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# Macrocycles by the trillions

By *Joanne Kotz, Senior Editor*

Japanese researchers have developed a method for creating large libraries of N-methylated peptide macrocycles,<sup>1</sup> a class of molecules that are sized between small molecules and biologics and have the potential to combine the pharmacological versatility of the former and the therapeutic specificity of the latter. **PeptiDream Inc.** has exclusively licensed the technology and entered collaborations with six pharma.

Small molecules are typically less than 500 Da in size, whereas biologics start at approximately 5,000 Da and cover a range of one to two orders of magnitude. Macrocycles, a structure frequently found in natural products, range in size from 500–2,000 Da.

Due to their structural rigidity and high target affinity, the hope has been for these compounds to be able to modulate challenging targets typically reserved for biologics, such as protein-protein interactions, while retaining the advantages of small molecules—cell permeability and oral bioavailability.<sup>2</sup>

One challenge has been generating sufficiently large and diverse libraries of synthetic macrocycles to identify drug leads. To overcome this hurdle, a team led by Hiroaki Suga has now merged two technologies—one developed by Suga in 2008 to incorporate non-natural amino acids into large libraries of peptide macrocycles<sup>3</sup> and the other developed independently in 1997 by Jack Szostak and Hiroshi Yanagawa for displaying natural peptide and protein libraries on mRNA.<sup>4,5</sup>

Suga is a professor in the Department of Chemistry at **The University of Tokyo**. Yanagawa is a professor at **Keio University**. Szostak is a professor at **Harvard Medical School** and **Massachusetts General Hospital**.

The integrated method, called RaPID, starts from a cDNA library encoding non-natural peptides of 8–15 residues. The peptides contain a random mixture of 12 natural amino acids and 4 N-methylated (non-natural) amino acids. Non-natural amino acids can increase the types of chemical groups in peptides beyond what is offered by natural amino acids. In particular, N-methylated amino acids increase a peptide's cell permeability.

The cDNA library is then transcribed to an mRNA library and linked to a second mRNA oligonucleotide that ends in a puromycin residue. The residue causes the growing peptide chain to be covalently connected to and displayed by its own mRNA template. *In vitro* translation of these mRNAs resulted in a library of about 1,012 N-methylated peptide macrocycles displayed on mRNA (see **Figure 1**, “Making macrocycles RaPID-ly”).

As proof of principle, the Japanese team used the library to select for macrocycles that bound the ligase domain of ubiquitin protein ligase




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E3A (UBE3A; E6AP). Identifying potent and selective inhibitors that interfere with the protein-protein interactions made by ubiquitin ligases has proven challenging. The team identified three distinct macrocycles that each bound to E6AP with low or subnanomolar affinity.

Results were published in *Chemistry & Biology*.

“This is a very clever technology. Synthetic tRNAs to introduce new amino acids in combination with mRNA allows you to create vast libraries of novel peptides,” said Nick Terrett, CSO of macrocycle company **Ensemble Therapeutics Corp.**

To isolate drugs with more complex function, such as disrupting protein-protein interactions, researchers are turning to larger molecules like peptides. “The real value of [this] work is that extremely large and diverse libraries can be produced and used in affinity-based selections, which greatly increases the likelihood that highly potent protein-protein interaction inhibitors can be isolated. These arguments also apply to cases where highly specific drugs are needed, for example, when attempting to inhibit one member in a family of closely related proteins,” said Douglas Treco, president, CEO and cofounder of **Ra Pharmaceuticals Inc.**

Ra Pharma is using *in vitro* display technologies to produce libraries of cyclic peptidomimetics to identify therapeutics in a variety of diseases. The company was cofounded by Szostak.

“The affinities described for the ubiquitin ligase are impressive. It will be key to demonstrate that high-affinity binders can be isolated for a broad range of targets,” said Christian Heinis, assistant professor in the Institute of Chemical Sciences and Engineering at the **Swiss Federal Institute of Technology Lausanne**. “I like the RaPID approach very much since it allows the facile incorporation of non-natural amino acids.”

Heinis is a cofounder of **Bicycle Therapeutics Ltd.**, a company developing cyclic peptide therapeutics using phage display.

However, Terrett said the molecules generated by RaPID could be too big to become drug leads. “The molecular weight is too high,” as the macrocycles described in the paper were around 2,000 Da, he said. “My guess would be that cell membrane permeability and the *in vivo* bioavailability would be low.”

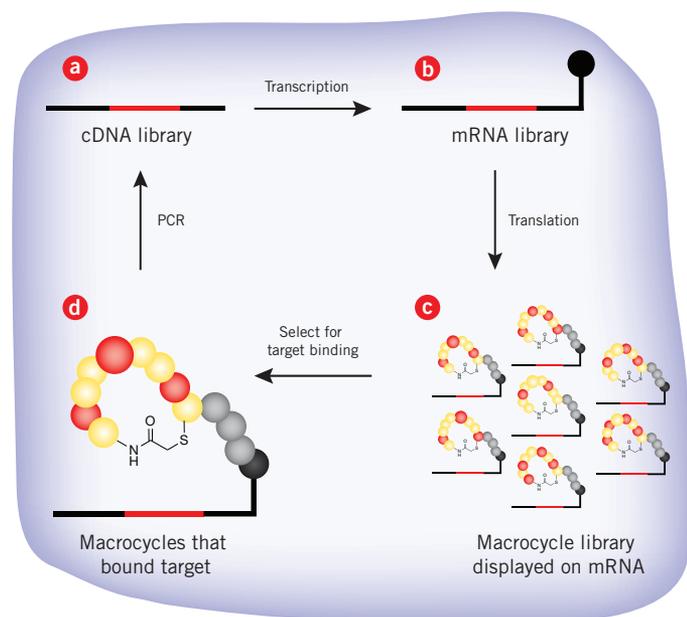
Ensemble’s macrocycles, which Terrett said are typically cell permeable, are in the range of 600–1,000 Da. For example, Ensemble’s macrocyclic IL-17 antagonists are 700 Da and have low nanomolar potency. The compounds are in preclinical development for autoimmune and inflammatory diseases.

Ensemble synthesizes macrocycles using a process called DNA-programmed chemistry that relies on DNA as a template but generates macrocycles using synthetic rather than peptide building blocks. “We are also using a purely synthetic process, so there is a lot of chemistry we can incorporate,” noted Terrett.

According to Terrett, Ensemble has generated a cumulative library of about 4 million macrocycles. He said Ensemble frequently has been able to find compounds with “micromolar to nanomolar potency against previously undruggable targets.”

**“This is a very clever technology. Synthetic tRNAs to introduce new amino acids in combination with mRNA allows you to create vast libraries of novel peptides.”**

—Nick Terrett,  
**Ensemble Therapeutics Corp.**



**Figure 1. Making macrocycles RaPID-ly.** A team from **The University of Tokyo** has developed a method called RaPID for generating libraries of trillions of N-methylated peptide macrocycles displayed on mRNA. First, a cDNA library is generated (red bar) that encodes 8–15 residue-long peptides containing a mixture of natural and non-natural amino acids [a]. The cDNA library is transcribed to an mRNA library and subsequently linked to a second mRNA oligonucleotide that terminates in a puromycin residue (black circle) [b]. When the mRNA library is translated, the puromycin causes the growing peptide chain to remain linked to its mRNA template. The displayed macrocyclic peptides contain a linker region (gray), natural amino acids (yellow) and N-methylated amino acids (red) [c]. After selecting for macrocycles that bind to a desired target, binding molecules can be identified and/or amplified for a second round of selection by PCR of the linked mRNA template [d].

