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# Probing the character of proteins

By Michael J. Haas, Senior Writer

A team from **The Scripps Research Institute** has developed a high throughput technology that can screen compound libraries against proteins whose biochemical activities are poorly characterized.<sup>1</sup> The method, which relies on fluorescent activity-based chemical probes to identify hits, can screen libraries containing tens of thousands of compounds, an increase of two orders of magnitude over the capacity of existing activity-based protein binding screens.

About 30–50% of human proteins have unknown biochemical activity<sup>2</sup> and thus are not amenable to conventional high throughput screens, which require detailed knowledge of a target protein's activity or binding partners. Activity-based protein profiling (ABPP) overcame these limitations by using chemical probes capable of binding the active site on a large number of mechanistically related enzymes, thus obviating the need for specific information about a given target. But the approach required gel-based assays—a laborious and time-consuming process that limited activity-based screens to small libraries.

The Scripps team set out to overcome this low throughput hurdle by combining two screening approaches: activity-based probes and a microtiter plate-based high throughput screening technique. They dubbed the technique fluorescence polarization technology for competitive ABPP (fluopol-ABPP).

The team dispensed purified target protein into a 384-well microtiter plate, spiked each well with an individual library compound and added a polarized fluorescent probe. This setup allowed the fluorescence signals to be detected in the plate, bypassing the need for gel-based separation and detection.

Using fluopol-ABPP, the team screened libraries against two uncharacterized proteins implicated in human cancers: retinoblastoma binding protein 9 (RBBP9) and glutathione *S*-transferase  $\omega$ 1 (GSTO1). A screen of a 19,000-member library against RBBP9 identified a lead, the alkaloid emetine, that inhibited the protein at low micromolar concentrations. A screen of a 2,000-member library against GSTO1 identified an  $\alpha$ -chloroacetamide that inhibited the protein at nanomolar concentrations. Gel-based assays confirmed the results of both screens.

Next, the team screened emetine and 75 structurally similar compounds against RBBP9 with activity-based probes and gel-based detection assays. They used the results to develop structure-activity relationships that shed light on the binding behavior of RBBP9 and the mechanism by which it is inhibited.

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“We hope to use the inhibitors discovered by fluopol-ABPP as pharmacological tools to map the biochemical activities of enzymes,” team leader Benjamin Cravatt told *SciBX*. Cravatt is chairman of chemical physiology at Scripps.

The team’s report on fluopol-ABPP technology was published in *Nature Biotechnology*.

**Out of the shadows**

Experts contacted by *SciBX* said the Scripps team’s method provided a good starting point for characterizing poorly understood proteins that have roles in human disease. Indeed, the key limitation may lie not in the method itself but in the availability of suitable probes.

Matthew Bogyo, associate professor of pathology at **Stanford University School of Medicine**, said fluopol-ABPP offered the dual advantages of increasing throughput relative to gel-based assays and simplifying the assay design relative to conventional high throughput approaches.

Bogyo has used activity-based probes to screen libraries containing at most a few thousand compounds and then used a gel-based assay to resolve and identify the hits. “This was certainly a low throughput method—not one I’d want to use on a library” containing tens of thousands of compounds as the Scripps team did in its study, he said.

Bogyo did note that the detection of fluorescence signals in the microtiter plates required screening of purified protein. That involves an information trade-off, he said, because “no off-target effects or selectivity could be assessed this way.” In contrast, he said gel-based assays can screen proteins in mixtures and even in cells, thereby providing some selectivity information about the hits.

The two screening methods don’t have to be mutually exclusive, Bogyo added. Fluopol-ABPP “could be a starting point for early-stage drug discovery research. You could use it to get at a scaffold that could lead to basic medicinal chemistry, X-ray crystallography

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studies and assessment of the biochemical functions of the protein,” he told *SciBX*.

Jinyan Du, a research fellow at **Dana-Farber Cancer Institute** and the **Broad Institute of MIT and Harvard**, said fluopol-ABPP “will enable the identification of inhibitors for a much broader range of enzymes,” in contrast to existing high throughput screening methods, which focus primarily on well-studied proteins such as kinases.

She said she would be interested in using this technology in her own research because it bypassed the need to identify suitable substrates for the target or develop robust *in vitro* assays around the target-substrate binding interaction. Du was lead author on a paper published in January that described a high throughput method for profiling activated tyrosine kinases in cancer cells.<sup>3</sup>

According to Du, another benefit of fluopol-ABPP is that use of activity-based probes requires no specialized knowledge, only knowledge of the general mechanistic classes of enzymes. “The method uses standard assays and equipment, so its adaptation by medicinal chemists should be quite straightforward,” she said.

Bogyo agreed that the technology should be readily exportable to any academic and industrial facility with high throughput screening technology. “This is a great application that has real value,” he said. “It will continue to have even more value as more probes become available.”

Indeed, Bogyo suggested that the chief limitation of the new technology might be the lack of probes suitable for screening some proteins. Most available activity-based probes target serine or cysteine proteases because these proteins are well known, although he said several researchers are working on probes for different classes of enzymes.

At the same time, Bogyo acknowledged that it might not be necessary to develop new probes to screen new classes of proteins with the Scripps method. “Some existing probes might work well enough on a purified protein target” to yield hits, he said.

Cravatt said that suitable probes are typically straightforward to synthesize and can be produced at sufficient scale and in a cost-effective manner for use with his team’s method.

Cravatt said the team is using fluopol-ABPP to screen a range of uncharacterized proteins that appear to play roles in human disease. “We are also interested in expanding the technology to address enzymes from distinct mechanistic classes,” he said.

Cravatt added that the team plans to optimize leads from their screens via conventional medicinal chemistry. He declined to disclose the IP status of the findings.

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**Broad Institute of MIT and Harvard**, Cambridge, Mass.  
**Dana-Farber Cancer Institute**, Boston, Mass.  
**The Scripps Research Institute**, La Jolla, Calif.  
**Stanford University School of Medicine**, Stanford, Calif.

**“This is a great application that has real value. It will continue to have even more value as more probes become available.”**

**—Matthew Bogyo,  
Stanford University  
School of Medicine**

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# Toll gate against allergic asthma

By *Tim Fulmer, Senior Writer*

Marketed treatments for allergic asthma, including corticosteroids and adrenergic receptor  $\beta_2$  agonists, have focused on intervening downstream from the initial inhalation of an allergen. Now, a team of Belgian and American researchers has proposed treating allergic asthma by antagonizing toll-like receptor 4 on cells that line the airway and have direct contact with airborne allergens.<sup>1</sup>

The group thinks that the ability to decrease multiple proinflammatory factors in the allergic asthma cascade could give the compounds an advantage over other asthma therapeutics and is looking for industry partners to take the approach into the clinic.

Previous work has shown that, in addition to serving as a physical barrier, airway epithelial cells sense the presence of airborne allergens via toll-like receptor 4 (TLR4). The epithelial cells then activate dendritic cells (DCs) and potentially contribute to downstream inflammation and allergic asthma<sup>2-4</sup> (see **Figure 1, "Allergens take their toll on asthma"**).

Bart Lambrecht and colleagues decided to test whether inhibiting TLR4 on airway epithelial cells was sufficient to decrease or prevent bronchial hyper-reactivity associated with allergic asthma. Lambrecht is professor of immunology and respiratory medicine at **Ghent University** and professor of pulmonary medicine at the **Erasmus University Medical Center**.

As reported in *Nature Medicine*, the team used mice with TLR4-deficient airway epithelial cells. In these mice, exposure to lipopolysaccharide (LPS) in the trachea resulted in lower influx of proinflammatory neutrophils, monocytes and DCs into lung tissue compared with that seen in wild-type mice. Importantly, mucosal DCs from the TLR4-deficient mice had a lower ability to drive the proliferation and differentiation of T cells, which are central players in allergic asthma.

Next, the researchers administered house dust mite extracts to the TLR4-deficient mice. The extracts were a complex mixture of multiple allergens and also contained LPS. The TLR4-deficient mice

had fewer monocytes and DCs in airway tissue and lower levels of proinflammatory cytokines and chemokines in the bronchoalveolar lavage than wild-type controls.

Finally, in wild-type mice exposed to house dust mite extract, intrapulmonary delivery of a TLR4 antagonist in combination with extract challenge led to less airway inflammation and hyper-reactivity than that seen in wild-type mice that received vehicle control in combination with extract challenge.

Lambrecht, the corresponding author, told *SciBX* that targeting TLR4 on airway epithelial cells could have advantages over targeting individual cytokines to treat asthma.

"By antagonizing TLR4 on airway epithelial cells, our strategy targets a receptor that sits most upstream in the allergy cascade. Blocking the initial interaction of TLR4 with an airborne allergen should thus prevent or at least reduce activation of multiple downstream proinflammatory cytokines that play a role in allergic asthma. This could offer a real advantage over compounds that target a single downstream cytokine to treat disease," he said.

## All about allergens

Lambrecht said he is in talks with potential industry partners that have TLR4 antagonists. He added that he wants to design and help run a small proof-of-concept trial in allergic asthma patients.

Disclosed TLR4 antagonist programs include NI-0101, a humanized mAb that antagonizes TLR4 from **NovImmune S.A.** The compound is in preclinical testing to treat autoimmune and inflammatory diseases.

At least three companies have small molecule TLR4 antagonists. **GlaxoSmithKline plc** gained CRX-526 when it acquired Corixa Corp. in 2005. **Eisai Co. Ltd.**'s Eritoran (E5564) is in Phase III testing to treat severe sepsis. Earlier this year, **Takeda Pharmaceutical Co. Ltd.** discontinued a Phase III trial of TAK-242 to treat sepsis. The company did not give a reason for the decision.

