretreatment with a control antibody or control serum.

“Our new study extends the list of PNAG-expressing organisms to most major human pathogens, including 9 of the top 10 causes of nosocomial infections” as reported by the **Centers for Disease Control and Prevention (CDC)**, Pier told *SciBX* (see Table 2, “Nine out of ten for PNAG”). “This implies that a PNAG vaccine or passive immunotherapy with the anti-PNAG antibody could target a huge range of organisms with just one inoculation or treatment.”

Pier noted that *Pseudomonas aeruginosa* is the only bacterium on the CDC’s top 10 list that does not express PNAG.

Pier’s team included researchers from **Boston University School of Medicine, Dana-Farber Cancer Institute, Harvard School of Public Health, University of Massachusetts Medical School, The Ohio State University College of Medicine, The Research Institute at Nationwide Children’s Hospital, Walter Reed Army Institute of Research, N.D. Zelinsky Institute of Organic Chemistry** and **Sanofi**, which contributed some of the bacteria studied and tested F598 in the animals

challenged with *S. pneumoniae*.

Data were reported in *Proceedings of the National Academy of Sciences*.

“The new study underscores that we have something unusual and even unique in our PNAG vaccine,” said Daniel Vlock. “First, we have a target that is expressed incredibly broadly in pathogens. Second, we can produce the vaccine via chemical synthesis, which is certainly cleaner than recombinant methods, and we hope it will be simpler and cheaper as well.”

In 2006, Pier and Vlock cofounded Alopexx Pharmaceuticals to develop F598 as a passive immunotherapy to protect against bacterial infections. Four years later, the duo cofounded Alopexx Vaccine, which has the dPNAG-based vaccine AV0318 in preclinical development to prevent bacterial infections in humans and production animals.

Vlock is CEO of both companies, which are part of the group **Alopexx Enterprises LLC**, which provides investment, managerial and development capabilities to its multiple subsidiaries.

In 4Q13, Alopexx Vaccine plans to begin testing AV0318 in cows to prevent mastitis caused by *S. aureus* and *Escherichia coli* and in pigs to prevent a severe form of pneumonia caused by *Actinobacillus pleuropneumoniae*, Vlock said.

“The immunogenicity and any toxicity we see in these animals will have an impact on what we can do in humans,” he added.

Alopexx Vaccine expects to begin a Phase I trial of AV0318 in humans next year. Vlock declined to disclose the target populations or indications.

Meanwhile, Pier’s team is testing F598 *in vitro* and in animals challenged with *E. coli* K1, Group B Streptococcus and other pathogens that cause neonatal infections in humans.

Pier said Brigham and Women’s Hospital and **Beth Israel Deaconess Medical Center** hold a portfolio of patents covering the PNAG technology.

The antibody-related IP from that portfolio is licensed to Alopexx Pharmaceuticals, while the vaccine-related IP is licensed to Alopexx Vaccine, Vlock said.

In 2010, Sanofi exercised an option from Alopexx Pharmaceuticals to in-license F598 (SAR279356), which the pharma now has in Phase II testing to prevent bacterial infections.

**Table 2. Nine out of ten for PNAG.** Multiple studies have determined that the surface antigen poly-*N*-acetylglucosamine (PNAG) is expressed on all but one of the pathogens responsible for the 10 most frequent nosocomial infections as reported to the **Centers for Disease Control and Prevention (CDC)** for 2006–2007.<sup>14</sup> These 10 pathogens accounted for 87% of reported nosocomial infections in the U.S., including central line-associated bloodstream infections, catheter-associated urinary tract infections, ventilator-associated pneumonia and surgical-site infections.

Source: Refs. 1, 10, 13, 15; **Alopexx Vaccine LLC**

Pathogen	Type	PNAG expression <sup>A</sup>	% of all nosocomial infections
<i>Staphylococcus epidermidis</i> and other coagulase-negative staphylococci	Bacteria	Yes	15
<i>S. aureus</i>	Bacteria	Yes <sup>13</sup>	15
<i>Enterococcus</i> species, including <i>E. faecalis</i>	Bacteria	Yes ( <i>E. faecalis</i> ) <sup>1</sup>	12
<i>Candida albicans</i>	Yeast	Yes <sup>1</sup>	11
<i>Escherichia coli</i>	Bacteria	Yes	10
<i>Pseudomonas aeruginosa</i>	Bacteria	No <sup>1</sup>	8
<i>Klebsiella pneumoniae</i>	Bacteria	Yes	6
<i>Enterobacter</i> species, including <i>E. cloacae</i>	Bacteria	Yes ( <i>E. cloacae</i> ) <sup>10</sup>	5
<i>Acinetobacter baumannii</i>	Bacteria	Yes <sup>15</sup>	3
<i>K. oxytoca</i>	Bacteria	Yes	2

<sup>A</sup>Indicates whether the pathogen expresses PNAG on its surface, as reported by the source cited.

(Continues on p. 8)

# Shrinking old hearts

By Lev Osherovich, Senior Writer

Boston researchers have discovered a blood-borne protein, growth differentiation factor 11, that can reverse age-related cardiac hypertrophy in mice.<sup>1</sup> The protein could be used as a therapeutic agent once its long-term effects are understood.

Cardiac hypertrophy, the pathological enlargement of one or more ventricles, can occur in old age or in response to chronic hypertension and myocardial infarction (MI). Chronically enlarged hearts develop fibrosis and eventually fail.

Cardiologists primarily try to prevent cardiac hypertrophy by reducing hypertension and the risk of MI. However, hypertrophy also may be reversible.

When triggered by hypertension or other stress, cardiomyocytes can become larger. Conversely, when demand on the heart falls, heart muscle cells can shrink.

“When you remove the growth trigger, the heart is capable of remarkable plasticity back to its normal state,” said Joseph Hill, professor of medicine and chief of cardiology at **The University of Texas Southwestern Medical Center**.

Hill said a variety of intracellular signaling pathways act as “brakes and accelerators in heart growth,” but the upstream factors that regulate these pathways are not well understood.

Now, a team co-led by Amy Wagers and Richard Lee has found evidence that growth differentiation factor 11 (GDF11) is a master regulator of heart size.

Wagers is a professor of stem cell and regenerative biology at **Harvard University** and an investigator at the **Howard Hughes Medical Institute**.