Ensemble recently extended their partnership with **Bristol-Myers Squibb Co.** to develop macrocycles against undisclosed targets.<sup>6</sup>

Terrett suggested adapting the RaPID technology “to make compounds that are smaller from the get-go. If you could make smaller cyclic peptides, you’d be at a better starting point for drug discovery. The compromise would be lower structural diversity. It’s a trade-off.”

### PeptiDreaming

PeptiDream, which was founded by Suga, is identifying macrocyclic drug leads using technology that is similar to RaPID but with a different, undisclosed display method.

“We developed an alternative to mRNA display that is simplified,” said CSO Patrick Reid.

He said PeptiDream has identified hits with nanomolar to subnanomolar potency against enzymes and protein-protein interactions. “Macrocyclic peptides seem to be able to target most anything— $\alpha$ -sheets,  $\alpha$ -helices, random coils—we have found peptides that have bound to them all.”

Reid disagreed with Terrett that size was the critical factor governing cell permeability. He said PeptiDream’s technology can make cell-permeable macrocycles of 800–2,000 Da. “In the studies that we have done, size doesn’t seem to matter that much,” he said.

Reid added that hydrophobicity and the 3D structure of the macrocycle seem to be more important than size in determining cell permeability.

PeptiDream’s most advanced program is a macrocycle that blocks influenza A virus hemagglutinin, an extracellular target, and prevents the virus from penetrating cells. The project is being funded by the Japanese government.

Reid said about half of the company’s targets are extracellular and the other half are intracellular. PeptiDream’s most advanced program against an intracellular target is an undisclosed protein-protein interaction being pursued as part of a pharma collaboration. PeptiDream and its undisclosed partner hope to start mouse studies in the next few months, according to Reid.

The next steps for Suga include designing new libraries with different scaffolds and developing new selection techniques, with an eye toward increasing cell permeability. “We need to look at the structural requirements for cell permeability. That is really the major direction that we are taking right now,” he said.

Suga told *SciBX* that the University of Tokyo has received a patent covering technology for generating the engineered tRNAs that introduce non-natural amino acids into peptides. The university has filed for patents covering both the use of the engineered tRNAs for *in vitro* translation and the integrated RaPID method. The university also has filed for patents covering technologies for introducing N-methyl peptides, cyclizing the peptides and for other modifications. All have been exclusively licensed to PeptiDream.

Reid said the company has collaborations with **AstraZeneca plc’s MedImmune LLC** subsidiary, two undisclosed Japanese pharmas and three undisclosed non-Japanese pharmas.

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### COMPANIES AND INSTITUTIONS MENTIONED

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# Visum sees the light

By Chris Cain, Staff Writer

Researchers at Case Western Reserve University have identified 16 approved drugs that could help treat Stargardt's disease and dry age-related macular degeneration by preventing the toxic buildup of visual cycle byproducts.<sup>1</sup> **Visum Therapeutics Inc.** has licensed the findings and has variants of the drugs in preclinical development.

The visual cycle is a metabolic process in the retina required for vision, but aberrant accumulation of toxic byproducts produced by the cycle can cause cellular damage. Stargardt's disease is a heritable genetic disorder of the visual cycle that affects about 1 in 10,000 people. Patients are highly susceptible to light and glare and develop severely impaired vision and blindness as they age.

The orphan disease is primarily caused by mutations in *ATP-binding cassette sub-family A member 4* (*ABCA4*; *ABCR*), which is expressed in the eye and is required to properly localize *N*-retinylidene phosphatidylethanolamine (*N*-ret-PE), an intermediate of the visual cycle. When *N*-ret-PE is not localized properly in the eye, it can react with free all-*trans*-retinal, one of the metabolites of the visual cycle, to form *N*-retinylidene-*N*-retinylethanolamine (A2E). A2E is a toxic compound that induces apoptosis in retinal pigment epithelial cells. High levels of A2E also are associated with the development of dry age-related macular degeneration (AMD).

A team at Case Western hypothesized that lowering the level of free all-*trans*-retinal in the eye could decrease the buildup of A2E and improve visual function.

"The fundamental idea is to temporarily lower levels of all-*trans*-retinal," said William Harte, CEO of Visum. "You need all-*trans*-retinal to generate 11-*cis*-retinal for normal vision, but what we are doing is temporarily sequestering any excess all-*trans*-retinal so it does not generate toxic byproducts."

To temporarily lower all-*trans*-retinal levels, the team reasoned that drugs containing a primary amine group would chemically react with and reversibly convert free all-*trans*-retinal into an inactive form.

"We narrowed it down to 24 compounds with primary amine groups that could be applied at a relatively high dose and were likely to penetrate the CNS," said Krzysztof Palczewski, chair of the Department of Pharmacology at Case Western and CSO of Visum.

To test the compounds, the group used a mouse model of Stargardt's disease that is driven in part by the deletion of *Abca4*. In the model, which was previously developed by Palczewski's lab, 16 of 24 drugs tested significantly lowered retinal degeneration compared with vehicle controls.

The researchers also suggested that the primary targets of the drugs were not responsible for the protective effects on the retina. In one study, for example, the researchers looked at *R*- and *S*-stereoisomers of Lyrica pregabalin, a  $\alpha$ -aminobutyric acid receptor (GABAR) agonist from **Pfizer Inc.** that is approved to treat pain and other neurological

indications. The isomers had similar efficacy in the mouse model, even though the *R*-stereoisomer has much weaker affinity for GABAR.

To nail down how the drugs were working *in vivo*, Palczewski performed mass spectrometry analysis of all-*trans*-retinal and related retinoids extracted from the eyes of treated animals. Specific chemical signatures in the eyes indicated a primary amine group had reacted with all-*trans*-retinal and converted it to an inactive form that could no longer generate toxic byproducts.

Results were published in *Nature Chemical Biology*. Palczewski was the paper's senior author.

"This is a very elegant approach to preventing the accumulation of A2E," said Jay Lichter, a partner at **Avalon Ventures** and president and CEO of **ReVision Therapeutics Inc.** "Palczewski has shown you can administer a compound and get it to the eye in sufficient quantities to prevent A2E accumulation, and that is a significant breakthrough. An added benefit of this approach is that it is not targeting the visual cycle, but a toxic byproduct. Inhibition of the visual cycle can often cause side effects including a delay in dark adaptation."

ReVision's fenretinide (RT-101) has completed Phase IIb testing in patients with geographic atrophy, an advanced form of dry AMD. The compound acts in part as a visual cycle modulator that inhibits retinol binding

protein, which leads to decreased levels of retinol in the eye and lower A2E production. Lichter added that RV-101 also has anti-inflammatory properties because it inhibits the production of ceramide.

Lichter said the company decided not to run a Phase III trial in dry AMD because the cost was prohibitive. Unrelated to the current paper, ReVision plans to start a short Phase II trial in patients with Stargardt's disease this summer.

Another company targeting the visual cycle is **Acucela Inc.** ACU-4429, a small molecule that targets retinal pigment epithelium-specific protein 65 kDa (RPE65), another component of the visual cycle, is in Phase II testing with partner **Otsuka Pharmaceutical Co. Ltd.** to treat dry AMD. Acucela declined to comment. Palczewski was formerly on the company's scientific advisory board.

