

## THIS WEEK

### ANALYSIS

#### COVER STORY

##### 1 Europe's upwelling

SciBX's third annual comprehensive analysis of public-private partnerships and early stage venture financing activity shows that Europe's PPP activity in 2013 surpassed that of the U.S. in dramatic fashion.

#### TRANSLATIONAL NOTES

##### 6 BAND-aid for PD and AD

Evidence for overlaps between PD and AD have led three foundations to launch the BAND grant program to fund cross-disease research. The studies will use outputs from both the Parkinson's Progression Markers Initiative and the Alzheimer's Disease Neuroimaging Initiative.

#### TARGETS & MECHANISMS

##### 8 Preserving the oocyte reserve

A Cornell team has preserved fertility in mice by knocking out *checkpoint kinase 2*. The target offers companies a new opportunity for preventing chemotherapy- and radiotherapy-induced premature menopause and infertility.

#### TOOLS

##### 10 Degradation from within

A Cornell group has proof of concept for proteasomal degradation of intracellular proteins using designer binding proteins to deliver ubiquitin to their targets. The challenge for Ubiquizyme, a newco formed around this concept, is to deliver its molecules in a therapeutic setting.

#### THE DISTILLERY

##### 12 This week in therapeutics

Inhibiting TREM1 to reduce inflammation associated with infection; antagonizing pknB to treat tuberculosis; activating the Nrf2 pathway to limit progression of PD; and more...

##### 17 This week in techniques

Diagnosing and monitoring treatment responses in patients with NPC1 using fluorescence-based volumetric measurement of lysosomes; bone marrow niche-sensitizing chemotherapy to enhance antibody-based ALL elimination; viral insertion of inducible aptazymes to improve the safety of oncolytic viral therapy; and more...

#### INDEXES

##### 20 Company and institution index

##### 20 Target and compound index

## Europe's upwelling

By Steven Edelson, Executive Editor, and Kai-Jye Lou, Senior Writer

SciBX's third annual comprehensive analysis of public-private partnerships and early stage venture financing activity shows that Europe's public-private partnership activity in 2013 surpassed that of the U.S. in dramatic fashion. At least 314 companies and institutions based in Europe were involved in forming new partnerships last year versus 182 in the U.S.

Europe has steadily upped its public-private partnership (PPP) activity over the past three years. In 2011, there were 13% fewer European companies and institutions participating in new PPPs than in the U.S. In 2012, 4% fewer European companies and institutions participated in PPPs<sup>1</sup> (see Figure 1, "Regional breakdown of public-private partnerships, 2011–2013").

Two drivers of Europe's PPP activity last year were the **European Commission** via its Seventh Framework Programme (FP7) and **Cancer Research UK**. The two organizations took the top positions with respect to the number of disclosed PPPs in 2013.

"There is no question that for the biotech companies in Europe, where venture capital is relatively more scarce, they have to seek whatever alternative source of funding there is available, and engagement with a foundation or a PPP initiative is attractive," said Stephan Christgau, investment director at **Novo Nordisk A/S's** Novo Seeds unit.

He added, "I am convinced that there are more—at least relatively—foundations and PPP financiers available here in Europe. Many companies and family offices are anchored in foundations that have a hybrid

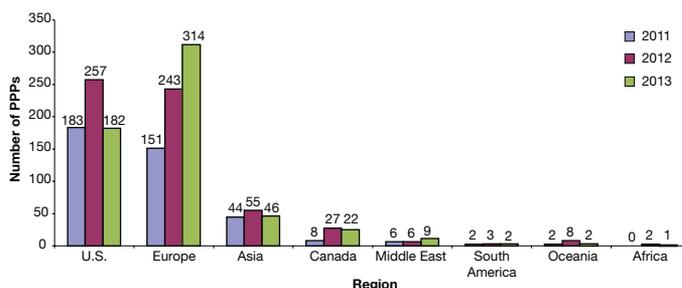


Figure 1. Regional breakdown of companies and institutes in public-private partnerships, 2011–2013. The number of disclosed public-private partnerships (PPPs) worldwide by year for 2011–2013. Data include double counting as many partnerships involve companies and/or institutions from more than one region. Total number of disclosed PPPs is 301 for 2013, 387 for 2012 and 241 for 2011.

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purpose of not only donating money but also seeking commercial gains. I see these types of long-term, committed and well-capitalized organizations playing an increasingly important role here, as the traditional European venture funds have had increasing difficulties in raising funds from traditional limited partners such as pension funds.”

In the U.S., PPP activity for 2013 mirrored that of 2011. The unanswered question is whether the spike to 257 companies and institutions that participated in 2012 was an aberration. As a group, California was the most active in the U.S., with 33 companies and 32 institutions participating in PPPs. The U.K. led the charge in Europe, with 52 companies and 56 institutions entering PPPs (see Figure 2, “Regional leaders in public-private partnerships”).

Elsewhere across the globe, PPP activity has either stayed on course or returned to 2011 levels—as is the case for Asia and Oceania. The Middle East did show a slight increase in 2013 compared with the prior two years, driven primarily by Israeli institutions.

In addition to the regional shifts, specific business areas showed differences in 2013 versus the prior two years. Cancer again took the top spot in terms of PPPs by business area but last year showed much more separation from the runner-up sector—neurology (see Figure 3, “Therapeutic areas covered by public-private partnerships and seed or series A financings”).

There were 84 cancer PPPs in 2013 (23% of the total), 70 cancer PPPs in 2012 (15%) and 50 in 2011 (18%). For early stage venture financings by business area, cancer remained the leading area for the third consecutive year.

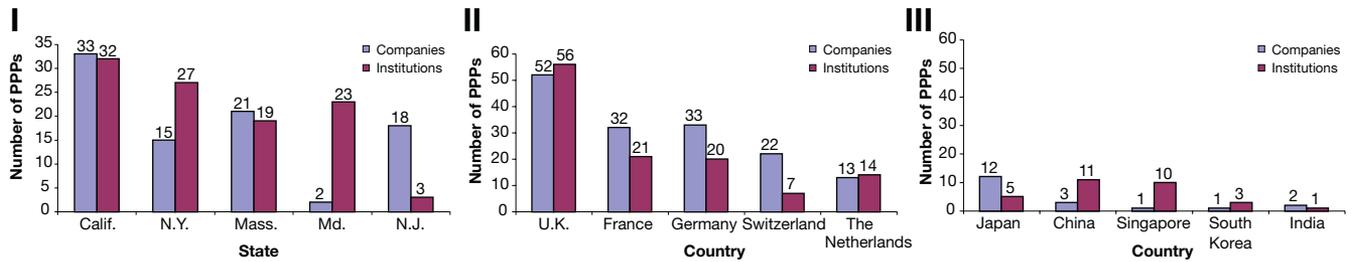
**Pharma shuffle**

On the company side, the same 5 pharmas that topped the chart in 2012 in terms of their involvement in new PPPs did so again in 2013, albeit

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**Figure 2. Regional leaders in public-private partnerships.** A breakdown of companies and institutions involved in public-private partnerships (PPPs) in the top five 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. Data include double counting as some partnerships involve companies and/or institutions from more than one state and/or country.

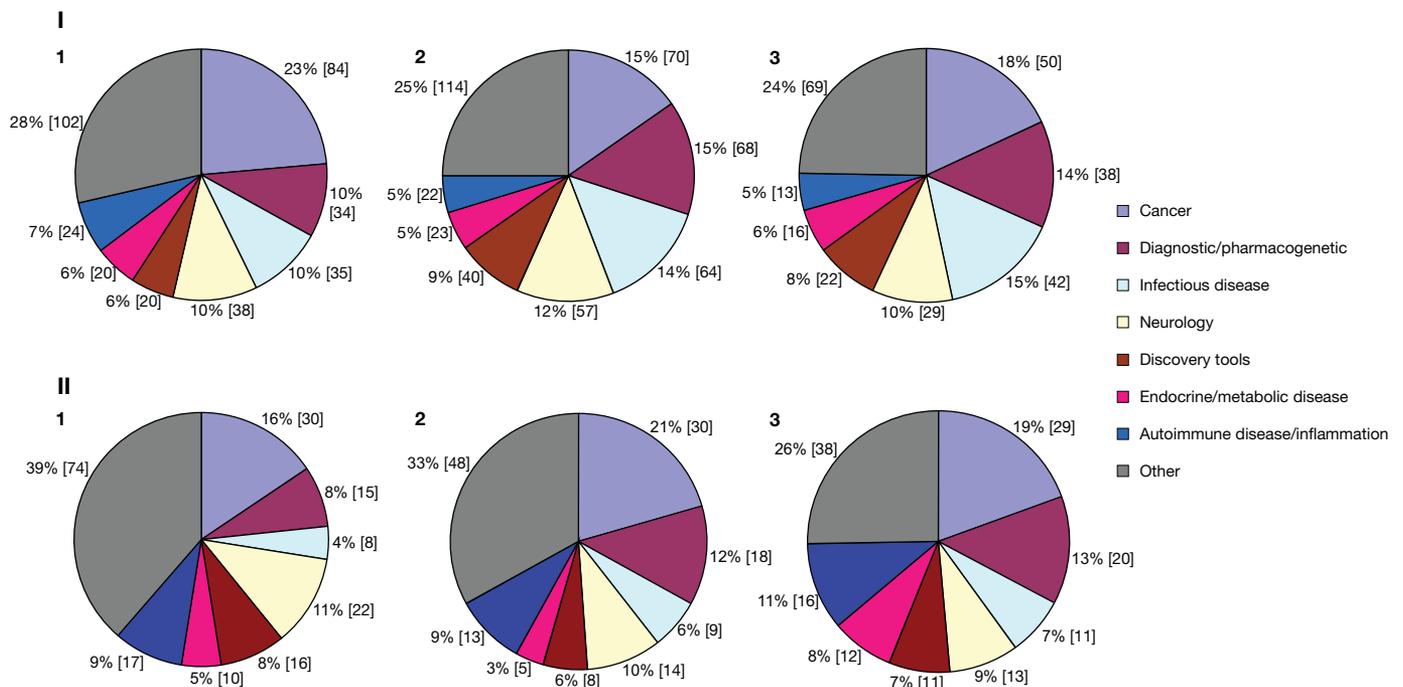
in a different order. **AstraZeneca plc** took the top company spot, and **Johnson & Johnson** was second (see Table 1, “Leaders in the number of public-private partnerships”).