Asthma researcher Christopher Karp wanted to see additional proof of concept in preclinical allergy models. Karp is director of the Division of Molecular Immunology and professor of pediatrics at the **Cincinnati Children's Hospital Medical Center** and the **University of Cincinnati College of Medicine**.

"The *Nature Medicine* paper does an excellent job illustrating the critical role that TLR4 on airway epithelial cells plays in driving

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**Figure 1. Allergens take their toll on asthma.** Research published in *Nature Medicine* suggests that blocking interactions between toll-like receptor 4 (TLR4) and allergens on airway epithelial cells could help treat allergic asthma.

**[a]** Airborne allergens bind TLR4 expressed on the surface of airway epithelial cells, triggering the release of multiple cytokines and chemokines including monocyte chemoattractant protein-1 (CCL2; MCP-1) and chemokine CC motif ligand 20 (CCL20; MIP3A).

**[b]** Increased levels of chemokines attract and activate airway dendritic cells (DCs), which subsequently activate T helper cells.

**[c]** Activated T helper cells secrete multiple proinflammatory cytokines, including IL-4 and IL-13, which activate antibody-producing B cells.

**[d]** High levels of the resulting IgE antibodies induce degranulation of mast cells and histamine release, leading to the classic symptoms of allergic asthma.

A number of strategies are in development or marketed to intervene at various points in the allergic cascade to decrease or prevent symptoms associated with allergic asthma.

allergic response to the house dust mite allergen extracts,” he said. “An interesting therapeutic question is how central TLR4 is to the recognition of many other common allergens. The researchers might now try antagonizing TLR4 in preclinical allergy models driven by other allergens—such as from *Aspergillus* mold or the cockroach—to see if they get similar results.”

Lambrecht said his lab is indeed looking at TLR4 antagonism in additional preclinical models, although for now they are focusing on dust mite allergen.

“We plan to look at the TLR4 antagonists in a humanized murine model of asthma driven by dust mite allergen,” Lambrecht told *SciBX*. “These mice are reconstituted with peripheral blood mononuclear cells from house dust mite allergy patients, and efficacy in these animals should lend further support to using TLR4 antagonists in patients.”

Karp also wanted to see the TLR4 antagonist delivered after allergen challenge and the establishment of asthma, rather than together with challenge. He said that could give insight into the potential importance of timing of treatment.

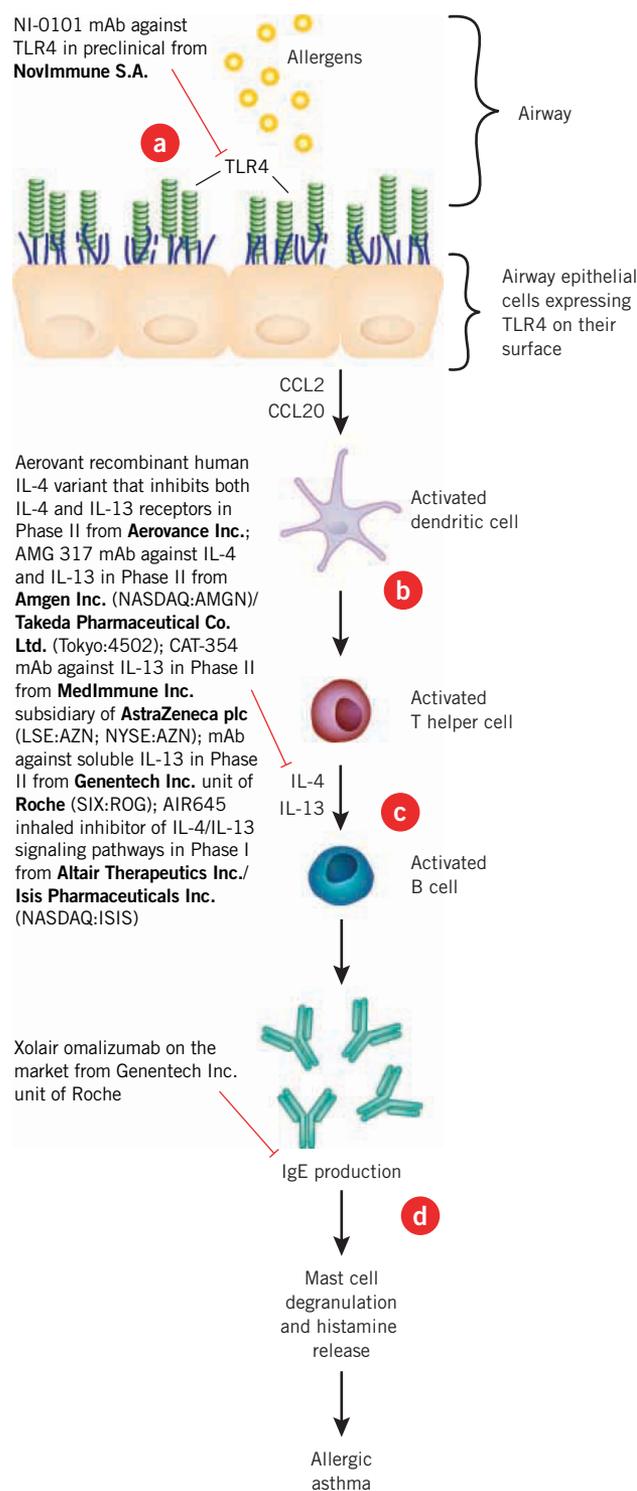
Earlier this year, Karp and colleagues published data that showed a single allergen, Der p 2, isolated from a house dust mite allergen extract elicited allergic asthma in murine models in a TLR4-dependent manner.<sup>5</sup>

Lambrecht told *SciBX* the *Nature Medicine* findings have not been patented.

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- Eisai Co. Ltd. (Tokyo:4523; Osaka:4523), Tokyo, Japan
- Erasmus University Medical Center, Rotterdam, The Netherlands
- Ghent University, Ghent, Belgium
- GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, UK
- NovImmune S.A., Geneva, Switzerland
- Takeda Pharmaceutical Co. Ltd. (Tokyo:4502), Osaka, Japan
- University of Cincinnati College of Medicine, Cincinnati, Ohio

# Charging up MS treatment

By Lauren Martz, Staff Writer

Researchers at **MediGene AG** have identified cationic liposomes that potentially could function as drug delivery vehicles or diagnostics tools for neuroinflammatory diseases such as multiple sclerosis.<sup>1</sup> The company has data showing that the liposomes specifically target the inflamed blood brain barrier, although it's still unknown whether the delivery system can improve the safety or activity of MS therapeutics.

The preferential absorption of liposomes in specific tissues has been attributed to increased permeability of the capillaries supplying both tumor and inflamed tissue types, which can allow increased liposome diffusion.<sup>2</sup>

Cationic liposomes are known to specifically bind angiogenic endothelial cells. Thus, they initially were employed as tumor-targeting agents formulated with cancer therapeutics.<sup>3</sup> Indeed, MediGene's EndoTAG-1 is a cationic liposome formulation of i.v. paclitaxel that has completed Phase II testing to treat inoperable, advanced or metastatic prostate cancer.

In a paper published in *Molecular Pharmaceutics*, Heinrich Haas and company colleagues now suggest that cationic liposomes could be used to target angiogenesis associated with acute inflammation, such as that of the spinal cord in MS patients.

Haas is associate director at MediGene and lead author on the paper.

In rats with experimental autoimmune encephalomyelitis (EAE), an animal model of MS, positively charged liposomes injected into the tail vein accumulated at the damaged blood brain barrier (BBB), as shown using laser scanning confocal microscopy.

Cationic liposome binding to the spinal cord of EAE rats was directly correlated with lower severity of disease and inflammation. In addition, the binding was detected even before the rats showed real signals of EAE, suggesting that the liposomes could prevent early changes in the neuroinflammatory process.

In contrast, the positively charged liposomes did not bind the spinal cords of healthy rats, and negatively charged liposomes did not bind to the spinal cords of either healthy or diseased rats.

"It will be interesting to see what happens when they actually use it to deliver drugs," said Simon Jones, VP of biology and ADMET at **Epix Pharmaceuticals Inc.** "The next step is to incorporate a drug known to work in MS into the liposomes and to use it in the EAE model to see if it can reduce inflammatory response. It could have been an extremely strong paper had they taken it this one step further."

Epix's EPX-102216, an oral CC chemokine receptor 2 (CCR2) antagonist, is in preclinical testing to treat MS.

**"Cationic targeting offers determination of inflammatory events with a mechanism that does not depend on elevated blood brain barrier permeability."**  
—Heinrich Haas, MediGene AG

## Targeting for safety

If therapeutics delivered via liposomes do show efficacy, the hope is that the compounds would have fewer side effects because of the more targeted delivery. In addition, the delivery method could be used to rescue compounds that were previously considered too toxic.

Haas told *SciBX* that "the local concentration of active agents at the sites of the affected blood brain barrier can be improved with respect to systemic administration," via cationic liposomes. The selective action of the active agent at these sites "will enable lower doses of drugs compared to systemic administration to reduce side effects or antibody production," he added.

Jones also noted that liposomes are passive targeting agents—they don't have surface elements that bind specific receptors, which can complicate the design of other types of carriers.

Haas did caution that the cationic lipids won't offer a cookie-cutter approach to formulating therapeutics. "The technology of loading/encapsulating an active compound to the liposome has to be selected on the basis of the molecular properties of the compound," he said.

Jones also said the large size of liposomes could be an issue. The molecules are in the range of "10 to 100s of nanometers. They will be taken up by the reticuloendothelial system in the liver and spleen, which can lead to toxicity of its own," he said. "The toxicity of the

liposome-drug constructs will have to be compared with that of the drugs alone."