Lee is a professor of medicine at **Brigham and Women’s Hospital** and **Harvard Medical School**.

The team reported that GDF11, a secreted member of the transforming growth factor- $\beta$  (TGFB; TGF $\beta$ ) family, wards off cardiac hypertrophy in young mice and can reverse the condition in old mice.

Wagers and Lee discovered GDF11’s role using heterochronic parabiotic mice, in which an old and young mouse are surgically connected so that they share a circulatory system.

Wagers previously used this technique to study the effect of circulating factors that promote tissue regeneration, which involves the proliferation of cells rather than changes in cell size. The adult heart does not typically regenerate new cardiomyocytes to replace damaged ones, so Wagers did not expect to see an effect from youthful serum on the heart itself.

“We usually focus on tissues that repair themselves well during youth but don’t do so well in old age,” said Wagers. “I thought the heart would not respond, since it’s not known for its regenerative capacity. I was dramatically wrong in this hypothesis.”

## Young blood

Wagers and Lee surgically joined old and young mice and kept the paired mice immobilized for four weeks, then separated the animals to examine cardiovascular function.

Ordinarily, old mice have enlarged hearts compared with younger controls. However, after sharing blood with young mice, the older animals had smaller, more youthful-looking hearts and smaller cardiomyocytes than did controls (old mice connected to other old mice).

To find the factor responsible for the heart-rejuvenating effect of heterochronic parabiosis, the team analyzed the metabolic  
(Continues on p. 9)

(Continued from "PNAG: broadening infection protection," p. 7)

Last December, Sanofi terminated a Phase II trial of SAR279356 for patients on mechanical ventilation in intensive care units because of difficulties with patient recruitment.

Sanofi declined to discuss the antibody’s status or how Pier’s new study might affect its development plans.

Haas, M.J. *SciBX* 6(23); doi:10.1038/scibx.2013.566

Published online June 13, 2013

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## COMPANIES AND INSTITUTIONS MENTIONED

**Alopecx Enterprises LLC**, Concord, Mass.  
**Alopecx Pharmaceuticals LLC**, Concord, Mass.  
**Alopecx Vaccine LLC**, Concord, Mass.  
**Beth Israel Deaconess Medical Center**, Boston, Mass.  
**Boston University School of Medicine**, Boston, Mass.  
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**Dana-Farber Cancer Institute**, Boston, Mass.  
**Harvard Medical School**, Boston, Mass.  
**Harvard School of Public Health**, Boston, Mass.  
**N.D. Zelinsky Institute of Organic Chemistry**, Moscow, Russia  
**The Ohio State University College of Medicine**, Columbus, Ohio  
**The Research Institute at Nationwide Children’s Hospital**, Columbus, Ohio  
**Sanofi** (Euronext:SAN; NYSE:SNY), Paris, France  
**University of Massachusetts Medical School**, Worcester, Mass.  
**Walter Reed Army Institute of Research**, Silver Spring, Md.

and proteomic profiles of old and young mice and converged on GDF11.

Young mice had high GDF11 levels, whereas old ones had low levels. In cell culture, murine cardiomyocytes with recombinant GDF11 had lower growth rates than did saline-treated controls. Injection of recombinant GDF11 into old mice reduced heart size and molecular markers of cardiac hypertrophy compared with saline.

Results were reported in *Cell*.

Wagers said her next step is to learn more about the basic functions of GDF11 in mice and humans.

“Not a lot is known about GDF11, which is a member of a broad superfamily of molecules with transforming growth factor- $\beta$  and bone morphogenetic protein (BMP) homology,” she said. “We want to understand how GDF11 is regulated during human aging.”

Along these lines, the team reported that in human cardiomyocytes, recombinant GDF11 activates components of the TGF $\beta$  signaling pathway and controls the activity of transcription factors involved in cardiac muscle remodeling.

Junichi Sadoshima, professor of cell biology and molecular medicine at the **University of Medicine and Dentistry of New Jersey**, said it would be necessary to characterize the functional effects of reversing cardiac hypertrophy with GDF11.

“They particularly look at the hypertrophy but they don’t look much at cardiac function,” said Sadoshima. In patients with cardiac hypertrophy, “diastolic heart failure is a significant problem, but

[the researchers] don’t show whether this is improved by young serum or parabiosis. Old hearts are susceptible to stress and reperfusion injury, so it would be nice to see functional assays” of these conditions.

Hill said it was unclear whether GDF11 could reverse

more severe forms of cardiac hypertrophy than those caused by aging.

“Pathological remodeling in the heart is not just about cell growth,” said Hill. “They should evaluate GDF11’s effect on fibrosis and other elements” of advanced heart disease.

### Stressing out

Wagers said she indeed plans to test the effect of GDF11 in a variety of cardiac injury and stress models. Her ultimate goal is to make a recombinant version of GDF11 that could be administered to patients. The biggest challenges will involve improving the protein’s specificity and stability.

She noted GDF11 is a close homolog of myostatin (GDF8), a blood-borne factor encoded by the gene *MSTN* that inhibits growth of skeletal muscle.

Companies previously have tried to block GDF-8 signaling to promote skeletal muscle regeneration in Duchenne muscular dystrophy (DMD) and muscular atrophy.

The most advanced GDF-8 inhibitor was **Accelaron Pharma Inc.**’s activin receptor type 2b (ACVR2B) antagonist ACE-031, which failed a Phase II trial in DMD in 2011 because of vascular safety concerns. In May, partner **Shire plc** handed rights to ACE-031 back to Accelaron.

“ACE-031 is a receptor for GDF-8 that is soluble,” said Accelaron CSO Ravi Kumar. “We have published that it also binds to GDF11.”

Kumar said development of ACE-031 was on hold for strategic reasons. Further details were not disclosed.

In 2010, **Amgen Inc.** suspended development of AMG 745, a GDF-8 inhibitor that was in Phase I testing for muscular atrophy.

It is unclear whether ACVR2B is the principal receptor for GDF11 *in vivo*, but one possibility is that the vascular side effects of ACE-031 resulted from cross-inhibition of GDF11.

A related concern is whether interaction of GDF11 with ACVR2B or related receptors would shrink muscles other than the heart.

“The question is whether GDF11 has effects in other tissues,” said Hill. “If GDF11’s receptor is expressed in other tissues, you need to see if GDF11 has effects there.”

