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## CRISPR genome editing

By *Chris Cain, Senior Writer*

Five separate research teams have developed a Cas9 endonuclease-based method for sequence-specific genome modification that is guided by DNA-RNA base pairing, and at least two companies are commercializing the findings.<sup>1-6</sup> Although the approach is technically more straightforward than existing methods, such as zinc finger nucleases and transcription activator-like effector nucleases, its specificity has yet to be fully determined.

At least four companies are using zinc finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs) to engineer point mutations, deletions and insertions into the genomes of organisms ranging from plants to humans. These technologies have enabled functional genetic studies in model systems including rats, pigs and zebrafish in which it was previously difficult to make targeted knockouts.

**Sangamo BioSciences Inc.** has advanced ZFN-based therapeutics into the clinic.

The success of both ZFN- and TALEN-based methods hinges on designing and synthesizing complex DNA-binding domains that have a high level of target sequence specificity.

"These approaches can provide exquisite target specificity; however, protein-DNA recognition, just as with antibody-antigen specificity, is a complex interaction that is difficult to engineer from the point of view of writing it down on a piece of paper," noted Sangamo CSO and VP of research Philip Gregory.

Zinc finger motifs represent the most common and best understood DNA-binding domain in eukaryotes, although there is no single blueprint that can be followed to design a multi-zinc finger motif that will bind a given DNA sequence. Because of this, successfully designing ZFNs often requires specialized expertise.

By comparison, TALENs are relatively easy to design. The DNA specificity of TALENs derives from peptides consisting of 33-35 amino acid repeats, each of which specifically recognizes a single cognate nucleotide. By stringing together multiple peptides, a TALEN can be directed to bind to almost any target gene of interest.<sup>7,8</sup>

Since this DNA-binding code was cracked in 2009, the use of TALENs for targeted gene knockouts in unconventional model systems has increased rapidly. However, the large size and repetitive nature of TALENs can make cloning difficult, which limits their use in some systems and makes it hard for researchers to efficiently construct the proteins in their own labs.

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Thus, five separate teams of researchers set out to design a simplified genome-engineering method guided solely by DNA-RNA base pairing.

The groups built upon recent biochemical studies describing a bacterial acquired immunity-like system that relies on clustered regularly interspaced short palindromic repeats (CRISPR) to cleave unwanted exogenous DNA from phages, plasmids and other sources.

CRISPR units form the backbone of this protection system. Bacteria use CRISPR-associated (Cas) proteins to cleave foreign DNA into short fragments that are subsequently incorporated into CRISPR. These DNA fragments are then transcribed into RNA and are incorporated into a complex with other Cas proteins, including the Cas9 endonuclease.<sup>9</sup>

When foreign DNA homologous to a particular CRISPR RNA-Cas9 complex enters the bacterial cell, the complex recognizes it and triggers its cleavage.

Last year, a team from the **University of California, Berkeley** and **Umea University** showed that the CRISPR-Cas9 system could be used to target and cleave any chosen DNA sequence *in vitro*.<sup>10</sup>

The logical next step was to determine whether CRISPR RNA-Cas9 complexes could be engineered to direct precise DNA cleavage in an intact genome.

The five teams took up this challenge, designing similar systems in which Cas9 was expressed in conjunction with a guide RNA containing CRISPR-specific sequences framing a region of about 20 base pairs complementary to a specific locus in the target genome.

Four teams used the approach to precisely cleave specific genomic sites and induce deletions or point mutations in human and mouse cells,<sup>1,2,4,6</sup> whereas the fifth group demonstrated the approach's utility in zebrafish.<sup>3</sup> One of the teams also adapted the approach to edit the genomes of two distinct bacterial species.<sup>5</sup>

In addition to targeting an individual genomic locus, some of the groups showed that multiple loci could be simultaneously targeted by a CRISPR RNA containing multiple regions of complementarity.

The approach's efficacy was comparable to that of ZFN and TALEN approaches. None of the studies provided detailed comparative data on specificity or a comprehensive genomewide specificity analysis.

The teams included researchers from the University of California, Berkeley, the **Broad Institute of MIT and Harvard**, the **Wyss Institute for Biologically Inspired Engineering at Harvard University**, **Massachusetts General Hospital**, **The Rockefeller University**, **Seoul National University** and **Harvard Medical School**.

Results were published in two *Science* papers, in three *Nature Biotechnology* papers and in *eLife*.

**Practical advantages**

The simplicity offered by the new approach could fuel uptake and acceptance of genome-editing approaches throughout the scientific community.

"Practically, it's not only easier to design an oligonucleotide, it's a lot cheaper to synthesize. Instead of going through rounds of molecular biology in order to build a DNA-binding protein, we can just order oligos from standard suppliers," said Feng Zhang, lead investigator on one of the *Science* papers and a member of the Broad Institute.

In contrast to short oligonucleotides, which can be synthesized for a few dollars on average, **Collectis S.A.** sells custom-engineered TALENs for

about \$5,000 each, and **Sigma-Aldrich Corp.** prices custom ZFNs at about \$6,000 under a license from Sangamo.

Zhang plans to use the CRISPR system in his own research to study the effect of point mutations on cellular disease phenotypes. “It really allows us to scale up our ability to study these mutations. With TALENs it takes a lot of effort to build each one, but it is easy to design 50 RNAs,” he said.

Jennifer Doudna, corresponding author on the *eLife* paper, told *SciBX* that the rapid development of this system by five separate teams is a testament to its real-world utility. “It’s been an exciting opportunity to see it working in so many people’s hands—that says a lot,” she said.

Doudna is a professor of biochemistry, biophysics and structural biology at UC Berkeley and a **Howard Hughes Medical Institute** investigator.

Gregory predicted that uptake of CRISPR could create a knock-on effect for more established genome-editing methods. “Between zinc finger proteins and these newer methods, my guess is you will see a displacement of RNAi as the research reagent of choice for asking gene function–related questions in the future,” he said.

J. Keith Joung, lead investigator on one of the *Nature Biotechnology* papers and associate professor of pathology at Massachusetts General Hospital, said it is important to have all the options on the table when designing experiments. “We really go on a case-by-case basis,” he said. “It depends on the needs for a particular project and the limitations of the experimental system we are working in. This is why we have all three capabilities in our lab. There is no approach at this point that is necessarily one size fits all.”

For example, he said, “some projects might require very precise targeting of DNA sequences, in which case we would favor the use of TALENs with their essentially limitless targeting range. Alternatively, other projects might require the use of lentiviral vectors to deliver nuclease-encoding DNA to cells, and so in those cases we would favor the use of ZFNs.”

Joung has published detailed resource papers containing protocols for researchers to produce customized ZFNs and TALENs, and he maintains an open-source software package that can be used to design genome-editing experiments using all three [systems](#).<sup>7,11</sup> Zhang also maintains [a website](#) with tools for CRISPR and TALEN engineering.

Luciano Marraffini, assistant professor of bacteriology at Rockefeller University and a corresponding author on the bacterial genome-editing paper, acknowledged that most of the excitement is focused on eukaryotic cells but noted that there will be uses for the approach even in some bacterial systems.

“I believe that the use of CRISPR-Cas systems for bacterial mutagenesis will open the door for many high throughput studies that will certainly advance our understanding of gene networks,” he said.

### Commercial aspirations

At least two companies, **Caribou Biosciences Inc.** and **ToolGen Inc.**, see commercial potential in the new approach.

Caribou president, CEO and cofounder Rachel Haurwitz told *SciBX* that the company was founded to develop and commercialize DNA and RNA manipulation tools using CRISPR-based systems. “Caribou plans to commercialize the Cas9 platform technology via internal product development and strategic partnerships with key entities in a variety of potential fields of use,” she said.

Caribou was founded in October 2011 by a Berkeley team that includes Doudna, and the company is currently housed at the **California Institute for Quantitative Biosciences (QB3)** incubator at UC Berkeley. Doudna has filed a patent covering her work on CRISPR editing.