The authors of the *Molecular Pharmaceutics* article also suggested that cationic liposomes might have diagnostic applications.

"Cationic targeting offers determination of inflammatory events with a mechanism that does not depend on elevated blood brain barrier permeability," said Haas. Although increased permeability of the BBB is a characteristic of MS, it is not the first change associated with the disease.

Haas added that labeling cationic liposomes for *in vivo* imaging, such as MRI contrast, could be a suitable way to use them for diagnostic applications.

MediGene is not pursuing use of the cationic liposomes in MS. The patent status of the findings is undisclosed.

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## COMPANIES AND INSTITUTIONS MENTIONED

**Epix Pharmaceuticals Inc.** (NASDAQ:EPIX), Lexington, Mass.  
**MediGene AG** (Xetra:MDG), Martinsried, Germany

# NO: more muscles

By Kai-Jye Lou, Staff Writer

Researchers at the **University of Manitoba** and the **Carolinas Medical Center** have uncovered myogenesis-promoting properties in an over-the-counter expectorant and have boosted the effect by synthesizing an analog that also releases the myogenic booster nitric oxide.<sup>1</sup> The next step will be to see if these effects translate into a meaningful therapeutic benefit in animal models of muscular dystrophy and atrophy.

The Manitoba team, led by Judy Anderson, had previously shown that nitric oxide (NO) activates quiescent satellite precursor cells in skeletal muscle, which generate new precursor cells for muscle growth and repair.<sup>2</sup> Anderson, who heads the Department of Biological Sciences at the university, has also shown that increased NO levels in both normal and dystrophic muscle can promote regeneration.<sup>2,3</sup>

In a paper in *Molecular Pharmaceutics*, Anderson and colleagues now report the synthesis and preliminary evaluation of guaifenesin dinitrate, a compound that delivers NO to skeletal muscle and can be given orally or transdermally.

The parent compound guaifenesin is available over the counter to help clear phlegm from the respiratory tract. The compound also has muscle relaxant properties.

In adult mice, a transdermal ointment formulation of guaifenesin dinitrate increased DNA synthesis—an indicator of muscle satellite cell activation and proliferation—in the back and quadriceps muscles compared with what was seen using placebo. Mice given an oral formulation of the compound showed greater satellite cell activation and myoblast production than oil-treated controls.

“The fact that they showed a 30–50% increase in DNA synthesis in the muscle satellite cells was very interesting and this clearly suggests efficacy,” said Ryszard Kole, SVP of discovery research at **AVI BioPharma Inc.**, which has compounds in Phase Ib and preclinical development for Duchenne muscular dystrophy (DMD).

The academics also showed that the muscle relaxant methocarbamol—an analog of guaifenesin—can promote muscle proliferation on its own, and that this effect was additive with NO.

Anderson told *SciBX* that the formulation is the first of a new family of NO donor molecules that boosts the myogenesis-promoting effects of muscle relaxants via NO.

“Previous work has demonstrated the capability of nitric oxide, possibly via a pharmacological action on the regulatory protein follistatin, to induce satellite cell myogenesis,” noted Csaba Szabo, CSO and SVP at **Ikaria Holdings Inc.** “The current work builds upon these data and demonstrates that both the classical NO donor compound, isosorbide dinitrate, and a novel NO donor compound synthesized by the authors, guaifenesin dinitrate, are able to produce satellite cell myogenesis in the skeletal muscle of mice.”

Ikaria markets INOmax inhaled nitric oxide to treat persistent pulmonary hypertension in newborns.

Looking forward, Ellen Welch, associate director of biology at

**PTC Therapeutics Inc.**, suggested that “this may be a good starting point to identify and develop muscle-specific nitric oxide-based therapies.”

PTC’s ataluren, which is partnered with **Genzyme Corp.**, is a small molecule that facilitates the complete translation of proteins containing nonsense mutations. The compound is in a pivotal Phase IIb trial to treat the 15% of DMD patients with a nonsense mutation in the gene encoding dystrophin. Ataluren has also completed a Phase IIa trial in cystic fibrosis (CF).

## A combinatorial approach

Anderson thinks the myogenesis-promoting effects of NO-donating compounds like guaifenesin dinitrate would be most applicable in muscular dystrophy and age-related muscular atrophy.

DMD is caused by mutations in the *dystrophin* gene that result in the loss of protein function. The loss of dystrophin results in muscle damage and eventual muscle necrosis and leads to premature death.<sup>4</sup> For the former indication, Anderson thinks the compounds probably would have an adjuvant role.

Kole agreed. “In muscle-wasting diseases other than DMD, the myogenesis-promoting properties of the NO-donating compound may be sufficient, but I don’t think this would be viable in the long run as a stand-alone approach for DMD. The reason is because even if you increase myogenesis in patients with DMD, these new muscle cells will still produce nonfunctional dystrophin.”

“While a molecule that modulates muscle growth and regeneration will not cure DMD, the fact that it will delay the progression of the disease is still very significant,” added Welch.

With regard to atrophy, Anderson thinks that a transdermal NO-based treatment tar-

geted to skeletal muscle would be useful as a complement to exercise.

Indeed, the benefits and risks associated with each mode of delivery will need to be carefully assessed in future studies.

Guaifenesin dinitrate’s systemic availability is important, noted Kole, because in certain musculoskeletal diseases like DMD, all muscles in the body are affected. “This means a candidate therapeutic approach will need to be able to demonstrate efficacy via systemic delivery,” he said.

Conversely, because NO exerts a broad range of pharmacological effects on various biological systems, targeting its delivery to a specific region or tissue could help decrease side effects.

## Translating forward

An unanswered question is whether guaifenesin dinitrate’s myogenesis-promoting effects in mice will translate into a meaningful improvement in disease symptoms.

“The main caveat I have is that the researchers only showed the myogenic effects in normal mice,” Kole told *SciBX*. “I will feel much better about these findings when the group also shows these results in the context of a disease model like the *mdx* mouse, either as a stand-alone treatment or in combination with another approach.”

“This may be a good starting point to identify and develop muscle-specific nitric oxide-based therapies.”

—Ellen Welch,  
PTC Therapeutics Inc.

Szabo said it will be important to show the compound's specificity for skeletal muscle. "The authors did not show regional distribution of the guaifenesin dinitrate compound. It is unclear whether the parent compound and/or the NO released from it will enter tissues other than skeletal muscle" and produce known side effects of NO such as systemic vascular relaxation and a fall in blood pressure, he said.

In addition, Szabo said the study only looked at the number of satellite cells induced by guaifenesin dinitrate. "The studies did not investigate whether this actually translates into detectable increases in muscle mass, muscle strength and other relevant functional parameters," he said.

Welch said she would like to see guaifenesin dinitrate evaluated in longer term safety and efficacy studies, given that it is likely to be used chronically. She also wanted to see how long the effects of the NO-donating compound will last in muscle, which would provide insights into a dosing schedule.

Anderson said her group has preliminary data suggesting that guaifenesin dinitrate promotes muscle regeneration in the *mdx* mouse model of muscular dystrophy. She added that her group is continuing with studies to evaluate the compound in both muscular atrophy and additional muscular dystrophy models.

According to Anderson, a patent application has been filed covering compositions and methods for increasing NO delivery to

promote muscle growth and repair under normal and diseased states. She said the university has transferred the rights to the inventors, which include herself, Gu Qi Wang and Frank Burczynski. The work is available for licensing.

Wang is a research faculty member in the McColl-Lockwood Laboratory for Muscular Dystrophy Research at the Carolinas Medical Center. Burczynski is a professor in the faculty of pharmacy at the University of Manitoba.

Lou, K.-J. *SciBX* 2(15); doi:10.1038/scibx.2009.607  
Published online April 16, 2009

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e-mail: [janders@ms.umanitoba.ca](mailto:janders@ms.umanitoba.ca)
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## COMPANIES AND INSTITUTIONS MENTIONED

**AVI BioPharma Inc.** (NASDAQ:AVI), Portland, Ore.  
**Carolinas Medical Center**, Charlotte, N.C.  
**Genzyme Corp.** (NASDAQ:GENZ), Cambridge, Mass.  
**Ikaria Holdings Inc.**, Clinton, N.J.  
**PTC Therapeutics Inc.**, South Plainfield, N.J.  
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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>				
Crohn's disease	Caspase recruitment domain family member 15 (CARD15; NOD2); IL-10	A study in patient samples and mice suggests that inhibiting a mutant form of NOD2 may help treat Crohn's disease. Patients homozygous for an insertion mutation at nucleotide 3020 of <i>NOD2</i> usually have severe disease. Patient-derived primary monocytes expressing the mutant <i>NOD2</i> had lower production of the anti-inflammatory cytokine IL-10 than monocytes expressing wild-type <i>NOD2</i> . A series of cell-culture studies showed the mutant <i>NOD2</i> inhibited IL-10 transcription, whereas the wild-type form did not. Next steps include the development of small molecule inhibitors of the mutant form of NOD2.	Work unpatented; licensing status not applicable	Noguchi, E. <i>et al. Nat. Immunol.</i> ; published online April 6, 2009; doi:10.1038/ni.1722 <b>Contact:</b> Xiaojing Ma, Weill Medical College of Cornell University, New York, N.Y. e-mail: <a href="mailto:xim2002@med.cornell.edu">xim2002@med.cornell.edu</a>
Multiple sclerosis (MS)	CC chemokine receptor 6 (CCR6)	A study in mice suggests that antagonizing CCR6 could help prevent MS. CCR6 knockout mice, which produce T helper type 17 (Th17) cells devoid of CCR6, were resistant to induction of the MS-like condition experimental autoimmune encephalomyelitis (EAE) compared with what was seen in wild-type controls. CCR6 knockout mice treated with wild-type Th17 cells developed EAE. In CCR6 knockouts, Th17 cells accumulated in the choroid plexus, a tissue that separates the brain from the ventricles, unlike in wild-type controls, where there was no accumulation. Next steps include testing whether CCR6 plays a role in periodic MS relapses.	Unpatented; licensing status not applicable	Reboldi, A. <i>et al. Nat. Immunol.</i> ; published online March 22, 2009; doi:10.1038/ni.1716 <b>Contact:</b> Federica Sallusto, Institute for Research in Biomedicine, Bellinzona, Switzerland e-mail: <a href="mailto:federica.sallusto@irb.unisi.ch">federica.sallusto@irb.unisi.ch</a>