Testing the effects of long-term GDF11 treatment may be difficult because the protein has poor solubility and stability.

“These proteins are notoriously hydrophobic and very hard to work with,” said Kumar. “They are very short proteins and have a very short half-life.”

“The problem with administering GDF11 is that it’s probably unstable or not long-lasting,” added Sadoshima. “It would be very difficult to keep it at high levels of circulation.”

“You might need to administer this chronically,” said Hill. “The ideal thing would be a small molecule agonist of cardiac-specific receptors” that mimics the effect of GDF11 but has better pharmacodynamics.

Brigham and Women’s Hospital has filed a patent on the therapeutic use of GDF11 in heart disease. That patent is available for licensing.

Osherovich, L. *SciBX* 6(23); doi:10.1038/scibx.2013.567  
Published online June 13, 2013

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### COMPANIES AND INSTITUTIONS MENTIONED

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**Harvard Medical School**, Boston, Mass.  
**Harvard University**, Cambridge, Mass.  
**Howard Hughes Medical Institute**, Chevy Chase, Md.  
**Shire plc** (LSE:SHP; NASDAQ:SHPG), Dublin, Ireland  
**The University of Texas Southwestern Medical Center**, Dallas, Texas  
**University of Medicine and Dentistry of New Jersey**, Newark, N.J.

**“I thought the heart would not respond, since it’s not known for its regenerative capacity. I was dramatically wrong in this hypothesis.”**