A second company, South Korea–based service-provider ToolGen, is planning to offer custom CRISPR-based services to researchers based on the method published by Seoul National University in *Nature Biotechnology*, dubbed RNA-guided endonucleases (RGENs). ToolGen provided research funding to corresponding author Jin-Soo Kim, an associate professor at the university and cofounder of the company.

Kim told *SciBX* that he sees a commercial opportunity in offering researchers a convenient, validated product. “We have found that not all RGENs are equally efficient, and some RGENs have no activity at all. ToolGen plans to provide high activity, validated RGENs.”

He added that the company also plans to use the method to provide custom gene knockout and knock-in services in cell lines and animals. Kim has filed a patent covering his work on RGENs.

Zhang has also filed a patent application covering his CRISPR-editing work, as has George Church, corresponding author on the second *Science* paper and a founding core faculty member of the Wyss Institute.

Joung and Doudna noted that Church shared results from his team with them prior to publication, whereas Zhang collaborated with Marraffini.

### Specific questions

The scope of the commercial and possible clinical utility of the CRISPR approach is likely to be determined by ongoing attempts to further characterize and improve specificity.

Gregory wanted to see more data detailing the off-target effects of genome modification using the CRISPR system. He noted that none of the papers measured the genomewide specificity of the approach.

“Work from Jennifer Doudna and others has shown that 12–14 bases are all that is necessary to induce Cas9 cleavage, and outside of this core region mismatches are perfectly well tolerated. To put that into perspective, any given 12-bp region would be predicted to occur by chance about 200 times in the human genome,” he said.

Although at least one recent paper has shown that some ZFNs have off-target effects,<sup>12</sup> Gregory noted that Sangamo published a whole-genome sequencing study in 2011 that showed a ZFN could correct a point mutation in a single cell and that the only change attributable to the ZFN action was the intended correction.<sup>13</sup>

Sangamo’s lead therapeutic ZFN program is SB-728-T, an autologous CD4<sup>+</sup> T cell therapy for patients with HIV that uses cells modified at *CC chemokine receptor 5 (CCR5; CD195)* by a ZFN.

“Between zinc finger proteins and these newer methods, my guess is you will see a displacement of RNAi as the research reagent of choice for asking gene function–related questions in the future.”

—Philip Gregory,  
Sangamo BioSciences Inc.

Collectis CSO Philippe Duchateau agreed that specificity is a key issue for CRISPR. “Only 12–14 base pairs seem to be important, and thus one can imagine that the specificity of such molecules will not be as stringent as the TALENs or zinc finger approaches,” he said.

In addition to providing fee-for-service TALEN design for research labs, Collectis is collaborating with the **University College London** to use its technology to engineer T cells for cancer immunotherapy.

Gregory was not hopeful about the prospect of improving the approach’s specificity. “The danger with the CRISPR system is that because it is so simple, I am not convinced it can be engineered to be completely specific,” said Gregory.

However, Doudna told *SciBX* that she was more optimistic. “The Cas9 system is one example of dozens if not hundreds of proteins with similar properties, which I suspect will be investigated very quickly by many labs. I personally think it’s going to be possible to find ways to make it more selective than it is currently.”

Zhang added that a better structural understanding of the Cas9 system may provide clues to improving the approach’s specificity. He noted that no Cas9-CRISPR crystal structure has been published and agreed with Doudna that studying the cleavage requirements of Cas9 homologs in other bacterial species could provide additional insight. Doudna said next steps in her lab include additional structural studies.

Joung said future work in his lab will include studying the determinants of CRISPR RNA specificity. He emphasized that the key next step to understanding the specificity of the approach is to more clearly define the rules governing CRISPR RNA-mediated cleavage of DNA. Marraffini noted that deep sequencing performed by his group has shown that some variation may be tolerated by Cas9 in certain CRISPR RNA sequences previously thought to be strictly invariant.

Doudna said that genomewide specificity analyses are ongoing in her lab and will be essential going forward.

Joung added that this system will benefit from the years of experience that have gone into developing ZFNs and TALENs. “It’s important to keep in mind that ZFNs were described in ‘96, and we have had more than 15 years of experience optimizing and delivering them. It’s been a little over three years since the TALEN code was described, and their rapid progress was because we were able to leverage what was done with the zinc fingers. With CRISPR it will be even faster.”

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## COMPANIES AND INSTITUTIONS MENTIONED

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**Seoul National University**, Seoul, South Korea  
**Sigma-Aldrich Corp.** (NASDAQ:SIAL), St. Louis, Mo.  
**ToolGen Inc.**, Seoul, South Korea  
**Umea University**, Umea, Sweden  
**University College London**, London, U.K.  
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**Wyss Institute for Biologically Inspired Engineering at Harvard University**, Cambridge, Mass.

# Translational globe-trotting

By Steve Edelson, Executive Editor

Six like-minded translational research centers have partnered to help speed the commercialization of academic research. The international cadre, dubbed the **Global Alliance of Leading Drug Discovery and Development Centres**, comprises more than 400 drug developers working on at least 165 projects.

The origin of the Global Alliance dates to 2010, when **The Centre for Drug Research and Development (CDRD)** in Canada began to look for other translational research organizations with which to potentially partner.

“There really are only a handful of organizations that have fully integrated drug discovery and development platforms, including infrastructure, expertise in industrial drug development and a mandate in the preclinical translational space,” said CDRD president and CEO Karimah Es Sabar.

Es Sabar had started talks with Belgium’s **Centre for Drug Design and Discovery**, Germany’s **Lead Discovery Center GmbH** and **The Scripps Research Institute’s Scripps Florida** drug discovery center.

The final pieces fell into place last year when Mike Johnson, director of corporate partnerships at **MRC Technology**, read an article about CDRD and how it receives funding from the Canadian federal government, the provincial governments of British Columbia and Alberta, and a handful of pharma companies.

“I got in touch with their CEO and said we should be talking,” noted Johnson. “We’re expanding and are looking to be global, and I liked their model. We met with CDRD in Europe and it was astounding—their slide presentation was virtually the same as ours.”

MRC Technology (MRCT) began life as the internal technology transfer company of the **Medical Research Council**, which is the U.K.’s largest publicly funded biomedical research organization. MRCT became independent in 2000, although the vast majority of its business came from MRC for the next decade.

Since 2010, however, MRCT has been searching for assets elsewhere. Now, about 70%–80% of its projects are non-MRC. For example, MRCT last year partnered with the **Shanghai Institute of Biochemistry and Cell Biology**, which is part of the **Chinese Academy of Sciences**. The institute is providing therapeutic targets, which can be further developed at MRCT’s **Centre for Therapeutics Discovery**.<sup>1</sup>

“We’ve been looking globally for good science, and we now have more projects than we can handle,” said Mike Johnson, director of corporate partnerships at MRCT. “The question was whether we could prioritize and share these projects. Now, we’ve pulled in global organizations to push the science forward.”

At the meeting with CDRD, MRCT found out that CDRD was discussing a potential alliance with the other translational centers. “We decided to pull together and create this alliance,” added Johnson.

The resulting Global Alliance also includes drug discovery center also includes **Cancer Research UK’s Cancer Research Technology Ltd.** commercial arm.

## Conversion rates

The overarching goal of the alliance is to help accelerate the conversion of early stage research into drugs. Johnson also said the alliance should help increase the international visibility of each member. “Some are only really seen well nationally,” he noted.

The organization’s success metrics include the number of spinouts from academic collaborators, the number of deals between the alliance’s academic collaborators and biotech or pharma companies and the number of patents granted to the alliance’s collaborators in academia.

Johnson told *SciBX* that he wants the alliance to “be demonstrating new models of drug discovery in the next two years. There’s an absolute need for pharma to access innovation in academia, and we can act as a catalyst.”