One of AstraZeneca’s most significant PPPs in 2013 was a deal with the **Karolinska Institute** to create the Karolinska Institutet/AstraZeneca Integrated Cardio Metabolic Center, a research center focused on cardiac regeneration, islet health and diabetic nephropathy. The pharma will provide up to \$20 million to the center annually, whereas Karolinska will contribute expertise and facilities.

Last year, J&J launched a series of incubators, which are key components of its focus on external regional partnerships to help fuel its early R&D pipeline.<sup>2</sup>

J&J’s innovation access strategy, first announced in 2011, aims to increase early stage deal flow by building a network of incubators and partnering hubs that cultivate connections with academics in research centers throughout the world.

Since 2012, J&J Innovation has launched three U.S. regional incubators. These include the Janssen Labs site in San Diego, a facility at



**Figure 3. Therapeutic areas covered by public-private partnerships and seed or series A financings.** A breakdown of therapeutic areas covered by public-private partnerships (PPPs) in 2013 (I.1) and seed or series A financings (II.1). PPPs by business area (I.2 (2012) and I.3 (2011)) and financings by business area (II.2 (2012) and II.3 (2011)) from the previous two years are provided for comparison. For (I), percentages are out of the total number of PPPs worldwide; bracketed values are actual numbers. For (II), 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. Data include double counting as some partnerships and companies are tied to more than one business and/or disease area.

**Table 1. Leaders in the number of public-private partnerships.** The European Commission and Cancer Research UK took the top positions with respect to the number of disclosed public-private partnerships (PPPs) in 2013. AstraZeneca took the top spot on the company side, and Johnson & Johnson took the second spot. Excludes deals that only involve IP transfer.

Source: BioCentury Archives

Institution	Number of PPPs
European Commission	21
Cancer Research UK	10
Agency for Science, Technology and Research (A*STAR)	8
Harvard University	8
University of California, San Francisco; University of California, Los Angeles; University of California, Davis	8
Company	Number of PPPs
AstraZeneca plc (LSE:AZN; NYSE:AZN)	14
Johnson & Johnson (NYSE:JNJ)	11
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK)	10
Pfizer Inc. (NYSE:PFE)	9
Sanofi (Euronext:SAN; NYSE:SNY)	9

the University of California, San Francisco's Institute for Quantitative Biology and the LabCentral facility in Boston.

J&J Innovation also operates three partnering hubs in Boston, Menlo Park and London. A fourth center in Shanghai is expected to open this year.

### Bites of the Big Apple

PPPs receiving direct support from governments and/or government-run institutions accounted for the largest PPPs by value (see Table 2, "Top public-private partnerships in 2013 by value").

The biggest such deal came as 2013 wound down. In December, New York City Economic Development Corp. partnered with Celgene Corp., Eli Lilly and Co. and General Electric Co.'s GE Ventures to invest at least \$100 million in early stage life science companies in New York City.

The parties will invest at least a combined \$50 million in a life sciences fund, and additional VC firms are expected to contribute at least \$50 million in matching funds. The fund plans to invest in the seed and series A rounds of 15–20 companies by 2020.

Notably, the state of New York was also home to one of the largest PPPs that had no direct government support. In October, the Memorial Sloan-Kettering Cancer Center, The Rockefeller University and Weill Cornell Medical College formed Tri-Institutional Therapeutics Discovery Institute Inc. (Tri-I TDI) to expedite early stage discovery into clinical treatments and therapies. The institute partnered with Takeda Pharmaceutical Co. Ltd. to develop small molecules.

Tri-I TDI was founded with a \$15 million gift from Lewis and Ali Sanders and a \$5 million gift from Howard and Abby Milstein, and it is funded through philanthropy and direct contributions from the three academic institutions, along with a yearly \$1.5 million contribution from Takeda.

### 'A' for effort

In addition to boasting the most PPP activity, Europe also saw some of the largest series A rounds for biotechs founded in 2013 (see Table 3, "Largest series A financing rounds for companies founded in 2013").

**Table 2. Top public-private partnerships in 2013 by value.** Public-private partnerships (PPPs) that include grants, awards and/or other types of direct funding support from national governments and/or government institutions are included in the 2013 list but are ranked separately from those without such support. Only 90 of the 301 PPPs reported in 2013 had disclosed dollar amounts. Excludes deals that only involve IP transfer.

Source: BioCentury Archives

Companies	Institutions	Disclosed value (\$M)
<b>PPPs without direct support from national governments and/or government institutions</b>		
AstraZeneca plc (LSE:AZN; NYSE:AZN)	Karolinska Institute	\$20 per year
Takeda Pharmaceutical Co. Ltd. (Tokyo:4502)	Memorial Sloan-Kettering Cancer Center; The Rockefeller University; Weill Cornell Medical College	\$20 plus \$1.5 per year
Not applicable	Canadian Partnership Against Cancer; Heart and Stroke Foundation	C\$16 (\$15.3)
illumina Inc. (NASDAQ:ILMN); Intel Corp. (NASDAQ:INTC)	Oregon Health & Science University; Leukemia & Lymphoma Society; Stanford University; The University of Texas Southwestern Medical Center; The University of Utah	\$8.2
Sarepta Therapeutics Inc. (NASDAQ:SRPT)	The University of Western Australia	\$7.1
<b>PPPs with direct support from national governments and/or government institutions</b>		
Celgene Corp. (NASDAQ:CELG); Eli Lilly and Co. (NYSE:LLY); General Electric Co. (NYSE:GE); undisclosed VC partners	New York City Economic Development Corp.	\$100
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK); Merck & Co. Inc. (NYSE:MRK); Pfizer Inc. (NYSE:PFE); JPMorgan Chase & Co. (NYSE:JPM); Lion's Head Global Partners LLP	Bill & Melinda Gates Foundation; Children's Investment Fund Foundation; Federal Ministry for Economic Cooperation and Development; Grand Challenges Canada; Swedish International Development Cooperation Agency	\$94
AbbVie Inc. (NYSE:ABBV); Boehringer Ingelheim GmbH; Eli Lilly; GlaxoSmithKline; Johnson & Johnson (NYSE:JNJ); Novartis AG (NYSE:NVS; SIX:NOVN); Pfizer; Takeda Pharmaceutical	Li Ka Shing Foundation; University of Oxford; U.K. government	£40 (\$61.8) plus a one-time payment of \$8
Eli Lilly; Roche (SIX:ROG; OTCQX:RHHBY); Biomet Inc.; BioCrossroads; Cook Group Inc.; Dow Chemical Co. (NYSE:DOW)	Indiana University; Purdue University; University of Notre Dame	\$50 <sup>A</sup>
Caprion Proteomics Inc.; Oncozyme Pharma Inc.; Pfizer; Sanofi (Euronext:SAN; NYSE:SNY)	Quebec Clinical Research Organization in Cancer; TELUS Health	C\$21.1 (\$20.9)

<sup>A</sup>Reflects initial amount, but PPP will seek another \$310 million in capital funding from corporate and philanthropic sources.

**Table 3. Largest series A financing rounds for companies founded in 2013.** Unlike in 2011 and 2012, European biotechs boasted some of the largest series A rounds last year. Table includes only companies that were founded in 2013 and raised series A money that same year.

Source: BCIQ: BioCentury Online Intelligence

Companies founded in 2013	Business area	Location	Amount raised (\$M)
Jounce Therapeutics Inc.	Cancer	Cambridge, Mass.	\$47.0
Seragon Pharmaceuticals Inc.	Cancer	San Diego, Calif.	\$30.0
Pulmocide Ltd.	Infectious disease	London, U.K.	\$27.4
Envisia Therapeutics Inc.	Ophthalmic disease	Research Triangle Park, N.C.	\$25.0
Allegra Therapeutics GmbH	Infectious disease	Lorrach, Germany	\$19.6

This is in contrast to the two prior years, in which none of the top five series A rounds went to companies based in Europe.

Among the 43 companies founded in 2013 that disclosed venture financing, there were 28 U.S. companies, 5 based in the U.K., 2 in France, 2 in Israel and 1 each in Australia, Austria, Denmark, Finland, Germany and Switzerland.

The largest series A round in 2013 for a company founded that year was a \$47 million financing by **Jounce Therapeutics Inc.** The Cambridge, Mass.-based company is using multiple protein-based methods of cancer immunotherapy.<sup>3</sup>

The European companies represented in the top five were both infectious disease companies. **Pulmocide Ltd.** raised \$27.4 million. The London-based biotech is developing therapies to treat viral and fungal respiratory tract infections. **Allegra Therapeutics GmbH** raised

\$19.6 million. The Lorrach, Germany-based company is developing antibiotics to treat multidrug-resistant Gram-negative infections.

The largest series A round last year was \$54 million by **Cleave Biosciences Inc.**, a California-based cancer company working on small molecule protein homeostasis inhibitors to treat cancer. The company was founded in 2011.

Edelson, S. & Lou, K.-J. *SciBX* 7(7); doi:10.1038/scibx.2014.188  
Published online Feb. 20, 2014

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3. Fisher, A. *BioCentury* 21(7), A14; Feb. 18, 2013

#### COMPANIES AND INSTITUTIONS MENTIONED

**Allegra Therapeutics GmbH**, Lorrach, Germany  
**AstraZeneca plc** (LSE:AZN; NYSE:AZN), London, U.K.  
**Cancer Research UK**, London, U.K.  
**Celgene Corp.** (NASDAQ:CELG), Summit, N.J.  
**Cleave Biosciences Inc.**, Burlingame, Calif.  
**Eli Lilly and Co.** (NYSE:LLY), Indianapolis, Ind.  
**European Commission**, Brussels, Belgium  
**General Electric Co.** (NYSE:GE), Fairfield, Conn.  
**Johnson & Johnson** (NYSE:JNJ), New Brunswick, N.J.  
**Jounce Therapeutics Inc.**, Cambridge, Mass.  
**Karolinska Institute**, Stockholm, Sweden  
**Memorial Sloan-Kettering Cancer Center**, New York, N.Y.  
**New York City Economic Development Corp.**, New York, N.Y.  
**Novo Nordisk A/S** (CSE:NVO; NYSE:NVO), Bagsvaerd, Denmark  
**Pulmocide Ltd.**, London, U.K.  
**The Rockefeller University**, New York, N.Y.  
**Takeda Pharmaceutical Co. Ltd.** (Tokyo:4502), Osaka, Japan  
**Tri-Institutional Therapeutics Discovery Institute Inc.**, New York, N.Y.  
**University of California, San Francisco**, Calif.  
**Weill Cornell Medical College**, New York, N.Y.