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## This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
<b>Cancer</b>				
Brain cancer	Transforming growth factor- $\beta$ (TGFB1; TGFB $\beta$ ); leukemia inhibitory factor (LIF); SMAD family member 4 (SMAD4; MADH4; DPC4)	<i>In vitro</i> and mouse studies suggest that targeting TGF $\beta$ or LIF could help treat glioblastoma. In patient-derived glioma cells, TGF $\beta$ increased self-renewal, induced expression of the cytokine LIF and increased protein secretion through activation of the SMAD complex. A neutralizing antibody against LIF or knockdown of <i>SMAD4</i> prevented self-renewal. In mice, implanted glioma cells that were stimulated with TGF $\beta$ or LIF generated tumors faster than nonstimulated cells, and TGF $\beta$ inhibitors decreased tumorigenic potential. Next steps include confirming the findings in additional patients. Antisense Pharma GmbH's AP 11014, a TGF $\beta$ 1 antisense oligonucleotide, is in preclinical testing to treat several cancers.  <b>SciBX 2(15); doi:10.1038/scibx.2009.610</b> <b>Published online April 16, 2009</b>	Priority patent application filed in Spain; available for licensing	Penuelas, S. <i>et al. Cell</i> ; published online April 6, 2009; doi:10.1016/j.ccr.2009.02.011 <b>Contact:</b> Joan Seoane, Autonomous University of Barcelona, Barcelona, Spain e-mail: <a href="mailto:jseoane@ir.vhebron.net">jseoane@ir.vhebron.net</a>
Breast cancer	Fyn-related kinase (FRK; RAK); phosphatase and tensin homolog deleted on chromosome ten (PTEN; MMAC1; TEP1)	A study in mice and in cell culture suggests that increasing RAK levels could help treat breast cancer. Mice receiving RAK-overexpressing breast cancer cells failed to form tumors at eight weeks. All mice receiving RAK-deficient mammary epithelial cells developed tumors at three weeks, whereas mice receiving RAK-expressing control cells did not. Cell-culture studies showed that RAK phosphorylated and increased the stability of the tumor suppressor PTEN. Next steps include ongoing screening for compounds that increase PTEN protein stability in cancer cells.  <b>SciBX 2(15); doi:10.1038/scibx.2009.611</b> <b>Published online April 16, 2009</b>	Work unpatented; licensing status undisclosed	Yim, E.-Y. <i>et al. Cancer Cell</i> ; published online April 6, 2009; doi:10.1016/j.ccr.2009.02.012 <b>Contact:</b> Shiaw-Yih Lin, The University of Texas M.D. Anderson Cancer Center, Houston, Texas e-mail: <a href="mailto:shilin@mdanderson.org">shilin@mdanderson.org</a>
Cancer	Not applicable	A study in cell culture identified derivatives of pyridylbenzo[ <i>b</i> ]thiophene-2-carboxamides and benzo[ <i>b</i> ]thieno[2,3- <i>c</i> ]naphthyridin-2-ones that may be useful for treating cancer. In a panel of five human cancer cell lines, four of the compounds inhibited proliferation with nanomolar to low single-digit micromolar IC <sub>50</sub> values. The compounds induced cell-cycle arrest in the cancer cells. Next steps could include evaluating the derivatives in preclinical cancer models.  <b>SciBX 2(15); doi:10.1038/scibx.2009.612</b> <b>Published online April 16, 2009</b>	Patent and licensing status unavailable	Ester, K. <i>et al. J. Med. Chem.</i> ; published online March 30, 2009; doi:10.1021/jm801573v <b>Contact:</b> Grace Karminski-Zamola, University of Zagreb, Zagreb, Croatia e-mail: <a href="mailto:gzamola@fkit.hr">gzamola@fkit.hr</a> <b>Contact:</b> Marijeta Kralj, Ruđer Boković Institute, Zagreb, Croatia e-mail: <a href="mailto:marijeta.kralj@irb.hr">marijeta.kralj@irb.hr</a>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Cancer	Histone deacetylase 1 (HDAC1); HDAC6; BCR-ABL tyrosine kinase; platelet derived growth factor receptor (PDGFR)	<p><i>In vitro</i> studies suggest that a hybrid compound targeting protein kinases and HDACs could help treat cancer. <i>In vitro</i>, a scaffold derived from the protein kinase inhibitor Gleevec imatinib and modified with benzamide or hydroxamate inhibited HDACs 1 and 6 with efficacy comparable to that of HDAC-specific inhibitors. Several of the structures also inhibited BCR-ABL tyrosine kinase and PDGFR. <i>In vitro</i>, all of the hybrid compounds had cytotoxicity against cancer cell lines. Next steps include <i>in vivo</i> studies in tumor-bearing xenografts.</p> <p>The BCR-ABL inhibitor Gleevec is marketed by Novartis AG to treat gastrointestinal stromal tumors (GIST), chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL), myelodysplastic syndromes (MDS), myeloproliferative diseases and certain other cancer indications.</p> <p><b>SciBX 2(15); doi:10.1038/scibx.2009.613</b> Published online April 16, 2009</p>	Findings patented by Nycomed Group A/S; patent sold to 4SC AG; contact 4SC AG for licensing information	<p>Mahboobi, S. <i>et al. J. Med. Chem.</i>; published online March 20, 2009; doi:10.1021/jm800988r</p> <p><b>Contact:</b> Thomas Beckers, Nycomed GmbH, Konstanz, Germany e-mail: <a href="mailto:Thomas.Beckers@oncotest.de">Thomas.Beckers@oncotest.de</a></p> <p><b>Contact:</b> Siavosh Mahboobi, University of Regensburg, Regensburg, Germany e-mail: <a href="mailto:siavosh.mahboobi@chemie.uni-regensburg.de">siavosh.mahboobi@chemie.uni-regensburg.de</a></p>
Cancer	Macrophage scavenger receptor 1 (MSR1; SR-A; CD204); toll-like receptor 4 (TLR4)	<p>Studies in mice and in cell culture suggest that inhibiting CD204 could increase the efficacy of TLR4 agonists as immunotherapy adjuvants for cancer. CD204 knockout mice had less tumor growth when vaccinated with ovalbumin plus a TLR4 agonist than CD204-expressing controls. In cultured CD204-deficient dendritic cells (DCs), a TLR4 agonist increased the cells' capacity to activate antigen-specific T cells compared with that seen in wild-type DCs. Ongoing work is seeking to confirm the results in human antigen-presenting cells and to elucidate the mechanism by which CD204 regulates TLR4 signaling.</p> <p>GlaxoSmithKline plc's AS04 vaccine adjuvant contains the TLR4 agonist monophosphoryl lipid A. GSK's Cervarix, a vaccine against human papillomavirus (HPV) types 16 and 18 formulated with AS04, is under FDA review and is approved in more than 90 countries to prevent cervical cancer.</p> <p><b>SciBX 2(15); doi:10.1038/scibx.2009.614</b> Published online April 16, 2009</p>	Patented; available for licensing	<p>Yi, H. <i>et al. Blood</i>; published online April 6, 2009; doi:10.1182/blood-2008-11-190033</p> <p><b>Contact:</b> Xiang-Yang Wang, Roswell Park Cancer Institute, Buffalo, N.Y. e-mail: <a href="mailto:xiang-yang.wang@roswellpark.org">xiang-yang.wang@roswellpark.org</a></p>
Cancer	NEDD8 activating enzyme (NAE)	<p>Studies in cell culture and in mice suggest that inhibiting NAE could help treat cancer. In cultured human colon cancer cells, Millennium Pharmaceuticals Inc.'s NAE inhibitor MLN4294, an N<sup>6</sup>-benzyl adenosine derivative, dysregulated DNA replication and caused cell death. In mice with colon and lung xenograft tumors, MLN4294 decreased tumor volume with no significant side effects.</p> <p>Millennium, a unit of Takeda Pharmaceutical Co. Ltd., is running Phase I studies of MLN4294 to treat lymphoma, multiple myeloma (MM) and advanced nonhematological malignancies.</p> <p><b>SciBX 2(15); doi:10.1038/scibx.2009.615</b> Published online April 16, 2009</p>	Patented; unavailable for licensing	<p>Soucy, T. <i>et al. Nature</i>; published online April 8, 2009; doi:10.1038/nature07884</p> <p><b>Contact:</b> Teresa Soucy, Millennium Pharmaceuticals Inc., Cambridge, Mass. e-mail: <a href="mailto:teresa.soucy@mpi.com">teresa.soucy@mpi.com</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Cancer; brain cancer; neuroendocrine tumors	Netrin 1 (NTN1); unc-5 homolog A (UNC5A; UNC5H1); UNC5C (UNC5H3); UNC5D (UNC5H4)	<p>Studies in primary tumors, cell cultures and animals suggest that inhibiting NTN1 could help treat aggressive neuroblastoma. In infants and children with stage 4 neuroblastoma tumors, high levels of NTN1 correlated with a five-year survival rate of &lt;50%. In neuroblastoma cell cultures, NTN1 inhibition triggered apoptosis by blocking interactions between NTN1 and its receptors UNC5H1, UNC5H3 and UNC5H4. In a chicken embryo model of neuroblastoma, inhibiting NTN1 blocked primary tumor growth and the formation of lung metastases. Next steps include finding inhibitors of NTN1-UNC5H interactions, elucidating the antiapoptotic mechanism triggered by NTN1 inhibition and identifying interactions between NTN1 and other receptors.</p> <p>Netris Pharma is developing leads that target NTN1-UNC5H interactions to treat cancer. Molecular Insight Pharmaceuticals Inc.'s Azedra, a radiolabeled norepinephrine analog, is in Phase I testing to treat neuroendocrine cancer, including neuroblastomas. PharmaGap Inc.'s protein kinase C (PKC) inhibitor PhGa1 is in preclinical development to treat neuroblastoma and other cancers.</p> <p><b>SciBX 2(15); doi:10.1038/scibx.2009.616</b> <b>Published online April 16, 2009</b></p>	Patented; exclusively licensed to Netris	<p>Delloye-Bourgeois, C. <i>et al. J. Exp. Med.</i>; published online April 6, 2009; doi:10.1084/jem.20082299 <b>Contact:</b> Patrick Mehlen, University of Lyon, Lyon, France e-mail: <a href="mailto:mehlen@lyon.fnclcc.fr">mehlen@lyon.fnclcc.fr</a></p>