—Amy Wagers, Harvard University

## This week in therapeutics

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

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

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Autoimmune disease</b>				
Autoimmune	CD4; CD52; sialic acid binding Ig-like lectin 10 (SIGLEC10)	<p>Studies in mice and patient samples suggest T cells with high CD52 levels could help prevent autoimmune diseases such as type 1 diabetes. In samples from patients who have type 1 diabetes, CD4<sup>+</sup> T cells expressing high levels of CD52 showed impaired responsiveness to an autoantigen and were present at lower levels compared with samples from healthy controls and from patients with type 2 diabetes. In nonobese diabetic mice, adoptive transfer of T cell populations depleted of cells with high CD52 expression led to accelerated disease onset compared with transfer of nondepleted T cell populations. In cell culture, the immunosuppressive activity of T cells with high CD52 expression was mediated by the binding of soluble CD52 to SIGLEC10. Next steps could include determining how the CD52-SIGLEC10 interaction could be targeted to prevent autoimmune disease.</p> <p><b>SciBX 6(23); doi:10.1038/scibx.2013.568</b> Published online June 13, 2013</p>	Patent and licensing status unavailable	<p>Bandala-Sanchez, E. <i>et al. Nat. Immunol.</i>; published online May 19, 2013; doi:10.1038/ni.2610</p> <p><b>Contact:</b> Leonard Harrison, The Walter and Eliza Hall Institute of Medical Research, Parkville, Victoria, Australia e-mail: <a href="mailto:harrison@wehi.edu.au">harrison@wehi.edu.au</a></p>
Multiple sclerosis (MS)	Ciliary neurotrophic factor (CNTF)	<p><i>In vitro</i> studies suggest aspirin could help treat demyelinating disorders such as MS. In primary human and mouse astrocytes, aspirin increased levels of myelin-promoting CNTF compared with no treatment. In cultured mouse oligodendrocytes, supernatant from mouse astrocytes treated with aspirin increased levels of myelin-associated proteins and decreased cell death compared with supernatant from <i>Cntf</i><sup>-/-</sup> astrocytes. Next steps could include testing the effects of aspirin in animal models for demyelinating disorders.</p> <p><b>SciBX 6(23); doi:10.1038/scibx.2013.569</b> Published online June 13, 2013</p>	Patent and licensing status unavailable	<p>Modi, K.K. <i>et al. J. Biol. Chem.</i>; published online May 7, 2013; doi:10.1074/jbc.M112.447268</p> <p><b>Contact:</b> Kalipada Pahan, Rush University Medical Center, Chicago, Ill. e-mail: <a href="mailto:kalipada_pahan@rush.edu">kalipada_pahan@rush.edu</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Osteoarthritis (OA)	Transforming growth factor $\beta$ 1 (TGF $\beta$ 1; TGFB1); TGF $\beta$ receptor II (TGF $\beta$ -R2; TGFBR2)	<p>Patient sample and rodent studies suggest inhibiting TGF<math>\beta</math>1 signaling in bone could help treat OA. Subchondral bone samples from patients with OA showed elevated TGF<math>\beta</math>1 levels compared with samples from healthy controls. In a mouse model for OA, deletion of <i>Tgfb2</i> decreased severity of OA symptoms compared with no deletion. In a rat model for OA, an antibody that blocks Tgf<math>\beta</math> signaling improved bone architecture compared with vehicle. Next steps include clinical trials to evaluate inhibitors of TGF<math>\beta</math>1 signaling.</p> <p>InterMune Inc., Ildong Pharmaceutical Co. Ltd. and Shionogi &amp; Co. Ltd. market Esbriet pifrenidone, a small molecule inhibitor of proinflammatory cytokines such as tumor necrosis factor-<math>\alpha</math> (TNF-<math>\alpha</math>) and IL-1<math>\beta</math>, as well as profibrotic cytokines including platelet derived growth factor (PDGF) and TGF<math>\beta</math></p> <p>At least 11 other companies have compounds that inhibit TGF<math>\beta</math>1 in Phase II or earlier testing to treat various diseases.</p> <p><b>SciBX 6(23); doi:10.1038/scibx.2013.570</b> Published online June 13, 2013</p>	Patent application filed; available for licensing	<p>Zhen, G. <i>et al. Nat. Med.</i>; published online May 19, 2013; doi:10.1038/nm.3143</p> <p><b>Contact:</b> Xu Cao, Johns Hopkins University, Baltimore, Md. e-mail: <a href="mailto:xcao11@jhmi.edu">xcao11@jhmi.edu</a></p>
<b>Cancer</b>				
Breast cancer	Interleukin-6 (IL-6); interleukin-8 (IL-8; CXCL8)	<p>Mouse and cell culture studies suggest dual blockade of IL-6 and IL-8 could be useful for treating triple-negative breast cancer.</p> <p>In a human triple-negative breast cancer cell line, small hairpin RNA-mediated knockdown of the two targets decreased anchorage-independent growth and increased apoptosis compared with knockdown of either interleukin alone. In a mouse xenograft model for triple-negative breast cancer, shRNA-mediated knockdown of both IL-6 and IL-8 inhibited tumor growth, whereas knockdown of either interleukin alone did not. Next steps could include developing and evaluating inhibitors of IL-6 and IL-8 signaling in models for triple-negative breast cancer.</p> <p><b>SciBX 6(23); doi:10.1038/scibx.2013.571</b> Published online June 13, 2013</p>	Patent and licensing status unavailable	<p>Hartman, Z.C. <i>et al. Cancer Res.</i>; published online April 30, 2013; doi:10.1158/0008-5472.CAN-12-4524-T</p> <p><b>Contact:</b> Powel H. Brown, The University of Texas MD Anderson Cancer Center, Houston, Texas e-mail: <a href="mailto:phbrown@mdanderson.org">phbrown@mdanderson.org</a></p>
Cancer	Histone deacetylase 6 (HDAC6); histone deacetylase 8 (HDAC8)	<p><i>In vitro</i> studies suggest dual inhibition of HDAC6 and HDAC8 could help treat cancer. Inhibition of HDAC6 or HDAC8 has been shown to promote cancer cell death. In a panel of HDACs, BRD73954 selectively inhibited HDAC6 and HDAC8 with nanomolar IC<sub>50</sub> values. Next steps include testing BRD73954 in models for neuroblastoma and using the compound to identify substrates for HDAC6 and HDAC8.</p> <p>Acetylon Pharmaceuticals Inc.'s rocilinoestat, an oral selective HDAC6 inhibitor, is in Phase I/II testing to treat multiple myeloma.</p> <p>At least three other companies have compounds that inhibit HDAC6 or HDAC8 in preclinical development to treat various cancers or inflammation.</p> <p><b>SciBX 6(23); doi:10.1038/scibx.2013.572</b> Published online June 13, 2013</p>	Patent application filed; available for licensing	<p>Olson, D.E. <i>et al. J. Med. Chem.</i>; published online May 14, 2013; doi:10.1021/jm400390r</p> <p><b>Contact:</b> Edward Holson, Broad Institute of MIT and Harvard, Cambridge, Mass. e-mail: <a href="mailto:edholson@broadinstitute.org">edholson@broadinstitute.org</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cancer	Nuclear receptor subfamily 5 group A member 2 (NR5A2; LRH-1)	<p>Mouse and <i>in vitro</i> studies identified an LRH-1 antagonist that could be useful for treating cancer. In <i>in vitro</i> binding studies, the compound bound LHR-1 with a <math>K_d</math> value of about 1.8 <math>\mu</math>M. In human cancer cells, the compound inhibited proliferation of LHR-1-positive cell lines. Next steps could include evaluating the LRH-1 antagonist in mouse xenograft models.</p> <p><b>SciBX 6(23); doi:10.1038/scibx.2013.573</b> Published online June 13, 2013</p>	Patent and licensing status not available	<p>Benod, C. <i>et al. J. Biol. Chem.</i>; published online May 10, 2013; doi:10.1074/jbc.M112.411686 <b>Contact:</b> Robert Fletterick, University of California, San Francisco, Calif. e-mail: <a href="mailto:robert.fletterick@ucsf.edu">robert.fletterick@ucsf.edu</a></p>