The Global Alliance does not charge its members any fees—each organization shoulders its own costs.

A steering committee consisting of one representative per member manages the Global Alliance. The chair of the committee rotates every year. The committee expects to meet two times annually, and decisions will be based on majority votes, including other organizations’ applications to join the alliance.

A key condition for joining the Global Alliance is integration—meaning a would-be member needs

to have in place the full spectrum of drug discovery and development capabilities.

Those criteria, according to the alliance website, will differentiate it from “upcoming, not fully integrated, purely academic drug discovery initiatives, or contract research organizations.”

Es Sabar said the Global Alliance also hopes to tackle large-scale projects that are beyond the scope of a single translational center. She declined to provide specifics but noted there will be at least one “massive initiative that will be a joint initiative between the centers. It’s very much needed, and none of us could do it on our own.”

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# Toll-erating AD

By Lev Osherovich, Senior Writer

Laval University and GlaxoSmithKline plc have shown that peripheral administration of the adjuvant monophosphoryl lipid A can help treat Alzheimer's disease in mice.<sup>1</sup> Although the findings point to a potential immunomodulatory approach for addressing the neurodegenerative disorder, the pharma is now focusing on elucidating the mechanism before advancing the program.

The joint academic-industry team made the discovery while examining the interplay between the innate immune system and AD pathology. The group looked at how activation of toll-like receptor 4 (TLR4), a sensor of bacterial lipids, affects the activity of microglia, which are brain-specific innate immune cells.

The group found that monophosphoryl lipid A (MPL), a mild TLR4 agonist, can stimulate clearance of  $\beta$ -amyloid (A $\beta$ ) from the brains of mice and prevent the onset of AD symptoms.

"We have been working on priming microglia to remove A $\beta$  from the brain without triggering massive inflammation," said team co-leader Serge Rivest, professor of medicine at Laval.

"Our study shows for the first time that high doses of MPL, a mild immunopotentiator, induce beneficial activities in terms of amyloid clearance in mice," said the other co-leader, Daniel Larocque, in an e-mail to SciBX. Larocque is leader of Alzheimer's vaccine R&D at the GlaxoSmithKline Vaccines unit of GSK.

The findings are the latest piece of evidence suggesting a key role for inflammatory signaling and innate immune cell activity in AD pathogenesis. Until recently, immunotherapeutic strategies for AD have focused on mAbs that directly hit A $\beta$ , but a spate of studies have suggested that stimulated microglia can clear up A $\beta$ .<sup>2-5</sup>

## Eat it up

The team compared the effect of MPL and a much stronger adjuvant, lipopolysaccharide (LPS), in a microglia-derived cell line. MPL modestly promoted proinflammatory signaling, cytokine production and morphological changes, whereas LPS had a strong effect on all of these proinflammatory markers.

The mild inflammatory response caused by MPL proved beneficial, whereas the strong effect of LPS did not.

Among the microglial behaviors the team examined was the uptake of fluorescently labeled bacteria, which are targeted and ingested by activated microglia through a process known as phagocytosis. Treatment with MPL or LPS stimulated the uptake of fluorescent labeled bacteria into microglia, suggesting that both TLR4 agonists enhanced phagocytosis.

Activation of TLR4 in the periphery drew innate immune cells toward the edge of the brain. *In vivo*, intraperitoneal injection of MPL caused moderate levels of peripheral monocyte proliferation, activation and migration into the brain parenchyma and choroid plexus, which are brain structures associated with the blood brain barrier (BBB).

In contrast, LPS caused high levels of proliferation, activation and migration.

The surprise was that peripheral activation of TLR4 by MPL injection protected mice from AD pathology. The animals had decreased A $\beta$  accumulation in the hippocampus and increased cognitive function compared with vehicle-treated controls. LPS did not improve AD pathology.

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

## Prophylactic potential

Rivest thinks MPL could be used to slow AD progression in patients with early forms of the disease.

"Most clinical trials with vaccines or antibodies against A $\beta$  have not worked very well because they are intervening too late," he said. "Innate immune cells can recognize and clear A $\beta$ , so this could be used early in disease for prevention."

He noted that the mouse studies involved repeated high doses of MPL and that "we don't know if this dose would be tolerated in patients." He said dose-ranging studies are needed to find a minimal effective regimen in mice.

MPL, which is about 100-fold less potent than LPS in inducing an inflammatory response, is a component of the adjuvant used for Cervarix, GSK's bivalent vaccine against HPV types 16 and 18. In the mouse AD studies, MPL was delivered at a 200–300-fold higher dose per body weight than Cervarix.

Larocque said GSK is testing the effect of MPL treatment, either alone or in combination with mAbs against A $\beta$ , in mouse models of more advanced AD.

It remains unclear how MPL activates innate immune cells and how this activation translates into clearance of A $\beta$ . The biggest mystery is why peripheral treatment with MPL enhances brain clearance of A $\beta$  because neither MPL nor activated peripheral monocytes can enter the brain structures affected by AD.

"MPL does not diffuse in the brain because of the large size of the molecules. Moreover, we did not observe a significant increase in the number of peripheral monocytes going into the brain following repeated injections of MPL," said Larocque. "Therefore, there are no direct interactions of MPL and brain cells."

The idea that peripheral innate immune cells can affect AD is not without precedent. Larocque cited prior evidence that agonizing TLR9 also elicits protective effects in a mouse model of AD.<sup>6</sup>

Larocque and Rivest suspect MPL causes brain microglia and peripheral monocytes to work together to clear up accumulated A $\beta$ .

One possibility is that MPL works indirectly by triggering production of BBB-diffusible factors that communicate a proinflammatory signal from peripheral monocytes into the brain. Those signals presumably stimulate microglia to ingest A $\beta$ .

Another question is why both LPS and MPL promote proinflammatory microglial activity but only MPL ameliorates AD pathology.

Michael Heneka, professor of clinical neuroscience at the University of Bonn, said the *in vitro* phagocytosis studies suggest LPS is more effective than MPL at promoting uptake of A $\beta$  but MPL is more effective in the *in vivo* AD model.

**"Most clinical trials with vaccines or antibodies against A $\beta$  have not worked very well because they are intervening too late. Innate immune cells can recognize and clear A $\beta$ , so this could be used early in disease for prevention."**

—Serge Rivest, Laval University

“The compound they’re using is 100 times less potent than LPS, but it’s not that much less potent at inducing inflammatory cytokines *in vivo*,” he said.

Heneka noted that the findings were consistent with emerging evidence that microglia can have different levels of proinflammatory activation that exert different effects on AD pathology. In December 2012, Heneka’s team reported that blocking a variety of proinflammatory signaling pathways in microglia could ameliorate AD in mice.<sup>3,7</sup>

It is also unclear whether phagocytosis of A $\beta$  by microglia is the real reason for MPL’s effect in AD. Heneka wanted to see pulse-chase studies showing that A $\beta$  ingested by MPL-activated cells actually gets degraded rather than just building up inside of the cells.

GSK’s sole AD compound in the clinic is rilapladib. The small molecule inhibitor of lipoprotein-associated phospholipase A<sub>2</sub> (PLA<sub>2</sub>G7; PAFAH; Lp-PLA<sub>2</sub>) is in Phase II testing.

GSK has filed patents in connection to the discoveries described in the *PNAS* paper, and the licensing status of the IP is undisclosed.

Osherovich, L. *SciBX* 6 (4); doi:10.1038/scibx.2013.79  
Published online Jan. 31, 2013

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e-mail: [serge.rivest@crchul.ulaval.ca](mailto:serge.rivest@crchul.ulaval.ca)
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## COMPANIES AND INSTITUTIONS MENTIONED

**GlaxoSmithKline plc** (LSE:GSK; NYSE:GSK), London, U.K.  
**Laval University**, Quebec City, Quebec, Canada  
**University of Bonn**, Bonn, Germany



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# Evotec's growing Ivy

By Kai-Jye Lou, Staff Writer

Evotec AG is double dipping into the Ivy League, this time partnering with **Yale University** to move early stage research from the university's labs into late preclinical and IND-ready assets for third parties to license. The Yale collaboration is upstream of the biotech's 2011 deal with **Harvard University** because the projects are not predefined.

