

THIS WEEK

ANALYSIS

COVER STORY

1 Spreadin' the news

SciBX's roundup of 2011 public-private partnership data shows the emergence of New York as a translational hub, the impact of nongovernmental funding on infectious disease research compared with the more muted VC support of this area, and the high interest of foreign companies in funding research in China.

TRANSLATIONAL NOTES

5 Seeing the (En)light

AstraZeneca and Novo Nordisk have come off the sidelines to partner with Enlight Biosciences, making them the sixth and seventh pharmas currently working with Enlight to form platform companies.

6 Scripps' partnering rethink

The Scripps Research Institute has decided that the kinds of broad deals it used to do with industry do not work anymore. Instead, the institute now hopes to forge a series of smaller, more focused collaborations with midsize biotechs.

TARGETS & MECHANISMS

8 Heat shock and awe

U.S. researchers have identified several small molecules that decrease toxic protein aggregation *in vitro*. The first-generation compounds have been licensed by Proteostasis and are proof of concept for the biotech's approach to treating protein misfolding diseases like Huntington's and cystic fibrosis.

THE DISTILLERY

10 This week in therapeutics

Treating cancer with FN1-targeting antibody-drug conjugates; ameliorating type 2 diabetes with an agonist mAb of FGFR1; preventing SIRS by inhibiting RIP kinases; and more...

17 This week in techniques

iPS cell model for Timothy syndrome; isoxazole compounds for pancreatic islet β cell regeneration; and more...

INDEXES

18 Company and institution index

18 Target and compound index

Spreadin' the news

By Kai-Iye Lou, Staff Writer

One of the most active areas of strategic repositioning in the translational space in 2011 occurred at the level of public-private partnerships established to expand corporate research portfolios and strengthen institutional research programs.

To gain an accurate picture of what really went on, SciBX performed a comprehensive analysis of public-private partnership (PPP) activity worldwide and contrasted it to early stage venture investing during the same period.

Highlights include the emergence of New York as a translational hub, the impact of nongovernmental funding on infectious disease research compared with the more muted VC support of this area, and the high interest of foreign companies in funding research in China.

Location, location

Globally, the U.S. continued to dominate the PPP landscape, with about half of the deals involving a U.S. institution or a U.S. company

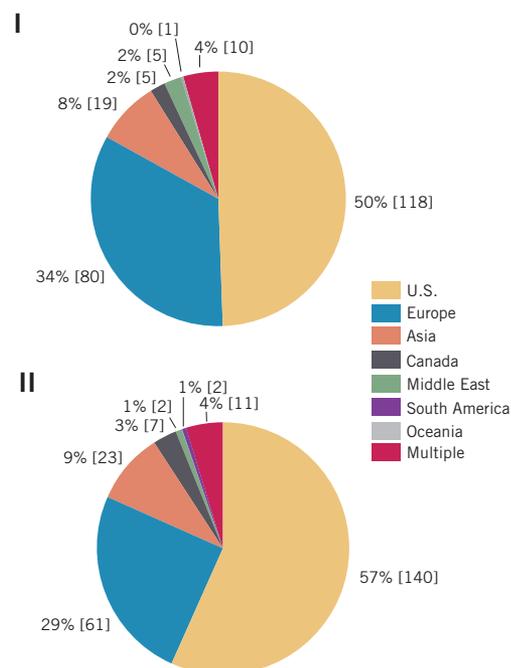


Figure 1. Breakdown of global public-private partnerships by companies (I) and institutions (II). Percentages are out of total number of public-private partnerships worldwide; bracketed values are actual number.

**EDITORIAL****Editor-in-Chief:** Karen Bernstein, Ph.D.**Managing Editor:** Gaspar Taroncher-Oldenburg, Ph.D.**Executive Editor:** Steve Edelson**Senior Editors:** Tracey Baas, Ph.D.; Joanne Kotz, Ph.D.**Writers:** Aaron Bouchie; Chris Cain, Ph.D.; Michael Flanagan; Tim Fulmer, Ph.D.; Michael J. Haas; Stephen Hansen; Kai-Jye Lou; Lauren Martz; Lev Osherovich, Ph.D.; Steve Usdin**Research Director:** Walter Yang**Research Manager:** Kevin Lehnbeuter**Production Editors:** Brandy Cafarella; Sabina Eberle; Carol Evangelista**Copy Editor:** Nicole DeGennaro**Editorial Assistant:** Mark Zipkin**Design:** Claudia Bentley; Miles DaviesFor inquiries, contact editorial@scibx.com**PUBLISHING****Publisher:** Peter Collins, Ph.D.**Associate Publishers:** Gaspar Taroncher-Oldenburg, Ph.D.; Eric Pierce**Marketing:** Sara Girard; Rosy Rogers**Technology:** Anthony Barrera; Julia Kulikova**Sales:** Ron Rabinowitz; Dean Sanderson; Tim Tulloch**OFFICES****BioCentury Publications, Inc.**San Francisco
PO Box 1246
San Carlos, CA 94070-1246
T: +1 650 595 5333Chadds Ford
223 Wilmington-West Chester Pike
Chadds Ford, PA 19317
T: +1 610 558 1873Chicago
20 N. Wacker Drive, Suite 1465
Chicago, IL 60606-2902
T: +1 312 755 0798Oxford
287 Banbury Road
Oxford OX4 7JA
United Kingdom
T: +44 (0)18 6551 2184Washington, DC
2008 Q Street, NW, Suite 100
Washington, DC 20009
T: +1 202 462 9582**Nature Publishing Group**New York
75 Varick Street, 9th Floor
New York, NY 10013-1917
T: +1 212 726 9200London
The Macmillan Building
4 Crinan Street
London N1 9XW
United Kingdom
T: +44 (0)20 7833 4000Tokyo
Chiyoda Building 6F
2-37 Ichigayatamachi
Shinjuku-ku, Tokyo 162-0843
Japan
T: +81 3 3267 8751

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 Inchcoombe, Managing Director, Nature Publishing Group; Peter Collins, Ph.D., Publishing Director, NPG; Christoph Hesselmann, Ph.D., Chief Financial Officer, NPG.

Copyright © 2012 Nature Publishing Group ALL RIGHTS RESERVED.

No part of the SciBX publication or website may be copied, reproduced, retransmitted, disseminated, sold, distributed, published, broadcast, circulated, commercially exploited or used to create derivative works without the written consent of the Publishers. Information provided by the SciBX publication and website is gathered from sources that the Publishers believe are reliable; however, the Publishers do not guarantee the accuracy, completeness, or timeliness of the information, nor do the Publishers make any warranties of any kind regarding the information. The contents of the SciBX publication and website are not intended as investment, business, tax or legal advice, and the Publishers are not responsible for any investment, business, tax or legal opinions cited therein.

(see Figure 1, “Breakdown of global public-private partnerships by companies and institutions” and Table 1, “Leaders in the number of public-private partnerships”). A more detailed look at the data, however, provides several interesting regional insights (see Figure 2, “Regional breakdown of companies and institutions involved in public-private partnerships in the top six U.S. states, top five European countries and top five Asian countries”).

Table 1. Leaders in the number of public-private partnerships.

U.S. institutes were involved in over half of the reported public-private partnerships (PPPs) in 2011, with such institutes taking four of the five top spots in terms of the number of deals done. Although U.S. companies were involved in about half of the reported PPPs in 2011, France’s Sanofi was by far the most active single company. Excludes deals that only involve IP transfer.

Source: BioCentury Archives

Institute	Number of PPPs
University of California (UCSF/UCSD/UCD/UCLA)	10
NIH (includes NCI/NHGRI/NIAID)	7
Columbia University	6
Harvard University	6
BGI (formerly the Beijing Genomics Institute)	5
Company	Number of PPPs
Sanofi (Euronext:SAN; NYSE:SNY)	12
AstraZeneca plc (LSE:AZN; NYSE:AZN)	9
Pfizer Inc. (NYSE:PFE)	9
Roche (SIX:ROG; OTCQX:RHHBY)	9
Johnson & Johnson (NYSE:JNJ)	6
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK)	6

SciBX: Science–Business eXchange

*SciBX welcomes editorial queries,
comments and press releases.*

To contact the editorial team at SciBX
please e-mail editorial@scibx.com

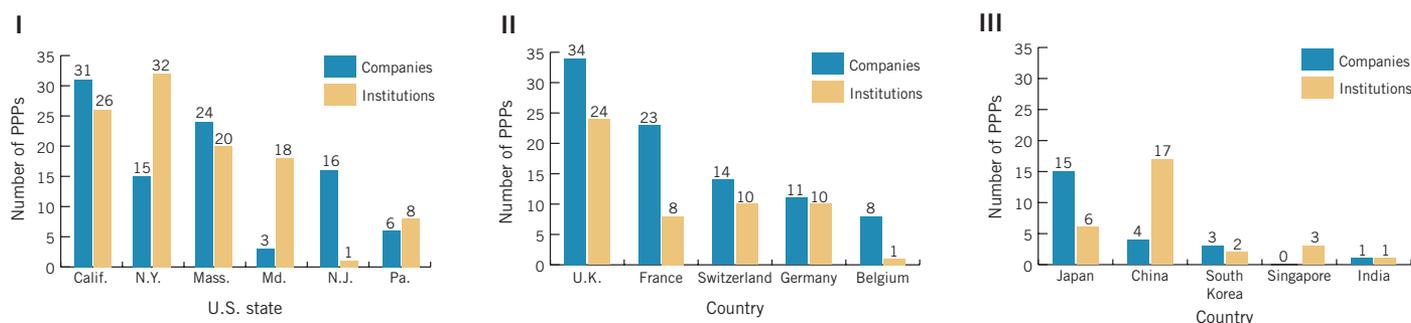


Figure 2. Regional breakdown of companies and institutions involved in public-private partnerships in the top six U.S. states (I), top five European countries (II) and top five Asian countries (III). Values refer to the actual number of companies or institutions.