## Seeing the money

Harte and Palczewski cofounded Visum, which has exclusively licensed a patent from Case Western covering the findings. The company is fundraising and conducting additional preclinical work on a lead candidate to treat Stargardt's disease.

"The challenge with using these FDA-approved drugs is removing the 'on mechanism' approved pharmacological effect of the agent. We were able to modify one of the drugs, demonstrate retinal protection in this model and are now performing IND-enabling studies," said Harte. He would not disclose which drug is being modified.

Whichever drug is chosen as a starting point, Lichter said the key will be developing a distinct new chemical entity.

**"The challenge with using these FDA-approved drugs is removing the 'on mechanism' approved pharmacological effect of the agent. We were able to modify one of the drugs, demonstrate retinal protection in this model and are now performing IND-enabling studies."**

— William Harte,  
Visum Therapeutics Inc.

(Continues on p. 5)

# Unleashing NK cells

By Lev Osherovich, Senior Writer

A French-led team has devised a new strategy to increase the activity of NK cells, a type of innate immune cell that combats infections and tumors. The approach involves antagonizing an NK cell surface protein called NCR1 that ordinarily holds the NK cells in check.<sup>1</sup> The findings offer a new entry point into modulating innate immunity, and **Innate Pharma S.A.** is collaborating with the team to explore potential therapeutic applications.

NK cells “distinguish normal cells from target cells infected by microbes or tumor cells using two types of receptors—activating and inhibitory ones,” said team co-leader Eric Vivier. “Normal cells express a lot of inhibitory molecules that engage NK cells. The presence or absence of these inhibitory signals governs whether the NK cells kill or spare a potential target cell.”

Vivier is director of the **Immunology Center of Marseille-Luminy**, professor of immunology at **Aix-Marseille University’s** medical school and cofounder of Innate Pharma.

The French-led team found that NCR1 (natural cytotoxicity triggering receptor 1; NKP46; CD335) is the likely receptor for such an inhibitory signal. Antagonizing NCR1 increased the innate immune response against a range of threats including tumor cells and the murine version of cytomegalovirus (CMV), a model viral pathogen.

## Mutant mouse

In a genetic screen for mouse mutants with unusual innate immune responses to CMV, the French team found a mouse strain with hyperactive innate immunity. When exposed to murine CMV, the animal had more robust cytokine production and better survival than similarly treated wild-type controls. The team traced the phenotype to a loss-of-function mutation in *Ncr1*.

(Continued from “**Visum sees the light**,” p. 4)

“It would be a serious uphill battle to get patent protection that is meaningful,” he said. “Say you get a method-of-use patent for using pregabalin to treat Stargardt’s disease. That’s great, but once the drug becomes generic, how are you going to make any money?” Lyrica loses patent protection in 2018.

Harte said Visum has a pending patent that broadly covers the use of primary amine-containing compounds to treat ophthalmic disease.

Visum plans to measure A2E levels as a biomarker of disease progression during the clinical development of its lead candidate. The company noted that A2E is a highly fluorescent molecule and can be noninvasively measured.

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The *Ncr1*-mutant mice appeared to have an otherwise normal immune system.

In cell culture, NK cells derived from mice with the *Ncr1* mutation also had a more vigorous response than wild-type NK cells against cocultured tumor cells and cells infected with an intracellular bacterium expressing a model antigen.

Vivier suspected pharmacological inactivation of *Ncr1* could produce similar results. To find out, his team made a murine mAb against *Ncr1*, injected it into mice and extracted NK cells. Indeed, the NK cells were more active against tumor cells in culture than NK cells from mice treated with a control mAb.

“We asked whether we could recapitulate these genetic effects using a mAb directed against NCR1,” said Vivier. “The good news is that we can recapitulate the mutations. We see that NK cell activity is boosted by this antibody.”

Results were reported in *Science*. The team was co-led by Sophie Ugolini, senior researcher at the **Institut National de la Santé et de la Recherche Médicale (INSERM)**. INSERM has filed patents covering the *Ncr1*-targeting mAb and is negotiating a license with Innate Pharma.

**“Normal cells express a lot of inhibitory molecules that engage NK cells. The presence or absence of these inhibitory signals governs whether the NK cells kill or spare a potential target cell.”**  
—Eric Vivier, Aix-Marseille University

## Natural utility

The findings are unexpected because NCR1 previously was thought to be a stimulatory receptor. Now, the receptor appears to have different effects on NK cell activity depending on when and where it is targeted.

“NCR1 is one of the main activating receptors of NK cells. Thus, the results presented in the paper are sort of surprising,” said Innate Pharma CSO and cofounder François Romagné. “Why would blocking an activating receptor cause gain of function of NK cells—this is counterintuitive.”

The answer, he said, appears to be in the timing of NCR1’s activity during the development of NK cells. He said the lack of NCR1 activity in Vivier’s mutant mice and in animals treated with anti-NCR1 mAbs causes NK cells to develop with a lower threshold for activation, leading to a hypervigilant innate immune response.

(Continues on p. 6)

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## COMPANIES AND INSTITUTIONS MENTIONED

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**Otsuka Pharmaceutical Co. Ltd.**, Tokyo, Japan  
**Pfizer Inc.** (NYSE:PFE), New York, N.Y.  
**ReVision Therapeutics Inc.**, San Diego, Calif.  
**Visum Therapeutics Inc.**, Cleveland, Ohio

However, it is possible that blocking NCR1 in mature NK cells could prevent their activation, said Romagné. Vivier's mAb thus "would not be very easy to use as a therapeutic agent."

Instead, he said the mAbs could be used prophylactically to prime a more potent innate immune response in patients undergoing hematopoietic cell reconstitution following bone marrow transplantation. He noted that CMV infections are a significant concern in such patients.

Innate Pharma has a panel of mAbs that block various members of the killer cell immunoglobulin-like receptor (KIR) family, which are NK cell proteins that play a purely inhibitory role.

Last year, Innate Pharma partnered with **Bristol-Myers Squibb Co.** to co-develop the biotech's lead compound, the KIR-targeting mAb IPH2101, which is in Phase I testing for acute myelogenous leukemia (AML).

Vivier is open about which indications the approach will be most useful in treating. He said his team is now testing the effect of antagonizing NCR1 in influenza, cancer and inflammation.

Another open question is what the natural ligand for NCR1 is and whether that protein can be targeted to achieve effects similar to those caused by blocking NCR1.

Vincent Serra, CEO, CSO and cofounder of **Wittycell S.A.S.**, said that although antagonizing NCR1 could improve the innate immune response against a variety of pathogens and tumors, having a hyperactive innate immune system "could degrade the specificity of the acquired immune response."

He cited evidence in Vivier's paper that NCR1-mutant mice had lower T cell responses compared with wild-type animals. These data,

said Serra, are in line with evidence that chronic activation of innate immunity leads to anergic or blunted acquired immune response. This occurs because T cells, which are normally activated by brief bursts of innate immune activity, become insensitive to constant stimulation by NK cells.

Serra said targeting NCR1 could be most useful in patients with HIV who are unable to mount an effective acquired immune cell response against pathogens but still have working innate immune systems. He also said the receptor could be a good target for vaccine adjuvants.

Wittycell is developing glycolipid vaccine adjuvants that stimulate NK T cells, which resemble NK cells. WTCc, the company's most advanced adjuvant, is in Phase I testing for cancer and viral indications.