Evotec and Yale will jointly assess and develop assays, screens, models, compounds and targets for projects that are taken up under the collaboration. The partners initially will focus on metabolic, CNS, immunology and cancer projects, although they have not yet selected any programs.

"Evotec is engaged in the development and validation of new targets and technologies, and we have the assay systems and infrastructure needed to bring the innovative science at Yale forward into industry-scale drug development programs," said Evotec CSO Cord Dohrmann. "Thus far, we've established a framework agreement that gives sufficient comfort to both

parties to take forward early stage research projects. What we need to do now to move forward is to have more in-depth discussions with principal investigators at Yale on potential project ideas."

The biotech will have an option to license any technologies developed under the deal. Costs will be shared by Evotec and Yale, as well as revenues from any deals with third parties. Details were not disclosed.

## Going earlier

Dohrmann said Evotec hopes to repeat the success it had with its March 2011 collaboration with Harvard to discover diabetes therapies targeting  $\beta$  cell regeneration.

The resulting portfolio of molecules and biologics from the Harvard deal were picked up by the Janssen Pharmaceuticals Inc. unit of **Johnson & Johnson** in July 2012 for an \$8 million upfront payment to the

partners and potential milestone payments of up to \$300 million per product plus royalties.<sup>1</sup>

"The Yale alliance is part of a larger initiative at Evotec to collaborate more tightly with academia, get involved in the innovation process as early as possible and accelerate the transition of innovative science to product development," said Dohrmann. "We want to make the early stages of drug discovery more efficient and establish a system that seamlessly integrates research coming out of academia with industry-scale drug R&D."

He added that Evotec and Yale will still be involved in the R&D process after an asset is picked up by a pharma partner. "We're not just taking technologies out of academic labs and moving them over the fence to pharma," he told *SciBX*.

"We think this collaboration will increase the odds of our technologies being developed and commercialized," added Christopher Unsworth, associate director at the Office of Cooperative Research at Yale. "Evotec has an established record of doing partnerships with pharma and in putting together asset packages that could be partnered."

Evotec has ongoing drug discovery and development deals with over 10 pharmas. With the Yale deal, the biotech now has at least four collaborations with universities and research organizations (see Table 1, "Evotec's partnerships with universities and research organizations").

In its earnings report for the first 9 months of 2012, Evotec reported €16 million (\$20.4 million) in milestone, upfront and license payments from its partnerships.

"From the university side, we've been seeing in recent years that it is becoming more and more difficult to partner university-stage research assets with pharma and biotech as they've become more risk averse," Unsworth told *SciBX*. "The perspective from pharma is that university technologies are interesting, but those that you would actually be comfortable bringing in through the door are few and far between. The collaboration with Evotec puts in place a mechanism whereby our

**"We have the assay systems and infrastructure needed to bring the innovative science at Yale forward into industry-scale drug development programs."**

—Cord Dohrmann, Evotec AG

**Table 1. Evotec's partnerships with universities and research organizations.** Evotec AG's Open Innovation Alliance with Yale University is among the few drug discovery and development partnerships it has with a university or research organization. The biotech already has ongoing partnerships with more than 10 pharmas.

Source: *BioCentury Archives*

Partners	Disease area	Description	Status	Announced
Yale University	Various	Open Innovation Alliance to jointly assess and develop technologies from the university into late preclinical and IND-ready assets that could be licensed to pharma	Project selection	January 2013
Brigham and Women's Hospital/Harvard University	Renal damage/ renal disease	CureNephron collaboration to jointly discover biomarkers implicated in kidney damage and develop therapies against kidney disease	Preclinical testing	January 2012
Harvard/Howard Hughes Medical Institute/Johnson & Johnson (NYSE:JNJ)	Diabetes	CureBeta collaboration to jointly discover and develop therapies that target pancreatic $\beta$ cell regeneration	Preclinical testing; portfolio of small molecules and biologics licensed to J&J's Janssen Pharmaceuticals Inc. unit	March 2011 (Harvard/HHMI); July 2012 (J&J)
CHDI Foundation Inc.	Huntington's disease	Strategic partnership to provide the foundation with medicinal chemistry, assay development, screening and library synthesis services	Not applicable	August 2006; third deal extension in October 2012

faculty will be able to rapidly transition a concept in the lab into an early stage therapeutic package that's ready for partnering."

### Moving past the startup

Evotec and Yale think their model will be more efficient than forming new companies to commercialize technologies in academia and will reduce the time that technologies spend in early stage development.

"When forming companies around new technologies, the time spent developing the technology itself often ends up being very little relative to the time spent on other necessary activities," Dohrmann said. "For example, it usually takes at least a year to just raise an initial round of funding, and another year to get the labs and the right people in place. And at this point, the new company will usually need to seek an additional round of financing. This process of getting an industry-scale drug development program in place can take three to five years."

He said Evotec's partnership model shortcuts all of this.

"Nothing has to be built, and projects could be pursued and developed in a very efficient manner from day one," he said. "And from day one, we could already be looking for potential partners from biotech

and pharma that could complement our efforts to take the early stage technology into the clinic."

Unsworth said the immediate goals of the partnership are to start the dialog between Evotec and Yale scientists and to get projects up and running. Success will be measured by the number of projects that are started, he said.

"Of course, the key measure of success for the collaboration itself is going to be whether we are generating assets that are being licensed by pharma," Unsworth told *SciBX*.

Lou, K.-J. *SciBX* 6(4); doi:10.1038/scibx.2013.80

Published online Jan. 31, 2013

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**Evotec AG** (Xetra:EVT), Hamburg, Germany

**Harvard University**, Cambridge, Mass.

**Johnson & Johnson** (NYSE:JNJ), New Brunswick, N.J.

**Yale University**, New Haven, Conn.

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## This week in therapeutics