Chronic myelogenous leukemia (CML)	BCR-ABL tyrosine kinase	<p><i>In vitro</i> studies suggest that disrupting BCR-ABL protein complexes could help treat CML. Tandem affinity purification of the BCR-ABL protein complex identified seven proteins that are highly associated with BCR-ABL. In CML cells, kinase inhibitors disrupted some of the interactions between BCR-ABL and the seven proteins, suggesting that therapeutics targeting those interactions could potentially help treat CML. Next steps include targeting either the enzymatic functions or the protein-protein interactions in combination with kinase inhibitors in cellular systems and mouse models of CML.</p> <p>At least seven companies have BCR-ABL tyrosine kinase inhibitors in development stages ranging from clinical to marketed to treat CML.</p> <p><b>SciBX 2(15); doi:10.1038/scibx.2009.617</b> <b>Published online April 16, 2009</b></p>	Findings unpatented; unavailable for licensing	<p>Brehme, M. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online April 13, 2009; doi:10.1073/pnas.0900653106 <b>Contact:</b> Giulio Superti-Furga, Austrian Academy of Sciences, Vienna, Austria e-mail: <a href="mailto:gsuperti@cemm.oeaw.ac.at">gsuperti@cemm.oeaw.ac.at</a></p>
Melanoma	Family with sequence similarity 129, member B (FAM129B; MINERVA)	<p>Studies in cell culture suggest that levels of phosphorylated FAM129B could help predict therapeutic response in melanoma. In FAM129B-deficient melanoma cells, expression of a mutant FAM129B containing a substitution at one of its phosphorylation sites repressed cell invasion, whereas expression of wild-type FAM129B promoted cell invasion. Next steps include validating the results in clinical melanoma samples.</p> <p><b>SciBX 2(15); doi:10.1038/scibx.2009.618</b> <b>Published online April 16, 2009</b></p>	Unpatented; unlicensed	<p>Old, W. <i>et al. Mol. Cell</i>; published online April 9, 2009; doi:10.1016/j.molcel.2009.03.007 <b>Contact:</b> Natalie G. Ahn, University of Colorado Boulder, Boulder, Colo. e-mail: <a href="mailto:natalie.ahn@colorado.edu">natalie.ahn@colorado.edu</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Prostate cancer	Androgen receptor (AR)	<p>Studies in cell culture and in mice identified noncompetitive inhibitors of AR that could help treat prostate cancer. In human prostate cancer cell lines, the compounds pyrvinium and harmol lowered expression of androgen-responsive genes and inhibited cell proliferation. Wild-type mice receiving the AR competitive inhibitor bicalutamide alone or in combination with pyrvinium had prostate reductions of 35% and 74%, respectively, compared with those seen in untreated controls. Future studies could include testing the potential therapeutic effect of pyrvinium and harmol in other AR-related diseases. The generic pyrvinium pamoate is approved to treat parasitic worm infections. Harmol is a natural product found in many plants.</p> <p>AstraZeneca plc markets Casodex bicalutamide to treat prostate cancer. Bristol-Myers Squibb Co.'s AR antagonist BMS-641988 is in Phase I testing to treat prostate cancer.</p> <p><b>SciBX 2(15); doi:10.1038/scibx.2009.619</b> <b>Published online April 16, 2009</b></p>	Patent and licensing status undisclosed	<p>Jones, J. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online April 6, 2009; doi:10.1073/pnas.0807282106 <b>Contact:</b> Marc I. Diamond, University of California, San Francisco, Calif. e-mail: <a href="mailto:marc.diamond@ucsf.edu">marc.diamond@ucsf.edu</a></p>
Sarcoma	Microsomal glutathione S-transferase 1 (MGST1)	<p><i>In vitro</i> studies suggest that MGST1 expression could help predict response to chemotherapy and guide choice of therapy for Ewing sarcoma. In 30 primary tumor samples, a genetic screen showed that <i>MGST1</i> expression was associated with doxorubicin sensitivity. Similar results were seen in Ewing sarcoma cell lines. An inhibitor of glutathione S-transferase enzymes was effective against six Ewing sarcoma cell lines. Next steps could include further mechanistic studies to determine the function of MGST1 in drug resistance.</p> <p>Telik Inc.'s TLK286, a glutathione analog activated by glutathione S-transferase P1-1 (GSTP1; GST P1-1), is in Phase III testing to treat ovarian cancer and non-small cell lung cancer (NSCLC) and Phase II testing to treat breast and colorectal cancer.</p> <p><b>SciBX 2(15); doi:10.1038/scibx.2009.620</b> <b>Published online April 16, 2009</b></p>	Patent and licensing status unavailable	<p>Scotlandi, K. <i>et al. J. Clin. Oncol.</i>; published online March 23, 2009; doi:10.1200/JCO.2008.19.2542 <b>Contact:</b> Katia Scotlandi, Orthopaedic Institute Rizzoli, Bologna, Italy e-mail: <a href="mailto:katia.scotlandi@ior.it">katia.scotlandi@ior.it</a></p>
<b>Dermatology</b>				
Wounds	Platelet derived growth factor B (PDGFB); integrin $\alpha_3\beta_1$	<p>A lipopeptide-plasmid complex delivery system may be useful as a single-dose, nonviral gene therapy approach to treat chronic wounds. In a diabetic rat model of chronic wound, an integrin <math>\alpha_3\beta_1</math> receptor-targeting Arg-Gly-Asp-Lys (RGDK) lipopeptide-rhPDGFB complex significantly increased the rate of wound healing compared with the effect of using a complex containing a control lipopeptide or an uncomplexed RGDK lipopeptide (<math>p &lt; 0.01</math> for both). Next steps include evaluating the systemic potential of the <i>RGDK-rhPDGFB</i> gene complex in humans.</p> <p><b>SciBX 2(15); doi:10.1038/scibx.2009.621</b> <b>Published online April 16, 2009</b></p>	Patent and licensing status undisclosed	<p>Bhattacharyya, J. <i>et al. Mol. Pharm.</i>; published online April 2, 2009; doi:10.1021/mp800231z <b>Contact:</b> Arabinda Chaudhuri, Indian Council of Medical Research, Hyderabad, India e-mail: <a href="mailto:arabinda@iict.res.in">arabinda@iict.res.in</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Endocrine disease</b>				
Diabetes	Peroxisome proliferator-activated receptor- $\gamma$ (PPARG; PPAR $\gamma$ )	SAR studies identified a selective PPAR $\gamma$ agonist that could be safer than other PPAR $\gamma$ -targeting compounds for treating diabetes. <i>In vitro</i> , the indole-based agonist with a modified tail incorporating 4-phenylbenzophorine had 80–100 times greater selectivity for PPAR $\gamma$ over PPAR $\alpha$ and showed 2–4 times better agonist activity for PPAR $\gamma$ than the marketed drug Avandia rosiglitazone. X-ray cocrystallization of the modified indole compound with PPAR $\gamma$ identified structural properties to support its potency and selectivity for the receptor. Next steps could include testing the agonists in animal models of diabetes. GlaxoSmithKline plc markets Avandia to treat diabetes. At least nine other companies have PPAR $\gamma$ agonists in development stages ranging from clinical to marketed to treat diabetes.  <b>SciBX 2(15); doi:10.1038/scibx.2009.622</b> <b>Published online April 16, 2009</b>	Patent and licensing status unavailable	Lin, C. <i>et al. J. Med. Chem.</i> ; published online March 20, 2009; doi:10.1021/jm801594x <b>Contact:</b> Hsing-Pang Hsieh, National Health Research Institutes, Taiwan e-mail: <a href="mailto:hphsieh@nhri.org.tw">hphsieh@nhri.org.tw</a> <b>Contact:</b> Su-Ying Wu, same affiliation as above e-mail: <a href="mailto:suying@nhri.org.tw">suying@nhri.org.tw</a>
<b>Hematology</b>				
Anemia; hemochromatosis	Hypoxia-inducible factor 2 $\alpha$ (EPAS1; HIF2A); solute carrier family 11 (proton-coupled divalent metal ion transporters), member 2 (SLC11A2; DMT1)	Studies in mice suggest that upregulating HIF2A could help treat anemia, whereas inhibiting the transcription factor could help decrease iron absorption to treat iron accumulation disorders such as hemochromatosis. In mice, specific <i>hif2a</i> deletion led to lower expression of <i>dmt1</i> , the principal intestinal iron transporter, and decreased serum and liver iron levels compared with what was seen in wild-type controls. Next steps could include screening for compounds that modulate HIF2A activity and testing them in models of iron disorders.  <b>SciBX 2(15); doi:10.1038/scibx.2009.623</b> <b>Published online April 16, 2009</b>	Patent and licensing status unavailable	Mastrogiannaki, M. <i>et al. J. Clin. Invest.</i> ; published online April 6, 2009; doi:10.1172/JCI38499 <b>Contact:</b> Carole Peyssonnaud, University Paris Descartes, CNRS, Paris, France e-mail: <a href="mailto:carole.peyssonnaud@inserm.fr">carole.peyssonnaud@inserm.fr</a>
<b>Infectious disease</b>				
Fungal infection	IL-1 $\beta$ ; NLR family pyrin domain containing 3 (NLRP3; NALP3); syk tyrosine kinase (SYK)	A study in mice and in cell culture suggests that activating the SYK-NLRP3 inflammasome pathway could help treat fungal infections. In a mouse model of <i>Candida albicans</i> challenge, <i>Nlrp3</i> knockout led to significantly less survival than that seen in wild-type controls ( $p < 0.0001$ ), and it also led to defective production of IL-1 $\beta$ , a cytokine that mediates fungal immunity. Studies in bone marrow-derived dendritic cells (DCs) showed that SYK signaling is involved in fungus-mediated activation of the NLRP3 inflammasome. Next steps include studying the functions of SYK in inflammasome activation. Tamatnib fosdium, a SYK kinase inhibitor from Rigel Pharmaceuticals Inc., is in Phase II testing for various cancers and autoimmune diseases.  <b>SciBX 2(15); doi:10.1038/scibx.2009.624</b> <b>Published online April 16, 2009</b>	Patent and licensing status unavailable	Gross, O. <i>et al. Nature</i> ; published online April 2, 2009; doi:10.1038/nature07965 <b>Contact:</b> Jürgen Ruland, Technical University of Munchen, Munich, Germany e-mail: <a href="mailto:jruland@lrz.tum.de">jruland@lrz.tum.de</a>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
HCV	HCV nonstructural protein 5B (NS5B)	<i>In vitro</i> studies suggest that fluorinated analogs of 4'-azidocytidine could help treat HCV infection. HCV replication assays identified a mono-fluorinated analog that inhibited NS5B at concentrations of 24 nM, which is 50-fold more potent than nonfluorinated 4'-azidocytidine. Cell viability and cell proliferation studies showed that the analogs had no significant toxic effects. Next steps include using SAR studies of the derivatives to help design and optimize additional NS5B inhibitors. R1626, a prodrug of nucleoside analog R1479 that inhibits NS5B, from Roche, is in Phase II testing to treat HCV.  <b>SciBX 2(15); doi:10.1038/scibx.2009.625</b> <b>Published online April 16, 2009</b>	Patent and licensing status undisclosed	Smith, D. <i>et al. J. Med. Chem.</i> ; published online April 2, 2009; doi:10.1021/jm801595c <b>Contact:</b> Mark Smith, Roche Palo Alto LLC, Palo Alto, Calif. e-mail: <a href="mailto:Mark.Smith@Roche.com">Mark.Smith@Roche.com</a>