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**Wittycell S.A.S.**, Reims, France

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# Stemming the tide of HeLa cells

By **Tim Fulmer**, Senior Writer

Max Planck cell biologists have challenged the scientific research community to replace one of the most entrenched tools of preclinical studies—the HeLa cell line—with stem cell lines.<sup>1</sup> The latter, they contend, more accurately reflect the underlying molecular complexity of healthy and diseased tissue, but technical and economic considerations may slow stem cells' adoption by the wider research community.

Stem cells have not been widely adopted as basic research tools because they are far more complex to grow and maintain than HeLa and many other cell lines. As a result, much of the translational research with stem cells has focused on their therapeutic applications, not on their use as *in vitro* screens and models.

HeLa cells were derived from a postmortem cervical cancer biopsy obtained in 1951 at **The Johns Hopkins University** from a woman named Henrietta Lacks and were the first immortalized human cell line ever created.<sup>2</sup>

“Unfortunately, it has remained unclear how well, if at all, the HeLa cell actually reflects the cellular diversity we know exists at the tissue level. For that reason we are proposing that new and better *in vitro* models of cellular diversity are needed for studying healthy and diseased tissue” because tissues are a mosaic of cell types with varying functional machineries and architectures that cannot be adequately modeled by a single cell line, said Kai Simons, a group leader at the **Max Planck Institute of Molecular Cell Biology and Genetics**.

In a commentary in *Nature*, Simons and Anthony Hyman, director at the same institute, wrote that HeLa cells and other immortalized cell lines “are completely inadequate for addressing the next big topic in cell biology: cellular diversity in normal tissue.”

The authors suggested researchers should either “use embryonic stem [ES] cells derived from mice or other model organisms, or convert differentiated cells into precursors using a cocktail of transcription factors,” creating induced pluripotent stem (iPS) cells.

“As the stem cell field moves forward, and our knowledge of stem cell biology improves, it only makes sense that stem cells—ES or iPS cells—would replace immortalized cell lines as the basic cell type biologists rely on in their preclinical research,” Hyman told *SciBX*. “As the fundamental cell underlying biological development, the stem cell should serve as the platform of any *in vitro* research project investigating cellular processes in health and disease.”

Simons and Hyman also proposed that cell and developmental biologists should generate “a large library or panel of stem cell–derived cell lines that better represent the various cell types of the body than immortalized cell lines. Such a panel would be ideal for studying cellular processes unique to each cell type, as well as useful for *in vitro* disease models and drug screens.”

“If developed in combination with a publicly available set of protocols and reagents, it should also be possible to standardize the library across the labs of cell biologists throughout the world,” said Hyman.

Hyman said organizations like the **NIH** need to provide additional funding to academic labs to encourage training in the growth, maintenance and differentiation of stem cell lines, as well as help oversee the development of the stem cell library. He declined to speculate on what would be a suitable sum of money for the endeavor.

## How to build a library

“The *Nature* commentary almost reads like part of our company’s original business plan,” said Chris Parker, VP and chief commercial officer of **Cellular Dynamics International Inc.** The company’s iCell platform differentiates iPS cells into highly homogenous, functional cell types for screening and optimization of compounds as well as *in vitro* modeling.

The company markets iCell cardiomyocytes, endothelial cells, neurons and hepatocytes, and has iCell hematopoietic cells in development.

“We produce our own cells on an industrialized scale, which removes perhaps the only remaining advantage of immortalized cells—that they can be produced in massive quantities,” said Parker.

“Our small company has commercialized four iPS-derived cell types in about four years. Much time and expense go into confirming that the derived cells have definitive functional and morphological characteristics that separate them from other cell types. Equally important is showing that the cells can be matured into a homogeneous adult phenotype, making them suitable for a drug discovery platform. Considering there are about 200 cell types in the body, you can see that a truly comprehensive library would be quite an undertaking,” continued Parker. “Obviously, not every one of those cell types is important to drug developers, so prioritizing helps make the task more manageable.”

Another company, **iPierian Inc.**, is developing a platform that generates iPS cells from patient-derived fibroblasts, which ensures that genetic variation unique to the patient will be reflected in the cell types differentiated from the iPS cells.

“The better your preclinical screens and models reflect the different cell types in diseased tissue, the easier you can understand how compounds affect phenotypes and the earlier you can weed out suboptimal compounds, thus increasing the efficiency of your drug development program. That makes an iPS cell–based screen much more powerful than a screen based on HeLa cells,” said iPierian president and CEO Nancy Stagliano.

“Our goal is to use those cells to create a disease-in-a-dish model that is a useful drug discovery platform for neurological diseases such as Alzheimer’s disease, amyotrophic lateral sclerosis and spinal muscular atrophy,” Stagliano told *SciBX*. “We believe an iPS cell–based platform is essential for incorporating the patient’s genetic background, which would otherwise be missing if we used HeLa cells as the basis for our *in vitro* studies.”

## New and improved immortality

Stem and IPS cells are not the only candidates for replacing HeLa cells in preclinical research.

**“The stem cell should serve as the platform of any *in vitro* research project investigating cellular processes in health and disease.”**

—Anthony Hyman,  
**Max Planck Institute of Molecular Cell Biology and Genetics**

“The authors’ essential point—that one needs to complement studies using immortal cancer lines with studies examining normal cells—is completely valid. However, they are way too global in their insistence on only using ES or iPS cells,” said Woodring Wright.

Wright, a professor of genetics and cell biology at **The University of Texas Southwestern Medical Center**, has shown that normal human cells, which undergo senescence in culture, can be immortalized by engineering them to express the telomerase protein.<sup>3</sup> The resulting cell line shows most of the functional characteristics of the parent cell, making it a much better tool for *in vitro* research than a HeLa cell line.

In some instances, telomerase-immortalized cell lines are easier to produce than stem cell–derived lines because the immortalization method can be applied to any cell along the developmental pathway and does not require starting from an ES or iPS cell, Wright said.

“For example, if you want to generate bronchial epithelial cells, telomerase-immortalized airway stem cells provide a much better starting point than ES or iPS cells, which have to undergo a complex and poorly understood process coaxing them forward to eventually become bronchial epithelial cells,” said Wright.

Parker acknowledged that starting from iPS cells means some cell types are indeed harder to generate than others. “Cell types like cardiomyocytes, which form early in development, are certainly easier to generate than cells like hepatocytes and  $\beta$  cells, which form late in development,” he said. “The barrier to development is higher for the latter. Nonetheless, we have shown it is possible.”

Fulmer, T. *SciBX* 5(4); doi:10.1038/scibx.2012.90  
Published online Jan. 26, 2012

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2. Lucey, B.P. *et al. Arch. Pathol. Lab. Med.* **133**, 1463–1467 (2009)
3. Bodnar, A.G. *et al. Science* **279**, 349–352 (1998)

#### COMPANIES AND INSTITUTIONS MENTIONED

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**iPierian Inc.**, South San Francisco, Calif.