During 2011, New York's desire to become a bona fide hub for biopharma was bolstered by the level of PPP activity at the state's research institutes and universities. Indeed, universities in the state were involved in the three PPPs with the highest disclosed values last year (see Table 2, "Top five public-private partnerships by value").

The state also is being buoyed by the recent appointments of Marc Tessier-Lavigne as president of **The Rockefeller University** and Laurie Glimcher as dean of **Weill Cornell Medical College**.¹

In addition to boasting the biggest deals, New York institutions also had the most PPPs in 2011 with 32 disclosed collaborations. The state edged out the 26 deals by universities in California (see Figure 2.I).

On the corporate side, California biopharma companies were the most active in the U.S. and entered into 31 PPPs last year.

In Europe, the U.K. was the clear leader in PPP activity in 2011. U.K. institutes announced 24 PPPs, whereas U.K. companies entered into 34 (see Figure 2.II).

Overall, the single most active company was **Sanofi**, which did 12 PPPs last year. This includes two R&D partnerships with the **University of California, San Francisco**² and a three-year research collaboration with **Columbia University** to investigate the use of osteocalcin as a diabetes therapeutic.³

In Asia, Japanese companies and Chinese institutes had the most PPP activity last year (see Figure 2.III). Companies in Japan partnered

with an even mix of institutes within the country's own borders and in the U.S. In contrast, Chinese institutes found most of their partners in the U.S. Among these is **Huya Bioscience International LLC**, which has operations in both Shanghai and San Diego.

Huya is focused on establishing collaborations to develop and commercialize China-sourced therapeutic candidates outside of China.

Follow the money

The specific areas of PPPs mirrored early stage financing activity in 2011, with cancer taking the top spot in both cases. The notable exception was infectious diseases, which took the second spot in terms of the number of PPPs in 2011 but placed fifth in terms of seed and series A financing activity (see Figure 3, "Breakdown of therapeutic areas covered by seed or series A financing and public-private partnerships in 2011").

Not surprisingly, the largest series A round in 2011 went to cancer and infectious diseases company **Ascleptis Inc.**, which pulled in \$50 million in the first tranche of a planned \$100 million series A round led by **Hangzhou Binjiang Investment Holding Co. Ltd.** The biotech was founded in April 2011 and has operations in Chapel Hill and Hangzhou (see Table 3, "Top five venture financing rounds for companies founded in 2011").

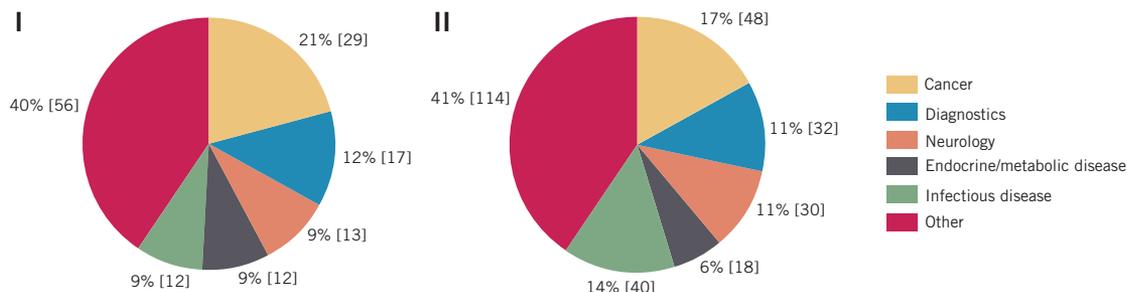
Table 2. Top five public-private partnerships by value. Three of the five largest public-private partnerships (PPPs) in 2011 are valued at \$100 million or more. Listed PPPs do not include award and grant programs established by government institutes. Only 58 of the 247 PPPs reported in 2011 had disclosed dollar amounts. Excludes deals that only involved IP transfer.

Source: BioCentury Archives

Companies	Institutes	Business area	Disclosed value (\$M)
Illumina Inc. (NASDAQ:ILMN)/ Roche (SIX:ROG; OTCQX:RHHBY)	New York Genome Center /11 U.S. institutes	Genomics	\$125 ^A
Gilead Sciences Inc. (NASDAQ:GILD)	Yale University	Cancer	\$100
Pfizer Inc. (NYSE:PFE)	The Rockefeller University / New York University Langone Medical Center / Mount Sinai Medical Center / Columbia University Medical Center / Albert Einstein College of Medicine of Yeshiva University / Weill Cornell Medical College	Pharmaceuticals	\$100
Advance BioChina	Institut Pasteur of Shanghai	Pharmaceuticals	\$47.5–\$95 ^B
Vertex Pharmaceuticals Inc. (NASDAQ:VRTX)	Cystic Fibrosis Foundation	Pulmonary disease	\$75

^A\$100 million of \$125 million has already been raised. ^BRange is calculated based on Advance BioChina disclosing that it would invest €1.5–€3 million (\$1.9–\$3.8 million) per company in up to 25 companies.

Figure 3. Breakdown of therapeutic areas covered by seed or series A financing (I) and public-private partnerships in 2011 (II). For (I), percentages are out of total financing events across all therapeutic areas; bracketed values



are the actual number of companies that received financing for a given therapeutic area. For (II), percentages are out of the total number of public-private partnerships worldwide; bracketed values are actual numbers.

Table 3. Top five venture financing rounds for companies founded in 2011. The five largest series A rounds for companies founded in 2011 went to those with U.S. operations. Among the 31 companies founded in 2011 that disclosed they received venture financing that year, there were 21 U.S. companies, 5 based in the U.K., 2 in Canada, 2 in Austria and 1 in Singapore.

Source: BCIQ: BioCentury Online Intelligence

Companies founded in 2011	Business area	Financing type	Amount raised (\$M)
Ascletris Inc. ^A	Cancer; infectious disease	Venture (series A)	\$50 ^B
Cleave Biosciences Inc.	Cancer	Venture (series A)	\$42
Blueprint Medicines	Cancer	Venture (series A)	\$40
Sage Therapeutics Inc.	Neurology	Venture (series A)	\$35
Lotus Tissue Repair Inc.	Dermatology	Venture (series A)	\$26

^ACompany has operations in both U.S. and China. ^BAmount raised is first half of a \$100 million series A round.

Within the cancer space, an overarching theme was targeted therapies. Indeed, the specific oncology indications were all over the map, but at least 20 of 48 PPPs were aimed towards developing targeted molecules.

One reason for the disconnect between partnering activity and startup money in infectious diseases is due to the availability of funding from sources such as nongovernmental organizations (NGOs) that are focused on eradicating tropical diseases and tuberculosis. Of the 40 reported PPPs covering infectious diseases, at least nine covered mosquito-borne illnesses such as malaria and dengue and another six focused on TB. At least 1 NGO was involved in 11 of these 15 PPPs.

Other top areas for PPPs last year were diagnostics, endocrine and metabolic diseases and neurology.

Lou, K.-J. *SciBX* 5(3); doi:10.1038/scibx.2012.59
Published online Jan. 19, 2012

REFERENCES

1. Kotz, J. *SciBX* 5(2); doi:10.1038/scibx.2012.31
2. Osherovich, L. *SciBX* 4(4); doi:10.1038/scibx.2011.92
3. Cain, C. *SciBX* 4(15); doi:10.1038/scibx.2011.417

COMPANIES AND INSTITUTIONS MENTIONED

Ascletris Inc., Chapel Hill, N.C.
Columbia University, New York, N.Y.
Hangzhou Binjiang Investment Holding Co. Ltd., Hangzhou, China
Huya Bioscience International LLC, San Diego, Calif.
The Rockefeller University, New York, N.Y.
Sanofi (Euronext:SAN; NYSE:SNY), Paris, France
University of California, San Francisco, Calif.
Weill Cornell Medical College, New York, N.Y.

SciBX

SciBX: Science–Business eXchange—transform your ability to efficiently identify and evaluate new developments in science and technology that have commercial and investment potential within the biotechnology and pharmaceutical arena.

Subscribe today at scibx.com

Seeing the (En)light

By Chris Cain, Staff Writer

AstraZeneca plc and Novo Nordisk A/S have come off the sidelines and joined up with Enlight Biosciences LLC, an entrepreneurial partnership that has established four platform technology companies in less than four years with input from its pharma partners.

Enlight was launched July 2008 with \$39 million in funding from PureTech Ventures in collaboration with Merck & Co. Inc., Pfizer Inc. and Eli Lilly and Co.

In addition to the three founding partners, Johnson & Johnson and Abbott Laboratories joined in 2009, bringing Enlight's total partner count to seven.

CEO Michelle Browner told *SciBX* that Enlight was founded to address the lack of support for platform technology companies in the VC community.