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# BAND-aid for PD and AD

By Michael J. Haas, Senior Writer

Spurred by emerging evidence of biological overlaps between Parkinson's disease and Alzheimer's disease, **The Michael J. Fox Foundation for Parkinson's Research**, the **Alzheimer's Association** and **The W. Garfield Weston Foundation** have launched a grant program to jump-start cross-disease research. The partners are soliciting project proposals and expect to announce awards in July.

The Biomarkers Across Neurodegenerative Disease (BAND) initiative will award grants of up to \$150,000 to about 6 projects this year, according to MJFF CEO Todd Sherer. The funded projects would run for one to two years and could focus on marker discovery, assay standardization, genetic profiling, imaging modalities, or diagnostic or therapeutic development, he said.

Heather Snyder, director of medical and scientific operations at the Alzheimer's Association, said that the partners will decide on a per-project basis how much each organization would contribute to the award.

Snyder said that her association has allocated a total of \$500,000 to BAND.

Sherer declined to disclose how much MJFF has allocated. He noted that funds from Weston will be for Canadian researchers. The foundation is a not-for-profit organization that supports science, education and land conservation in Canada.

## Getting the BAND together

BAND projects must use existing data or biological samples from two large-scale clinical studies—the Parkinson's Progression Markers Initiative (PPMI) and the Alzheimer's Disease Neuroimaging Initiative (ADNI).

MJFF launched the five-year PPMI in 2010 to identify biological markers of PD. PPMI initially enrolled about 150 patients and age-matched controls in the U.S. and EU<sup>1</sup> and later expanded to include about 600 patients and controls at 24 sites in the U.S., EU and Australia.<sup>2</sup>

A public-private partnership that includes the Alzheimer's Association and the **Foundation for the National Institutes of Health** launched the ADNI in 2004 to identify markers for early detection of AD and for monitoring disease progression. The study has enrolled more than 1,000 participants, including patients with AD or mild cognitive impairment (MCI), individuals at risk of developing AD and controls who have no memory problems.<sup>3</sup>

Indeed, the genesis of the BAND program was presentations related to the two studies at the Alzheimer's Association International Conference last July that hinted at biological overlaps between PD and AD.

The most convincing link came from Kenneth Marek, who reported preliminary data from the first 100 participants in PPMI and drew comparisons between those findings and results from ADNI. For example,

cerebrospinal fluid levels of  $\beta$ -amyloid ( $A\beta$ ) were lower in both PD and AD patients than in healthy controls, whereas cerebrospinal fluid levels of microtubule-associated protein- $\tau$  (MAPT; tau; FTDP-17) were lower in PD patients but higher in AD patients than in healthy controls. Together, these findings suggest that  $A\beta$  and tau play roles in both diseases.<sup>2</sup>

Marek is a clinical professor of neurology at **Yale University** and senior scientist at the university's Institute for Neurodegenerative Disorders. The preliminary PPMI data—but not the ADNI comparisons—were published in *JAMA Neurology* in October.<sup>4</sup>

Snyder said that Marek's presentation—as well as other presentations at the meeting that drew on both ADNI and preliminary PPMI data—stimulated discussions between MJFF and the Alzheimer's Association about leveraging the two datasets and led to the development of the grant program.

At that time, MJFF and the W. Garfield Weston Foundation were discussing plans for a grant program to fund research into PD markers, said C. Alexandra Stewart, executive director of neuroscience at Weston. Once MJFF pointed out the shared interests of the three organizations,

“we all agreed a three-way program would be beneficial,” she said.

## Opening acts

The guidelines for BAND highlight several areas on which funded projects could focus—such as analyzing cross-talk between PD and AD markers and investigating common mechanisms across PD, AD and other neurodegenerative diseases. However, Snyder and Sherer said that these are just suggestions and do not reflect the partners' expectations or priorities for funded projects.

“We all agree that the highlighted areas are important, but we don't want to rank them or give priority to any one of them,” Snyder said. “We know researchers will have innovative ideas for leveraging the datasets.”

With the BAND program, “we are trying to break down the silos around research into each disease,” Sherer said. “We want researchers to use these large datasets from PPMI and ADNI and find out whether the data could change how we think about and define each disease from a biological perspective.”

Sherer said that the partners have two broad goals for research that will be funded by the program: identifying commonalities between PD and AD, and drawing distinctions between PD, AD and the natural processes of aging.

“Identifying a common factor between the diseases might lead to the discovery that something previously considered only as a therapy for Parkinson's disease might actually treat a subset of both Parkinson's and Alzheimer's patients,” he said. “Finding a distinguishing factor between the diseases could lead to better differential diagnoses or targeted therapies for each disease.”

The well-characterized age-matched controls in PPMI and ADNI “will also allow researchers to take a close look at normal aging and neurodegeneration, which could help make distinctions between changes that are part of natural aging and changes that result from pathological disease mechanisms,” said Sherer.

**“We are trying to break down the silos around research into each disease. We want researchers to use these large datasets from PPMI and ADNI and find out whether the data could change how we think about and define each disease from a biological perspective.”**

— Todd Sherer,  
The Michael J. Fox Foundation  
for Parkinson's Research

Snyder added that cross-disease research funded by the BAND program could lead to new treatments for other neurodegenerative disorders. She also said that the partners have not yet decided whether BAND will continue beyond the launch phase.

Sherer said that PPMI is now recruiting individuals who have one of three risk factors for PD: loss of the sense of smell, REM sleep behavior disorder (loss of normal motor inhibition during REM sleep) or mutations in either *leucine-rich repeat kinase 2 (LRRK2)* or *α-synuclein (SNCA)*.

“We want to look at markers in these groups of individuals and see whether we can predict who might convert to a diagnosis of PD in the future,” he said. He added that a paper reporting full baseline data from the original cohort of 600 PPMI participants is in the press.

Snyder said that ADNI began its third phase, ADNI-2, in 2011 to identify individuals at risk of AD, track disease progression and develop tests to measure the effectiveness of treatments. The third phase will conclude in 2016.

BAND is not the only program that could lead to new ways of classifying PD and AD.

Last month, the **Innovative Medicines Initiative (IMI)** and the **European Federation of Pharmaceutical Industries and Associations (EFPIA)** launched Aetionomy, a consortium of 17 pharmas, research institutions and clinical centers that seeks to develop new classification

systems for PD and AD based on the underlying mechanisms specific to each disease and then validate each new system in the clinic. The consortium does not aim to develop a single classification system that would encompass both diseases on the basis of their shared biology.

IMI and EFPIA have each contributed €8 million (\$10.8 million) to fund Aetionomy over the next 5 years.

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4. Kang, J.-H. *et al. JAMA Neurol.* 70, 1277–1287 (2013)

#### COMPANIES AND INSTITUTIONS MENTIONED

**Alzheimer’s Association**, Chicago, Ill.  
**European Federation of Pharmaceutical Industries and Associations**, Brussels, Belgium  
**Foundation for the National Institutes of Health**, Bethesda, Md.  
**Innovative Medicines Initiative**, Brussels, Belgium  
**The Michael J. Fox Foundation for Parkinson’s Research**, New York, N.Y.  
**The W. Garfield Weston Foundation**, Toronto, Ontario, Canada  
**Yale University**, New Haven, Conn.

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# Preserving the oocyte reserve

By Tracey Baas, Senior Editor

A **Cornell University** team has shown how knocking out *checkpoint kinase 2* can preserve fertility in mice.<sup>1</sup> The results suggest that companies have an opportunity with this kinase, which is less pursued than the well-trodden cancer target checkpoint kinase 1, to prevent chemotherapy- and radiotherapy-induced premature menopause and infertility.

Oocytes that contain genetic errors, such as unrepaired DNA double-strand breaks (DSBs), can lead to birth defects and spontaneous abortions. Under normal conditions, the body repairs such breaks by homologous recombination.

Known molecular repair mechanisms in humans include ataxia telangiectasia mutated (ATM) kinase, which responds primarily to DSBs, and ataxia telangiectasia and Rad3 related (ATR; FRP1), which responds primarily to single-stranded DNA breaks.<sup>2,3</sup>

If these repair mechanisms fail to correct the mutations, unknown checkpoint triggers are activated that lead to elimination of defective oocytes and possible primordial ovarian follicle depletion. The result can be infertility.

In women undergoing cancer radiotherapy or chemotherapy, the incidence of genetic damage is substantially elevated, often leading to oocyte and ovarian follicle depletion and to premature ovarian failure and menopause.

In these patients, options to preserve fertility are oocyte or ovarian tissue cryopreservation or gonadal suppression with gonadotropin-releasing hormone (GnRH) agonist therapy. The former approach works but does not impede premature menopause. The latter approach has yielded mixed results and is not an option for women with estrogen-dependent tumors.

Previous research has shown that *Atm* and *Atr* are needed to ensure fertility and oocyte viability in mice.<sup>2</sup> However, a downstream effector of *Atm* kinase called checkpoint kinase 2 (*Chk2*; *Chek2*) was not required.

Those findings prompted a team led by John Schimenti to hypothesize that inhibiting this checkpoint effector could reduce the number of oocytes that are eliminated while allowing other mechanisms to complete DSB repair and maintain viable oocytes.

Schimenti is a professor of genetics and director of the Center for Vertebrate Genomics at Cornell.

In female mice with genetically induced meiotic failure, Schimenti's team showed that *Chk2* deficiency increased the number of ovarian follicles compared with normal *Chk2* expression. Oocytes in *Chk2*-deficient mice were viable, despite abundant DSBs, and resulted in multiple litters of pups with no visible abnormalities at one year of age.

Similar results occurred in mice with DSBs induced by irradiation.

Irradiated wild-type animals showed complete elimination of the follicle pool, whereas *Chk2*<sup>-/-</sup> mice retained follicles, did not undergo DSB-mediated oocyte elimination and remained fertile.

The knockouts produced litter sizes that were comparable to those of unirradiated controls, and the resulting pups did not exhibit visible abnormalities at one year of age.

Results were published in *Science*.

## Deeper dive

The team's next steps include sequencing the genomes of the pups to check for potential mutations and other defects and identifying the mechanism responsible for repairing oocyte DSB damage.