Cancer	Phosphodiesterase $\delta$ subunit (PDE $\delta$ ); Ras	<p>Mouse studies suggest inhibiting an interaction between Ras and the PDE<math>\delta</math> subunit could help treat cancer. PDE<math>\delta</math> binds lipid-modified Ras and facilitates Ras relocalization and activation. An <i>in vitro</i> high throughput screen and subsequent SAR study identified deltarasin as a small molecule inhibitor of the Ras-PDE<math>\delta</math> interaction. In a mouse xenograft model for human pancreatic cancer, deltarasin decreased tumor growth compared with vehicle. Next steps include identifying new chemotypes that target the PDE<math>\delta</math>-Ras binding site and developing a drug candidate based on deltarasin.</p> <p><b>SciBX 6(23); doi:10.1038/scibx.2013.574</b> Published online June 13, 2013</p>	Compound class is patented; available for licensing	<p>Zimmerman, G. <i>et al. Nature</i>; published online May 22, 2013; doi:10.1038/nature12205 <b>Contact:</b> Herbert Waldmann, Max Planck Institute of Molecular Physiology, Dortmund, Germany e-mail: <a href="mailto:herbert.waldmann@mpi-dortmund.mpg.de">herbert.waldmann@mpi-dortmund.mpg.de</a> <b>Contact:</b> Philippe I.H. Bastiaens, same affiliation as above e-mail: <a href="mailto:philippe.bastiaens@mpi-dortmund.mpg.de">philippe.bastiaens@mpi-dortmund.mpg.de</a> <b>Contact:</b> Alfred Wittinghofer, same affiliation as above e-mail: <a href="mailto:alfred.wittinghofer@mpi-dortmund.mpg.de">alfred.wittinghofer@mpi-dortmund.mpg.de</a></p>
Colon cancer	p53	<p>Mouse and cell culture studies suggest gain-of-function mutations in p53 can raise colorectal cancer risk by increasing susceptibility to chronic inflammation. In mouse intestinal epithelial cells, expression of a gain-of-function mutant p53 prolonged the inflammatory response to tumor necrosis factor-<math>\alpha</math> (TNF-<math>\alpha</math>) compared with expression of wild-type p53. In mice, expression of the p53 mutant increased susceptibility to chronic inflammation-induced colon cancer compared with expression of wild-type p53. Next steps could include confirming the association between mutant p53, colon cancer and chronic inflammation in additional models. At least six companies have compounds that target p53 signaling in Phase II or earlier testing to treat various cancers.</p> <p><b>SciBX 6(23); doi:10.1038/scibx.2013.575</b> Published online June 13, 2013</p>	Patent and licensing status unavailable	<p>Cooks, T. <i>et al. Cancer Cell</i>; published online May 13, 2013; doi:10.1016/j.ccr.2013.03.022 <b>Contact:</b> Moshe Oren, Weizmann Institute of Science, Rehovot, Israel e-mail: <a href="mailto:moshe.oren@weizmann.ac.il">moshe.oren@weizmann.ac.il</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Melanoma	Pyruvate dehydrogenase kinase 1 (PDK1)	<p>Cell culture and mouse studies suggest inhibiting PDK1 could help treat melanoma. In a mouse xenograft model for BRAF V600E mutant melanoma, small hairpin RNA-mediated knockdown of PDK1 slowed tumor growth. In cultured human BRAF V600E mutant melanoma cells, PDK1 knockdown plus Zelboraf vemurafenib increased cell death compared with Zelboraf alone. Next steps include developing PDK1 inhibitors and examining the therapeutic potential of inhibiting PDK1 in solid tumors. Daiichi Sankyo Co. Ltd., Chugai Pharmaceutical Co. Ltd. and Roche market Zelboraf, an oral small molecule inhibitor of oncogenic BRAF V600E, to treat melanoma.</p> <p><b>SciBX 6(23); doi:10.1038/scibx.2013.576</b> Published online June 13, 2013</p>	Patent application filed; available for licensing	<p>Kaplon, J. <i>et al. Nature</i>; published online May 19, 2013; doi:10.1038/nature12154 <b>Contact:</b> Daniel Peeper, The Netherlands Cancer Institute, Amsterdam, the Netherlands e-mail: <a href="mailto:d.peeper@nki.nl">d.peeper@nki.nl</a> <b>Contact:</b> Eyal Gottlieb, Cancer Research UK, Beatson Institute for Cancer Research, Glasgow, U.K. e-mail: <a href="mailto:e.gottlieb@beatson.gla.ac.uk">e.gottlieb@beatson.gla.ac.uk</a></p>
Sarcoma	Sphingosine 1-phosphate (S1P); S1P receptor 1 (S1PR1; EDG1)	<p>Cell culture and mouse studies suggest inhibiting S1P-S1PR1 signaling could help treat rhabdomyosarcoma. In normal mice, radiotherapy or chemotherapy increased S1P levels in multiple tissues. In multiple human rhabdomyosarcoma cell lines, S1P bound to S1PR1 and led to increased migration and adhesion compared with vehicle. In mice pretreated with radiotherapy and engrafted with human rhabdomyosarcoma cells, the anti-S1P L-aptamer NOX-S93 decreased the number of metastases compared with no treatment. Ongoing work includes testing the aptamer in rhabdomyosarcoma models pretreated with chemotherapy. Noxxon Pharma AG's spiegelmer NOX-S93 is in preclinical testing to treat undisclosed cancer, ophthalmic and autoimmune indications.</p> <p><b>SciBX 6(23); doi:10.1038/scibx.2013.577</b> Published online June 13, 2013</p>	Patent and licensing status of findings unavailable; NOX-S93 patented by Noxxon Pharma AG; available for licensing	<p>Schneider, G. <i>et al. Mol. Cancer Res.</i>; published online April 24, 2013; doi:10.1158/1541-7786.MCR-12-0600 <b>Contact:</b> Mariusz Z. Ratajczak, University of Louisville, Louisville, Ky. e-mail: <a href="mailto:mzrata01@louisville.edu">mzrata01@louisville.edu</a></p>
<b>Endocrine/metabolic disease</b>				
Infertility	Phosphoinositide 3-kinase (PI3K); phosphatase and tensin homolog deleted on chromosome 10 (PTEN; MMAC1; TEP1); protein kinase B (PKB; PKBA; AKT; AKT1)	<p>Mouse studies suggest AS101 could help prevent cyclophosphamide-induced depletion of ovarian follicles, which leads to infertility. In female mice, cyclophosphamide enhanced Pi3k-Pten-Akt signaling and decreased primordial ovarian follicles compared with vehicle. In female mice, the Pi3k-Pten-Akt pathway inhibitor AS101 decreased cyclophosphamide-induced follicle loss and rescued fertility compared with saline. Next steps include evaluating the ability of AS101 to protect ovarian follicles in nonhuman primates. BioMAS Ltd.'s AS101 is in Phase II testing to prevent chemotherapy-associated hematological toxicity. Cyclophosphamide is a generic chemotherapeutic.</p> <p><b>SciBX 6(23); doi:10.1038/scibx.2013.578</b> Published online June 13, 2013</p>	<p>Patented; available for licensing from BioMAS Ltd.</p> <p><b>Contact:</b> Ayelet Dilion-Mashiah, BioMAS Ltd., Jerusalem, Israel e-mail: <a href="mailto:ayelet@biomas-pharma.com">ayelet@biomas-pharma.com</a></p>	<p>Kalich-Philosoph, L. <i>et al. Sci. Trans. Med.</i>; published online May 15, 2013; doi:10.1126/scitranslmed.3005402 <b>Contact:</b> Dror Meirou, Tel Aviv University, Tel Aviv, Israel e-mail: <a href="mailto:meirou@post.tau.ac.il">meirou@post.tau.ac.il</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Infectious disease</b>				