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**Max Planck Institute of Molecular Cell Biology and Genetics**, Dresden, Germany

**National Institutes of Health**, Bethesda, Md.

**The University of Texas Southwestern Medical Center**, Dallas, Texas

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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>Cancer</b>				
Acute lymphoblastic leukemia (ALL)	Not applicable	<p>Genomewide association studies suggest it may be possible to repurpose therapies for myeloid leukemias to treat early T cell precursor ALL. Patients with early T cell precursor ALL had a spectrum of mutations that were similar to those found in patients with myeloid tumors. The gene expression profile in early T cell precursor ALL showed enrichment of gene expression signatures associated with both normal and myeloid leukemia stem cells. Next steps could include evaluating therapies for myeloid leukemia in patients with early T cell precursor ALL.</p> <p><b>SciBX 5(4); doi:10.1038/scibx.2012.91</b> Published online Jan. 26, 2012</p>	Patent and licensing status unavailable	<p>Zhang, J. <i>et al. Nature</i>; published online Jan. 11, 2012; doi:10.1038/nature10725 <b>Contact:</b> Charles G. Mullighan, St. Jude Children's Research Hospital, Memphis, Tenn. e-mail: <a href="mailto:charles.mullighan@stjude.org">charles.mullighan@stjude.org</a></p>
Brain cancer	N-Methylpurine-DNA glycosylase (MPG; APNG)	<p>A study in cells and in patient tissue suggests inhibiting the DNA repair enzyme APNG may help treat Temodal-resistant glioblastoma multiforme (GBM). In Temodal-resistant primary GBM cells, anti-APNG small hairpin RNA sensitized cells to Temodal compared with scrambled shRNA. In 37 GBM patients treated with Temodal, expression of APNG in tumor tissue correlated with decreased overall survival compared with no APNG expression. Next steps include a clinical trial of the DNA repair inhibitor methoxyamine plus Temodal in patients with GBM.</p> <p>Merck &amp; Co. Inc. markets the DNA-alkylating agent Temodal temozolomide to treat brain cancer.</p> <p><b>SciBX 5(4); doi:10.1038/scibx.2012.92</b> Published online Jan. 26, 2012</p>	Unpatented; licensing status not applicable	<p>Agnihotri, S. <i>et al. J. Clin. Invest.</i>; published online Dec. 12, 2011; doi:10.1172/JCI59334 <b>Contact:</b> Sameer Agnihotri, University of Toronto, Toronto, Ontario, Canada e-mail: <a href="mailto:sameer.agnihotri@utoronto.ca">sameer.agnihotri@utoronto.ca</a></p>
Cancer	Smoothened (SMO)	<p><i>In vitro</i> studies identified an oxysterol-binding site on SMO that could guide development of new drugs targeting the hedgehog pathway. Oxysterols were known to activate hedgehog signaling, but their molecular target in the pathway was unclear. <i>In vitro</i>, 20(S)-hydroxycholesterol activated hedgehog signaling at low micromolar concentrations and was noncompetitively blocked by the SMO inhibitor cyclopamine. Next steps include exploring whether oxysterol-targeted drugs could be used as anti-hedgehog agents and discovering new sterol-based modulators of hedgehog signaling.</p> <p>At least six companies have SMO antagonists in preclinical to Phase II development for cancer.</p> <p><b>SciBX 5(4); doi:10.1038/scibx.2012.93</b> Published online Jan. 26, 2012</p>	Unpatented; unavailable for licensing	<p>Nachtergaele, S. <i>et al. Nat. Chem. Biol.</i>; published online Jan. 8, 2012; doi:10.1038/nchembio.765 <b>Contact:</b> Rajat Rohatgi, Stanford University School of Medicine, Stanford, Calif. e-mail: <a href="mailto:rrohbatgi@stanford.edu">rrohbatgi@stanford.edu</a> <b>Contact:</b> Douglas Covey, Washington University in St. Louis School of Medicine, St. Louis, Mo. e-mail: <a href="mailto:dcovey@wustl.edu">dcovey@wustl.edu</a></p>

## This week in therapeutics

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Chronic myelogenous leukemia (CML)	CD27; CD70 (CD27L)	<p>Cell culture and mouse studies suggest blocking CD27-CD70 interactions could help treat CML. In a mouse model of CML, deletion of Cd27 or an anti-CD70 antibody decreased wntless-type MMTV integration site (WNT) signaling and prolonged survival compared with normal Cd27 expression or an IgG control, respectively. Next steps could include clinical development of anti-CD27 or anti-CD70 antibodies to treat CML.</p> <p>CDX-1127, a human mAb against CD27 from Celldex Therapeutics Inc., is in Phase I testing to treat cancer.</p> <p>Seattle Genetics Inc.'s SGN-75, an antibody-drug conjugate composed of an anti-CD70 mAb and monomethyl auristatin F, is in Phase I trials to treat cancer.</p> <p>MDX-1203, a cytotoxic prodrug chemically linked with a human anti-CD70 antibody from Bristol-Myers Squibb Co., is in Phase I testing to treat cancer.</p> <p><b>SciBX 5(4); doi:10.1038/scibx.2012.94</b> Published online Jan. 26, 2012</p>	Patent and licensing status unavailable	<p>Schürch, C. <i>et al. J. Clin. Invest.</i>; published online Jan. 9, 2012; doi:10.1172/JCI45977</p> <p><b>Contact:</b> Adrian F. Ochsenbein, University Hospital Bern, Bern, Switzerland e-mail: <a href="mailto:adrian.ochsenbein@insel.ch">adrian.ochsenbein@insel.ch</a></p>
<b>Cardiovascular disease</b>				
Atherosclerosis	Acyl-CoA synthetase long-chain family member 1 (ACSL1)	<p>Studies in mice and in patient samples suggest inhibiting ACSL1 could help prevent diabetes-associated atherosclerosis. Macrophages from two mouse models of type 1 diabetes and monocytes from patients with type 1 diabetes had higher levels of ACSL1 mRNA than cells from nondiabetic controls. In a mouse model of diabetes, myeloid-specific ACSL1 deficiency decreased aortic macrophage accumulation and atherosclerotic lesion severity compared with normal expression of ACSL1. Next steps could include cell-based screening and developing molecules that inhibit ACSL1.</p> <p><b>SciBX 5(4); doi:10.1038/scibx.2012.95</b> Published online Jan. 26, 2012</p>	Unpatented; licensing status not applicable	<p>Kanter, J.E. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Jan. 17, 2012; doi:10.1073/pnas.1111600109</p> <p><b>Contact:</b> Karin E. Bornfeldt, University of Washington School of Medicine, Seattle, Wash. e-mail: <a href="mailto:bornf@uw.edu">bornf@uw.edu</a></p>
Atherosclerosis	Netrin 1 (NTN1)	<p>Studies in mice and in human samples suggest blocking NTN1 could help treat atherosclerosis. Immunohistochemical staining of human atherosclerotic plaque samples detected NTN1 expression in macrophages. In a mouse model of atherosclerosis, mice with macrophages lacking Ntn1 developed smaller atherosclerotic lesions than mice with Ntn1-expressing macrophages. Next steps could include testing the effect of NTN1-blocking antibodies in models of atherosclerosis.</p> <p><b>SciBX 5(4); doi:10.1038/scibx.2012.96</b> Published online Jan. 26, 2012</p>	Patent and licensing status unavailable	<p>Van Gils, J.M. <i>et al. Nat. Immunol.</i>; published online Jan. 8, 2012; doi:10.1038/ni.2205</p> <p><b>Contact:</b> Kathryn J. Moore, New York University Langone Medical Center, New York, N.Y. e-mail: <a href="mailto:kathryn.moore@nyumc.org">kathryn.moore@nyumc.org</a></p>
<b>Endocrine/metabolic disease</b>				
Diabetes; obesity	Fibronectin type III domain containing 5 (FNDC5; irisin)	<p>A study in mice and in patient serum identified irisin as a hormone that may help treat obesity and type 2 diabetes. In mice and humans, exercise led to increased blood levels of irisin, which is produced by cleavage of the muscle cell-expressed membrane protein FNDC5. In mice, adenoviral-mediated FNDC5 expression increased levels of irisin in the blood and the conversion of white fat to brown fat and decreased weight gain compared with adenoviral control. Next steps include studying a stabilized version of irisin in the mouse models and identifying irisin's receptor.</p> <p><b>SciBX 5(4); doi:10.1038/scibx.2012.97</b> Published online Jan. 26, 2012</p>	Patent application filed; licensed to Ember Therapeutics	<p>Boström, P. <i>et al. Nature</i>; published online Jan. 11, 2012; doi:10.1038/nature10777</p> <p><b>Contact:</b> Bruce M. Spiegelman, Harvard Medical School and Dana-Farber Cancer Institute, Boston, Mass. e-mail: <a href="mailto:bruce_spiegelman@dfci.harvard.edu">bruce_spiegelman@dfci.harvard.edu</a></p>