HIV/AIDS; influenza virus	IL-28B	<i>In vitro</i> and mouse studies suggest that IL-28B could be a useful adjuvant for DNA vaccines. In mice, co-delivery of an adjuvant plasmid encoding IL-28B and an HIV-1 Gag protein increased Gag-specific immune responses compared with the effect of co-delivery using an IL-12 plasmid adjuvant. In mice, co-delivery of the IL-28B plasmid and a plasmid encoding the influenza nucleoprotein protected all mice from lethal influenza virus compared with the effect of using the plasmid encoding the influenza nucleoprotein alone. Next steps could include evaluating the IL-28B-encoding plasmid as an adjuvant in DNA vaccines to treat cancer or infectious disease.  <b>SciBX 2(15); doi:10.1038/scibx.2009.626</b> <b>Published online April 16, 2009</b>	Patent and licensing status unavailable	Morrow, M. <i>et al. Blood</i> ; published online March 20, 2009; doi:10.1182/blood-2008-11-190520 <b>Contact:</b> David B. Weiner, University of Pennsylvania School of Medicine, Philadelphia, Pa. e-mail: <a href="mailto:dbweiner@mail.med.upenn.edu">dbweiner@mail.med.upenn.edu</a>
Leishmaniasis	Not applicable	<i>In vitro</i> studies suggest that Kahalalide F analogs could help treat leishmaniasis. <i>In vitro</i> , micromolar concentrations of seven depsipeptide Kahalalide F analogs inhibited proliferation of <i>Leishmania</i> in both its promastigote and amastigote phases. Also <i>in vitro</i> , the analogs caused a concentration-dependent decrease in membrane permeability, depolarizing the parasite's plasma membrane and impairing the parasite's bioenergetic metabolism. Next steps could include testing the analogs in animal models of the infection. PharmaMar S.A.'s Kahalalide F is in Phase II testing to treat psoriasis and Phase I and II testing for cancer.  <b>SciBX 2(15); doi:10.1038/scibx.2009.627</b> <b>Published online April 16, 2009</b>	Patent and licensing status unavailable	Albericio, F. <i>et al. Mol. Pharm.</i> ; published online March 24, 2009; doi:10.1021/mp8001039 <b>Contact:</b> Luis Rivas, Center for Biological Investigations, Madrid, Spain e-mail: <a href="mailto:luis.rivas@cib.csic.es">luis.rivas@cib.csic.es</a> <b>Contact:</b> Fernando Albericio, University of Barcelona, Barcelona, Spain e-mail: <a href="mailto:albericio@irbbarcelona.org">albericio@irbbarcelona.org</a>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Malaria	Not applicable	An SAR study identified a series of acridone compounds that could be useful for treating malaria. <i>In vitro</i> , the lead compound T3.5 had potency against several strains of chloroquine-sensitive and chloroquine-resistant <i>Plasmodium falciparum</i> . In combination with traditional quinoline antimalarials, T3.5 was able to reverse resistance in quinoline-resistant <i>P. falciparum</i> . In mice, T3.5 showed dose-dependent efficacy and no adverse effects. Next steps include further optimization of the compounds and testing in larger animal models.  <b>SciBX 2(15); doi:10.1038/scibx.2009.628</b> <b>Published online April 16, 2009</b>	Compounds covered under a patent cooperation treaty patent application; available for licensing <b>Contact:</b> Michele Gunness, Oregon Health and Science University, Portland, Ore. e-mail: <a href="mailto:gunnessm@ohsu.edu">gunnessm@ohsu.edu</a>	Kelly, J. <i>et al. Nature</i> ; published online April 8, 2009; doi:10.1038/nature07937 <b>Contact:</b> Jane Kelly, Veteran Affairs Medical Center, Portland, Ore. e-mail: <a href="mailto:kellyja@ohsu.edu">kellyja@ohsu.edu</a>
Malaria	<i>Plasmodium falciparum</i> histone deacetylase 1 (PFI1260c; HDAC1)	An <i>in vitro</i> study identified <i>P. falciparum</i> -specific HDAC1 inhibitors that may be useful for treating malaria. <i>In vitro</i> , four of the compounds inhibited <i>P. falciparum</i> HDAC1 and parasite proliferation with nanomolar IC <sub>50</sub> values. Next steps include optimizing the compounds and evaluating their efficacy in murine models of malaria infection. Zolinza vorinostat, an HDAC inhibitor from Merck & Co. Inc., is marketed to treat cutaneous T cell lymphoma (CTCL). Belinostat, a small molecule HDAC inhibitor from TopoTarget A/S, is in Phase III testing to treat T cell lymphoma. At least 18 other companies have HDAC inhibitors in Phase II or earlier development.  <b>SciBX 2(15); doi:10.1038/scibx.2009.629</b> <b>Published online April 16, 2009</b>	Patent and licensing status unavailable	Patel, V. <i>et al. J. Med. Chem.</i> ; published online March 24, 2009; doi:10.1021/jm801654y <b>Contact:</b> Jon Clardy, Harvard University, Cambridge, Mass. e-mail: <a href="mailto:jon_clardy@hms.harvard.edu">jon_clardy@hms.harvard.edu</a>
Malaria; toxoplasmosis	Calpain 1 (CAPN1)	Studies in cell culture suggest that inhibiting host calpain activity could be useful for treating malaria and toxoplasmosis. In cultured human erythrocytes, inhibition of CAPN1 prevented <i>Plasmodium falciparum</i> parasites from escaping infected cells, thus preventing the parasites from proliferating. Similarly, small interfering RNA-mediated suppression or genetic deletion of calpain activity blocked escape of <i>Toxoplasma gondii</i> parasites in infected mammalian fibroblasts. Next steps include studies in mice to verify that parasitic escape is mediated by host calpains.  <b>SciBX 2(15); doi:10.1038/scibx.2009.630</b> <b>Published online April 16, 2009</b>	Unpatented; unlicensed	Chandramohanadas, R. <i>et al. Science</i> ; published online April 2, 2009; doi:10.1126/science.1171085 <b>Contact:</b> Doron C. Greenbaum, University of Pennsylvania, Philadelphia, Pa. e-mail: <a href="mailto:dorong@upenn.edu">dorong@upenn.edu</a>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Metabolic disease</b>				
Dyslipidemia	Arrestin $\beta$ 1 (ARRB1); G protein-coupled receptor 109A (GPR109A; HM74A)	<i>In vitro</i> and mouse studies suggest that GPR109A agonists that do not stimulate ARRB1 could help treat dyslipidemia with fewer flushing side effects. The GPR109A agonist nicotinic acid lowers triglycerides and high-density lipoprotein but also causes flushing. In cell culture, nicotinic acid caused ARRB1-mediated release of a prostaglandin D <sub>2</sub> precursor that causes vasodilation and flushing. In ARRB1-deficient mice treated with nicotinic acid, cutaneous flushing was decreased, but serum free fatty acid levels were similar to those of wild-type mice. The next steps include identifying a G protein-based ligand that activates GPR109A in an ARRB1-independent way. Incyte Corp's INCB1902, a GPR109A agonist, is in Phase I testing to treat diabetes. Taisho Pharmaceutical Co. Ltd. and Arena Pharmaceuticals Inc. have a GPCR modulator targeting GPR109A in Phase I testing in neurology.	Provisional patent application filed; screening concept for biased niacin receptor ligands or parathyroid receptor hormones available for licensing	Walters, R. <i>et al. J. Clin. Invest.</i> ; published online April 6, 2009; doi:10.1172/JCI36806 <b>Contact:</b> Robert J. Lefkowitz, Duke University Medical Center, Durham, N.C. e-mail: <a href="mailto:lefk001@receptor-biol.duke.edu">lefk001@receptor-biol.duke.edu</a>
<b>SciBX 2(15); doi:10.1038/scibx.2009.631 Published online April 16, 2009</b>				
<b>Musculoskeletal disease</b>				
Bone repair	Wnt	Studies in mice suggest that mesenchymal stem cells overexpressing Wnt could be useful for increasing bone formation to help heal bone fractures. In a mouse model of ectopic bone formation, implants of Wnt-overexpressing human mesenchymal stem cells mixed with hydroxyapatite (HA)/tri-Ca phosphate (TCP) ceramic powder increased bone formation by up to 25% compared with that seen in controls that overexpressed control LacZ protein. Next steps could include testing the approach in animal models of fracture repair.	Patent application filed; unlicensed	Liu, G. <i>et al. J. Cell Biol.</i> ; published online April 6, 2009; doi:10.1083/jcb.200810137 <b>Contact:</b> Stuart A. Aaronson, Mount Sinai School of Medicine, New York, N.Y. e-mail: <a href="mailto:stuart.aaronson@mssm.edu">stuart.aaronson@mssm.edu</a>
<b>SciBX 2(15); doi:10.1038/scibx.2009.632 Published online April 16, 2009</b>				
<b>Neurology</b>				
Alzheimer's disease (AD)	Dynamin 1-like (DNM1L; DRP1)	A study in cell culture suggests that blocking S-nitrosylation of DRP1 could help treat AD. Cultured mouse neurons exposed to AD-associated $\beta$ -amyloid (A $\beta$ ) oligomers had higher levels of nitric oxide and S-nitrosylated Drp1, which coordinates mitochondrial fusion, compared with what was seen in mock-treated controls. Mutation of cysteine residue Cys664 prevented S-nitrosylation and lowered the extent of mitochondrial fragmentation and synaptic dysfunction compared with what was seen in mock-treated controls. Next steps include identifying small molecule inhibitors of DRP1 nitrosylation and testing their efficacy in animal models of AD.	Patents pending for unpublished discoveries of compounds to modulate Drp1 nitrosylation; available for licensing or partnering	Cho, D.-H. <i>et al. Science</i> ; published online April 3, 2009; doi:10.1126/science.1171091 <b>Contact:</b> Stuart A. Lipton, Burnham Institute for Medical Research, La Jolla, Calif. e-mail: <a href="mailto:slipton@burnham.org">slipton@burnham.org</a>
<b>SciBX 2(15); doi:10.1038/scibx.2009.633 Published online April 16, 2009</b>				