Bacterial infection; candidiasis; malaria	Poly-N-acetylglucosamine (PNAG)	<p><i>In vitro</i> and mouse studies suggest an anti-PNAG antibody could help prevent infections from a range of pathogens. PNAG was expressed on the surface of <i>Candida albicans</i>, <i>Neisseria meningitidis</i>, <i>Plasmodium</i> species, <i>Streptococcus pneumoniae</i>, <i>S. pyogenes</i> and multiple other pathogens. In mouse models for <i>C. albicans</i>, <i>N. meningitidis</i>, <i>S. pneumoniae</i>, <i>S. pyogenes</i> or <i>P. burghei</i> infection, pretreatment with the anti-PNAG antibody F598 decreased pathogen burden and markers of disease compared with control antibody or control serum. Ongoing work includes testing F598 against <i>Escherichia coli</i> K1, Group B <i>Streptococcus</i> and other pathogens that cause neonatal infections.</p> <p>Alopexx Pharmaceuticals LLC and Sanofi have F598 (SAR279356) in Phase II testing to prevent bacterial infections.</p> <p>Alopexx Vaccine LLC has a vaccine based on deacetylated PNAG in preclinical development to prevent bacterial infections in humans and animals (see PNAG: broadening infection protection, page 6).</p> <p><b>SciBX 6(23); doi:10.1038/scibx.2013.579</b> Published online June 13, 2013</p>	Patented by Brigham and Women's Hospital and Beth Israel Deaconess Medical Center; licensed to Alopexx Pharmaceuticals LLC and Sanofi	<p>Cywes-Bentley, C. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online May 28, 2013; doi:10.1073/pnas.1303573110</p> <p><b>Contact:</b> Gerald B. Pier, Brigham and Women's Hospital and Harvard Medical School, Boston, Mass. e-mail: <a href="mailto:gpier@rics.bwh.harvard.edu">gpier@rics.bwh.harvard.edu</a></p>
Bacterial infection	Toll-like receptor 2 (TLR2); CD14	<p>Patient sample and mouse studies identified CD14-targeting peptides that could help treat bacterial infections. In mouse models for Gram-positive and Gram-negative bacterial peritonitis, CD14-binding peptides derived from leucine-rich repeat motifs in TLR2 accelerated bacterial clearance compared with saline. In whole blood samples from patients with sepsis-associated immunosuppression, two of the peptides restored chemokine responses to a challenge with bacteria and bacteria-derived antigens. Next steps could include testing the antibacterial effects in additional models of bacterial infection.</p> <p>Implicit Biosciences Pty. Ltd.'s IC14, an antibody targeting CD14, is in Phase II testing to treat acute lung injury.</p> <p><b>SciBX 6(23); doi:10.1038/scibx.2013.580</b> Published online June 13, 2013</p>	Patent and licensing status unavailable	<p>Raby, A.-C. <i>et al. Sci. Transl. Med.</i>; published online May 15, 2013; doi:10.1126/scitranslmed.3005544</p> <p><b>Contact:</b> Mario Labéta, Cardiff University, Cardiff, U.K. e-mail: <a href="mailto:wmdmol@cardiff.ac.uk">wmdmol@cardiff.ac.uk</a></p> <p><b>Contact:</b> Ann-Catherine Raby, same affiliation as above e-mail: <a href="mailto:rabya@cardiff.ac.uk">rabya@cardiff.ac.uk</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Neurology</b>				
Pain	Adenylate cyclase 1 (ADCY1; AC1); NMDA receptor NR2B subtype (GRIN2B; NR2B)	<p>Mouse studies suggest inhibiting GRIN2B in the insular cortex of the brain could help treat neuropathic pain. In mice, surgery to induce peripheral nerve injury led to increased synaptic NMDA receptor levels in the insular cortex compared with sham surgery, and this increase was dependent on AC1 signaling. In a mouse model for neuropathic pain, microinjection of a nonspecific or GRIN2B-selective NMDA receptor antagonist into the insular cortex significantly decreased mechanical allodynia compared with microinjection of saline (<math>p &lt; 0.05</math>). Next steps include developing more GRIN2B-selective NMDA receptor antagonists and studying the pathways that lead to upregulation of NMDA receptor expression after nerve injury.</p> <p><b>SciBX 6(23); doi:10.1038/scibx.2013.581</b> Published online June 13, 2013</p>	AC1 inhibitor patented; unavailable for licensing; available for partnering	<p>Qiu, S. <i>et al. Sci. Signal.</i>; published online May 14, 2013; doi:10.1126/scisignal.2003778 <b>Contact:</b> Ming-gao Zhao, Fourth Military Medical University, Xi'an, China e-mail: <a href="mailto:minggao@fmmu.edu.cn">minggao@fmmu.edu.cn</a> <b>Contact:</b> Min Zhuo, University of Toronto, Toronto, Ontario, Canada e-mail: <a href="mailto:min.zhuo@utoronto.ca">min.zhuo@utoronto.ca</a></p>
Parkinson's disease (PD)	$\alpha$ -Synuclein (SNCA)	<p><i>In vitro</i> fruit fly and mouse studies suggest mannitol, a known disrupter of the blood brain barrier (BBB), could help treat PD. In biochemical studies, mannitol inhibited amyloid fibril formation and disrupted the formation of <math>\alpha</math>-synuclein aggregates. In a fruit fly model for PD, mannitol decreased <math>\alpha</math>-synuclein aggregation in the brain and increased locomotion compared with no treatment. In a human <math>\alpha</math>-synuclein (SNCA) transgenic mouse model for PD, mannitol conferred a neuroprotective effect in dopaminergic neurons and decreased <math>\alpha</math>-synuclein levels in specific brain regions compared with saline. Next steps include confirming the behavioral effects of mannitol in mouse models for PD and evaluating the compound in combination with amyloid inhibitors that do not efficiently cross the BBB.</p> <p><b>SciBX 6(23); doi:10.1038/scibx.2013.582</b> Published online June 13, 2013</p>	Patent and licensing status undisclosed	<p>Shaltiel-Karyo, R. <i>et al. J. Biol. Chem.</i>; published online May 1, 2013; doi:10.1074/jbc.M112.434787 <b>Contact:</b> Ehud Gazit, Tel Aviv University, Tel Aviv, Israel e-mail: <a href="mailto:ehudg@post.tau.ac.il">ehudg@post.tau.ac.il</a> <b>Contact:</b> Daniel Segal, affiliation same as above e-mail: <a href="mailto:dsegal@post.tau.ac.il">dsegal@post.tau.ac.il</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Transplantation</b>				