## This week in therapeutics

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Hematology</b>				
Hemolytic uremic syndrome	Golgi integral membrane protein 4 (GOLIM4; GPP130)	<i>In vitro</i> and mouse studies suggest GPP130 inhibitors or Mn <sup>2+</sup> could help prevent Shiga toxin–induced hemolytic uremic syndrome. In cultured cells exposed to Shiga toxin, Mn <sup>2+</sup> protected cells from cytotoxicity compared with no treatment. In a mouse model of Shiga toxin exposure, daily Mn <sup>2+</sup> protected all mice from lethal toxin doses, whereas mice given no treatment died. Next steps include identifying the optimal dose and mode of delivery in mice and testing in combination with antibiotics.  <b>SciBX 5(4); doi:10.1038/scibx.2012.98</b> <b>Published online Jan. 26, 2012</b>	Patent application filed; licensing status unknown	Mukhopadhyay, S. & Linstedt, A.D. <i>Science</i> ; published online Jan. 20, 2012; doi:10.1126/science.1215930 <b>Contact:</b> Adam D. Linstedt, Carnegie Mellon University, Pittsburgh, Pa. e-mail: <a href="mailto:linstedt@andrew.cmu.edu">linstedt@andrew.cmu.edu</a>
<b>Infectious disease</b>				
Cytomegalovirus (CMV)	Natural cytotoxicity triggering receptor 1 (NCR1; NKP46; CD335)	Studies in mice suggest antagonizing NCR1 could help treat CMV. Mice with a loss-of-function mutation in the <i>Ncr1</i> gene had greater NK cell activity and higher resistance to murine CMV infection than wild-type controls. NK cells from wild-type mice treated with an anti-NCR1 mAb had greater NK cell activity than mice receiving control mAbs. Next steps include testing anti-NCR1 mAbs in mouse models of diseases modulated by NK cell activity, including influenza and cancer. Innate Pharma S.A., which was cofounded by study author Eric Vivier, is evaluating therapeutics that target NCR1 ( <i>see Unleashing NK cells, page 5</i> ).  <b>SciBX 5(4); doi:10.1038/scibx.2012.99</b> <b>Published online Jan. 26, 2012</b>	Patent filed; licensing status undisclosed	Narini-Mancinelli, E. <i>et al. Science</i> ; published online Jan. 20, 2012; doi:10.1126/science.1215621 <b>Contact:</b> Sophie Ugolini, Aix-Marseille University, Marseille, France e-mail: <a href="mailto:ugolini@ciml.univ-mrs.fr">ugolini@ciml.univ-mrs.fr</a> <b>Contact:</b> Eric Vivier, same affiliation as above e-mail: <a href="mailto:vivier@ciml.univ-mrs.fr">vivier@ciml.univ-mrs.fr</a>
Smallpox; viral infection	Viral type I interferon binding protein	Mouse studies suggest antibodies against viral type I interferon (IFN) binding protein could help treat diseases caused by orthopoxviruses such as smallpox. In a mouse model of lethal mousepox, injection of type I IFN binding protein antisera lowered liver viral loads and lethality up to five days postinfection compared with injection of naïve sera ( $p=0.0014$ and $p=0.0377$ , respectively). Next steps include testing antibodies against viral type I IFN binding protein in animal models of monkeypox infection, which also is caused by an orthopoxvirus.  <b>SciBX 5(4); doi:10.1038/scibx.2012.100</b> <b>Published online Jan. 26, 2012</b>	Patented; available for licensing from Fox Chase Cancer Center <b>Contact:</b> Kurt Schwinghammer, Fox Chase Cancer Center, Philadelphia, Pa. phone: 215-214-3985 e-mail: <a href="mailto:kurt.schwinghammer@fccc.edu">kurt.schwinghammer@fccc.edu</a>	Xu, R.-H. <i>et al. PLoS Pathog</i> ; published online Jan. 5, 2012; doi:10.1371/journal.ppat.1002475 <b>Contact:</b> Luis J. Sigal, Fox Chase Cancer Center, Philadelphia, Pa. e-mail: <a href="mailto:luis.sigal@fccc.edu">luis.sigal@fccc.edu</a>
<b>Inflammation</b>				
Inflammation	IL-33 (NF-HEV)	<i>In vitro</i> and mouse studies suggest inhibiting the cleavage products of IL-33 could help treat inflammatory diseases. In mice, injection of IL-33 cleavage products increased spleen weight and inflammatory responses compared with saline injection. Next steps include testing inhibition of the IL-33 cleavage products in undisclosed indications.  <b>SciBX 5(4); doi:10.1038/scibx.2012.101</b> <b>Published online Jan. 26, 2012</b>	Patent application filed; available for licensing	Lefrançois, E. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Jan. 17, 2012; doi:10.1073/pnas.1115884109 <b>Contact:</b> Corinne Cayrol, Institute of Pharmacology and Structural Biology, Toulouse, France e-mail: <a href="mailto:corinne.cayrol@ipbs.fr">corinne.cayrol@ipbs.fr</a> <b>Contact:</b> Jean-Philippe Girard, same affiliation as above e-mail: <a href="mailto:jean-philippe.girard@ipbs.fr">jean-philippe.girard@ipbs.fr</a>