"Venture capitalists have needed to make sure they can realize high returns from specific therapeutic opportunities. The rationale for creating Enlight, as envisioned by PureTech and senior executives within pharma, was the need to address the decline in creation and investment in technology-focused companies," she said.

Enlight hopes to solve this problem by working with a collective of interested pharma partners to fund new companies developing technology of direct interest to them.

Enlight operates like a venture firm but receives financial support and input from its pharma partners. Thus, investment risk is shared between parties that have a vested interest in developing a given technology for their own use.

Each partner invests an undisclosed amount in Enlight and then can evaluate platform technologies identified by Enlight's network of academics.

"We bring together scientists from across pharmas, determine what the critical needs are in a given focus area and discuss where they see the challenges and the opportunity for transformational change," said Browner.

"Then with the help of academic experts we identify and evaluate technologies that can address the need, we develop an IP position, potentially combining IP from multiple sources and creating IP ourselves, and put together a company proposal, including the business plan that we will execute on," she added.

Once Enlight identifies a technology platform its pharma partners are interested in, it acquires rights to the IP, develops a business plan and founds a company. Enlight first applied this approach to Endra Inc.,

which was founded in 2008 to develop a photoacoustic imaging system that can take high-resolution tomography images without researchers needing to inject contrast agents.

"Each pharma partner can decide if and how it will be involved with a new company—participation may be based around a research collaboration or be a strategic partnership, which may include an equity investment," noted Browner.

Alan Lamont, business development director at AstraZeneca, said joining Enlight gives the pharma "the opportunity to leverage investment across a number of pharma partners to generate new collaborations and companies to address these challenges. We are also excited by the opportunity to collaborate with pharma colleagues to access different thinking and solutions to problems."

"Clearly when it comes to platform technologies, cross-pharma validation of applicability may lead to investments which we would otherwise be more reluctant to consider," said Tomas Landh, director of strategy and sourcing at the diabetes research unit of Novo Nordisk. "In the case of Enlight, establishing networks and exploring precompetitive pharma-pharma relations are positive outcomes in and of themselves."

Precompetitive for-profit

In addition to Endra, Enlight has also founded Entrega Inc., Knode Inc. and Ensōf Biosystems Inc. (See Table 1, "Enlight's offspring.") Browner said pharmas have

participated in each company but would not disclose which pharma invested in which startup.

"Because we focus on platform technologies, the magnitude of exits can be smaller than those realized by therapeutic-based companies but the timelines may be shorter. For our portfolio companies we can envision business plans where revenues may be realized in 2–3 years, and the companies can potentially become profitable relatively quickly—and there is usually a longer-term business strategy for continued value creation," said Browner.

She pointed to Endra as an example, saying the company's photoacoustic imaging system has short-term use in pharma preclinical development and long-term potential as a clinical imaging tool. Their preclinical photoacoustic imaging system was commercially launched in 2010.

Browner said Enlight falls squarely into a precompetitive space that pharma has been increasingly comfortable with. "Something like preclinical imaging technology doesn't need to be owned outright by pharma; it's not their core business. These days the technology toolbox that is needed in pharma is very large; no one can have all the expertise and technology development in-house in every area, so they are looking for ways to access both the technology and expertise without necessarily having to buy it outright, and Enlight provides a means to that goal," she said.

Lamont pointed to the growth of Enlight's portfolio of companies and the scope of technology evaluated by Enlight over the past three years as key reasons AstraZeneca decided the time was ripe to join,

(Continues on p. 6)

"We bring together scientists from across pharmas, determine what the critical needs are in a given focus area and discuss where they see the challenges and the opportunity for transformational change."

—Michelle Browner,
Enlight Biosciences LLC

Table 1. Enlight's offspring.

Company	Technology	Founded
Endra Inc.	Photoacoustic molecular imaging	2008
Entrega Inc.	Formulation technology for oral delivery of peptides and proteins	2010
Knode Inc.	Web application to identify research experts	2011
Ensōf Biosystems Inc.	Systems-level proteomics platform	2011

Scripps' partnering rethink

By Lev Osherovich, Senior Writer

Following a long run of funding a substantial portion of its research through institute-wide deals with pharmas, **The Scripps Research Institute** is now shifting to more focused collaborations with midsize biotechs. Scripps believes biotechs are a better fit for the institute's platform technologies than pharmas, where platforms can get lost in the companies' disease-oriented franchise structure.

Over the last two decades, Scripps has had a sequential series of campus-wide partnerships with pharmas including **Eli Lilly and Co.**, **Johnson & Johnson**, **Novartis AG** and, most recently, **Pfizer Inc.**

Under the 2007 Pfizer deal, the pharma had right of first refusal to technology emerging from Scripps' 280 labs at its main campus in La Jolla and its drug discovery institute in Florida. In exchange, the institute received \$100 million over 5 years and retained royalty rights to products emerging from the collaboration.

Scott Forrest, VP of business development at Scripps, said Pfizer and the institute will continue collaborating in certain undisclosed areas, but the pharma will no longer have preferred access to new Scripps discoveries.

"Historically, we've always had a broad agreement with a major pharma," said Forrest. "Those relationships were a mix of sponsored research and flat payments in exchange for the right to license Scripps' technology. We discovered empirically that those deals were great at providing short-term access to cash, but not all of the technologies we produced were amenable to pharma in-licensing."

At its end, the Scripps-Pfizer deal is a case study in how ill-defined academic-industry collaborations can lead to lost opportunities for both sides.

"We discovered empirically that those deals were great at providing short-term access to cash, but not all of the technologies we produced were amenable to pharma in-licensing."

— Scott Forrest,
The Scripps Research Institute

Mathew Mitchell, technology licensing officer at Scripps and manager of the Pfizer alliance, said that the company ultimately in-licensed very little Scripps technology over the course of the deal.

Mitchell said Pfizer gave Scripps *carte blanche* for spending the upfront money on salary support and new facilities, but the pharma did not specify what it was hoping to get from Scripps.

The Pfizer deal called for Scripps to file technology disclosures with the pharma on everything coming out of the institute, but Mitchell said the review process for disclosures was not clearly structured and could take months to complete.

Mitchell added that one of the most fruitful collaborations with Pfizer was in high throughput screening at the **Scripps Florida** drug discovery institute. Those projects had clearly defined aims and focused on compounds rather than new technology.

In retrospect, Mitchell suspects that because Pfizer and Scripps did not clearly communicate up front about what sort of technologies the pharma wanted, the deal "didn't bear the fruit that it could have."

Forrest said the disease-focused structure of pharmas proved to be a barrier to entry for Scripps' core technologies, which include platforms for target discovery, protein engineering and drug screening.

During the genomics bubble, most companies forged multiple platform technology deals, often creating overarching tool groups designed to serve their therapeutic area groups. Forrest said those days are over, as anticipated declines in revenue due to patent expiry have driven aggressive cost cutting in research areas without an immediate path to market.

"For us or any early stage research alliance with pharma, the money available for projects" has diminished, said Forrest. "We're a part of their research spending, and we ended up on the wrong side of their cost-cutting equation."

One major obstacle in working with Pfizer was the pharma's inability to convey Scripps' technologies to the right people within the company, said Forrest.

(Continues on p. 7)

(Continued from "Seeing the (En)light," p. 5)

adding that the companies and technologies aligned with strategic areas of interest for AstraZeneca.

Landh also told *SciBX*, "Enlight's reach has clearly been shown to be effective in areas highly relevant for Novo Nordisk."

Going forward, Browner believes "that what is defined as precompetitive will change and expand, and so we are now thinking about novel ways to address the needs in areas of more basic biology and disease understanding. The focus could be on identifying opportunities for drug discovery and development—the pharmas would then compete on how to capitalize on those opportunities."

She declined to be more specific but said many pharmas are investing in basic disease biology through partnerships with academics and that sharing such information could improve efficiency.

Cain, C. *SciBX* 5(3); doi:10.1038/scibx.2012.60
Published online Jan. 19, 2012

COMPANIES AND INSTITUTIONS MENTIONED

Abbott Laboratories (NYSE:ABT), Abbott Park, Ill.
AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K.
Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
Endra Inc., Ann Arbor, Mich.
Enlight Biosciences LLC, Boston, Mass.
Ensōf Biosystems Inc., Boston, Mass.
Entrega Inc., Boston, Mass.
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Knobe Inc., Boston, Mass.
Merck & Co. Inc. (NYSE:MRK), Whitehouse Station, N.J.
Novo Nordisk A/S (CSE:NVO; NYSE:NVO), Bagsvaerd, Denmark
Pfizer Inc. (NYSE:PFE), New York, N.Y.
PureTech Ventures, Boston, Mass.

“Platform technologies are very difficult for large companies to position internally,” said Forrest. “Pharmas are siloed by therapeutic areas, but platforms are usually application-agnostic at an early stage. These technologies often have data packages that pharma licensing offices don’t know how to interpret.”

Forrest thinks Scripps will be better served by not giving any one company the exclusive right to license all of the institute’s technology. He said the ideal industry partner going forward would be a “midsize company with positive cash flow and a relatively narrow focus.”

Compared with fledgling startups and big companies, midsize companies are in a better position to evaluate and advance Scripps’ technologies to market and generate revenue for the institute, said Forrest.

Partnering with nimble but seasoned biotechs will make it easier for Scripps researchers to find and work directly with the right people, he added.

“Under the old structure, not enough of our compounds or technologies were advancing to market,” said Forrest. “If we really work together with these companies, we are more likely to hit the market.”