Transplant	Thrombopoietin (TPO) receptor (CD110; Mpl)	<p>Mouse studies suggest TPO mimetics or CD110 agonists could help enhance engraftment of hematopoietic stem cells (HSCs) following bone marrow transplant (BMT). In mice with ablated bone marrow, CD110 deficiency or an anti-CD110 antibody decreased megakaryocyte recruitment to HSC niches and subsequent osteoblast expansion compared with normal CD110 expression or no treatment, respectively. In mouse models for BMT, TPO pretreatment increased HSC engraftment compared with no pretreatment. Next steps could include testing marketed TPO receptor agonists in mouse models for BMT. GlaxoSmithKline plc and Ligand Pharmaceuticals Inc. market Promacta eltrombopag, a small molecule TPO receptor agonist, to treat thrombocytopenia and idiopathic thrombocytopenic purpura (ITP). The compound is under regulatory review to treat HCV and is in Phase III testing to reduce the need for platelet transfusion in patients with thrombocytopenia and chronic liver disease who are undergoing elective invasive procedures.</p> <p>Amgen Inc. and Kyowa Hakko Kirin Co. Ltd. market Nplate romiplostim, a recombinant fusion protein containing a pair of TPO receptor-binding domains, to treat ITP. Eisai Co. Ltd.'s avatrombopag (E5501), an oral TPO receptor agonist, is in Phase III testing to treat ITP.</p> <p><b>SciBX 6(23); doi:10.1038/scibx.2013.583</b> Published online June 13, 2013</p>	Patent and licensing status unavailable	<p>Olson, T.S. <i>et al. Blood</i>; published online May 10, 2013; doi:10.1182/blood-2012-10-463414 <b>Contact:</b> Edwin M. Horwitz, Children's Hospital of Philadelphia, Philadelphia, Pa. e-mail: <a href="mailto:horwitze@email.chop.edu">horwitze@email.chop.edu</a></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
<b>Assays &amp; screens</b>			
Screening platform for detecting RAF dimerization in cells	<p>A high throughput screening platform for RAF dimerization could help identify bona fide inhibitors of RAF signaling. ATP-competitive inhibitors of RAF kinases can paradoxically stimulate RAF signaling and tumor cell growth by inducing Ras-dependent RAF dimerization. The current screening approach uses membrane tethered RAF kinase domains and quantitatively detects RAF dimerization in cells. A high throughput screen using the platform identified activators and inhibitors of RAF dimerization. Researchers did not disclose next steps, which could include using the screen to identify kinase inhibitors that induce RAF dimerization and evaluating compounds that inhibit RAF dimerization in cancer models.</p> <p><b>SciBX 6(23); doi:10.1038/scibx.2013.584</b> Published online June 13, 2013</p>	Patented; licensing status undisclosed	<p>Lavoie, H. <i>et al. Nat. Chem. Biol.</i>; published online May 19, 2013; doi:10.1038/nchembio.1257  <b>Contact:</b> Marc Therrien, University of Montreal, Montreal, Quebec, Canada            e-mail: <a href="mailto:marc.therrien@umontreal.ca">marc.therrien@umontreal.ca</a>  <b>Contact:</b> Frank Sicheri, Mount Sinai Hospital, Toronto, Ontario, Canada            e-mail: <a href="mailto:sicheri@lunenfeld.ca">sicheri@lunenfeld.ca</a></p>
<b>Computational models</b>			
Database of human phosphatase-substrate interactions	<p>A compilation of protein phosphatase-substrate interaction data could help identify new phosphatase-class drug targets. A list of phosphatases was assembled using sequence and structural information and combined with data from protein-protein interaction and gene expression databases. The data were computationally analyzed and correlated with phosphatase target-site predictions and known kinase substrates to generate a map of phosphatase-substrate interactions. Next steps could include experimental validation of predicted interactions in pathways of therapeutic interest. The human dephosphorylation database is hosted by the European Molecular Biology Laboratory and is available at <a href="http://www.koehn.embl.de/depod/">http://www.koehn.embl.de/depod/</a>.</p> <p><b>SciBX 6(23); doi:10.1038/scibx.2013.585</b> Published online June 13, 2013</p>	Unpatented; licensing status not applicable	<p>Li, X. <i>et al. Sci. Signal.</i>; published online May 9, 2013; doi:10.1126/scisignal.2003203  <b>Contact:</b> Maja Köhn, European Molecular Biology Laboratory, Heidelberg, Germany            e-mail: <a href="mailto:koehn@embl.de">koehn@embl.de</a></p>
<b>Drug platforms</b>			
Human embryonic stem cell (hESC)-derived thymic epithelial cells capable of supporting T cell production	<p>A protocol to generate thymic epithelial cells from hESCs could help restore thymus function and induce immune tolerance. hESCs were exposed to a series of cocktails containing multiple growth factors, including modulators of signaling by wingless-type MMTV integration site (WNT) and bone morphogenetic protein (BMP), which converted the cells into thymic epithelial progenitors. In athymic immunodeficient mice, transplanted progenitor cells differentiated into thymic epithelial cells that could produce functional T cells. Next steps include exploring the therapeutic uses of the derived thymic epithelial cells in mouse models.</p> <p>Corresponding authors Matthias Hebrok and Mark Anderson have cofounded ThyGen to commercialize the approach.</p> <p><b>SciBX 6(23); doi:10.1038/scibx.2013.586</b> Published online June 13, 2013</p>	Patent application filed; exclusively licensed to ThyGen	<p>Parent, A.V. <i>et al. Cell Stem Cell</i>; published online May 16, 2013; doi:10.1016/j.stem.2013.04.004  <b>Contact:</b> Matthias Hebrok, University of California, San Francisco, Calif.            e-mail: <a href="mailto:mhebrok@diabetes.ucsf.edu">mhebrok@diabetes.ucsf.edu</a>  <b>Contact:</b> Mark S. Anderson, same affiliation as above            e-mail: <a href="mailto:manderson@diabetes.ucsf.edu">manderson@diabetes.ucsf.edu</a></p>
Phage display system for rapid mammalian expression of library hits	<p>A phage display system designed to facilitate expression in mammalian cells could be used to rapidly screen libraries against therapeutic targets. A time-consuming step in phage display is the cloning of library candidates into a mammalian expression system. An expression vector was designed to take advantage of splicing machinery unique to mammalian cells. One version of a candidate fusion protein is produced in bacterial cells, and another, distinct version of the fusion protein is produced in mammalian cells. The system was used to discover a CD4-mimetic peptide that binds to HIV-1 envelope glycoprotein and neutralizes the virus. Next steps include modifying the expression vector to enable rapid antibody selection and expression.</p> <p><b>SciBX 6(23); doi:10.1038/scibx.2013.587</b> Published online June 13, 2013</p>	Provisional patent application filed; available for licensing from Harvard University Office of Technology Development	<p>Quinlan, B.D. <i>et al. J. Biol. Chem.</i>; published online May 10, 2013; doi:10.1074/jbc.M113.452839  <b>Contact:</b> Michael Farzan, The Scripps Research Institute, Jupiter, Fla.            e-mail: <a href="mailto:mfarzan@scripps.edu">mfarzan@scripps.edu</a>  <b>Contact:</b> Brian Quinlan, same affiliation as above            e-mail: <a href="mailto:bquinlan@scripps.edu">bquinlan@scripps.edu</a></p>