"Because females with DSBs were able to produce litters of pups that showed no visible abnormalities, the results suggest that all or most DSBs were eventually repaired," said Schimenti, who is corresponding author on the paper. "We have genetic experiments under way to identify the mechanism responsible for repairing the remaining DNA damage and also to determine what other types of defects are monitored by CHK2. We will also be sequencing the genomes of the mouse pups to check for mutations."

Schimenti also said that the team is testing CHK2 inhibitors in mouse ovaries. "We are almost certain that the checkpoint pathways work the same in mice and humans; the basic pathway even exists in yeast," he said.

**AstraZeneca plc's** AZD7762, a CHK1 and CHK2 inhibitor, was in Phase I testing for cancer as monotherapy and in combination with gemcitabine or irinotecan but has now been terminated.

A more selective CHK2 inhibitor, CCT241533 from **The Institute of Cancer Research's Cancer Research UK** Cancer Therapeutics Unit at Surrey, is in preclinical development as a combination therapy with poly(ADP-ribose) polymerase (PARP) inhibitors for cancer.<sup>4</sup>

"If CHK2 inhibitors actually do help fight cancer—presumably by disrupting normal DNA repair processes and imposing an insurmountable load of DNA damage—then women would get the dual benefit of oocyte protection plus anticancer activity," said Schimenti. "If ovarian follicles can be protected, young women undergoing cancer treatment will not have to undergo the additional challenge of facing premature menopause. Additionally, reproductive-aged women with cancer would not have to delay therapy until after they cryopreserve oocytes or embryos."

"The reproductive system is highly regulated by a network of hormonal signaling, and it will be very important to assess and compare the long- and short-term effects of CHK2 inhibition on DNA damage repair signaling as well as on hormonal regulation," said Antonio Giordano, director of the **Sbarro Health Research Organization's** Institute for Cancer Research and Molecular Medicine and of the Center for Biotechnology at **Temple University**.

"It would be ideal to implement conditional knockouts where *Chk2* function is preserved up to puberty of mice and then genetically silenced prior to exposure to ionizing radiation or chemotherapy," said Stephen Palmer. "This experimental paradigm more closely resembles the progression of oncologic disease in women, where the disease is diagnosed and therapy applied after oocytes have become follicle enclosed and attained meiotic arrest."

Palmer is CSO of genitourinary company **TocopheRx**, which was launched by **Merck KGaA's** EMD Serono subsidiary to develop preclinical, oral follicle-stimulating hormone (FSH) agonists to treat infertility.

**"The reproductive system is highly regulated by a network of hormonal signaling, and it will be very important to assess and compare the long- and short-term effects of CHK2 inhibition on DNA damage repair signaling as well as on hormonal regulation."**

**—Antonio Giordano,  
Temple University**

“There also would need to be thorough analysis of the impact of CHK2 inhibition prior to fertilization on subsequent embryonic and prenatal development in rodents and primates,” added Palmer.

“Even if experiments in mice show that offspring of females exposed to both cancer treatment and CHK2 inhibitors do not have a higher mutational load, the same cannot be assumed for humans, so careful testing would be essential. Especially important would be to evaluate the range of chemotherapies that are commonly used and the genotoxicity of each upon CHK2-treated or untreated human oocytes,” cautioned Schimenti.

“Ultimately, a clinical study could be designed where a woman of reproductive age has been prescribed a regimen of radiotherapy, is seeking fertility preservation, would elect to have one ovary protected by cryopreservation techniques and the remaining ovary subjected to CHK2 inhibition,” Palmer said. “Subsequently, these women would have mandatory preimplantation genetic screening of embryos by karyotype as well as comparative genomic hybridization analysis from blastocyst biopsy. In this manner, the efficacy and safety of CHK2 inhibition can be directly compared to cryopreservation techniques for each patient.”

But Palmer thought that the real importance of the study was the ability to push innovation at the interface of varying expertise: fertility and oncology.

“An important outcome of this publication is that it will prompt more conversations between oncologists and fertility specialists, giving patients more potential options,” said Palmer.

According to Schimenti, “Fertility preservation in cancer patients, an area of study often called oncofertility, is becoming increasingly important as both men and women have children later in life, thus expanding the number of cancer patients wishing to have children post-treatment. Our work with CHK2 not only provides a promising oncofertility target for fertility preservation but also expands the range of potential targets to other proteins in its signaling pathway.”

The Cornell team’s findings are not patented.

Baas, T. *SciBX* 7(7); doi:10.1038/scibx.2014.190

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# Degradation from within

By Lev Osherovich, Senior Writer

Cornell University researchers have devised a way to selectively destroy intracellular proteins of interest using ubiquibodies—engineered molecules coupled to an enzyme that marks targets for degradation by the proteasome.<sup>1</sup> The technique could be useful for screening the effects of knocking down targets that cannot be readily hit by siRNA.

Team leader Matthew DeLisa, a professor of engineering at Cornell, said that ubiquibodies are a type of intracellular antibody—a transgenic antibody fragment expressed within a cell to block the activity of a target protein.<sup>2</sup>

“We had long been working on intracellular antibodies, which are single-chain fragments expressed inside the cytosol. These have found some use in interfering with the targets they bind to,” said DeLisa.

The problem is that intracellular antibodies have been hard to work with because of the difficulty in achieving the high levels of protein expression needed to inactivate targets.

With intracellular antibodies, “you have to get expression levels at one-to-one stoichiometry toward your target, so their activity depends critically on the expression level,” said DeLisa. “To address the problem of expression, we thought about arming intracellular antibodies with a mechanism for clearance of the target. We have now achieved this by conjugating them to proteins that are targeted for intracellular degradation.”

DeLisa’s new technique uses antibody-derived designer binding proteins to first bind their targets and then tag them with ubiquitin. Ubiquitin is a small protein that directs proteins toward the proteasome.

As the target protein undergoes degradation, the ubiquibody falls off and moves on to find and bind the next target molecule.

“With this system, one ubiquibody can cause the degradation of many copies of its target, reducing the need for high expression,” said DeLisa.

## Designer destruction

DeLisa’s team created ubiquibodies from engineered gene fusions encoded by a viral vector.

One half of each ubiquibody is a minimized portion of a type of E3 ubiquitin ligase called CHIP (STIP1 homology and U-box containing protein 1; STUB1) (*see Figure 1, “Ubiquibodies”*). CHIP performs the last in a series of enzymatic steps that leads to ubiquitination of targets.

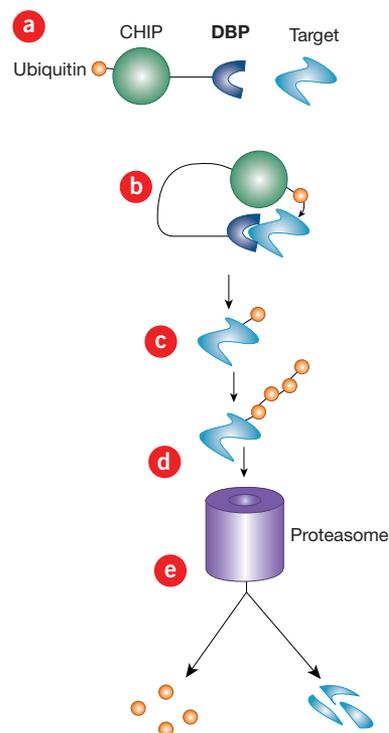
The target specificity of ubiquibodies comes from the other half of the fusion—a target-binding domain that is derived from a class of engineered intracellular proteins with antibody-like binding specificity.

As proof of principle, the team made ubiquibodies against two bacterial proteins—*Escherichia coli*  $\beta$ -galactosidase and *E. coli* maltose binding protein.

In bacterial cell lysates, the two ubiquibodies bound their targets and caused them to become ubiquitinated.

In mammalian cells expressing the two bacterial targets, concurrent expression of matching ubiquibodies led to ubiquitination and degradation of the target proteins.

Results were reported in *The Journal of Biological Chemistry*.



**Figure 1. Ubiquibodies.** Portnoff *et al.* have demonstrated a strategy for targeted destruction of intracellular proteins using engineered intracellular antibodies that deliver ubiquitin to a target protein. Ubiquitin is a small protein that tags intracellular proteins for degradation by the proteasome, a cellular garbage disposal system.

The team constructed a transgene encoding the E3 ubiquitin ligase domain of STIP1 homology and U-box containing protein 1 (STUB1; CHIP) fused to a mAb-derived designer binding protein (DBP) that targets a model substrate (a). The resulting fusion protein is called a ubiquibody.

In cell culture, DBP trapped a model target protein (b), and the CHIP domain of the fusion protein added ubiquitin to the captive target (c), triggering the addition of further ubiquitin molecules (d) and degradation of the target by the proteasome (e).

**Arvinas Inc.** and **GlaxoSmithKline plc** are independently developing proteolysis-targeting chimeric molecules, or PROTACs, that recruit a different E3 ubiquitin ligase to target disease-linked proteins. PROTAC compounds from Arvinas are in lead optimization to treat cancer, and GSK has PROTACs in lead discovery for undisclosed indications.

## Post-translational knockdown

DeLisa thinks that the best application for the technology is in target validation studies focused on proteins that are hard to hit with gene knockdown methods.

“There are things that we can go after that wouldn’t be possible with RNA-targeting methods,” said DeLisa. “RNAi is a sledgehammer that goes after everything so the protein doesn’t even get made, whereas we can go after protein isoforms.”

“You could imagine isoform-specific ubiquibodies that eliminate the

phosphorylated form of a protein but leave the unphosphorylated form alone,” he added.

DeLisa’s study “is a clever combinatorial strategy to utilize antibodies to recruit things to the ligase. By swapping out the ligase’s binding site, you can get the ligase to bind whatever you want,” said Timothy Shannon, CEO of **Arvinas Inc.**

Arvinas is developing small molecules to promote targeted protein degradation.

Shannon said that ubiquibodies could be rapidly adapted to hit a variety of intracellular targets thanks to their recombinant, modular design. However, he said that more work is needed to demonstrate the technology’s potential for hitting mammalian cell proteins implicated in disease.

“I’d like to see if this is scalable for a broad array of targets,” said Shannon.

DeLisa said that his next steps are to optimize delivery methods for the transgenic construct that encodes ubiquibodies and test whether ubiquibodies could be delivered from outside the cell.