Another potential partnering scenario is a disease-focused collaborative research program like the December 2010 and January 2011 deals the **Sanford-Burnham Medical Research Institute** made with the pharmas **Takeda Pharmaceutical Co. Ltd.** and **J&J**, respectively, Forrest said. The J&J deal covers target and drug discovery in Alzheimer’s disease (AD) and neuropsychiatric disorders, whereas the Takeda deal covers obesity.¹

Scripps will continue to host the Genomics Institute of the Novartis Research Foundation (GNF), a Novartis-backed research outfit that predates the Pfizer deal.

Getting a head

Scripps’ change in partnering strategy coincides with a change of leadership. At the start of the year, Michael Marletta became president of the institute in addition to professor of chemistry. He formerly was chair of chemistry at the **University of California, Berkeley**.

Marletta told *SciBX* that fundraising for discovery science, which he said is a strength of Scripps, has become harder than fundraising for translational research. He noted that constrained research and partnering budgets at pharmas have led to a more milestone-driven, disease-focused attitude toward academic collaborators.

“Pharmas have changed how they invest and think about research,” said Marletta. “Their interest in places like Scripps was previously something like, ‘Here’s a bunch of money, go off and do your own thing, and we’ll have a chance to look at it’. Now they’re much more targeted, to the detriment of discovery science.”

Marletta noted that the end of the Pfizer deal also comes at a time

“Pharmas have changed how they invest and think about research. Their interest in places like Scripps was previously something like, ‘Here’s a bunch of money, go off and do your own thing, and we’ll have a chance to look at it’. Now they’re much more targeted, to the detriment of discovery science.”

—*Michael Marletta,*
The Scripps Research Institute

when government support for basic research is diminishing, thus putting further stress on Scripps’ finances.

“The support of pharmas and the federal government has allowed Scripps to undergo unprecedented growth, but both of these partners are disappearing on us,” Marletta noted.

Marletta said Scripps will make up some of the lost money from royalties on drugs based on Scripps technology. He expects the coming years will bring a significant uptick in royalty income from **Benlysta** belimumab from **GlaxoSmithKline plc** and **Human Genome Sciences Inc.** and Pfizer’s **Vyndaqel** tafamidis.

Benlysta was approved last year to treat

active, autoantibody-positive systemic lupus erythematosus (SLE) in patients who are receiving standard therapy. Vyndaqel, a small molecule that corrects a structural defect in a mutant form of transthyretin, was approved last year in the EU for familial amyloid polyneuropathy. In April 2011, the FDA issued a refusal to file letter for Vyndaqel.

Vyndaqel was developed by FoldRx Pharmaceuticals Inc., which was cofounded by Jeffery Kelly, a chemistry professor at Scripps. FoldRx was based on IP developed prior to the Pfizer deal, and Pfizer subsequently acquired FoldRx for an undisclosed amount in 2010.

Marletta also hopes to derive more income from increased licensing. He said Scripps plans to scale up its technology transfer office staffing to handle a higher volume of IP filings. Rather than routinely handing its technology over to Pfizer, the office now will need to proactively seek out potential partners.

“We’re going to increase the revenue that Scripps generates from its IP,” said Marletta. “We’re going to invest in the technology transfer office to handle the greater workload, and to justify that expense there needs to be more income.”

He also said Scripps will now seek philanthropic funding, a source of dollars the institute previously had not explored.

Osheroich, L. *SciBX* 5(3); doi:10.1038/scibx.2012.61
Published online Jan. 19, 2012

REFERENCES

1. Cain, C. *SciBX* 4(5); doi:10.1038/scibx.2011.123

COMPANIES AND INSTITUTIONS MENTIONED

Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Human Genome Sciences Inc. (NASDAQ:HGS1), Rockville, Md.
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Pfizer Inc. (NYSE:PFE), New York, N.Y.
Sanford-Burnham Medical Research Institute, La Jolla, Calif.
Scripps Florida, Jupiter, Fla.
The Scripps Research Institute, La Jolla, Calif.
Takeda Pharmaceutical Co. Ltd. (Tokyo:4502), Osaka, Japan
University of California, Berkeley, Calif.

Heat shock and awe

By *Tim Fulmer, Senior Writer*

U.S. researchers have identified several small molecules that decrease toxic protein aggregation *in vitro*.¹ The first-generation compounds have been licensed by **Proteostasis Therapeutics Inc.** and are proof of concept for the biotech's approach to treating protein misfolding diseases like Huntington's and cystic fibrosis.

Cells have evolved a complex network of quality control enzymes to prevent the formation and accumulation of misfolded proteins during normal cellular function. However, this protein homeostasis (or proteostasis) network often is overwhelmed in protein misfolding diseases, which generate high levels of protein aggregates that are impossible to clear and lead to cell death.

The challenge has been figuring out how to boost the activity of the network, which consists of hundreds of proteins involved in the folding, trafficking and degradation of misfolded proteins.²

Rather than tackling single components of the network, a research team led by Proteostasis Therapeutics founder and **Northwestern University** professor of biology Richard Morimoto hypothesized that activating a global regulator of many components simultaneously would improve the likelihood of a therapeutic effect.

The group turned to a known transcriptional factor of the network—heat shock transcription factor 1 (HSF1)^{3,4}—and set out to identify compounds that activated that target. Morimoto and colleagues first devised a high throughput cell-based screen that allowed them to measure activation of HSF1. The assay worked by monitoring the activity of the promoter of one of HSF1's many target genes, *heat shock protein 70 (Hsp70)*.

A screen of about 900,000 small molecules resulted in 233 compounds that increased *Hsp70* promoter activity. The compounds encompassed a variety of chemical scaffolds and were grouped into seven classes based on structural similarity.

Additional *in vitro* studies confirmed that the five best compounds upregulated multiple proteins in the protein homeostasis network, including *Hsp40* and *Hsp27*, and did so by acting through HSF1.

The next priority was determining whether any of the five HSF1 activators had a disease-modifying effect *in vitro*.

The researchers looked at cell culture models of Huntington's disease (HD), which is characterized by toxic huntingtin (HTT) protein aggregates, and of cystic fibrosis (CF), which is characterized by a misfolded and defective cystic fibrosis transmembrane conductance regulator (CFTR) protein.

In the HD model, compounds A1, D1 and F1 decreased the number of HTT aggregates compared with vehicle control. In the CF model, compounds A3, C1 and F1 increased CFTR ion conductance compared with vehicle.

Finally, in a *Caenorhabditis elegans* model of HD, compounds A1, D1 and F1 lowered toxic aggregation compared with vehicle.

The findings were published in *Nature Chemical Biology*.

Prioritize and optimize

"A basic part of our initial optimization process is the generation of a proteostasis network signature for each compound. The signature reflects how each compound affects pathways within the network and helps prioritize our choice of disease models for further testing," said Peter Reinhart, president and CSO of Proteostasis Therapeutics. "By focusing on several pathways at once, our approach differs from more traditional optimization strategies that focus on a single target from the outset."

Proteostasis Therapeutics founder Jeffrey Kelly said the strength of the approach and the screen used in the paper is that "distinct compounds with distinct mechanisms of action will likely be discovered. A more reductionist biochemical screen can then be added subsequently to identify actual targets and demonstrate mechanistic details."

Kelly is a professor of chemistry at **The Scripps Research Institute**.

Reinhart said the company plans to study some of the compounds in animal models of CF, Parkinson's disease (PD), HD and Alzheimer's disease (AD).

"By focusing on several pathways at once, our approach differs from more traditional optimization strategies that focus on a single target from the outset."

—Peter Reinhart,
Proteostasis Therapeutics Inc.

AD and PD are characterized by toxic aggregates of β -amyloid (A β) and α -synuclein (SNCA) proteins, respectively.

Screening the screens

Experiments reported in the paper confirmed that some of the most active compounds in the *in vitro* disease models did not have off-target effects on the proteasome or Hsp90 that might lead to toxicity.

Nevertheless, Matt Kaerberlein, associate professor of pathology at the **University of Washington**, said that beyond the screens and assays it will be important "to see if any of the compounds are effective in mouse models of human proteotoxic diseases without too many negative side effects."

"There are a variety of mechanisms of action that promote the heat shock response, and some of those MoAs are undesirable because they result from acute cellular stress, not from activation of HSF1," noted William Janzen, cofounder, president and CEO of **Chaperone Therapeutics Inc.** "For that reason, we designed our yeast-based screen to identify only compounds that have an HSF1-dependent MoA."

The screen described in *Nature Chemical Biology* cannot by itself distinguish heat shock-promoting compounds that have an HSF1-dependent mechanism of action from those that have an HSF1-independent one. For that reason, the researchers had to use additional *in vitro* experiments to confirm that their activators had an HSF1-dependent mechanism of action.

In contrast, Chaperone Therapeutics' screen is, by itself, sufficient to identify only compounds that have an HSF1-dependent mechanism of action.

Thus, while the two companies are seeking to identify the same types of compounds, they differ in the screening platforms they are using. It is not yet clear whether one approach will yield better therapeutic candidates than the other.

Last year, Chaperone Therapeutics cofounder Dennis Thiele published in *Public Library of Science Biology* that the company's screen identified multiple compounds that activated HSF1.⁵ This month,

The **Michael J. Fox Foundation for Parkinson's Research** announced it was funding research to test some of those HSF1 activators in preclinical models of PD. Thiele is professor of pharmacology and cancer biology at the **Duke University School of Medicine**.