## This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Epilepsy; seizures	Brain-derived neurotrophic factor (BDNF); fibroblast growth factor 2 (FGF2; FGF-2)	<p>A study in rats suggests that localized hippocampal delivery of FGF-2 and BDNF may be useful for decreasing seizure frequency. In a rat model of epilepsy, hippocampal delivery of a vector containing BDNF and FGF-2 decreased the incidence of spontaneous recurrent seizures, the number of seizures per day and seizure severity compared with what was seen using a control vector. The vector also increased hippocampal volume and neurogenesis compared with that seen using the control vector. Next steps include evaluating the approach in other epilepsy models and developing better delivery methods.</p> <p>BrainStorm Cell Therapeutics Inc. has glial cell-derived neurotrophic factor-expressing and BDNF-expressing stem cells in preclinical testing to treat amyotrophic lateral sclerosis (ALS) and Parkinson's disease (PD).</p> <p>Enkam Pharmaceuticals A/S's Defakin 1, an FGF receptor activator, is in preclinical testing to treat Huntington's disease (HD).</p> <p><b>SciBX 2(15); doi:10.1038/scibx.2009.634</b> Published online April 16, 2009</p>	Work unpatented; licensing status not applicable	<p>Paradiso, B. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online April 6, 2009; doi:10.1073/pnas.0810710106</p> <p><b>Contact:</b> Michele Simonato, University of Ferrara, Ferrara, Italy e-mail: <a href="mailto:michele.simonato@unife.it">michele.simonato@unife.it</a></p>
Huntington's disease (HD)	Caspase-6 apoptosis-related cysteine peptidase (CASP6; MCH2)	<p><i>In vitro</i> studies identified sulfonamide isatin Michael acceptor (IMA) analogs that could help treat HD. <i>In vitro</i>, the analogs selectively inhibited CASP6 with nanomolar potency over CASP3. CASP6 mediates cleavage of the huntingtin protein. Next steps include identifying more potent CASP6 inhibitors for therapeutic development.</p> <p>Miraxion, a caspase inhibitor from Amarin Corp. plc and Scil Group, is in Phase III testing to treat HD.</p> <p><b>SciBX 2(15); doi:10.1038/scibx.2009.635</b> Published online April 16, 2009</p>	Invention disclosure filed; findings unpatented; licensing status undisclosed	<p>Chu, W. <i>et al. J. Med. Chem.</i>; published online March 30, 2009; doi:10.1021/jm900135r</p> <p><b>Contact:</b> Robert H. Mach, Washington University School of Medicine, St. Louis, Mo. e-mail: <a href="mailto:rhmach@mir.wustl.edu">rhmach@mir.wustl.edu</a></p>
<b>Pulmonary disease</b>				
Chronic obstructive pulmonary disorder (COPD)	Muscarinic acetylcholine receptor M3 (CHRM3) (HM3)	<p><i>In vitro</i> and <i>in vivo</i> studies identified 4-hydroxyl(diphenyl)methyl-substituted quinuclidines as CHRM3 antagonists that could help treat COPD and other conditions related to bronchoconstriction. In a mouse model of bronchoconstriction, one of the quinuclidines had an <i>in vivo</i> IC<sub>50</sub> of &lt;10nM and its activity lasted more than 48 hours. In isolated human bronchus, the compound exhibited potency and its activity persisted after washout. Next steps include further optimization of the compounds before testing in humans.</p> <p>Boehringer Ingelheim GmbH and Pfizer Inc. market the CHRM3 antagonist Spiriva tiotropium to treat COPD.</p> <p>Chiesi Farmaceutici S.p.A.'s CHF 5407, also a CHRM3 antagonist, is in preclinical testing for the indication.</p> <p><b>SciBX 2(15); doi:10.1038/scibx.2009.636</b> Published online April 16, 2009</p>	Patent and licensing status unavailable	<p>Laine, D. <i>et al. J. Med. Chem.</i>; published online March 24, 2009; doi:10.1021/jm801601v</p> <p><b>Contact:</b> Dramane I. Laine, GlaxoSmithKline plc, King of Prussia, Pa. e-mail: <a href="mailto:dramane.i.laine@gsk.com">dramane.i.laine@gsk.com</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Various</b>				
Atherosclerosis; stroke	P selectin (SELP; CD62P)	<p>A study in mice suggests that decreasing soluble SELP levels may be useful for preventing atherosclerosis and stroke-induced tissue damage. In a mouse model of ischemic stroke, mice with upregulated soluble Selp expression had significantly larger infarct sizes than wild-type controls (<math>p&lt;0.05</math>). In a mouse model of atherosclerosis, mice with upregulated soluble Selp had significantly larger atherosclerotic lesions than controls that had normal expression (<math>p&lt;0.05</math>). Next steps could include developing compounds to lower soluble SELP levels and evaluating them in preclinical animal models of stroke and atherosclerosis.</p> <p>GMI-1070, a glycomimetic inhibitor of E, P and L selectin from GlycoMimetics Inc., is in Phase I testing to treat sickle cell disease.</p> <p><b>SciBX 2(15); doi:10.1038/scibx.2009.637</b> <b>Published online April 16, 2009</b></p>	Patent application filed; licensing status undisclosed	<p>Kisucka, J. <i>et al. Blood</i>; published online April 6, 2009; doi:10.1182/blood-2008-10-186650 <b>Contact:</b> Denisa D. Wagner, Harvard Medical School, Boston, Mass. e-mail: <a href="mailto:wagner@idi.harvard.edu">wagner@idi.harvard.edu</a></p>
Brain injury; spinal cord injury (SCI); stroke; multiple sclerosis (MS)	Cannabinoid CB <sub>2</sub> receptor (CNR2; CB <sub>2</sub> )	<p>Studies in cell culture suggest that CB<sub>2</sub> agonists could be useful for protecting central neurons from axonal damage associated with brain injuries, SCI, stroke and MS. In severed central neurons, the CB<sub>2</sub> agonist JWH-015 stimulated the phosphoinositide 3-kinase (PI3K)/protein kinase B (PKB; Akt) pathway, which decreased cell death and increased neurological recovery compared with what was seen in controls. Next steps include testing CB<sub>2</sub> agonists in other models of axonal damage.</p> <p>At least four companies have CB<sub>2</sub> agonists in development stages ranging from preclinical to Phase II for various neurology indications.</p> <p><b>SciBX 2(15); doi:10.1038/scibx.2009.638</b> <b>Published online April 16, 2009</b></p>	Unpatented; unlicensed	<p>Viscomi, M. <i>et al. J. Neurosci.</i>; published online April 8, 2009; doi:10.1523/JNEUROSCI.0786-09.2009 <b>Contact:</b> Marco Molinari, Santa Lucia Foundation, Rome, Italy e-mail: <a href="mailto:m.molinari@hsantalucia.it">m.molinari@hsantalucia.it</a></p>