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

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

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
<b>Autoimmune disease</b>				
Pemphigus vulgaris (PV)	Desmoglein 1 (DSG1); DSG3	<i>In vitro</i> and mouse studies identified a DSG-binding peptide that could help treat PV. In a mouse model of a skin disease caused by autoantibodies against DSG1 and DSG3, injection or topical administration of a tandem peptide that bound DSG decreased blistering compared with no peptide treatment. In skin lesions from the mouse model, the DSG-binding peptide prevented autoantibody-induced p38 mitogen-activated protein kinase (p38 MAPK; MAPK14) activation and resulting blistering. Next steps could include optimizing the peptide for topical delivery.	Patent and licensing status unavailable	Spindler, V. <i>et al. J. Clin. Invest.</i> ; published online Jan. 9, 2013; doi:10.1172/JCI60139 <b>Contact:</b> Jens Waschke, Ludwig Maximilian University of Munich, Munich, Germany e-mail: <a href="mailto:jens.waschke@med.uni-muenchen.de">jens.waschke@med.uni-muenchen.de</a>
<b>SciBX 6(4); doi:10.1038/scibx.2013.81</b> Published online Jan. 31, 2013				
<b>Cancer</b>				
Cancer	NADP-dependent malic enzyme 1 cytosolic (ME1); NADP-dependent malic enzyme 2 mitochondrial (ME2); p53	Cell culture and mouse studies suggest inhibiting ME1 or ME2 may help treat cancer. In mice injected with a human colorectal cancer cell line, pretreatment with anti-ME1 or anti-ME2 small interfering RNA decreased tumor growth compared with pretreatment using control siRNA. Next steps include developing small molecule inhibitors of ME1 and ME2.	Patent application filed; available for licensing from the University of Pennsylvania <b>Contact:</b> Heather Steinman, Center for Technology Transfer, University of Pennsylvania, Philadelphia, Pa. e-mail: <a href="mailto:steinman@ctt.upenn.edu">steinman@ctt.upenn.edu</a>	Jiang, P. <i>et al. Nature</i> ; published online Jan. 13, 2013; doi:10.1038/nature11776 <b>Contact:</b> Xiaolu Yang, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pa. e-mail: <a href="mailto:xyang@mail.med.upenn.edu">xyang@mail.med.upenn.edu</a>
<b>SciBX 6(4); doi:10.1038/scibx.2013.82</b> Published online Jan. 31, 2013				
Cancer	<i>NGFI-A binding protein 2 (EGR1 binding protein 2; NAB2); signal transducer and activator of transcription 6 (STAT6)</i>	Two separate genetic sequencing studies identified a <i>NAB2-STAT6</i> gene fusion associated with solitary fibrous tumors (SFTs), which could provide a new therapeutic target. In the first study, whole-exome sequencing of 53 SFT samples identified <i>NAB2-STAT6</i> fusion transcripts in 29 of the samples. In a second study, whole-genome and whole-transcriptome sequencing of tumor and matched normal tissues from a patient with meningeal malignant SFT identified a <i>NAB2-STAT6</i> fusion in the tumor tissue. The fusion also was found in all of the 51 other SFT samples tested. In benign prostate cells, lentiviral-mediated overexpression of the fusion protein increased cell proliferation compared with normal expression. Next steps for both groups include testing the effects of inhibiting STAT6 or downstream signaling targets.	Findings in first study unpatented; unavailable for licensing Patent application filed for findings in second study; available for licensing	Chmielecki, J. <i>et al. Nat. Genet.</i> ; published online Jan. 13, 2013; doi:10.1038/ng.2522 <b>Contact:</b> Matthew Meyerson, Harvard Medical School, Boston, Mass. e-mail: <a href="mailto:matthew_meyerson@dfci.harvard.edu">matthew_meyerson@dfci.harvard.edu</a>  Robinson, D.R. <i>et al. Nat. Genet.</i> ; published online Jan. 13, 2013; doi:10.1038/ng.2509 <b>Contact:</b> Arul M. Chinnaiyan, University of Michigan Medical School, Ann Arbor, Mich. e-mail: <a href="mailto:arul@umich.edu">arul@umich.edu</a> <b>Contact:</b> Cristina R. Antonescu, Memorial Sloan-Kettering Cancer Center, New York, N.Y. e-mail: <a href="mailto:antonesc@mskcc.org">antonesc@mskcc.org</a>
<b>SciBX 6(4); doi:10.1038/scibx.2013.83</b> Published online Jan. 31, 2013				

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Leukemia	BCR-ABL tyrosine kinase	<p>Cell culture and mouse studies suggest the BCR-ABL tyrosine kinase inhibitor GZD824 could help treat imatinib-resistant cancer. In leukemia cell lines expressing a BCR-ABL tyrosine kinase with drug-resistant mutations, GZD824 blocked BCR-ABL tyrosine kinase activation and signaling and inhibited proliferation. In mouse models of leukemia with wild-type or mutant BCR-ABL, oral dosing of GZD824 decreased proliferation and tumor burden compared with oral dosing of vehicle. Next steps include manufacturing sufficient amounts of GZD824 under GMP conditions for clinical trials. Novartis AG's BCR-ABL tyrosine kinase inhibitor Gleevec imatinib is marketed to treat multiple cancers. Novartis' BCR-ABL tyrosine kinase inhibitor Tasigna nilotinib is marketed to treat chronic myelogenous leukemia (CML).</p> <p><b>SciBX 6(4); doi:10.1038/scibx.2013.84</b> Published online Jan. 31, 2013</p>	Patent application filed; licensed to Guangzhou Shunjian Pharma Inc.	<p>Ding, K. <i>et al. J. Med. Chem.</i>; published online Jan. 9, 2013; doi:10.1021/jm301581y <b>Contact:</b> Ke Ding, Chinese Academy of Sciences, Guangzhou, China e-mail: <a href="mailto:ding_ke@gibh.ac.cn">ding_ke@gibh.ac.cn</a></p>
Thyroid cancer	VEGF	<p>Mouse and human studies suggest Votrient pazopanib, a VEGF signaling inhibitor, could help improve the efficacy of paclitaxel in anaplastic thyroid cancer. In a mouse xenograft model of human anaplastic thyroid cancer, paclitaxel plus Votrient decreased tumor volume compared with either compound alone. In a single patient who had anaplastic thyroid cancer with lung metastases, paclitaxel plus Votrient led to durable regression of metastatic disease. Next steps could include running a clinical trial of the combination in patients with anaplastic thyroid cancer.</p> <p>GlaxoSmithKline plc markets Votrient to treat renal cell carcinoma (RCC) and advanced soft tissue sarcomas. The drug is in Phase II testing to treat thyroid cancer.</p> <p><b>SciBX 6(4); doi:10.1038/scibx.2013.85</b> Published online Jan. 31, 2013</p>	Unpatented; licensing status not applicable	<p>Isham, C.R. <i>et al. Sci. Transl. Med.</i>; published online Jan. 2, 2013; doi:10.1126/scitranslmed.3004358 <b>Contact:</b> Keith C. Bible, Mayo Clinic, Rochester, Minn. e-mail: <a href="mailto:bible.keith@mayo.edu">bible.keith@mayo.edu</a></p>
<b>Cardiovascular disease</b>				
Cardiovascular disease	POU class 1 homeobox 1 (POU1F1; PIT1)	<p>Cell culture and mouse studies suggest spironolactone could help prevent calcification of vascular and other soft tissues, which is seen in patients who have chronic kidney disease (CKD). In a mouse model of soft tissue calcification, spironolactone decreased tissue calcification and Pit1-mediated osteoinductive signaling compared with vehicle. In human aortic smooth muscle cells, spironolactone and PIT1-targeted small interfering RNA both decreased PIT1-mediated osteoinductive signaling compared with vehicle or control siRNA. Next steps include a prospective clinical trial to determine whether patients with CKD receiving spironolactone or another mineralocorticoid receptor antagonist have less tissue calcification and fewer cardiovascular complications than placebo-treated patients.</p> <p>Spironolactone is a generic mineralocorticoid receptor antagonist and is used as a diuretic in patients who have cardiovascular diseases.</p> <p><b>SciBX 6(4); doi:10.1038/scibx.2013.86</b> Published online Jan. 31, 2013</p>	Patent application filed; available for licensing	<p>Voelkl, J. <i>et al. J. Clin. Invest.</i>; published online Jan. 9, 2013; doi:10.1172/JCI64093 <b>Contact:</b> Florian Lang, University of Tuebingen, Tuebingen, Germany e-mail: <a href="mailto:florian.lang@uni-tuebingen.de">florian.lang@uni-tuebingen.de</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Endocrine/metabolic disease</b>				
Diabetes	Free fatty acid receptor 1 (FFAR1; GPR40)	<i>In vitro</i> and mouse studies identified an alkyne series of FFAR1 agonists that could help treat type 2 diabetes. In healthy mice, an alkyne-based FFAR1 agonist with polar substituents on the terminal phenyl ring was orally bioavailable and increased glucose tolerance at least as much as the marketed type 2 diabetes drug Glactiv sitagliptin. Next steps include testing the compounds in rodent models of diabetes. Connexios Life Sciences Pvt. Ltd. has FFAR1 agonists including CNX-011-67 in preclinical testing to treat diabetes. Takeda Pharmaceutical Co. Ltd.'s FFAR1 agonist, TAK-875, is in Phase III testing for the indication. Merck & Co. Inc. and Ono Pharmaceutical Co. Ltd. market the dipeptidyl peptidase-4 (DPP-4) inhibitor Glactiv sitagliptin to treat diabetes.  <b>SciBX 6(4); doi:10.1038/scibx.2013.87</b> <b>Published online Jan. 31, 2013</b>	Patent application filed covering compounds; available for licensing	Christiansen, E. <i>et al. J. Med. Chem.</i> ; published online Jan. 8, 2013; doi:10.1021/jm301470a <b>Contact:</b> Trond Ulven, University of Southern Denmark, Odense, Denmark e-mail: <a href="mailto:ulven@sdu.dk">ulven@sdu.dk</a>
<b>Genitourinary disease</b>				
Uterine fibroids	Prolactin releasing hormone receptor (PRLHR; GPR10)	Patient sample and mouse studies suggest inhibiting PRLHR could help treat uterine fibroids. In patient uterine fibroid samples, PRLHR levels were higher than those in matched normal myometrial tissues. In mice, expression of human PRLHR in myometrial tissue increased uterine size, uterine thickness and fibroid development compared with no PRLHR expression. Next steps include screening for small molecule inhibitors of PRLHR.  <b>SciBX 6(4); doi:10.1038/scibx.2013.88</b> <b>Published online Jan. 31, 2013</b>	Unpatented; licensing status not applicable	Varghese, B.V. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Jan. 2, 2013; doi:10.1073/pnas.1215759110 <b>Contact:</b> Vargheese M. Chennathukuzhi, The University of Kansas Medical Center, Kansas City, Kan. e-mail: <a href="mailto:vchennathukuzhi@kumc.edu">vchennathukuzhi@kumc.edu</a>
<b>Infectious disease</b>				
Herpes simplex virus (HSV); cytomegalovirus (CMV)	Lysine-specific demethylase 4 (KDM4; JMJD2)	Cell culture and explanted mouse ganglia studies suggest JMJD2 inhibitors could be used to treat primary HSV-1 infection and prevent reactivation. In cultured human cell lines, the JMJD2 inhibitor ML324 blocked early expression of HSV-1 genes with an IC <sub>50</sub> of about 10 μM and caused dose-dependent decreases in viral replication compared with acyclovir. In mouse ganglia infected with latent HSV-1, the inhibitor decreased viral reactivation compared with acyclovir. Ongoing work includes studying the inhibitor in a mouse model of primary HSV infection. Acyclovir is a generic used to treat HSV infection.  <b>SciBX 6(4); doi:10.1038/scibx.2013.89</b> <b>Published online Jan. 31, 2013</b>	Patented; available for licensing from the National Institute of Allergy and Infectious Diseases (NIAID) <b>Contact:</b> Ken Pekoc, Office of Technology Development, NIAID, Bethesda, Md. e-mail: <a href="mailto:kpekoc@niaid.nih.gov">kpekoc@niaid.nih.gov</a> <b>Contact:</b> Tedd Fenn, same affiliation as above e-mail: <a href="mailto:tedd.fenn@nih.gov">tedd.fenn@nih.gov</a>	Liang, Y. <i>et al. Sci. Transl. Med.</i> ; published online Jan. 9, 2013; doi:10.1126/scitranslmed.3005145 <b>Contact:</b> Thomas M. Kristie, National Institutes of Health, Bethesda, Md. e-mail: <a href="mailto:thomas_kristie@nih.gov">thomas_kristie@nih.gov</a>