The *Nature Chemical Biology* findings are covered by patents from Northwestern University and licensed to Proteostasis Therapeutics.

Fulmer, T. *SciBX* 5(3); doi:10.1038/scibx.2012.62
Published online Jan. 19, 2012

REFERENCES

1. Calamini, B. *et al. Nat. Chem. Biol.*; published online Dec. 25, 2011; doi:10.1038/nchembio.763
Contact: Richard Morimoto, Northwestern University, Evanston, Ill.
e-mail: r-morimoto@northwestern.edu

2. Hartl, F.U. *et al. Nature* **475**, 324–332 (2011)
3. Neef, D.W. *et al. Nat. Rev. Drug Disc.* **10**, 930–944 (2011)
4. Westerheide, S.D. & Morimoto, R.I. *J. Biol. Chem.* **280**, 33097–33100 (2005)
5. Neef, D.W. *et al. PLoS Biol.* **8**, e1000291; published online Jan. 19, 2010; doi:10.1371/journal.pbio.1000291

COMPANIES AND INSTITUTIONS MENTIONED

Chaperone Therapeutics Inc., Research Triangle Park, N.C.
Duke University School of Medicine, Durham, N.C.
Northwestern University, Evanston, Ill.
The Michael J. Fox Foundation for Parkinson's Research, New York, N.Y.
Proteostasis Therapeutics Inc., Cambridge, Mass.
The Scripps Research Institute, La Jolla, Calif.
University of Washington, Seattle, Wash.



The Scientific Acumen of Nature Publishing Group
plus
The Business Intelligence of BioCentury Publications, Inc.
in a single publication

Can you afford not to subscribe?
Visit scibx.com for details on how to subscribe to SciBX

This week in therapeutics

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

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

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Autoimmune disease				
Celiac disease	Transglutaminase 2 (TGM2; TG2)	<i>In vitro</i> studies identified autoantibody binding sites of TG2 that could be blocked to help treat celiac disease. <i>In vitro</i> studies showed that mutation in any of three spatially adjacent residues on the TG2 protein prevented binding of celiac autoantibodies compared with mutation in other residues. In <i>ex vivo</i> placental tissue from celiac patients, a mAb targeting the identified epitope caused release of autoantibodies compared with an anti-TG2 mAb binding a different epitope. Next steps include testing the efficacy of the antibody in an animal model of celiac disease. SciBX 5(3); doi:10.1038/scibx.2012.63 Published online Jan. 19, 2012	Patent applications filed for diagnostic and therapeutic applications; available for licensing	Simon-Vecsei, Z. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Dec. 22, 2011; doi:10.1073/pnas.1107811108 Contact: Ilma R. Korponay-Szabó, University of Tampere and University of Tampere Hospital, Tampere, Finland e-mail: loikko@uta.fi
Cancer				
Breast cancer	ADP-ribosylation factor 1 (ARF1)	Mouse studies identified an ARF1 inhibitor that could help treat breast cancer. A computational method identified AMF-26 as an ARF1 inhibitor that was structurally distinct from brefeldin A, which has poor oral bioavailability. In a mouse xenograft model of breast cancer, oral treatment with AMF-26 induced tumor regression compared with vehicle treatment. Next steps could include testing AMF-26 in mouse models of other cancer types. SciBX 5(3); doi:10.1038/scibx.2012.64 Published online Jan. 19, 2012	Patent and licensing status unavailable	Ohashi, Y. <i>et al. J. Biol. Chem.</i> ; published online Dec. 9, 2011; doi:10.1074/jbc.M111.316125 Contact: Takao Yamori, Japanese Foundation for Cancer Research, Tokyo, Japan e-mail: yamori@jfcrc.or.jp
Breast cancer	Mucin 1 (MUC1; CD227)	Mouse studies suggest an immunotherapy based on a MUC1 glycopeptide could help treat breast cancer. In a mouse model of breast cancer with aberrant MUC1 glycosylation, a vaccine composed of a cancer-associated MUC1 glycopeptide linked with an adjuvant and a T cell epitope led to less tumor growth than a vaccine in which the three components were unlinked. Next steps include optimizing the T cell response elicited by the vaccine, followed by a Phase Ia trial. Oncothyreon Inc.'s MUC1-based vaccines, Stimuvax and ONT-10, are in Phase III testing for non-small cell lung cancer (NSCLC) and preclinical testing for cancer, respectively. Bavarian Nordic A/S's CV-301, a vaccine targeting carcinoembryonic antigen (CEA) and MUC1, is in Phase II testing for breast cancer. SciBX 5(3); doi:10.1038/scibx.2012.65 Published online Jan. 19, 2012	Patents pending; some aspects available for licensing; Viamune Inc., a company founded by Geert-Jan Boons, has an option to license the technology for cancer vaccine applications	Lakshminarayanan, V. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Dec. 14, 2011; doi:10.1073/pnas.1115166109 Contact: Geert-Jan Boons, The University of Georgia, Athens, Ga. e-mail: gjboons@ccrc.uga.edu Contact: Sandra J. Gendler, Mayo Clinic College of Medicine, Scottsdale, Ariz. e-mail: gendler.sandra@mayo.edu

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Breast cancer	Nerve growth factor (NGF)	<p>Cell culture and patient tissue studies suggest pro-NGF could be antagonized to treat breast cancer. NGF is typically proteolytically cleaved from an intracellular pro form to a secreted form. In breast cancer tumor biopsies, pro-NGF was overexpressed in malignant tumor tissue compared with benign tumor or normal tissue. In a breast cancer cell line, small interfering RNA against pro-NGF decreased invasiveness compared with siRNA controls. Next steps could include testing antibodies against NGF in cell culture and animal models of breast cancer.</p> <p>At least five anti-NGF mAbs are in Phase II and Phase III testing for osteoarthritis and pain indications.</p> <p>SciBX 5(3); doi:10.1038/scibx.2012.66 Published online Jan. 19, 2012</p>	Patent and licensing status undisclosed	<p>Demont, Y. <i>et al. J. Biol. Chem.</i>; published online Nov. 29, 2011; doi:10.1074/jbc.M110.211714</p> <p>Contact: Hubert Hondermarck, University of Lille, Lille, France e-mail: hubert.hondermarck@univ-lille1.fr</p>
Breast cancer; brain cancer	Taspase threonine aspartase 1 (TASP1)	<p>Cell culture and mouse studies identified a TASP1 inhibitor that could help treat breast cancer and gliomas. A cell-based screen of a National Cancer Institute small molecule library identified an arsonic acid-based molecule as a specific TASP1 inhibitor. In mouse xenograft models of TASP1-overexpressing human breast cancer and glioma, the inhibitor lowered tumor growth compared with vehicle. Next steps include developing more potent TASP1 inhibitors and identifying the most appropriate types of cancers to treat with such inhibitors.</p> <p>SciBX 5(3); doi:10.1038/scibx.2012.67 Published online Jan. 19, 2012</p>	<p>Patent application filed; available for licensing from Washington University in St. Louis</p> <p>Contact: Jon Kratochvil, Washington University in St. Louis, St. Louis, Mo. phone: 314-747-0923 e-mail: kratochj@wustl.edu</p>	<p>Chen, D.Y. <i>et al. Cancer Res.</i>; published online Dec. 13, 2011; doi:10.1158/0008-5472.CAN-11-2584</p> <p>Contact: James J.-D. Hsieh, Memorial Sloan-Kettering Cancer Center, New York, N.Y. e-mail: hsiehj@mskcc.org</p>
Cancer	Checkpoint kinase 1-short (Chk1-S)	<p><i>In vitro</i> and mouse studies suggest increasing levels of Chk1-S may help treat cancer. In mice bearing breast cancer tumors, overexpression of Chk1-S decreased tumor volume compared with normal Chk1-S expression. Next steps include identifying a way to increase the splicing that produces Chk1-S. Eli Lilly and Co. has checkpoint kinase 1 (Chk1) inhibitors in Phase I, Phase II and Phase I/II testing to treat cancer. Genentech Inc. has a Chk1 inhibitor to treat cancer in Phase I trials.</p> <p>SciBX 5(3); doi:10.1038/scibx.2012.68 Published online Jan. 19, 2012</p>	Unpatented; available for licensing	<p>Pabla, N. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Dec. 19, 2011; doi:10.1073/pnas.1104767109</p> <p>Contact: Zheng Dong, Georgia Health Sciences University, Augusta, Ga. e-mail: zdong@georgiahealth.edu</p>
Cancer	Fibronectin 1 (FN1; FN)	<p>Mouse studies identified an FN1-targeting antibody-drug conjugate that could help treat cancer. A variant of the cytotoxic peptide cemadotin was conjugated to a human antibody against the tumor vascular protein FN1. In a mouse tumor model, the conjugate decreased tumor growth and increased survival compared with the peptide conjugated to a control antibody or unconjugated peptide. Next steps include generating conjugates with different therapeutic payloads and testing them in additional models of cancer.</p> <p>SciBX 5(3); doi:10.1038/scibx.2012.69 Published online Jan. 19, 2012</p>	Patent applications filed by Philogen S.p.A.; available for licensing	<p>Bernardes, G.J.L. <i>et al. Angew. Chem. Int. Ed.</i>; published online Dec. 15, 2011; doi:10.1002/anie.201106527</p> <p>Contact: Dario Neri, Swiss Federal Institute of Technology Zurich (ETHZ), Zurich, Switzerland e-mail: dario.neri@pharma.ethz.ch</p>