He and study coauthor Jeffrey Varner, an associate professor of engineering at Cornell, cofounded **Ubiquizyme Inc.** to develop screening technology based on the technique. Ubiquizyme is in the process of licensing pending patents on the technology from Cornell.

DeLisa said that the company’s initial focus is to develop research tools, but the eventual goal is to develop therapeutics.

### PROTACs vs. ubiquibodies

Ubiquibodies are a biologic-based counterpart to proteolysis-targeting chimeric molecules (PROTACs), a class of small molecules developed in the laboratory of Craig Crews.<sup>3</sup> Crews is a professor of chemistry, pharmacology, and molecular, cellular and developmental biology at **Yale University**.

PROTACs work by bridging target proteins to a different E3 ubiquitin ligase called von Hippel-Lindau tumor suppressor (vHL) that also causes ubiquitination and degradation.

In 2012, Yale licensed patents on PROTACs to **GlaxoSmithKline plc** to pursue undisclosed cancer targets. Last year, Arvinas licensed PROTAC patents to pursue targets not covered by GSK’s license. Arvinas has PROTACs in lead optimization for undisclosed cancer indications, and GSK has PROTACs in lead discovery for undisclosed indications.

Raymond Deshaies, a professor of biology at the **California Institute of Technology**, said that ubiquibodies and PROTACs will likely serve two distinct roles, with the former being used for research and the latter for therapeutics.

The PROTAC technique “has potential as a therapeutic approach because it is based on small molecules. However, it is likely to be far more difficult to make custom-designed PROTACs that target specific proteins,” said Deshaies. “In general, it should be easier to get antibody mimetics that bind with high specificity and affinity to a target than it is to get a small molecule with the same properties.”

Deshaies said that the biggest challenge for ubiquibody-based therapeutics is the difficulty of delivering the bulky proteins directly into the cytoplasm. In contrast, small molecule PROTACs have better odds of getting into the cell.

“I don’t see PROTACs as being a practical approach for the development of research tools, but they could be a feasible approach for the development of therapeutics,” he added. “Ubiquibodies are the inverse.”

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**Ubiquizyme Inc.**, Ithaca, N.Y.  
**Yale University**, New Haven, Conn.

**“With this system, one ubiquibody can cause the degradation of many copies of its target, reducing the need for high expression.”**

**—Matthew DeLisa,  
Cornell 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>				
Inflammatory bowel disease (IBD)	Invariant NK T (iNKT) cells	<i>In vitro</i> and mouse studies suggest <i>Bacteroides fragilis</i> -derived glycosylceramide sphingolipids (GL-Cers) could help treat IBD by inhibiting activation of iNKT cells. In cocultures of bone marrow dendritic cells and iNKT cell hybridomas, <i>B. fragilis</i> -derived GL-Cers decreased IL-2-mediated activation of iNKT cells compared with ceramide sphingolipids. In a mouse model of ulcerative colitis, colonization with sphingolipid-defective <i>B. fragilis</i> increased disease severity compared with wild-type <i>B. fragilis</i> . In the same model, a GL-Cer increased colonic iNKT cell numbers and decreased disease symptoms compared with vehicle. Next steps could include testing <i>B. fragilis</i> -derived GL-Cers in additional models of IBD.	Patent application filed; licensing status unavailable	An, D. <i>et al. Cell</i> ; published online Jan. 16, 2014; doi:10.1016/j.cell.2013.11.042 <b>Contact:</b> Dennis L. Kasper, Harvard Medical School, Boston, Mass. e-mail: <a href="mailto:dennis_kasper@hms.harvard.edu">dennis_kasper@hms.harvard.edu</a> <b>Contact:</b> Richard S. Blumberg, same affiliation as above e-mail: <a href="mailto:rblumberg@partners.org">rblumberg@partners.org</a>
<b>SciBX 7(7); doi:10.1038/scibx.2014.192</b> Published online Feb. 20, 2014				
<b>Cancer</b>				
Acute myelogenous leukemia (AML)	SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily a member 4 (SMARCA4; BRG1)	Studies in cell culture and mice suggest inhibiting BRG1 could help treat AML. In a mouse model of AML, conditional <i>Brg1</i> knockout in hematopoietic cells decreased leukemia growth compared with wild-type <i>Brg1</i> expression and prolonged survival. In mice, <i>Brg1</i> knockout did not affect numbers of long-term repopulating hematopoietic stem cells in bone marrow but did reduce their proliferation potential. In AML cell lines, shRNA against <i>BRG1</i> decreased proliferation and survival compared with a control shRNA. Next steps could include further characterizing the role of BRG1 in human AML.	Patent and licensing status unavailable	Buscarlet, M. <i>et al. Blood</i> ; published online Jan. 29, 2014; doi:10.1182/blood-2013-02-483495 <b>Contact:</b> Julie A. Lessard, Institute for Research in Immunology and Cancer, Montreal, Quebec, Canada e-mail: <a href="mailto:j.lesard.1@umontreal.ca">j.lesard.1@umontreal.ca</a>
<b>SciBX 7(7); doi:10.1038/scibx.2014.193</b> Published online Feb. 20, 2014				
Breast cancer	TANK-binding kinase 1 (TBK1); estrogen receptor	<i>In vitro</i> , mouse and patient sample studies suggest inhibiting TBK1 could help treat tamoxifen-resistant breast cancer and that measuring <i>TBK1</i> expression could help predict response to tamoxifen. In breast cancer cell lines, overexpression of <i>TBK1</i> increased estrogen receptor transcriptional activation and decreased response to the estrogen receptor antagonist tamoxifen compared with normal <i>TBK1</i> expression, and siRNA against <i>TBK1</i> increased sensitivity to tamoxifen compared with scrambled siRNA. In mouse xenograft models of breast cancer, pharmacological inhibition of TBK1 plus tamoxifen synergistically inhibited tumor growth. In samples from patients with breast cancer, high TBK1 expression correlated with poor response to tamoxifen and high relapse potential. Next steps could include validating the association in additional samples and developing TBK1 inhibitors. Tamoxifen is a generic estrogen receptor antagonist marketed to treat breast cancer.	Patent and licensing status unavailable	Wei, C. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Jan. 21, 2014; doi:10.1073/pnas.1316255111 <b>Contact:</b> Hui Zhong, Beijing Institute of Biotechnology, Beijing, China e-mail: <a href="mailto:towall@yahoo.com">towall@yahoo.com</a>
<b>SciBX 7(7); doi:10.1038/scibx.2014.194</b> Published online Feb. 20, 2014				