## This week in therapeutics

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Neurology</b>				
Alzheimer's disease (AD)	$\beta$ -Amyloid (A $\beta$ ); $\beta$ -site APP-cleaving enzyme 1 (BACE1)	<p>Mouse studies identified tannic acid as a BACE1 inhibitor that could help treat and prevent AD. In a mouse model of cerebral amyloidosis, six months of oral tannic acid decreased hyperactivity and cognitive impairment compared with vehicle (<math>p &lt; 0.05</math>). In the same model, tannic acid lowered BACE1 protein abundance, A<math>\beta</math> production and neuroinflammation compared with vehicle. Next steps could include evaluating tannic acid in additional mouse models of AD.</p> <p>At least four companies have BACE1 antagonists in preclinical or Phase I testing for AD.</p> <p><b>SciBX 5(4); doi:10.1038/scibx.2012.102</b> Published online Jan. 26, 2012</p>	Patent and licensing status unavailable	<p>Mori, T. <i>et al. J. Biol. Cell</i>; published online Jan. 4, 2012; doi:10.1074/jbc.M111.294025 <b>Contact:</b> Terrence Town, Cedars-Sinai Medical Center, Los Angeles, Calif. e-mail: <a href="mailto:terrence.town@cshs.org">terrence.town@cshs.org</a> <b>Contact:</b> Takashi Mori, Saitama Medical University, Saitama, Japan e-mail: <a href="mailto:t_mori@saitama-med.ac.jp">t_mori@saitama-med.ac.jp</a></p>
Amyotrophic lateral sclerosis (ALS)	Superoxide dismutase 1 (SOD1)	<p>A study in mice identified aryloxyanyl pyrazolone derivatives that inhibit mutant SOD1 and could help treat ALS. In a mouse model of mutant SOD1-driven ALS, the lead SOD1 inhibitor extended lifespan compared with vehicle. Next steps include identifying a partner and pursuing alternative inhibitor scaffolds.</p> <p>Isis Pharmaceuticals Inc.'s ISIS-SOD1Rx, an antisense molecule that inhibits production of SOD1, is in Phase I trials to treat ALS.</p> <p>Amorfix Life Sciences Ltd. has a mAb against SOD1 in preclinical testing to treat ALS.</p> <p><b>SciBX 5(4); doi:10.1038/scibx.2012.103</b> Published online Jan. 26, 2012</p>	Patent applications filed; available for licensing	<p>Chen, T. <i>et al. J. Med. Chem.</i>; published online Dec. 22, 2011; doi:10.1021/jm2014277 <b>Contact:</b> Richard B. Silverman, Northwestern University, Evanston, Ill. e-mail: <a href="mailto:agman@chem.northwestern.edu">agman@chem.northwestern.edu</a></p>
Autism spectrum disorder (ASD)	$\mu$ -Opioid receptor (OPRM1; MOR); corticotropin-releasing factor receptor 1 (CRHR1; CRFR1)	<p>Studies in mice suggest antagonizing OPRM1 and/or CRHR1 could help treat a form of ASD caused by duplication of the <i>methyl CpG binding protein 2 (MECP2; RTT)</i> gene. In a mouse model of <i>Mecp2</i> duplication, <i>Crhr1</i><sup>+/-</sup> mice or wild-type mice treated with CRHR1 antagonists had lower anxiety than <i>Crhr1</i><sup>+/+</sup> controls. In the same model, <i>Oprm1</i><sup>+/-</sup> mice had fewer social behavior abnormalities than <i>Oprm1</i><sup>+/+</sup> controls. Next steps could include identification of CRHR1 and OPRM1 inhibitors for clinical development.</p> <p><b>SciBX 5(4); doi:10.1038/scibx.2012.104</b> Published online Jan. 26, 2012</p>	Patent and licensing status undisclosed	<p>Samaco, R.C. <i>et al. Nat. Genet.</i>; published online Jan. 8, 2012; doi:10.1038/ng.1066 <b>Contact:</b> Huda Y. Zoghbi, Baylor College of Medicine, Houston, Texas e-mail: <a href="mailto:hzoghbi@bcm.edu">hzoghbi@bcm.edu</a></p>
Huntington's disease (HD)	Not applicable	<p>Mouse studies suggest bone marrow transplantation could help treat HD. In two transgenic mouse models of HD, transplantation of bone marrow cells from wild-type donors decreased HD-associated behavior and motor deficits compared with no transplantation. In the transplanted mice, levels of cytokines known to be dysregulated in HD became comparable to levels in wild-type animals. Studies to identify immunomodulatory small molecules that could help treat neurodegenerative diseases are ongoing.</p> <p><b>SciBX 5(4); doi:10.1038/scibx.2012.105</b> Published online Jan. 26, 2012</p>	Work unpatented; licensing status not applicable	<p>Kwan, W. <i>et al. J. Neurosci.</i>; published online Jan. 4, 2012; doi:10.1523/JNEUROSCI.4846-11.2012 <b>Contact:</b> Paul J. Muchowski, Gladstone Institute of Neurological Disease, San Francisco, Calif. e-mail: <a href="mailto:pmuchowski@gladstone.ucsf.edu">pmuchowski@gladstone.ucsf.edu</a></p>

## This week in therapeutics

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Pain	$\mu$ -Opioid receptor (OPRM1; MOR)	Rat studies suggest brief high-dose delivery of OPRM1 agonists could help treat some forms of pain. In rats, a one-hour, high-dose i.v. infusion of Ultiva remifentanyl, an ultra-short-acting OPRM1 agonist, suppressed pain-associated responses in nerve fibers compared with pretreatment baseline. In rats, Ultiva significantly attenuated capsaicin-induced hyperalgesia compared with saline. Next steps include determining whether brief high-dose opioids could reverse or improve some forms of chronic pain in patients. Mylan Inc. markets Ultiva as an analgesic.  <b>SciBX 5(4); doi:10.1038/scibx.2012.106</b> <b>Published online Jan. 26, 2012</b>	Unpatented; unavailable for licensing	Drdla-Schutting, R. <i>et al. Science</i> ; published online Jan. 13, 2012; doi:10.1126/science.1211726 <b>Contact:</b> Jürgen Sandkühler, Medical University of Vienna, Vienna, Austria e-mail: <a href="mailto:juergen.sandkuehler@meduniwien.ac.at">juergen.sandkuehler@meduniwien.ac.at</a>
Rett syndrome	Sodium channels	Patient and mouse studies suggest inhibiting sodium channels could help prevent lethal cardiac arrhythmias in patients with Rett syndrome. In 379 female patients with Rett syndrome, 70 had prolonged QT intervals, which increased the risk of developing lethal cardiac arrhythmias. In a mouse model of Rett syndrome, the sodium channel blocker phenytoin decreased QT intervals to lengths comparable to those in healthy wild-type controls. Next steps include determining which sodium channel blockers would be most effective at correcting QT intervals in patients with Rett syndrome. Phenytoin is a generic antiepileptic.  <b>SciBX 5(4); doi:10.1038/scibx.2012.107</b> <b>Published online Jan. 26, 2012</b>	Findings covered by patent application; licensing information available from the Baylor Licensing Group at Baylor College of Medicine	McCauley, M.D. <i>et al. Sci. Transl. Med.</i> ; published online Dec. 14, 2011; doi:10.1126/scitranslmed.3002982 <b>Contact:</b> Jeffrey L. Neul, Baylor College of Medicine, Houston, Texas e-mail: <a href="mailto:jneul@bcm.edu">jneul@bcm.edu</a> <b>Contact:</b> Xander H.T. Wehrens, same affiliation as above e-mail: <a href="mailto:wehrens@bcm.edu">wehrens@bcm.edu</a>
<b>Ophthalmic disease</b>				
Age-related macular degeneration (AMD)	All-trans-retinal production	Studies in mice identified amine-containing FDA-approved compounds that could help treat dry AMD. A mouse model of retinal degeneration caused by toxic all-trans-retinal production was used to screen drugs. In the mice, Lyrica pregabalin or a stereoisomer of the compound decreased all-trans-retinal levels and improved retinal morphology compared with vehicle. Next steps include further preclinical testing of undisclosed lead candidates identified in the same screen. Pfizer Inc. markets Lyrica, a $\gamma$ -aminobutyric acid receptor (GABAR) agonist, for neurological pain, epilepsy and fibromyalgia. The corresponding author has cofounded Visum Therapeutics Inc. to commercialize the work ( <i>see Visum sees the light, page 4</i> ).  <b>SciBX 5(4); doi:10.1038/scibx.2012.108</b> <b>Published online Jan. 26, 2012</b>	Patent application filed; exclusively licensed to Visum Therapeutics	Maeda, A. <i>et al. Nat. Chem. Biol.</i> ; published online Dec. 25, 2011; doi:10.1038/nchembio.759 <b>Contact:</b> Krzysztof Palczewski, Case Western Reserve University, Cleveland, Ohio e-mail: <a href="mailto:kxp65@case.edu">kxp65@case.edu</a>