## Company and institution index

<b>A</b>		<b>P</b>		CD110	16	homolog deleted on chromosome 10	13
Acceleron Pharma Inc.	9	Prosensa B.V.	4	CD191	4	Phosphodiesterase $\delta$ subunit	12
Acetylon Pharmaceuticals Inc.	11	Proteostasis Therapeutics Inc.	3	CDw199	4	Phosphoinositide 3-kinase	13
Alopecx Enterprises LLC	7	<b>R</b>		CFTR	1	PI3K	13
Alopecx Pharmaceuticals LLC	6,14	Reata Pharmaceuticals Inc.	3	Ciliary neurotrophic factor	10	Pirfenidone	11
Alopecx Vaccine LLC	6,14	Research Institute at Nationwide Children's Hospital	7	CNTF	10	PKB	13
Amgen Inc.	9,16	Nationwide Children's Hospital	7	CXCL8	11	PKBA	13
		Roche	13	Cyclic AMP	2	Platelet derived growth factor	11
		Royal Netherlands Academy of Arts and Sciences	2	Cyclophosphamide	13	PNAG	6,14
		<b>S</b>		Cystic fibrosis transmembrane conductance regulator	1	PNAG vaccine	7
<b>B</b>		Sanofi	6,14	<b>D</b>		Poly- <i>N</i> -acetylglucosamine	7,14
Beth Israel Deaconess Medical Center	7,14	Shionogi & Co. Ltd.	11	Deltarasin	12	PRO051	4
BioMAS Ltd.	13	Shire plc	9	Drisapersen	4	Promacta	16
Boston University School of Medicine	7	<b>T</b>		<b>E</b>		Protein kinase B	13
Brigham and Women's Hospital	6,8,14	ThyGen	17	E5501	16	PTEN	13
<b>C</b>		<b>U</b>		EDG1	13	Pyruvate dehydrogenase kinase 1	13
ChemoCentryx Inc.	4	University Medical Center Utrecht	1	Eltrombopag	16	<b>R</b>	
Centers for Disease Control and Prevention	7	University of Massachusetts Medical School	7	Esbriet	11	RAF	17
Chugai Pharmaceutical Co. Ltd.	13	University of Medicine and Dentistry of New Jersey	9	<b>F</b>		Ras	12
<b>D</b>		University of Texas Southwestern Medical Center	3,8	F598	6,14	Rocilinostat	11
Daiichi Sankyo Co. Ltd.	13	<b>V</b>		Forskolin	2	Romiplostim	16
Dana-Farber Cancer Institute	7	Vertex Pharmaceuticals Inc.	1	<b>G</b>		<b>S</b>	
<b>E</b>		<b>W</b>		GDF-8	9	S1P	13
Eisai Co. Ltd.	16	Walter Reed Army Institute of Research	7	GDF11	8	S1P1	13
European Molecular Biology Laboratory	17	.....		GRIN2B	15	S1PR1	13
<b>G</b>		<b>Target and compound index</b>		Growth differentiation factor 11	8	S1P receptor 1	13
GlaxoSmithKline plc	4,16	<b>A</b>		<b>H</b>		SAR279356	6,14
<b>H</b>		$\alpha$ -Synuclein	15	HDAC6	11	Sialic acid binding Ig-like lectin 10	10
Harvard Medical School	6,8	AC1	15	HDAC8	11	SIGLEC10	10
Harvard School of Public Health	7	ACE-031	9	Histone deacetylase 6	11	SNCA	15
Harvard University	8	Activin receptor type 2b	9	Histone deacetylase 8	11	Sphingosine 1-phosphate	13
Harvard University Office of Technology Development	17	ACVR2B	9	<b>I</b>		<b>T</b>	
Howard Hughes Medical Institute	8	ADCY1	15	IC14	14	TEP1	13
Hubrecht Institute	2	Adenylate cyclase 1	15	IL-6	11	TGF $\beta$	8
<b>I</b>		AKT	13	IL-8	11	TGFB	8
Ildong Pharmaceutical Co. Ltd.	11	AKT1	13	Interleukin-6	11	TGF $\beta$ 1	11
Implicit Biosciences Pty. Ltd.	14	AMG 745	9	Interleukin-8	11	TGF $\beta$ 1	11
InterMune Inc.	11	AS101	1	Ivacaftor	1	TGF $\beta$ -R2	11
<b>K</b>		AV0318	7	<b>K</b>		TGFBR2	11
Kyowa Hakko Kirin Co. Ltd.	16	Avatrombopag	16	Kalydeco	1	TGF $\beta$ receptor II	11
<b>L</b>		<b>B</b>		<b>L</b>		Thrombopoietin receptor	16
Ligand Pharmaceuticals Inc.	16	BMP	9,17	LRH-1	12	TLR2	14
<b>M</b>		Bone morphogenetic protein	9,17	<b>M</b>		TNF- $\alpha$	11,12
McGill University	3	BRAF V600E	13	MMAC1	13	Toll-like receptor 2	14
<b>N</b>		BRD73954	11	Mpl	16	TPO	16
N.D. Zelinsky Institute of Organic Chemistry	7	<b>C</b>		Myostatin	9	Traficet-EN	4
Noxxon Pharma AG	13	cAMP	2	<b>N</b>		Transforming growth factor- $\beta$	8
<b>O</b>		CC chemokine receptor 1	4	NMDA receptor NR2B subtype	15	Transforming growth factor $\beta$ 1	11
Ohio State University College of Medicine	7	CC chemokine receptor 9	4	NOX-S93	13	Tumor necrosis factor- $\alpha$	11,12
		CCR1	4	Nplate	16	<b>V</b>	
		CCR9	4	NR2B	15	Vemurafenib	13
		CCX354	4	NR5A2	12	Vercirnon	4
		CD4	10	Nuclear receptor subfamily 5 group A member 2	12	VX-661	1
		CD14	14	<b>P</b>		VX-809	1
		CD52	10	p53	12	<b>W</b>	
				PDE $\delta$	12	Wingless-type MMTV integration site	17
				PDGF	11	WNT	17
				PDK1	13	<b>Z</b>	
				Phosphatase and tensin		Zelboraf	13