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Cancer	Procaspase-3	<i>In vitro</i> and mouse studies suggest combining compounds that activate procaspase-3 by different mechanisms could help treat cancer. The compound PAC-1 activates procaspase-3 by chelating inhibitory zinc, whereas the compound 1541B activates procaspase-3 by promoting enzyme maturation. In human lymphoma, breast cancer and lung cancer cell lines, a combination of 1541B and PAC-1 increased caspase activation faster and more potently than either agent alone. In multiple mouse and human cancer cell lines, 1541B and PAC-1 synergistically increased procaspase-3 activity and cell death. In a mouse xenograft model of lymphoma, the combination of 1541B and PAC-1 decreased tumor size more than either agent alone. Next steps could include optimizing 1541B and PAC-1 and testing the combination in additional tumor models.  <b>SciBX 7(7); doi:10.1038/scibx.2014.195</b> <b>Published online Feb. 20, 2014</b>	Patent and licensing status unavailable	Botham, R.C. <i>et al. J. Am. Chem. Soc. USA</i> ; published online Jan. 2, 2014; doi:10.1021/ja4124303 <b>Contact:</b> Paul J. Hergenrother, University of Illinois at Urbana-Champaign, Urbana, Ill. e-mail: <a href="mailto:hergenro@illinois.edu">hergenro@illinois.edu</a>
Glioma	Stage-specific embryonic antigen-4 (SSEA-4)	Human sample, <i>in vitro</i> and mouse studies suggest an anti-SSEA-4 mAb could be used to treat glioblastoma. In human tissue microarrays, 38 of 55 specimens from patients with glioblastoma expressed SSEA-4, whereas most samples from healthy individuals did not. In cultured human glioblastoma cell lines, an anti-SSEA-4 mAb increased cell death compared with IgG control. In a mouse xenograft model of glioblastoma, the mAb decreased tumor growth compared with IgG control. Next steps include studying the role of SSEA-4 in cancer progression.  <b>SciBX 7(7); doi:10.1038/scibx.2014.196</b> <b>Published online Feb. 20, 2014</b>	SSEA-4-targeted cancer vaccine patented; patent filed covering anti-SSEA-4 mAb; licensed to an undisclosed company	Lou, Y.-W. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Feb. 3, 2014; doi:10.1073/pnas.1400283111 <b>Contact:</b> Chi-Huey Wong, National Taiwan University, Taipei, Taiwan e-mail: <a href="mailto:chwong@gate.sinica.edu.tw">chwong@gate.sinica.edu.tw</a>
Hepatocellular carcinoma (HCC)	Spleen tyrosine kinase (SYK)	Primary tumor studies suggest measuring levels of two SYK isoforms could help predict treatment outcomes in patients with HCC. In 152 primary HCC tumors, levels of full-length SYK were lower and levels of a short SYK isoform were higher than those in surrounding normal tissue or liver tissue from healthy subjects. In patients with HCC tumors, overall survival and time to recurrence after surgical resection correlated positively with tumor levels of full-length SYK and correlated negatively with tumor levels of the short SYK isoform. Planned studies include validating both SYK isoforms as prognostic markers in a larger cohort of patients with HCC.  <b>SciBX 7(7); doi:10.1038/scibx.2014.197</b> <b>Published online Feb. 20, 2014</b>	Patent status undisclosed; unlicensed	Hong, J. <i>et al. Cancer Res.</i> ; published online Jan. 29, 2014; doi:10.1158/0008-5472.CAN-13-2104 <b>Contact:</b> Raymond T. Chung, Massachusetts General Hospital, Boston, Mass. e-mail: <a href="mailto:rtchung@partners.org">rtchung@partners.org</a>
Lung cancer	SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily a member 4 (SMARCA4; BRG1)	Cell culture studies suggest inhibiting BRG1 could help treat <i>MYC associated factor X (MAX)</i> mutant small cell lung cancer (SCLC). Sequencing of a panel of SCLC cell lines and primary tumors identified tumor-specific, homozygous, <i>MAX</i> -inactivating mutations in about 6% of cases. In <i>MAX</i> -mutant SCLC cells, shRNA against BRG1 decreased cell growth compared with scrambled control. Next steps could include developing and testing inhibitors of BRG1 in <i>MAX</i> -inactivated cancers.  <b>SciBX 7(7); doi:10.1038/scibx.2014.198</b> <b>Published online Feb. 20, 2014</b>	Patent and licensing status unavailable	Romero, O.A. <i>et al. Cancer Discov.</i> ; published online Dec. 20, 2013; doi:10.1158/2159-8290.CD-13-0799 <b>Contact:</b> Montse Sanchez-Céspedes, Bellvitge Biomedical Research Institute (IDIBELL), Barcelona, Spain e-mail: <a href="mailto:mcscedes@idibell.cat">mcscedes@idibell.cat</a>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Endocrine/metabolic disease</b>				
Infertility	Checkpoint kinase 2 (Chk2; CHEK2)	<p>Mouse studies suggest inhibiting CHK2 could prevent premature ovarian failure after radiotherapy or chemotherapy. In mice with genetically induced meiotic failure, <i>Chk2</i> deficiency increased numbers of ovarian follicles compared with normal <i>Chk2</i> expression. Oocytes in <i>Chk2</i>-deficient mice were viable despite abundant double-strand breaks, resulting in multiple litters of pups with no visible abnormalities. Wild-type mice subjected to irradiation showed complete elimination of the follicle pool, whereas <i>Chk2</i><sup>-/-</sup> mice retained follicles, remained fertile and did not undergo strand break-mediated oocyte elimination. Next steps include sequencing the genomes of the pups for mutations and identifying the mechanism responsible for repairing oocyte double strand-break damage (<i>see Preserving the oocyte reserve</i>, page 8).</p> <p><b>SciBX 7(7); doi:10.1038/scibx.2014.199</b> Published online Feb. 20, 2014</p>	Unpatented; licensing status not applicable	<p>Bolcun-Filas, E. <i>et al. Science</i>; published online Jan. 31, 2014; doi:10.1126/science.1247671</p> <p><b>Contact:</b> John C. Schimenti, Cornell University, Ithaca, N.Y. e-mail: <a href="mailto:jcs92@cornell.edu">jcs92@cornell.edu</a></p>
Mucopolysaccharidosis	$\alpha$ -L-iduronidase (IDUA)	<p><i>In vitro</i> and mouse studies suggest megakaryocyte-targeted gene therapy could help treat mucopolysaccharidosis I (MPS I; Hurler syndrome). In a human megakaryocytic cell line, an erythroid-targeting vector expressing <i>IDUA</i> increased IDUA protein secretion by 30-fold compared with no treatment. In MPS I mice, transplant of hematopoietic stem cells (HSCs) in which 1%–2% of cells were transfected with the <i>IDUA</i>-expressing vector increased IDUA levels in plasma and platelets to levels comparable to those observed in normal mice. In the MPS I mice, the HSC transplants decreased levels of glycosaminoglycans in liver, spleen and other organs compared with no treatment. Future studies could include testing the gene therapy in mouse models of other types of MPS.</p> <p>BioMarin Pharmaceutical Inc. markets Aldurazyme laronidase, a form of recombinant IDUA, to treat MPS I. Athersys Inc.'s MultiStem, allogeneic multipotent adult progenitor cells obtained from the bone marrow of healthy adult donors, is in preclinical testing to treat MPS I.</p> <p>ArmaGen Technologies Inc. has AGT-181, re-engineered human IDUA fused to IgG, in preclinical testing to treat MPS I.</p> <p><b>SciBX 7(7); doi:10.1038/scibx.2014.200</b> Published online Feb. 20, 2014</p>	Patent and licensing status unavailable	<p>Dai, M. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Feb. 3, 2014; doi:10.1073/pnas.1323155111</p> <p><b>Contact:</b> Dao Pan, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio e-mail: <a href="mailto:dao.pan@cchmc.org">dao.pan@cchmc.org</a></p> <p><b>Contact:</b> Roscoe O. Brady, National Institutes of Health, Bethesda, Md. e-mail: <a href="mailto:bradyr@ninds.nih.gov">bradyr@ninds.nih.gov</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Hematology</b>				
Anemia	Hepcidin	<i>In vitro</i> and mouse studies identified modified forms of heparin that could help treat chronic anemia. Heparin preparations were subjected to an oxidation-reduction modification process that removed their anticoagulant activity. In a mouse model of chronic anemia, injection of the modified heparins decreased serum and liver hepcidin levels and increased serum iron concentration compared with saline injection, without causing bleeding. Next steps include optimizing dose and timing of treatment in mice or rats. Noxxon Pharma AG has the hepcidin inhibitor Lexaptetid pegol in Phase II testing to treat anemia. At least two other companies have hepcidin inhibitors in Phase I or earlier testing to treat anemia.  <b>SciBX 7(7); doi:10.1038/scibx.2014.201</b> <b>Published online Feb. 20, 2014</b>	Patented; available for licensing	Poli, M. <i>et al. Blood</i> ; published online Jan. 7, 2014; doi:10.1182/blood-2013-07-515221 <b>Contact:</b> Paolo Arosio, University of Brescia, Brescia, Italy e-mail: <a href="mailto:arosio@med.unibs.it">arosio@med.unibs.it</a>
<b>Infectious disease</b>				
Bacterial infection	IgA	Mouse studies suggest secretory IgA could help prevent bacterial infections in formula-fed neonates. Maternal secretory IgA in breast milk protects infants from multiple bacterial infections. In mouse pups not receiving maternal secretory IgA during breast feeding, post-weaning gut levels of endogenous secretory IgA were lower than those in pups that did receive maternal secretory IgA. In the pups, post-weaning levels of endogenous secretory IgA altered the microbial composition of the gut and were inversely associated with numbers of opportunistic bacteria in mesenteric lymph nodes and colonic upregulation of genes linked to inflammatory bowel disease (IBD) and other conditions. Ongoing work includes investigating the role of secretory IgA in preventing infection in neonatal mouse pups.  <b>SciBX 7(7); doi:10.1038/scibx.2014.202</b> <b>Published online Feb. 20, 2014</b>	Patent application to be filed by the University of Kentucky; available for licensing	Rogier, E.W. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Feb. 3, 2014; doi:10.1073/pnas.1315792111 <b>Contact:</b> Charlotte S. Kaetzel, University of Kentucky, Lexington, Ky. e-mail: <a href="mailto:cskaet@uky.edu">cskaet@uky.edu</a>
Infectious disease	Triggering receptor expressed on myeloid cells 1 (TREM1)	Mouse studies suggest inhibiting the innate immune receptor TREM1 could help reduce inflammation caused by infection. In mouse models of colitis, <i>Trem1</i> knockout decreased weight loss, shortening of the colon and intestinal inflammation compared with normal <i>Trem1</i> expression. In mouse models of <i>Leishmania major</i> , influenza or <i>Legionella pneumonia</i> infection, <i>Trem1</i> knockout reduced disease severity without compromising the adaptive immune responses needed to clear the pathogens. Next steps include measuring <i>TREM1</i> expression in human tissue samples associated with chronic and noninfectious inflammatory conditions and identifying TREM1-inhibitory strategies.  <b>SciBX 7(7); doi:10.1038/scibx.2014.203</b> <b>Published online Feb. 20, 2014</b>	Unpatented; licensing status not applicable	Weber, B. <i>et al. PLoS Pathog.</i> ; published online Jan. 16, 2014; doi:10.1371/journal.ppat.1003900 <b>Contact:</b> Christoph Mueller, University of Bern, Bern, Switzerland e-mail: <a href="mailto:christoph.mueller@pathology.unibe.ch">christoph.mueller@pathology.unibe.ch</a> <b>Contact:</b> Leslie Saurer, same affiliation as above e-mail: <a href="mailto:leslie.saurer@pathology.unibe.ch">leslie.saurer@pathology.unibe.ch</a>

## This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Tuberculosis	<i>Mycobacterium tuberculosis</i> transmembrane serine/threonine-protein kinase B (pknB)	Cell culture studies suggest inhibiting <i>M. tuberculosis</i> pknB could be useful for treating tuberculosis. In cell culture, a small molecule inhibitor of pknB decreased recovery of <i>M. tuberculosis</i> from hypoxia-induced latency compared with vehicle. Next steps could include identifying selective <i>M. tuberculosis</i> pknB inhibitors and testing them in animal models of tuberculosis.	Unpatented; licensing status not applicable	Ortega, C. <i>et al. PLoS Biol.</i> ; published online Jan. 7, 2014; doi:10.1371/journal.pbio.1001746 <b>Contact:</b> Christoph Grundner, Seattle Biomedical Research Institute, Seattle, Wash. e-mail: christoph.grundner@seattlebiomed.org
<b>SciBX 7(7); doi:10.1038/scibx.2014.204</b> Published online Feb. 20, 2014				

## Neurology

Parkinson's disease (PD)	Nuclear factor (erythroid-derived 2)-like 2 (NFE2L2; NRF2); heme oxygenase decycling 1 (HMOX1; HO-1; Hsp32)	<i>In vitro</i> and mouse studies identified NRF2 pathway activators that could help treat PD. Chemical synthesis and testing of vinyl sulfone analogs in a mouse cell-based assay identified a lead compound that increased expression of the Nrf2 target gene <i>Hmox1</i> compared with vehicle. In mouse dopaminergic neurons, the compound increased levels of Nrf2, Hmox1 and other antioxidant proteins in the Nrf2 pathway compared with vehicle. In a mouse model of chemically induced PD, the compound decreased dopaminergic neuron loss and motor function deficits compared with vehicle. Ongoing work includes optimization of the lead compound. Biogen Idec Inc. markets the NRF2 pathway activator Tecfidera dimethyl fumarate to treat multiple sclerosis (MS). XenoPort Inc.'s XP23829, an oral prodrug of monomethyl fumarate (MMF) that induces and activates the NRF2 pathway, is in Phase I trials to treat MS.	Patented by the Korea Institute of Science and Technology and the University of Ulsan; available for licensing	Woo, S.Y. <i>et al. J. Med. Chem.</i> ; published online Jan. 27, 2014; doi:10.1021/jm401788m <b>Contact:</b> Ki Duk Park, Korea Institute of Science and Technology, Seoul, South Korea e-mail: kdpark@kist.re.kr <b>Contact:</b> Onyou Hwang, University of Ulsan College of Medicine, Seoul, South Korea e-mail: oyhwang@amc.seoul.kr
<b>SciBX 7(7); doi:10.1038/scibx.2014.205</b> Published online Feb. 20, 2014				