## This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Influenza	Influenza A virus matrix protein 2 (M2)	<i>In vitro</i> studies identified M2 inhibitors that could help treat amantadine-resistant influenza. The S31N M2 mutation in the influenza virus results in resistance to first-generation M2 inhibitors, including amantadine. In <i>Xenopus laevis</i> oocytes expressing the S31N M2 mutant protein, amantadine derivatives with a CH <sub>2</sub> -heteroaryl group conjugated to the drug's amine group inhibited the M2 proton channel. In a cellular assay using an influenza virus expressing the S31N mutant, derivatives of the new M2 inhibitor blocked viral replication. Next steps include testing in animals.  <b>SciBX 6(4); doi:10.1038/scibx.2013.90</b> <b>Published online Jan. 31, 2013</b>	Patent application filed; licensed to InfluxMedix Inc.; available for licensing	Wang, J. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Jan. 9, 2013; doi:10.1073/pnas.1216526110 <b>Contact:</b> William F. DeGrado, University of California, San Francisco, Calif. e-mail: <a href="mailto:william.degrado@ucsf.edu">william.degrado@ucsf.edu</a> <b>Contact:</b> Yibing Wu, same affiliation as above e-mail: <a href="mailto:yibing.wu@ucsf.edu">yibing.wu@ucsf.edu</a>
<b>Inflammation</b>				
Asthma	Leptin	Mouse studies suggest anticholinergic compounds could help treat obesity-induced asthma. In two obesity-related mouse models of asthma, the anticholinergic agent tiotropium bromide, which inhibits parasympathetic signaling in airway smooth cells, prevented bronchoconstriction. Next steps include determining whether anticholinergic agents are effective against obesity-induced asthma. Boehringer Ingelheim GmbH and Pfizer Inc. market Spiriva/Respimat tiotropium to treat chronic obstructive pulmonary disease (COPD). The compound is in Phase III testing to treat asthma.  <b>SciBX 6(4); doi:10.1038/scibx.2013.91</b> <b>Published online Jan. 31, 2013</b>	Findings unpatented; unavailable for licensing	Arteaga-Solis, E. <i>et al. Cell Metab.</i> ; published online Jan. 8, 2013; doi:10.1016/j.cmet.2012.12.004 <b>Contact:</b> Gerard Karsenty, Columbia University, New York, N.Y. e-mail: <a href="mailto:gk2172@columbia.edu">gk2172@columbia.edu</a>
<b>Neurology</b>				
Addiction	Histone deacetylase 3 (HDAC3)	Mouse studies suggest HDAC3 inhibition could help treat cocaine addiction. HDAC inhibitors are known to reduce drug-seeking behaviors, but the individual HDAC responsible was unknown. In mice, an HDAC3-specific inhibitor blocked cocaine-seeking behavior. Next steps include additional studies of HDAC3 inhibition on learning, memory and drug-seeking behaviors in animals. Repligen Corp.'s HDAC3-specific inhibitor, RG2833, is in Phase I testing to treat ataxia.  <b>SciBX 6(4); doi:10.1038/scibx.2013.92</b> <b>Published online Jan. 31, 2013</b>	Inhibitor and its use patented; licensed to Repligen; available for partnering to advance application in conditions including addiction	Malvaez, M. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Jan. 7, 2013; doi:10.1073/pnas.1213364110 <b>Contact:</b> Marcelo A. Wood, University of California, Irvine, Calif. e-mail: <a href="mailto:mwood@uci.edu">mwood@uci.edu</a>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Alzheimer's disease (AD)	Toll-like receptor 4 (TLR4)	<p>Cell culture and mouse studies suggest moderately agonizing TLR4 could help treat AD. In cell culture, mouse microglia treated with the moderate TLR4 agonist monophosphoryl lipid A (MPL) had increased levels of proinflammatory activity and phagocytic behavior compared with negative controls treated with vehicle but had a decreased inflammatory response compared with positive controls treated with the strong TLR4 agonist lipopolysaccharide (LPS). In a mouse model of AD, intraperitoneal injection of MPL decreased <math>\beta</math>-amyloid (<math>A\beta</math>) plaque levels in the brain compared with injection of vehicle or LPS and induced a modest proinflammatory response and stimulated blood monocyte activity. Next steps include optimizing MPL dosing and testing the compound in other mouse models of AD.</p> <p>MPL is a component of Cervarix, a bivalent vaccine against HPV types 16 and 18 that is marketed by GlaxoSmithKline plc (<i>see Toll-erating AD, page 6</i>).</p> <p><b>SciBX 6(4); doi:10.1038/scibx.2013.93</b> Published online Jan. 31, 2013</p>	Patents on the use of MPL as an immunomodulatory agent held by GlaxoSmithKline; licensing status undisclosed	<p>Michaud, J.-P. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Jan. 15, 2013; doi:10.1073/pnas.1215165110</p> <p><b>Contact:</b> Serge Rivest, Laval University, Quebec City, Quebec, Canada e-mail: <a href="mailto:serge.rivest@crchul.ulaval.ca">serge.rivest@crchul.ulaval.ca</a></p> <p><b>Contact:</b> Daniel Larocque, GlaxoSmithKline Vaccines, Laval, Quebec, Canada e-mail: <a href="mailto:daniel.a.larocque@gsk.com">daniel.a.larocque@gsk.com</a></p>
Neurology	Hypoxia-inducible factor prolyl hydroxylase (HIF-PH; EGLN); hypoxia-inducible factor 1 $\alpha$ (HIF1A; HIF1 $\alpha$ )	<p>Human and rabbit studies suggest compounds that inhibit HIF-PH could prevent neurogenesis deficits in preterm infants. Postmortem brain tissue samples from preterm infants had lower glutamatergic neurogenesis than tissue samples from fetuses. In rabbits, preterm pups showed decreased markers of neurogenesis, hypoxia and angiogenesis compared with full-term pups. In preterm rabbit pups, the HIF-PH inhibitor dimethyloxallyl glycine rescued neurogenesis deficits, whereas vehicle did not. Next steps could include testing additional compounds that inhibit HIF-PH or activate HIF1<math>\alpha</math> in animal models of premature birth.</p> <p>Dimethyloxallyl glycine is a research reagent.</p> <p><b>SciBX 6(4); doi:10.1038/scibx.2013.94</b> Published online Jan. 31, 2013</p>	Patent and licensing status unavailable	<p>Malik, S. <i>et al. J. Neurosci.</i>; published online Jan. 9, 2013; doi:10.1523/JNEUROSCI.4445-12.2013</p> <p><b>Contact:</b> Praveen Ballabh, Westchester Medical Center, Valhalla, N.Y. e-mail: <a href="mailto:pballabh@msn.com">pballabh@msn.com</a></p>
<b>Various</b>				
Colorectal cancer; colitis	Caspase recruitment domain family member 15 (CARD15; NOD2)	<p>Mouse studies suggest intestinal microbiota from organisms with functional NOD2 could help protect against colitis and colitis-associated colorectal cancer. Wild-type mice cohoused with <i>Nod2</i>-deficient mice showed greater susceptibility to chemically induced colitis and colitis-associated colorectal cancer than wild-type mice that were not housed with <i>Nod2</i>-deficient mice. In a mouse model of chemically induced colitis, <i>Nod2</i>-deficient animals that received a fecal transplant from wild-type animals showed decreased disease histopathology compared with those that received a fecal transplant from <i>Nod2</i>-deficient animals. Next steps include screening for probiotic bacterial strains that could reduce disease susceptibility and elucidating the mechanisms through which <i>Nod2</i> deficiency disrupts the gut microbiota.</p> <p><b>SciBX 6(4); doi:10.1038/scibx.2013.95</b> Published online Jan. 31, 2013</p>	Unpatented; licensing status not applicable	<p>Couturier-Maillard, A. <i>et al. J. Clin. Invest.</i>; published online Jan. 2, 2013; doi:10.1172/JCI62236</p> <p><b>Contact:</b> Mathias Chamaillard, Pasteur Institute in Lille, Lille, France e-mail: <a href="mailto:mathias.chamaillard@inserm.fr">mathias.chamaillard@inserm.fr</a></p>