## 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>Chemistry</b>			
Production of N-methylated macrocyclic peptide libraries	A method for producing libraries of N-methylated macrocyclic peptides displayed on mRNA could be used to identify compounds targeting protein-protein interactions. A library of 1,012 compounds was generated by <i>in vitro</i> translation and cyclization of mRNA-linked peptides. An <i>in vitro</i> screen of the library identified macrocycles that bound the ligase domain of ubiquitin protein ligase E3A (UBE3A; E6AP) with subnanomolar affinity. Ongoing work includes identifying macrocyclic inhibitors against a range of targets and looking at the activity of the molecules in cells and <i>in vivo</i> (see <i>Macrocycles by the trillions</i> , page 1).	Work covered by patents and patent applications; exclusively licensed to PeptiDream Inc.	Yamagishi, Y. <i>et al. Chem. Biol.</i> ; published online Dec. 23, 2011; doi:10.1016/j.chembiol.2011.09.013 <b>Contact:</b> Hiroaki Suga, The University of Tokyo, Tokyo, Japan e-mail: <a href="mailto:hsuga@chem.s.u-tokyo.ac.jp">hsuga@chem.s.u-tokyo.ac.jp</a>
<b>SciBX 5(4); doi:10.1038/scibx.2012.109</b> Published online Jan. 26, 2012			
<b>Drug platforms</b>			
Chimpanzee adenovirus vectors for vaccine development	Human, primate and mouse studies suggest chimpanzee adenovirus vectors could be used in vaccines. In nonhuman primates, a replication-deficient chimpanzee adenovirus serotype 3 (ChAd3) vector encoding an HIV antigen elicited an antigen-specific T cell response. In healthy volunteers, a ChAd3 vector encoding an HCV antigen and a ChAd63 vector encoding a <i>Plasmodium falciparum</i> antigen each induced T cell responses against their respective antigens. Clinical trials of the chimpanzee adenovirus vector-based malaria and HCV vaccines are ongoing. The University of Oxford is running a Phase II trial of Okairos AG's ChAd63 vector-based malaria vaccine AdCh63-MVA (formerly PlaMavax).	Multiple patent applications filed covering chimpanzee adenovirus vectors and specific vaccine applications; available for licensing	Colloca, S. <i>et al. Sci. Transl. Med.</i> ; published online Jan. 4, 2012; doi:10.1126/scitranslmed.3002925 <b>Contact:</b> Alfredo Nicosia, Okairos s.r.l., Rome, Italy e-mail: <a href="mailto:nicosia@okairos.com">nicosia@okairos.com</a>
<b>SciBX 5(4); doi:10.1038/scibx.2012.110</b> Published online Jan. 26, 2012			
Next-generation prime-boost HIV vaccine	A study in monkeys identified a prime and boost regimen that could be useful for vaccination against HIV infection. Macaques were vaccinated with combinations of modified vaccinia Ankara (MVA) and adenovirus serotype 26 (Ad26). An Ad26 prime and MVA boost regimen provided protection against repeated intra-rectal inoculation with a highly virulent strain of simian immunodeficiency virus (SIV) compared with other prime-boost combinations. Next steps include scaling up manufacturing of the vaccine formulation in preparation for an investigator-initiated Phase I trial. Johnson & Johnson's Crucell N.V. unit coauthored the study and is manufacturing this vaccine.	Multiple components of the vaccine used in this study covered by patents held by various companies and institutions; licensing status undisclosed	Barouch, D.H. <i>et al. Nature</i> ; published online Jan. 4, 2012; doi:10.1038/nature10766 <b>Contact:</b> Dan H. Barouch, Harvard Medical School, Boston, Mass. e-mail: <a href="mailto:dbarouch@bidmc.harvard.edu">dbarouch@bidmc.harvard.edu</a>
<b>SciBX 5(4); doi:10.1038/scibx.2012.111</b> Published online Jan. 26, 2012			
<b>Imaging</b>			
MRI detection of 2-hydroxyglutarate (2-HG) to diagnosis and monitor <i>isocitrate dehydrogenase 1 (IDH1)</i> -mutant gliomal tumors	Human and primary tumor studies suggest MRI could help diagnose and monitor treatment responses of <i>IDH1</i> -mutant gliomal tumors. Low-grade gliomas expressing <i>IDH1</i> mutations have higher 2-HG levels than gliomas expressing wild-type <i>IDH1</i> or normal brain tissue. In the first study, 2D MRI distinguished 2-HG from other metabolites in the brains of patients and healthy controls to correctly detect mutant <i>IDH1</i> gliomas, wild-type <i>IDH1</i> gliomas and absence of glioma. In the second study, 1D MRI identified associations in primary glioma tumor samples between 2-HG levels and cellular density, degree of abnormal vasculature and other features of tumor progression. Future studies could include using the MRI methods to monitor the treatment response of <i>IDH1</i> -mutant tumors by measuring the 2-HG-related tumor features.	Patent and licensing status unavailable	Andronesi, O.C. <i>et al. Sci. Transl. Med.</i> ; published online Jan. 11, 2012; doi:10.1126/scitranslmed.3002693 <b>Contact:</b> Ovidiu C. Andronesi, Massachusetts General Hospital and Harvard Medical School, Boston, Mass. e-mail: <a href="mailto:ovidiu@nmr.mgh.harvard.edu">ovidiu@nmr.mgh.harvard.edu</a>  Elkhaled, A. <i>et al. Sci. Transl. Med.</i> ; published online Jan. 11, 2012; doi:10.1126/scitranslmed.3002796 <b>Contact:</b> Sarah J. Nelson, University of California, San Francisco, Calif. e-mail: <a href="mailto:sarah.nelson@ucsf.edu">sarah.nelson@ucsf.edu</a>
<b>SciBX 5(4); doi:10.1038/scibx.2012.112</b> Published online Jan. 26, 2012			

## This week in techniques

Approach	Summary	Licensing status	Publication and contact information
<b>Markers</b>			
Hyperpolarized $^{13}\text{C}$ magnetic resonance spectroscopy (MRS) to predict tumors that will respond to anti-VEGF therapy	Mouse studies suggest hyperpolarized $^{13}\text{C}$ MRS could help detect early tumor response to anti-VEGF therapy. In mice with colorectal cancer xenografts, MRS using $^{13}\text{C}$ pyruvate and $^{13}\text{C}$ fumarate probes detected less metabolic label flux in tumors responding to Avastin than in nonresponding tumors. Clinical trials of the technology in undisclosed indications are ongoing. Chugai Pharmaceutical Co. Ltd. and the Genentech Inc. unit of Roche market Avastin bevacizumab to treat various cancers.	Technology patented by GE Healthcare and the University of Cambridge; licensing status undisclosed	Bohndiek, S.E. <i>et al. Cancer Res.</i> ; published online Jan. 5, 2012; doi:10.1158/0008-5472.CAN-11-2795 <b>Contact:</b> Kevin M. Brindle, University of Cambridge, Cambridge, U.K. e-mail: <a href="mailto:kmb@mole.bio.cam.ac.uk">kmb@mole.bio.cam.ac.uk</a>
<i>SciBX</i> 5(4); doi:10.1038/scibx.2012.113 Published online Jan. 26, 2012			



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