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cancer	Not applicable	<p>Mouse studies suggest activating autophagy or increasing ATP release from tumor cells could help treat cancer. In a mouse xenograft model of colorectal cancer, the generic chemotherapeutic mitoxantrone induced autophagy and increased immunogenic ATP release compared with saline. In mice with mitoxantrone-treated human colorectal cancer cells, transplantation of autophagy-deficient cells decreased ATP release and the antitumor immune response and increased tumor growth compared with transplantation of autophagy-competent cells. Next steps could include developing strategies to promote autophagy or immunogenic ATP release in autophagy-deficient cancers.</p> <p>Hydroxychloroquine, a generic inhibitor of autophagy, is in investigator-led Phase II trials for various cancers.</p> <p>SciBX 5(3); doi:10.1038/scibx.2012.70 Published online Jan. 19, 2012</p>	Patent and licensing status unavailable	<p>Michaud, M. <i>et al. Science</i>; published online Dec. 16, 2011; doi:10.1126/science.1208347 Contact: Laurence Zitvogel, Institut National de la Santé et de la Recherche Médicale (INSERM), Villejuif, France e-mail: zitvogel@igr.fr Contact: Guido Kroemer, same affiliation as above e-mail: kroemer@orange.fr</p>
Chronic myelogenous leukemia (CML)	Sirtuin 1 (SIRT1)	<p><i>In vitro</i> and mouse studies suggest inhibiting SIRT1 could increase the efficacy of Gleevec imatinib in CML. In CML cell lines, imatinib plus a SIRT1 inhibitor decreased cell growth and increased imatinib-induced apoptosis compared with either treatment alone. In mice receiving BCR-ABL tyrosine kinase-transformed bone marrow cells, those receiving <i>Sirt1</i>^{-/-} cells had delayed development of CML and increased survival compared with those receiving <i>Sirt1</i>^{+/+} cells. Next steps include developing a SIRT1 inhibitor.</p> <p>Elixir Pharmaceuticals Inc. has a SIRT1 inhibitor in preclinical testing to treat Huntington's disease (HD). Novartis AG markets Gleevec to treat CML and gastrointestinal stromal tumors (GISTs).</p> <p>SciBX 5(3); doi:10.1038/scibx.2012.71 Published online Jan. 19, 2012</p>	Patent application filed covering SIRT1 inhibition to treat cancer chemoresistance; available for licensing	<p>Yuan, H. <i>et al. Blood</i>; published online Dec. 29, 2011; doi:10.1182/blood-2011-06-361691 Contact: WenYong Chen, City of Hope, Duarte, Calif. e-mail: wchen@coh.org</p>
Endocrine/metabolic disease				
Diabetes	Fibroblast growth factor receptor 1 (FGFR1; CD331); fibroblast growth factor 21 (FGF21)	<p>A study in mice suggests an agonist mAb of FGFR1 could help treat type 2 diabetes. In a mouse model of diabetes, an agonistic mAb that mimics the effect of FGF21 decreased blood glucose, insulin and lipid levels as effectively as recombinant FGF21 while having a longer half-life and duration of action. Next steps include optimization and further preclinical development of the FGFR1 mAb as a type 2 diabetes candidate.</p> <p>Ambix Inc. and Bristol-Myers Squibb Co. have ARX618, a stabilized form of FGF21, in preclinical development for type 2 diabetes.</p> <p>SciBX 5(3); doi:10.1038/scibx.2012.72 Published online Jan. 19, 2012</p>	Patent pending; unavailable for licensing	<p>Wu, A.L. <i>et al. Sci. Transl. Med.</i>; published online Dec. 14, 2011; doi:10.1126/scitranslmed.3002669 Contact: Junichiro Sonoda, Genentech Inc., South San Francisco, Calif. e-mail: junichis@gene.com</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Diabetes	Sphingosine 1-phosphate receptor	<p>Studies in mice suggest that agonizing sphingosine 1-phosphate receptors could help treat diabetes. In a mouse model of type 2 diabetes, Gilenya fingolimod lowered fasting blood glucose concentrations and increased β cell mass and proliferation compared with no treatment. Next steps could include clinical testing in diabetic patients.</p> <p>Gilenya fingolimod (FTY720), a sphingosine 1-phosphate receptor agonist from Novartis AG and Mitsubishi Tanabe Pharma Corp., is approved to treat relapsing-remitting multiple sclerosis (RRMS).</p> <p>At least seven other companies have sphingosine 1-phosphate receptor agonists in preclinical to Phase II testing.</p> <p>SciBX 5(3); doi:10.1038/scibx.2012.73 Published online Jan. 19, 2012</p>	Patent application filed; available for licensing	<p>Zhao, Z. <i>et al. J. Biol. Chem.</i>; published online Dec. 22, 2011; doi:10.1074/jbc.M111.305359</p> <p>Contact: Zhongmin Alex Ma, Mount Sinai School of Medicine, New York, N.Y. e-mail: zhongmin.ma@mssm.edu</p>
Hematology				
Hemolytic uremic syndrome	CXC chemokine receptor 4 (CXCR4; NPY3R); chemokine CXC motif ligand 12 (CXCL12; SDF-1); CXCR7	<p><i>In vitro</i> and mouse studies suggest inhibiting the CXCR4/CXCR7/SDF-1 signaling pathway could help treat or prevent hemolytic uremic syndrome following <i>Escherichia coli</i> infection. In human microvascular endothelial cells, exposure to an <i>E. coli</i>-derived shiga toxin, which could cause hemolytic uremic syndrome, resulted in greater expression of CXCR4, CXCR7 and SDF-1 than exposure to vehicle. In mice injected with the toxin, the CXCR4 antagonist Mozobil plerixafor partially restored kidney function and increased survival compared with saline. Next steps include measuring SDF-1 levels in infected individuals during an <i>E. coli</i> outbreak. Sanofi markets Mozobil to treat multiple myeloma (MM) and non-Hodgkin's lymphoma (NHL).</p> <p>SciBX 5(3); doi:10.1038/scibx.2012.74 Published online Jan. 19, 2012</p>	Unpatented; available for strategic partnerships	<p>Petruzzello-Pellegrini, T.N. <i>et al. J. Clin. Invest.</i>; published online Jan. 9, 2012; doi:10.1172/JCI57313</p> <p>Contact: Philip A. Marsden, University of Toronto, Toronto, Ontario, Canada e-mail: p.marsden@utoronto.ca</p>
Infectious disease				
Bacterial infection	UDP-3-O-[3- hydroxymyristoyl] N-acetylglucosamine deacetylase (LpxC)	<p><i>In vitro</i> and mouse studies identified hydroxamic acid-based LpxC inhibitors that could help treat Gram-negative bacterial infections. <i>In vitro</i>, the compounds inhibited LpxC at low nanomolar IC₅₀ values. In a mouse model of systemic <i>Pseudomonas aeruginosa</i> infection, a lead compound decreased bacterial growth compared with no treatment. Next steps include further optimization of lead LpxC inhibitors.</p> <p>SciBX 5(3); doi:10.1038/scibx.2012.75 Published online Jan. 19, 2012</p>	Patent application filed; licensing status undisclosed	<p>Brown, M.F. <i>et al. J. Med. Chem.</i>; published online Dec. 18, 2011; doi:10.1021/jm2014748</p> <p>Contact: Matthew F. Brown, Pfizer Global Research and Development, Groton, Conn. e-mail: matthew.f.brown@pfizer.com</p>
HCV	Niemann-Pick C1-like protein (NPC1L1)	<p><i>In vitro</i> and mouse studies suggest NPC1L1 inhibitors could help prevent HCV infection. In human hepatocyte cell culture, small interfering RNA against NPC1L1 or antibodies against NPC1L1 prevented the entry of multiple HCV genotypes compared with scrambled siRNA or control IgG, respectively. In mice with chimeric human livers, daily Zetia ezetimibe for 1 or 2 weeks prior to HCV challenge prevented infection in up to 71% of animals compared with vehicle but had no effect in chimeric mice with established HCV infection. Ongoing work includes a Phase II trial of ezetimibe plus standard of care to treat HCV.</p> <p>Merck & Co. Inc. markets Zetia, a cholesterol uptake inhibitor that blocks NPC1L1, to treat coronary artery disease (CAD), hypercholesterolemia and hyperlipidemia.</p> <p>SciBX 5(3); doi:10.1038/scibx.2012.76 Published online Jan. 19, 2012</p>	Patented by the University of Illinois; available for licensing or partnering	<p>Sainz Jr., B. <i>et al. Nat. Med.</i>; published online Jan. 8, 2012; doi:10.1038/nm.2581</p> <p>Contact: Susan L. Uprichard, University of Illinois at Chicago, Chicago, Ill. e-mail: sluprich@uic.edu</p>