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## This week in techniques

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

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

Approach	Summary	Licensing status	Publication and contact information
<b>Assays &amp; screens</b>			
Diagnosing and monitoring treatment responses in patients with Niemann-Pick disease type C1 (NPC1) using fluorescence-based volumetric measurement of lysosomes	<p>A fluorescence-based assay in B cells could help monitor treatment responses and diagnose patients with NPC1. The assay measured uptake of a fluorescent probe by the acidic compartment of lysosomes to determine the volume of that compartment relative to total cell volume. In B cells from pediatric patients with NPC1, the method identified positive correlations between the relative compartment volume and NPC1 disease severity. In B cells from patients with NPC1 receiving Zavesca miglustat or bone marrow transplantation, the method identified a correlation between decreased relative compartment volume and treatment response. Future studies could include testing the assay in patients with other lysosomal storage disorders.</p> <p>Actelion Ltd.'s and UCB Group's Zavesca, a glucosylceramide synthase (GCS) inhibitor, is marketed to treat Gaucher's disease and Niemann-Pick disease.</p> <p><b>SciBX 7(7); doi:10.1038/scibx.2014.206</b> Published online Feb. 20, 2014</p>	Patent and licensing status unavailable	<p>te Vruchte, D. <i>et al. J. Clin. Invest.</i>; published online Feb. 3, 2014; doi:10.1172/JCI72835</p> <p><b>Contact:</b> Frances M. Platt, University of Oxford, Oxford, U.K. e-mail: frances.platt@pharm.ox.ac.uk</p> <p><b>Contact:</b> Mario Cortina-Borja, University College London, London, U.K. e-mail: m.cortina@ucl.ac.uk</p>
Screening antimetastatic compounds using microfluidic-based tracking of cell migration	<p>A microfluidic device that monitors cell migration could be used to screen antimetastatic compounds. On the chip-based device, chemoattractant loaded at one end of 10 separate microchannels induced the migration of cells loaded at the other end of each microchannel, which could be tracked with scanning electron microscopy. The device simultaneously screened nine research-grade, clinical or marketed small molecule inhibitors of metastasis-associated targets for their ability to increase or decrease the migration of paclitaxel-resistant metastatic human breast cancer cells compared with no treatment. Future studies could include using the device to screen new inhibitors of cell migration and metastasis.</p> <p><b>SciBX 7(7); doi:10.1038/scibx.2014.207</b> Published online Feb. 20, 2014</p>	Patent and licensing status unavailable	<p>Zhang, Y. <i>et al. Angew. Chem. Int. Ed.</i>; published online Jan. 29, 2014; doi:10.1002/anie.201309885</p> <p><b>Contact:</b> Lidong Qin, Houston Methodist Research Institute, Houston, Texas e-mail: lqin@tmhs.org</p>
<b>Drug platforms</b>			
Bone marrow niche-sensitizing chemotherapy to enhance antibody-based acute lymphoblastic leukemia (ALL) elimination	<p>Mouse and human sample studies suggest targeting tumor type-specific factors that suppress antitumor immunity could help eliminate residual ALL. In a humanized mouse model of ALL treated with Campath alemtuzumab, shRNA screening of residual leukemia cells identified secreted factors that suppressed antitumor macrophage activity in the bone marrow. In the same mice, Campath plus low doses of cyclophosphamide led to a synergistic, near-complete elimination of tumor cells in the bone marrow caused by cyclophosphamide-dependent blockade of a tumor cell secretory program that suppressed bone marrow-resident macrophages. Next steps include testing low-dose cyclophosphamide inhibition with therapeutic antibodies as treatment for refractory B cell malignancies and investigating specific tumor-secreted, macrophage-suppressing factors. Campath, an anti-CD52 antibody, is marketed by Sanofi to treat chronic lymphocytic leukemia (CLL) and multiple sclerosis (MS).</p> <p>Cyclophosphamide is a generic chemotherapeutic used to treat cancers including lymphoma and leukemia.</p> <p><b>SciBX 7(7); doi:10.1038/scibx.2014.208</b> Published online Feb. 20, 2014</p>	Patents filed covering the humanized ALL model and treatment with low-dose cyclophosphamide as an antibody-sensitizing agent; available for licensing	<p>Pallasch, D.P. <i>et al. Cell</i>; published online Jan. 30, 2014; doi:10.1016/j.cell.2013.12.041</p> <p><b>Contact:</b> Michael T. Hemann, Massachusetts Institute of Technology, Cambridge, Mass. e-mail: hemann@mit.edu</p> <p><b>Contact:</b> Jianzhu Chen, same affiliation as above e-mail: jchen@mit.edu</p>

## This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Improved brain delivery of anti-transferrin receptor (TFRC; TFR)-containing antibodies by reducing TFRC affinity	<p>Mouse studies suggest lowering anti-TFRC antibody affinity could increase brain uptake of blood brain barrier (BBB)-penetrant, bispecific antibodies. In mice, a bispecific, anti-TFRC and anti-<math>\beta</math>-amyloid cleaving enzyme 1 (BACE1) antibody with low affinity for TFRC led to increased surface-expressed Tfr levels on BBB endothelial cells and increased BBB trafficking and brain uptake compared with a related antibody with high affinity for TFRC. This relative increase in surface-expressed Tfr was seen because the low-affinity antibody induced less lysosome-mediated degradation of Tfr than the high-affinity antibody. Ongoing work includes validating the approach in nonhuman primates.</p> <p><b>SciBX 7(7); doi:10.1038/scibx.2014.209</b> Published online Feb. 20, 2014</p>	Patent and licensing status undisclosed	<p>Bien-Ly, N. <i>et al. J. Exp. Med.</i>; published online Jan. 27, 2014; doi:10.1084/jem.20131660 <b>Contact:</b> Ryan J. Watts, Genentech Inc., South San Francisco, Calif. e-mail: <a href="mailto:rwatts@gene.com">rwatts@gene.com</a> <b>Contact:</b> Inhee Chung, same affiliation as above e-mail: <a href="mailto:chung.inhee@gene.com">chung.inhee@gene.com</a></p>
Inducing multipotent progenitor cells from keratinocytes by depleting the tumor protein p63 (TP63; p63) $\Delta Np63$ isoform or DGCR8 microprocessor complex subunit (DGCR8)	<p><i>In vitro</i> studies suggest depleting <math>\Delta Np63</math> or <i>DGCR8</i> in keratinocytes could induce their conversion into multipotent stem cells. In mouse or human epidermal cells, shRNA against or knockout of <math>\Delta Np63</math> and <i>DGCR8</i> increased expression of pluripotency markers compared with control shRNA or no alteration and allowed differentiation into multiple cell types. Restoring <i>DGCR8</i> expression repressed expression of pluripotency markers. In mice, injection of green fluorescent protein-labeled <math>\Delta Np63</math> mutant epidermal cells into blastocyst-stage embryos led to their incorporation into differentiated tissues at levels similar to those for induced pluripotent stem (iPS) cells. Next steps include using the strategy to differentiate cells for cell therapy.</p> <p><b>SciBX 7(7); doi:10.1038/scibx.2014.210</b> Published online Feb. 20, 2014</p>	Patent application filed; available for licensing	<p>Chakravarti, D. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Jan. 21, 2014; doi:10.1073/pnas.1319743111 <b>Contact:</b> Elsa R. Flores, The University of Texas MD Anderson Cancer Center, Houston, Texas e-mail: <a href="mailto:elsaflores@mdanderson.org">elsaflores@mdanderson.org</a></p>
Intracellularly expressed antibodies linked to the E3 ubiquitin ligase domain of STIP1 homology and U-box containing protein 1 (STUB1; CHIP) to enable targeted protein degradation	<p><i>In vitro</i> and cell culture studies suggest intracellular expression of antibodies linked to the E3 ubiquitin ligase domain of CHIP could promote ubiquitin-mediated degradation of target proteins. <i>In vitro</i>, an E3 ubiquitin ligase domain-linked single-chain variable fragment (scFv) specific for a model target protein caused ubiquitination of the protein. In cultured mammalian cells, plasmid-based expression of an E3 ubiquitin ligase domain-linked antibody-like protein led to degradation of a plasmid-expressed protein from <i>Escherichia coli</i>. Next steps include developing extracellular or transgenic delivery methods and testing the effect of the molecules, called ubiquibodies, on disease-associated proteins in cell culture. GlaxoSmithKline plc and Arvinas Inc. each have discovery stage programs to find small molecules that promote ubiquitin-mediated protein degradation (<i>see Degradation from within</i>, page 10).</p> <p><b>SciBX 7(7); doi:10.1038/scibx.2014.211</b> Published online Feb. 20, 2014</p>	Patent pending; being licensed to Ubiquizyme Inc.	<p>Protstoff, A.D. <i>et al. J. Biol. Chem.</i>; published online Jan. 28, 2014; doi:10.1074/jbc.M113.544825 <b>Contact:</b> Matthew P. DeLisa, Cornell University, Ithaca, N.Y. e-mail: <a href="mailto:md255@cornell.edu">md255@cornell.edu</a></p>
Retinal progenitor cell therapy for retinal degeneration	<p>Rat studies suggest transplantation of retinal progenitor cells could help treat or prevent retinal degeneration. In a rat model of retinal degeneration, subretinal injection of expanded human retinal progenitor cells preserved visual acuity, photoreceptor distribution and outer nuclear layer thickness and cell count compared with vehicle control injection. Next steps include clinical testing.</p> <p><b>SciBX 7(7); doi:10.1038/scibx.2014.212</b> Published online Feb. 20, 2014</p>	Patented; licensed by ReNeuron Group plc	<p>Luo, J. <i>et al. J. Biol. Chem.</i>; published online Jan. 9, 2014; doi:10.1074/jbc.M113.513713 <b>Contact:</b> Kang Zhang, University of California, San Diego, La Jolla, Calif. e-mail: <a href="mailto:kang.zhang@gmail.com">kang.zhang@gmail.com</a> <b>Contact:</b> Xiaodong Sun, Shanghai JiaoTong University, Shanghai, China e-mail: <a href="mailto:xdsun@sjtu.edu.cn">xdsun@sjtu.edu.cn</a></p>