## This week in techniques

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

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

Approach	Summary	Licensing status	Publication and contact information
<b>Assays &amp; screens</b>			
DNA analysis of Pap smear samples to detect ovarian and endometrial cancer	DNA sequencing of Pap smear samples could help diagnose ovarian and endometrial cancer. In Pap smear samples isolated from patients with endometrial or ovarian tumors, targeted DNA amplification and sequencing identified tumor-associated mutations in all 24 endometrial cancer cases and 9 of 22 ovarian cancer cases. In Pap smear samples from patients with cancer and healthy controls, a multiplexed test that amplifies and sequences 50 commonly mutated genomic regions identified mutations in all 14 cancer cases and none of the 14 controls. Next steps include validating the PapGene test on a larger number of specimens to determine its specificity and sensitivity.  <b>SciBX 6(4); doi:10.1038/scibx.2013.96</b> <b>Published online Jan. 31, 2013</b>	Patent application filed; available for licensing from The Johns Hopkins University <b>Contact:</b> Keith Baker, Technology Transfer, The Johns Hopkins University, Baltimore, Md. e-mail: <a href="mailto:kbaker@jhmi.edu">kbaker@jhmi.edu</a>	Kinde, I. <i>et al. Sci. Transl. Med.</i> ; published online Jan. 9, 2013; doi:10.1126/scitranslmed.3004952 <b>Contact:</b> Bert Vogelstein, Ludwig Center for Cancer Genetics and Therapeutics, Baltimore, Md. e-mail: <a href="mailto:bertvog@gmail.com">bertvog@gmail.com</a> <b>Contact:</b> Luis A. Diaz Jr., same affiliation as above e-mail: <a href="mailto:ldiaz1@jhmi.edu">ldiaz1@jhmi.edu</a> <b>Contact:</b> Isaac Kinde, same affiliation as above e-mail: <a href="mailto:ik@jhmi.edu">ik@jhmi.edu</a>
<b>Disease models</b>			
Induced pluripotent stem (iPS) cell-derived models of familial hypertrophic cardiomyopathy (HCM)	Patient-derived iPS cell models of familial HCM could help identify new treatments for the disease. HCM is a hereditary heart disease caused by many distinct mutations that affect cardiac muscle function. iPS cell-derived cardiomyocytes were generated from fibroblasts from patients with HCM carrying a mutation in <i>myosin heavy chain 7 cardiac muscle-β</i> ( <i>MYH7</i> ). These cardiomyocytes showed disease-associated phenotypes including increased cell size and multinucleation compared with cardiomyocytes derived from healthy subjects and showed abnormal calcium signaling. In these cells, a calcium channel blocker decreased hypertrophy compared with no treatment. Ongoing work includes developing a patient-specific iPS cell disease library and screening for HCM therapeutics.  <b>SciBX 6(4); doi:10.1038/scibx.2013.97</b> <b>Published online Jan. 31, 2013</b>	Patent and licensing status undisclosed	Lan, F. <i>et al. Cell Stem Cell</i> ; published online Jan. 3, 2013; doi:10.1016/j.stem.2012.10.010 <b>Contact:</b> Joseph C. Wu, Stanford University School of Medicine, Stanford, Calif. e-mail: <a href="mailto:joewu@stanford.edu">joewu@stanford.edu</a>
Mouse model for lymphocytic choriomeningitis virus (LCMV) infection that produces hemorrhagic-like disease	A new mouse model could be used to screen for therapeutics or test vaccines against arenavirus infections that cause hemorrhagic-like disease. The arenavirus LCMV normally causes only mild infections in humans and mice, although related arenaviruses are capable of causing severe disease including hemorrhagic fever. In a strain of mice susceptible to viruses, LCMV infection caused hemorrhagic pathology that was fatal in seven of eight mice. Next steps include investigating the host-virus interactions that contribute to hemorrhagic symptoms in the mouse model.  <b>SciBX 6(4); doi:10.1038/scibx.2013.98</b> <b>Published online Jan. 31, 2013</b>	Mouse model patented; available for licensing	Schnell, F.J. <i>et al. PLoS Pathog.</i> ; published online Dec. 27, 2012; doi:10.1371/journal.ppat.1003073 <b>Contact:</b> Dan V. Mourich, Sarepta Therapeutics Inc., Cambridge, Mass. e-mail: <a href="mailto:dmourich@sareptatherapeutics.com">dmourich@sareptatherapeutics.com</a>