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Sepsis	Receptor-interacting serine-threonine kinase 1 (RIPK1; RIP1); RIPK3 (RIP3)	<p>Mouse studies suggest that inhibition of RIPK1 and/or RIPK3 could help prevent systemic inflammatory response syndrome (SIRS). In mice, Ripk3 deficiency or pretreatment with the RIPK1-specific kinase inhibitor necrostatin-1 decreased hypothermia and mortality from tumor necrosis factor (TNF)-induced SIRS compared with what was seen in wild-type controls or using vehicle, respectively. Next steps could include evaluating the RIPK1 inhibitor in a therapeutic as opposed to prophylactic setting.</p> <p>SciBX 5(3); doi:10.1038/scibx.2012.77 Published online Jan. 19, 2012</p>	Patent and licensing status unavailable	<p>Duprez, L. <i>et al. Immunity</i>; published online Dec. 23, 2011; doi:10.1016/j.immuni.2011.09.020 Contact: Peter Vandenebelee, Flanders Institute for Biotechnology (VIB), Ghent, Belgium e-mail: peter.vandenebelee@dmbr.ugent.be</p>
Inflammation				
Inflammation	Matrix metalloproteinase 9 (MMP9)	<p>Mouse studies identified antibodies that inhibit MMP9 to help treat inflammatory diseases. In mice, immunization with a synthetic organic metal-ligand designed to mimic the active site of MMP9 led to generation of anti-MMP9 antibodies. In a mouse model of colitis, the antibodies lowered disease severity compared with control antibodies. Next steps include humanizing the antibodies and evaluating toxicity.</p> <p>SciBX 5(3); doi:10.1038/scibx.2012.78 Published online Jan. 19, 2012</p>	Patent application filed; available for licensing	<p>Sela-Passwell, N. <i>et al. Nat. Med.</i>; published online Dec. 25, 2011; doi:10.1038/nm.2582 Contact: Irit Sagi, Weizmann Institute of Science, Rehovot, Israel e-mail: irit.sagi@weizmann.ac.il</p>
Neurology				
Depression	Nicotinic acetylcholine receptor $\alpha_4\beta_2$	<p><i>In vitro</i> and mouse studies suggest two new classes of nicotinic acetylcholine receptor $\alpha_4\beta_2$ partial agonists could help treat depression. Chemical synthesis and <i>in vitro</i> testing identified an isoxazole ether analog and several cyclopropylpyridine ether analogs that were selective partial agonists of nicotinic acetylcholine receptor $\alpha_4\beta_2$ at low micromolar and low nanomolar EC₅₀ values, respectively. In a mouse model of depression, the isoxazole ether analog and three lead cyclopropylpyridine ether analogs decreased immobility in the forced swim test compared with vehicle. Ongoing work by PsychoGenics Inc. includes showing efficacy for one of the lead cyclopropylpyridine ether analogs in an animal model of drug-resistant depression.</p> <p>Pfizer Inc. markets Chantix/Champix varenicline, a nicotinic acetylcholine receptor $\alpha_4\beta_2$ partial agonist, to treat addiction.</p> <p>Bulgarian Pharmaceutical Group Ltd. markets Tabex cytisine, a nicotinic acetylcholine receptor $\alpha_4\beta_2$ partial agonist, to treat addiction.</p> <p>AZD3480 (TC-1734), a neuronal nicotinic acetylcholine receptor $\alpha_4\beta_2$ agonist from Targacept Inc. and AstraZeneca plc, is in Phase IIb testing to treat Alzheimer's disease (AD) and Phase II testing to treat attention deficit hyperactivity disorder (ADHD).</p> <p>SciBX 5(3); doi:10.1038/scibx.2012.79 Published online Jan. 19, 2012</p>	Findings from both studies patented by the University of Illinois at Chicago; licensed to PsychoGenics	<p>Yu, L.-F. <i>et al. J. Med. Chem.</i>; published online Dec. 13, 2011; doi:10.1021/jm201301h Contact: Alan P. Kozikowski, University of Illinois at Chicago, Chicago, Ill. e-mail: kozikowa@uic.edu</p> <p>Zhang, H. <i>et al. J. Med. Chem.</i>; published online Dec. 15, 2011; doi:10.1021/jm201157c Contact: Alan P. Kozikowski, University of Illinois at Chicago, Chicago, Ill. e-mail: kozikowa@uic.edu</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Huntington's disease (HD)	Heat shock transcription factor 1 (HSF1)	An <i>in vitro</i> screen identified small molecule compounds that activated the heat shock response and could help treat HD and other protein misfolding diseases. Two cell-based high throughput screens of about 900,000 compounds identified 233 small molecules that activated HSF1 and the heat shock response. In cell culture and worm models of HD, three of the compounds suppressed toxic protein aggregation compared with vehicle. Next steps by Proteostasis Therapeutics Inc. include optimizing some of the compounds (<i>see Heat shock and awe, page 8</i>). SciBX 5(3); doi:10.1038/scibx.2012.80 Published online Jan. 19, 2012	Compounds patented by Northwestern University; licensed to Proteostasis Therapeutics	Calamini, B. <i>et al. Nat. Chem. Biol.</i> ; published online Dec. 25, 2011; doi:10.1038/nchembio.763 Contact: Richard I. Morimoto, Northwestern University, Evanston, Ill.; e-mail: r-morimoto@northwestern.edu
Parkinson's disease (PD)	Mitochondrial complex I (MC-1)	Rat studies suggest a fusion protein consisting of the rabies virus glycoprotein (RVG) linked to a cytomegalovirus (CMV)-derived RNA sequence could help treat PD. The noncoding p137 RNA, which is derived from a human CMV transcript, was fused to an arginine-modified RVG to facilitate delivery across the blood brain barrier (BBB). In adult rats, tail vein injection of the RVG-p137 RNA conjugate three days after neurotoxin-induced injury of dopaminergic neurons led to better postinjury motor performance than injection of the same RVG peptide conjugated with a control RNA sequence. Next steps include determining the minimal subdomain of the p137 RNA required for neuroprotection and the time window for the fusion peptide's effects. SciBX 5(3); doi:10.1038/scibx.2012.81 Published online Jan. 19, 2012	Patent application filed; available for licensing from Cambridge Enterprise Ltd.	Kuan, W.-L. <i>et al. J. Exp. Med.</i> ; published online Dec. 19, 2011; doi:10.1084/jem.20111126 Contact: John H. Sinclair, University of Cambridge, Cambridge, U.K. e-mail: js@mole.bio.cam.ac.uk Contact: Roger A. Barker, same affiliation as above e-mail: rab46@cam.ac.uk
Other				
Hyperthermia	Ryanodine receptor 1 (RyR1)	Mouse studies suggest 5-aminoimidazole-4-carboxamide ribonucleoside (AICAR) could help prevent heat-induced sudden death caused by RyR1 mutations. In a mouse model of RyR1-mutant hyperthermia, AICAR prevented heat-induced sudden death. The compound blocks Ca ²⁺ leak from the sarcoplasmic reticulum that leads to muscle dysfunction and sudden death. Next steps include testing AICAR in large animal models. Armgo Pharma Inc.'s RyR1 modulator, Rycals, is in Phase II testing to treat heart failure and arrhythmia. SciBX 5(3); doi:10.1038/scibx.2012.82 Published online Jan. 19, 2012	Unpatented; unavailable for licensing	Lanner, J.T. <i>et al. Nat. Med.</i> ; published online Jan. 8, 2012; doi:10.1038/nm.2598 Contact: Susan L. Hamilton, Baylor College of Medicine, Houston, Texas e-mail: susanh@bcm.edu
Transplantation				
Graft rejection	Haptoglobin (HP)	Mouse studies suggest that antagonizing HP could help prevent graft rejection. In a mouse model of skin graft, treatment with purified human HP increased levels of inflammatory cytokines compared with mock treatment. Skin grafts from Hp knockout mice showed lower inflammation and longer survival than grafts from wild-type controls. Next steps include identifying ways to locally antagonize HP and to test the role of HP in organ graft rejection. SciBX 5(3); doi:10.1038/scibx.2012.83 Published online Jan. 19, 2012	Patent pending; available for licensing	Hua, S. <i>et al. J. Clin. Invest.</i> ; published online Dec. 12, 2011; doi:10.1172/JCI58344 Contact: Daniel R. Goldstein, Yale School of Medicine, New Haven, Conn. e-mail: daniel.goldstein@yale.edu

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Various				
Cancer; inflammation	p38 Mitogen- activated protein kinase (p38 MAPK; MAPK14)	<i>In vitro</i> and mouse studies identified a compound that could help guide the development of selective p38 MAPK-targeted therapeutics for cancer and inflammatory diseases. In cell-free and whole-blood assays, a dibenzosuberone-based compound, skepinone-L, selectively bound to and inhibited p38 MAPK with a nanomolar IC ₅₀ value and did not show significant binding in a panel of 400 other kinases. In mice, skepinone-L inhibited inflammation-induced tumor necrosis factor- α (TNF- α) release compared with vehicle control. Next steps include testing the compound in disease models. At least seven companies have p38 MAPK inhibitors in clinical testing for various indications. <i>SciBX</i> 5(3); doi:10.1038/scibx.2012.84 Published online Jan. 19, 2012	Patent application filed covering skepinone-L and analogues by cair biosciences GmbH; available for licensing	Koerberle, S.C. <i>et al. Nat. Chem. Biol.</i> ; published online Dec. 25, 2011; doi:10.1038/nchembio.761 Contact: Stefan A. Laufer, University of Tuebingen, Tuebingen, Germany e-mail: thilo.stehle@uni-tuebingen.de Contact: Thilo Stehle, same affiliation as above e-mail: stefan.laufer@uni-tuebingen.de

Can You Afford Not to Read SciBX?