## This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Viral insertion of inducible aptazymes to improve the safety of oncolytic viral therapy	<i>In vitro</i> studies suggest inducible aptazymes that regulate viral gene expression could improve the safety of oncolytic viruses. Aptazymes are self-cleaving ribozymes linked to ligand-binding aptamers that enable ligand-triggered inhibition of target gene expression. In cancer cells infected with an adenovirus encoding an aptazyme in the <i>E1A</i> gene, viral genome replication, infectious particle production and cellular toxicity were decreased upon ligand exposure compared with what was seen using unmodified adenovirus or no ligand. The aptazyme also decreased infectivity of measles virus. Next steps could include assessing the therapeutic activity of aptazyme-modified oncolytic viruses.  <b>SciBX 7(7); doi:10.1038/scibx.2014.213</b> Published online Feb. 20, 2014	Patent and licensing status unavailable	Ketzer, P. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Jan. 21, 2014; doi:10.1073/pnas.1318563111 <b>Contact:</b> Dirk M. Nettelbeck, German Cancer Research Center, Heidelberg, Germany e-mail: <a href="mailto:d.nettelbeck@dkfz-heidelberg.de">d.nettelbeck@dkfz-heidelberg.de</a>

## Markers

A cytosine methylation signature that predicts overall survival in acute myelogenous leukemia (AML)	Studies of human samples suggest a cytosine methylation signature can predict overall survival of patients with AML. A nanoHELP (nano HpaII tiny fragment enrichment by ligation-mediated PCR) assay identified genome-wide cytosine methylation patterns in highly purified blood cells from individual patients with AML and healthy subjects. In the samples from healthy subjects, cytosine methylation in common myeloid progenitors was lower than that in hematopoietic stem cells, particularly near promoters of genes involved in hematopoiesis and leukemogenesis. In the samples from patients with AML, a signature based on methylation at 561 loci predicted poorer overall survival. Next steps include testing the signature in prospective clinical trials and developing a simpler assay to determine the methylation status of loci in the signature.  <b>SciBX 7(7); doi:10.1038/scibx.2014.214</b> Published online Feb. 20, 2014	Patent application filed; available for licensing from the Albert Einstein College of Medicine of Yeshiva University <b>Contact:</b> David Silva, Albert Einstein College of Medicine of Yeshiva University, Bronx, N.Y. e-mail: <a href="mailto:david.silva@einstein.yu.edu">david.silva@einstein.yu.edu</a>	Bartholdy, B. <i>et al. J. Clin. Invest.</i> ; published online Feb. 3, 2014; doi:10.1172/JCI71264 <b>Contact:</b> Ulrich Steidl, Albert Einstein College Of Medicine of Yeshiva University, Bronx, N.Y. e-mail: <a href="mailto:ulrich.steidl@einstein.yu.edu">ulrich.steidl@einstein.yu.edu</a> <b>Contact:</b> Amit Verma, same affiliation as above e-mail: <a href="mailto:amit.verma@einstein.yu.edu">amit.verma@einstein.yu.edu</a>
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**Company and institution index****A**

AbbVie Inc. 4  
 Actelion Ltd. 17  
 Agency for Science, Technology and Research 4  
 Albert Einstein College of Medicine of Yeshiva University 19  
 Allegra Therapeutics GmbH 5  
 Alzheimer's Association 6  
 ArmaGen Technologies Inc. 14  
 Arvinas Inc. 10,18  
 AstraZeneca plc 3,8  
 Athersys Inc. 14

**B**

Bill & Melinda Gates Foundation 4  
 BioCrossroads 4  
 Biogen Idec Inc. 16  
 BioMarin Pharmaceutical Inc. 14  
 Biomet Inc. 4  
 Boehringer Ingelheim GmbH 4

**C**

California Institute of Technology 11  
 Canadian Partnership Against Cancer 4  
 Cancer Research UK 1,8  
 Caprion Proteomics Inc. 4  
 Celgene Corp. 4  
 Children's Investment Fund Foundation 4  
 Cleave Biosciences Inc. 5  
 Cook Group Inc. 4  
 Cornell University 8,10

**D**

Dow Chemical Co. 4

**E**

Eli Lilly and Co. 4  
 Envisia Therapeutics Inc. 5  
 European Commission 1  
 European Federation of Pharmaceutical Industries and Associations 7

**F**

Federal Ministry for Economic Cooperation and Development 4  
 Foundation for the National Institutes of Health 6

**G**

General Electric Co. 4  
 GlaxoSmithKline plc 4,10,18  
 Grand Challenges Canada 4

**H**

Harvard University 4  
 Heart and Stroke Foundation 4

**I**

illumina Inc. 4  
 Indiana University 4  
 Innovative Medicines Initiative 7  
 Institute of Cancer Research 8  
 Intel Corp. 4

**J**

Johnson & Johnson 3  
 Jounce Therapeutics Inc. 5  
 JPMorgan Chase & Co. 4

**K**

Karolinska Institute 3  
 Korea Institute of Science and Technology 16

**L**

Leukemia & Lymphoma Society 4  
 Li Ka Shing Foundation 4  
 Lion's Head Global Partners LLP 4

**M**

Memorial Sloan-Kettering Cancer Center 4  
 Merck & Co. Inc. 4  
 Merck KGaA 8  
 Michael J. Fox Foundation for Parkinson's Research 6

**N**

New York City Economic Development Corp. 4  
 Novartis AG 4  
 Novo Nordisk A/S 1  
 Noxxon Pharma AG 15

**O**

Oncozyme Pharma Inc. 4  
 Oregon Health & Science University 4

**P**

Pfizer Inc. 4  
 Pulmocide Ltd. 5  
 Purdue University 4

**Q**

Quebec Clinical Research Organization in Cancer 4

**R**

ReNeuron Group plc 18  
 Roche 4  
 Rockefeller University 4

**S**

Sanofi 4,17  
 Sarepta Therapeutics Inc. 4  
 Sbarro Health Research Organization 8  
 Seragon Pharmaceuticals Inc. 5  
 Stanford University 4  
 Swedish International Development Cooperation Agency 4

**T**

Takeda Pharmaceutical Co. Ltd. 4  
 TELUS Health 4  
 Temple University 8  
 TocopheRx 8  
 Tri-Institutional Therapeutics Discovery Institute Inc. 4

**U**

U.K. government 4  
 Ubiquizyme Inc. 11,18

UCB Group 17  
 University of California, Los Angeles 4  
 University of California, San Francisco 4  
 University of California, Davis 4  
 University of Kentucky 15  
 University of Notre Dame 4  
 University of Oxford 4  
 University of Texas Southwestern Medical Center 4  
 University of Ulsan 16  
 University of Utah 4  
 University of Western Australia 4

**W**

W. Garfield Weston Foundation 6  
 Weill Cornell Medical College 4

**X**

XenoPort Inc. 16

**Y**

Yale University 6,11

.....

**Target and compound index**

1541B 13

**A**

$\alpha$ -L-iduronidase 14  
 $\alpha$ -Synuclein 7  
 A $\beta$  6  
 AGT-181 14  
 Aldurazyme 14  
 Alemtuzumab 17  
 Ataxia telangiectasia and Rad3 related 8  
 Ataxia telangiectasia mutated 8  
 ATM 8  
 ATR 8  
 AZD7762 8

**B**

$\beta$ -Amyloid 6  
 $\beta$ -Amyloid cleaving enzyme 1 18  
 BACE1 18  
 BRG1 12,13

**C**

Campath 17  
 CCT241533 8  
 CD52 17  
 Checkpoint kinase 1 8  
 Checkpoint kinase 2 8,14  
 CHEK2 8,14  
 CHIP 10,18  
 CHK1 8  
 Chk2 8,14  
 Cyclophosphamide 17

**D**

DGCR8 microprocessor complex subunit 18  
 DGCR8 18  
 Dimethyl fumarate 16

**E**

*E. coli* maltose binding protein 10  
 E3 ubiquitin ligase 10,18

*Escherichia coli*  $\beta$ -galactosidase 10  
 Estrogen receptor 12

**F**

Follicle-stimulating hormone 8  
 FRP1 8  
 FSH 8  
 FTDP-17 6

**G**

GCS 17  
 Gemcitabine 8  
 Glucosylceramide synthase 17  
 GnRH 8  
 Gonadotropin-releasing hormone 8

**H**

Heme oxygenase decycling 1 16  
 Heparin 15  
 Hepcidin 15  
 HMOX1 16  
 HO-1 16  
 Hsp32 16

**I**

IDUA 14  
 IgA 15  
 IgG 13,14  
 IL-2 12  
 Irinotecan 8

**L**

Laronidase 14  
*Leucine-rich repeat kinase 2* 7  
 Lexaptapid pegol 15  
 LRRK2 7

**M**

MAPT 6  
 MAX 13  
 Microtubule-associated protein- $\tau$  6  
 Miglustat 17  
 MMF 16  
 Monomethyl fumarate 16  
 MultiStem 14  
*MYC associated factor X* 13  
*Mycobacterium tuberculosis* transmembrane serine/threonine-protein kinase B 16

**N**

NFE2L2 16  
 NRF2 16  
 Nuclear factor (erythroid-derived 2)-like 2 16

**P**

p63 18  
 PAC-1 13  
 Paclitaxel 17  
 PARP 8  
 PknB 16  
 Poly(ADP-ribose) polymerase 8  
 Procasase-3 13  
 PROTAC 11  
 Proteolysis-targeting chimeric molecule 11

<b>S</b>							
SMARCA4	12,13	SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily a member 4	12,13	Tecfidera	16	Ubiquitin	10
SNCA	7			TFR	18	<b>V</b>	
Spleen tyrosine kinase	13	SYK	13	TFRC	18	vHL	11
SSEA-4	13	<b>T</b>		TP63	18	Von Hippel-Lindau tumor suppressor	11
Stage-specific embryonic antigen-4	13	Tamoxifen	12	Transferrin receptor	18	<b>X</b>	
STIP1 homology and U-box containing protein 1	10,18	TANK-binding kinase 1	12	TREM1	15	XP23829	16
STUB1	10,18	Tau	6	Triggering receptor expressed on myeloid cells 1	15	<b>Z</b>	
		TBK1	12	Tumor protein p63	18	Zavesca	17
				<b>U</b>			
				Ubiquibodies	10		