## This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Transgenic miniature pig model for hypercholesterolemia and atherosclerosis	A transgenic miniature pig model for hypercholesterolemia and atherosclerosis could aid the development of imaging technologies, intravascular devices and therapeutics. Yucatan miniature pigs were engineered to express a gain-of-function mutant of human <i>proprotein convertase subtilisin/kexin type 9</i> (PCSK9) in the liver, which causes hypercholesterolemia and accelerates atherosclerosis in humans. Transgenic pigs fed a high-fat, high-cholesterol diet had severe hypercholesterolemia and key pathophysiological features of human atherosclerosis, and faster development of atherosclerotic lesions compared with wild-type pigs fed the same diet. Ongoing studies include validating some of the imaging techniques used for clinical atherosclerosis studies.	Patent application filed by Aarhus University; licensed to PixieGene A/S	Al-Mashhadi, R.H. <i>et al. Sci. Transl. Med.</i> ; published online Jan. 2, 2013; doi:10.1126/scitranslmed.3004853 <b>Contact:</b> Jacob F. Bentzon, Aarhus University Hospital, Aarhus, Denmark e-mail: <a href="mailto:jben@ki.au.dk">jben@ki.au.dk</a>
<b>Drug platforms</b>			
Antigen-specific T cells generated from induced pluripotent stem (iPS) cells derived for adoptive immunotherapy	Two separate groups showed that iPS cells derived from mature CD8 <sup>+</sup> T cells can be differentiated into antigen-specific T cells that may be useful for overcoming T cell exhaustion during adoptive immunotherapy. Mature CD8 <sup>+</sup> T cells were reprogrammed into iPS cells and then differentiated into T cells with the same functionality and antigen specificity as the original CD8 <sup>+</sup> T cells. One group used mature CD8 <sup>+</sup> T cells from an HIV-infected patient to generate T cells that showed antigen-specific activity against HIV p27 (nef). The other group used CD8 <sup>+</sup> T cells from a patient with melanoma to generate T cells that showed antigen-specific activity against melan-A (MLANA; MART1). Next steps for both groups include testing the regenerated human T cells in animal models.	Patent application filed for findings in first study; available for licensing from Megakaryon Corp. <b>Contact:</b> Genjiro Miwa, Megakaryon Corp., Tokyo, Japan phone: 81-3-3536-6000 e-mail: <a href="mailto:gmiwa@megakaryon.com">gmiwa@megakaryon.com</a>  Findings in second study unpatented; licensing status not applicable	Nishimura, T. <i>et al. Cell Stem Cell</i> ; published online Jan. 3, 2013; doi:10.1016/j.stem.2012.11.002 <b>Contact:</b> Hiromitsu Nakauchi, The University of Tokyo, Tokyo, Japan e-mail: <a href="mailto:nakauchi@ims.u-tokyo.ac.jp">nakauchi@ims.u-tokyo.ac.jp</a>  Vizcardo, R. <i>et al. Cell Stem Cell</i> ; published online Jan. 3, 2013; doi:10.1016/j.stem.2012.12.006 <b>Contact:</b> Hiroshi Kawamoto, RIKEN Research Center for Allergy and Immunology, Yokohama, Japan e-mail: <a href="mailto:kawamoto@rcai.riken.jp">kawamoto@rcai.riken.jp</a>
Clustered, regularly interspaced short palindromic repeats (CRISPR) RNA editing system to modify mammalian DNA	A CRISPR-derived genome editing system could be used to modify mammalian DNA. CRISPR is a bacterial immune response system that uses host-expressed nucleases and RNA repeats to cleave foreign DNA. To adapt this system to cleave and edit mammalian genomes, two separate teams designed a DNA vector that expressed a bacteria-derived CRISPR-associated nuclease together with guide RNAs that contained CRISPR features and homology similar to mammalian genes. The system was used to induce site-specific insertions and deletions in multiple genomic loci in cultured mouse and human cells. Next steps include characterizing and optimizing the specificity of the approach (see <i>CRISPR genome editing</i> , page 1).	Patent applications filed for findings in both papers; licensing status undisclosed	Cong, L. <i>et al. Science</i> ; published online Jan. 3, 2013; doi:10.1126/science.1231143 <b>Contact:</b> Feng Zhang, Broad Institute of MIT and Harvard, Cambridge, Mass. e-mail: <a href="mailto:zhang_f@mit.edu">zhang_f@mit.edu</a>  Mali, P. <i>et al. Science</i> ; published online Jan. 3, 2013; doi:10.1126/science.1232033 <b>Contact:</b> George M. Church, Harvard Medical School, Boston, Mass. e-mail: <a href="mailto:gchurch@genetics.med.harvard.edu">gchurch@genetics.med.harvard.edu</a>
Sortase-mediated modification of a targeted mAb to improve antigen delivery and presentation	Sortase-mediated modification of therapeutic mAbs could be useful for developing vaccines and therapeutics to treat viral infections. Sortase A was used to generate conjugate molecules consisting of 1 out of 19 different peptide epitopes of a mouse $\gamma$ -herpes virus (MHV-68) linked to a mAb against lymphocyte antigen 75 (LY75; DEC205). In mice, immunization with the conjugated mAb prior to infection with MHV-68 led to a 10-fold decrease of viral titers compared with immunization using free peptide epitopes. Next steps could include using the method to modify other antibody-based vaccines.	Patent pending covering use of sortase enzymes for protein modification; available for licensing	Swee, L.K. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Jan. 7, 2013; doi:10.1073/pnas.1214994110 <b>Contact:</b> Hidde L. Ploegh, Whitehead Institute for Biomedical Research and Massachusetts Institute of Technology, Cambridge, Mass. e-mail: <a href="mailto:ploegh@wi.mit.edu">ploegh@wi.mit.edu</a>

## This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Structure-based design of peptide inhibitors and activators of ubiquitin enzymes	<i>In vitro</i> studies identified a strategy to develop peptide inhibitors and activators of ubiquitin pathway enzymes that could help treat various diseases. The crystal structures of ubiquitin with deubiquitinases or ligases were used to identify ubiquitin variants that could act as competitive inhibitors, allosteric inhibitors or activators of the enzymes. In human embryonic kidney cells, a ubiquitin variant with high binding affinity for the ubiquitin-specific peptidase 21 (USP21) blocked deubiquitination. Next steps include developing therapeutic delivery methods for the proteins.  <b>SciBX 6(4); doi:10.1038/scibx.2013.103</b> <b>Published online Jan. 31, 2013</b>	Provisional patent application filed covering inhibitors and activators of deubiquitinases and ubiquitin ligases; available for licensing	Ernst, A. <i>et al. Science</i> ; published online Jan. 3, 2013; doi:10.1126/science.1230161 <b>Contact:</b> Sachdev S. Sidhu, University of Toronto, Toronto, Ontario, Canada e-mail: <a href="mailto:sachdev.sidhu@utoronto.ca">sachdev.sidhu@utoronto.ca</a>
Terminally differentiated stem cell-derived cells with negligible immunogenicity	Terminally differentiated stem cell-derived cells show negligible immunogenicity, suggesting they could be useful for transplant and cell therapy applications. Terminally differentiated mouse skin and bone marrow cells derived from 10 different induced pluripotent stem (iPS) cell and 7 embryonic stem cell (ESC) lines had limited or no immunogenicity after transplantation into immunocompetent mice. Next steps include conducting additional immunogenicity studies on ESC- and iPS cell-derived cells.  <b>SciBX 6(4); doi:10.1038/scibx.2013.104</b> <b>Published online Jan. 31, 2013</b>	Unpatented; licensing status not applicable	Araki, R. <i>et al. Nature</i> ; published online Jan. 9, 2013; doi:10.1038/nature11807 <b>Contact:</b> Masumi Abe, National Institute of Radiological Sciences, Chiba, Japan e-mail: <a href="mailto:abemasum@nirs.go.jp">abemasum@nirs.go.jp</a>



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