According to MEDLINE®, the U.S. National Library of Medicine's® premier bibliographic database of articles in life sciences, over 775,000 articles were added to the database in 2009 alone—an average of almost 15,000 new articles every week.

Can you afford to miss investment opportunities?

Can you afford to miss emerging competition?

SciBX is the single source for scientific context, commercial impact and the critical next steps.

Visit scibx.com for details on how to subscribe to SciBX

SciBX: Science–Business eXchange

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
Disease models			
Induced pluripotent stem (iPS) cell model for Timothy syndrome	<p>A study in cell culture suggests patient-derived iPS cells could help identify therapies for Timothy syndrome, a form of autism spectrum disorder. Neuronal precursor cells derived from iPS cells from patients with Timothy syndrome displayed abnormal gene expression including higher levels of the dopamine-synthesizing enzyme tyrosine hydroxylase (TH) compared with neurons derived from healthy control iPS cells. In the precursors, the racemic form of roscovitine, an inhibitor with multiple targets, decreased TH expression compared with vehicle. Next steps could include screening for additional compounds that modify Timothy syndrome-associated biomarkers.</p> <p>Cyclacel Pharmaceuticals Inc. has Seliciclib (R-roscovitine) in Phase II testing for non-small cell lung cancer (NSCLC) and nasopharyngeal cancer.</p> <p>SciBX 5(3); doi:10.1038/scibx.2012.85 Published online Jan. 19, 2012</p>	Patent pending; available for licensing	<p>Paşca, S.P. <i>et al. Nat. Med.</i>; published online Nov. 27, 2011; doi:10.1038/nm.2576</p> <p>Contact: Ricardo E. Dolmetsch, Stanford University School of Medicine, Stanford, Calif. e-mail: ricardo.dolmetsch@stanford.edu</p>

Drug platforms			
Isoxazole compounds for pancreatic islet β cell regeneration	<p>A study in cell culture suggests 3,5-disubstitute isoxazoles could be useful for regenerating islet β cells in type 1 diabetes. In cultured human islets, an undisclosed isoxazole compound increased expression of both β cell markers and insulin compared with vehicle. Next steps could include testing the compound in rodent models of type 1 diabetes.</p> <p>SciBX 5(3); doi:10.1038/scibx.2012.86 Published online Jan. 19, 2012</p>	Patent and licensing status unavailable	<p>Dioum, E.M. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Dec. 5, 2011; doi:10.1073/pnas.1118526109</p> <p>Contact: Melanie H. Cobb, The University of Texas Southwestern Medical Center, Dallas, Texas e-mail: melanie.cobb@utsouthwestern.edu</p> <p>Contact: Jay W. Schneider, same affiliation as above e-mail: jay.schneider@utsouthwestern.edu</p>

SciBX: Science-Business eXchange

Kick-start your knowledge management—and leave your competitors behind...

Can you afford not to subscribe?

Visit scibx.com for details on how to subscribe to SciBX

Company and institution index

A					
Abbott Laboratories	5	New York University Langone Medical Center	3	CD227	10
Advance BioChina	3	Northwestern University	8,15	CD331	12
Albert Einstein College of Medicine of Yeshiva University	3	Novartis AG	6,12,13	CEA	10
Ambrx Inc.	12	Novo Nordisk A/S	5	Cemadotin	11
Armgo Pharma Inc.	15	O		CFTR	8
Asclepis Inc.	3	Oncothyreon Inc.	10	Champix	14
AstraZeneca plc	2,5,14	P		Chantix	14
B		Pfizer Inc.	2,5,6,14	Checkpoint kinase 1	11
Bavarian Nordic A/S	10	Philogen S.p.A.	11	Checkpoint kinase 1-short	11
BGI	2	Proteostasis Therapeutics Inc.	8,15	Chemokine CXC motif ligand 2	13
Blueprint Medicines	4	PsychoGenics Inc.	14	Chk1	11
Bristol-Myers Squibb Co.	12	PureTech Ventures	5	Chk1-S	11
Bulgarian Pharmaceutical Group Ltd.	14	R		Cholesterol	13
C		Roche	2	CV-301	10
cair biosciences GmbH	16	Rockefeller University	3	CXC chemokine receptor 4	13
Cambridge Enterprise Ltd.	15	S		CXCL12	13
Chaperone Therapeutics Inc.	8	Sage Therapeutics Inc.	4	CXCR4	13
Cleave Biosciences Inc.	4	Sanford-Burnham Medical Research Institute	7	CXCR7	13
Columbia University	2	Sanofi	2,13	Cyclopropylpyridine ether	14
Columbia University Medical Center	3	Scripps Florida	6	Cystic fibrosis transmembrane conductance regulator	8
Cyclacel Pharmaceuticals Inc.	17	Scripps Research Institute	6,8	Cytisine	14
Cystic Fibrosis Foundation	3	T		D	
D		Takeda Pharmaceutical Co. Ltd.	7	Dibenzosuberone	16
Duke University School of Medicine	9	Targacept Inc.	14	E	
E		U		Ezetimibe	13
Eli Lilly and Co.	5,6,11	University of California	2	F	
Elixir Pharmaceuticals Inc.	12	University of California, Berkeley	7	FGF21	12
Endra Inc.	5	University of California, San Francisco	3	FGFR1	12
Enlight Biosciences LLC	5	University of Illinois	13	Fibroblast growth factor 21	12
Ensōf Biosystems Inc.	5	University of Illinois at Chicago	14	Fibroblast growth factor receptor 1	12
Entrega Inc.	5	University of Washington	8	Fibronectin 1	11
G		V		Fingolimod	13
Genentech Inc.	11	Vertex Pharmaceuticals Inc.	3	FN	11
Gilead Sciences Inc.	3	Viamune Inc.	10	FN1	11
GlaxoSmithKline plc	2,7	W		FTY720	13
H		Washington University in St. Louis	11	G	
Hangzhou Binjiang Investment Holding Co. Ltd.	3	Weill Cornell Medical College	3	Gilenya	13
Harvard University	2	Y		Gleevec	12
Human Genome Sciences Inc.	7	Yale University	3	H	
Huya Bioscience International LLC	3		Haptoglobin	15
I		Target and compound index		Heat shock protein 70	8
Illumina Inc.	3	5-Aminoimidazole-4-carboxamide ribonucleoside	15	Heat shock transcription factor 1	8,15
Institut Pasteur of Shanghai	3	A		HP	15
J		α-Synuclein	8	HSF1	8,15
Johnson & Johnson	2,5,6	Aβ	8	Hsp27	8
K		ADP-ribosylation factor 1	10	Hsp40	8
Knode Inc.	5	AICAR	15	Hsp70	8
L		AMF-26	10	Hsp90	8
Lotus Tissue Repair Inc.	4	ARF1	10	HTT	8
M		Arsonic acid	11	Huntingtin	8
Merck & Co. Inc.	5,13	ARX618	12	Hydroxamic acid	13
Michael J. Fox Foundation for Parkinson's Research	9	ATP	12	Hydroxychloroquine	12
Mitsubishi Tanabe Pharma Corp.	13	AZD3480	14	I	
Mount Sinai Medical Center	3	B		Imatinib	12
N		β-Amyloid	8	Isoxazole	17
National Institutes of Health	2	BCR-ABL tyrosine kinase	12	Isoxazole ether	14
New York Genome Center	3	Belimumab	7	L	
		Benlysta	7	LpxC	13
		Brefeldin A	10	M	
		C		MAPK14	16
		Carcinoembryonic antigen	10	Matrix metalloproteinase 9	14
				MC-1	15
				Mitochondrial complex 1	15
				Mitoxantrone	12
				MMP9	14
				Mozobil	13
				MUC1	10
				Mucin 1	10
				N	
				Necrostatin-1	14
				Nerve growth factor	11
				NGF	11
				Nicotinic acetylcholine receptor	14
				α ₄ β ₂	14
				Niemann-Pick C1-like protein	13
				NPC1L1	13
				NPY3R	13
				O	
				ONT-10	10
				Osteocalcin	3
				P	
				p38 MAPK	16
				p38 Mitogen-activated protein kinase	16
				p137	15
				Plerixafor	13
				R	
				Rabies virus glycoprotein	15
				Receptor-interacting serine-threonine kinase 1	14
				RIP1	14
				RIP3	14
				RIPK1	14
				RIPK3	14
				Roscovitine	17
				R-roscovitine	17
				RVG	15
				Ryanodine receptor 1	15
				Rycals	15
				RyR1	15
				S	
				SDF-1	13
				Seliciclib	17
				Shiga toxin	13
				SIRT1	12
				Sirtuin 1	12
				Skepinone-L	16
				SNCA	8
				Sphingosine 1-phosphate receptor	13
				Stimuvax	10
				T	
				Tabex	14
				Tafamidis	7
				TASP1	11
				Taspase threonine aspartase 1	11
				TC-1734	14
				TG2	10
				TGM2	10
				TH	17
				TNF	14
				TNF-α	16
				Transglutaminase 2	10
				Transthyretin	7
				Tumor necrosis factor	14
				Tumor necrosis factor-α	16
				Tyrosine hydroxylase	17
				U	
				UDP-3-O-[3-hydroxyristoyl] N-acetylglucosamine deacetylase	13
				V	
				Varenicline	14
				Vyndaqel	7
				Z	
				Zetia	13