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## This week in techniques

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

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

Approach	Summary	Licensing status	Publication and contact information
<b>Chemistry</b>			
Multiplexed, high throughput, high accuracy array-based resequencing	A multiplexed, high throughput array-based resequencing platform could be useful for increasing the efficiency and sensitivity of large-scale genomewide association studies. In a proof-of-concept study, researchers used the platform to resequence 2,351 megabases of DNA from 473 genomic samples with a false-positive rate of about 1 per 500,000 base pairs and about 90% sensitivity. Next steps include decreasing the number, size and cost of the arrays used in the resequencing platform.  <b>SciBX 2(15); doi:10.1038/scibx.2009.639</b> <b>Published online April 16, 2009</b>	Patent and licensing status unavailable	Zheng, J. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online March 30, 2009; doi:10.1073/pnas.0901902106 <b>Contact:</b> Malek Faham, Affymetrix Inc., Santa Clara, Calif. e-mail: <a href="mailto:malekfaham@hotmail.com">malekfaham@hotmail.com</a> <b>Contact:</b> Ronald W. Davis, Stanford Genome Technology Center, Palo Alto, Calif. e-mail: <a href="mailto:dbowe@stanford.edu">dbowe@stanford.edu</a>
<b>Disease models</b>			
Fly model of the blood-brain barrier (BBB)	The fruit fly <i>Drosophila melanogaster</i> may serve as a more accurate model of the human BBB than existing animal models and could more effectively identify compounds that modulate the BBB. A genetic screen for fly mutants with a defective BBB identified multiple drug resistance 65 (Mdr65), a transporter that keeps foreign small molecules out of the nervous system. Mdr65 mutants had higher susceptibility to the neurotoxic compound vinblastine than did wild-type controls. BBB defects caused by a loss-of-function mutation in Mdr65 were corrected by transgenic expression of its human homolog, multidrug resistance (ABCB1; MDR1). Next steps include screening for small molecule antagonists of Mdr65 and testing the effects of those compounds on the BBB in higher organisms.  <b>SciBX 2(15); doi:10.1038/scibx.2009.640</b> <b>Published online April 16, 2009</b>	Patent pending on the <i>in vivo</i> blood-brain partitioning assay used in this study; available for licensing <b>Contact:</b> Joel Kirschbaum, Office of Technology Management, University of California, San Francisco, Calif. e-mail: <a href="mailto:joel.kirschbaum@ucsf.edu">joel.kirschbaum@ucsf.edu</a>	Mayer, F. <i>et al. J. Neurosci.</i> ; published online March 18, 2009; doi:10.1523/JNEUROSCI.5564-08.2009 <b>Contact:</b> Roland J. Bainton, University of California, San Francisco, Calif. e-mail: <a href="mailto:baintonr@anesthesia.ucsf.edu">baintonr@anesthesia.ucsf.edu</a>
Mouse models of acute myelogenous leukemia (AML) for predicting chemotherapy response	A series of mouse models of human AML could be useful for predicting responses to chemotherapy. Researchers generated a series of mice with common AML genotypes and treated the mice with cytarabine and doxorubicin. Mice expressing the <i>AML1-ETO9a</i> fusion oncogene were more responsive to chemotherapy and had better survival than mice expressing the <i>MLL-ENL</i> fusion oncogene. Loss of p53 accelerated AML and decreased survival to a greater extent in mice expressing <i>AML1-ETO9a</i> compared with what was seen in mice expressing <i>MLL-ENL</i> . The models are available for use.  <b>SciBX 2(15); doi:10.1038/scibx.2009.641</b> <b>Published online April 16, 2009</b>	Patent pending covering AML mouse models; available for licensing from the Office of Technology Transfer at Cold Spring Harbor Laboratory	Zuber, J. <i>et al. Genes Dev.</i> ; published online April 1, 2009; doi:10.1101/gad.1771409 <b>Contact:</b> Scott W. Lowe, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y. e-mail: <a href="mailto:lowe@cshl.edu">lowe@cshl.edu</a>

## This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
<b>Drug delivery</b>			
High stability, pH-responsive small interfering RNA-polymer conjugate for <i>in vivo</i> applications	A pH-responsive, endosomolytic siRNA-polymer conjugate could be useful for increasing the extracellular stability and effectiveness of siRNA. The conjugate consisted of polylysine (PLL)-bound RNA, polyethylene glycol (PEG) and the endosomolytic peptide melittin, which is released at endosomal pH levels. <i>In vitro</i> , the conjugate was stable in the presence of the anticoagulant heparin and displayed favorable biocompatibility and bioactivity. However, i.v. and intratumoral administration of the conjugate in mice showed high levels of toxicity. Next steps include developing a better nontoxic formulation of the conjugate.	Not applicable; unavailable for licensing	Meyer, M. <i>et al. Mol. Pharm.</i> ; published online April 6, 2009; doi:10.1021/mp9000124 <b>Contact:</b> Ernst Wagner, Ludwig Maximillians University, Munchen, Germany e-mail: <a href="mailto:ernst.wagner@cup.uni-muenchen.de">ernst.wagner@cup.uni-muenchen.de</a>
<b>SciBX 2(15); doi:10.1038/scibx.2009.642</b> Published online April 16, 2009			
<b>Drug platforms</b>			
Expansion of T <sub>reg</sub> cells using IL-2-mAb complexes to treat multiple sclerosis (MS)	Injections of IL-2-mAb complexes could be a useful approach for inducing rapid expansion of T <sub>reg</sub> cells to treat MS. High numbers of T <sub>reg</sub> cells can potentially help decrease the intensity of autoimmune responses. In mice, IL-2 mixed with an IL-2 mAb increased T <sub>reg</sub> cells by up to 10-fold in the liver, gut, spleen and lymph nodes compared with what was seen in controls. Mice pretreated with the IL-2-mAb complexes were resistant to induced experimental autoimmune encephalomyelitis (EAE), a model of MS. Next steps include testing the IL-2-mAb complexes in a relapsing/remitting model of disease.	Worldwide patent application filed by Nascent Biologics Inc. for IL-2-mAb complexes; unlicensed	Webster, K. <i>et al. J. Exp. Med.</i> ; published online March 30, 2009; doi:10.1084/jem.20082824 <b>Contact:</b> Jonathan Sprent, Garvan Institute of Medical Research, Darlinghurst, Australia e-mail: <a href="mailto:j.sprent@garvan.org.au">j.sprent@garvan.org.au</a>
<b>SciBX 2(15); doi:10.1038/scibx.2009.643</b> Published online April 16, 2009			
Plant-based production of a recombinant microbicidal protein to prevent HIV transmission	A recombinant protein produced in tobacco could be useful for preventing HIV transmission. Large-scale quantities of griffithsin, an algae-derived protein with antimicrobial properties, were prepared in transgenic tobacco and had comparable HIV binding properties to <i>Escherichia coli</i> -derived recombinant griffithsin. In human cervical explants, tobacco-derived griffithsin decreased HIV-1 proliferation after viral challenge compared with that seen in untreated controls. In a rabbit assay of vaginal irritancy, tobacco-derived griffithsin caused less epithelial irritation than Conceptrol, a marketed spermicidal gel. Next steps include human safety trials.	Manufacturing procedure patented by Kentucky Bioprocessing LLC; griffithsin is patented by the National Cancer Institute and is licensed to Intrucept Biomedicine LLC	O'Keefe, B.R. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online March 30, 2009; doi:10.1073/pnas.0901506106 <b>Contact:</b> Kenneth Palmer, Owensboro Cancer Research Program, Owensboro, Ky. e-mail: <a href="mailto:kepal02@gwise.louisville.edu">kepal02@gwise.louisville.edu</a>
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 Cannabinoid CB<sub>2</sub> receptor 19  
 CAPN1 16  
 CARD15 9  
 Casodex 13  
 CASP3 18  
 CASP6 18  
 Caspase-6 apoptosis-related cysteine peptidase 18  
 Caspase recruitment domain family member 15 9  
 CAT-354 5  
 CB<sub>2</sub> 19  
 CC chemokine receptor 2 6  
 CC chemokine receptor 6 9  
 CCL2 5  
 CCL20 5  
 CCR2 6  
 CCR6 9  
 CD204 11  
 CD62P 19  
 Cervarix 11  
 Chemokine C-C motif ligand 20 5  
 CHF 5407 18  
 Chloroquine 16  
 CHRM3 18  
 CNR2 19  
 Conceptrol 21  
 Corticosteroid 4  
 CRX-526 4  
 Cytarabine 20

**D**

Defakin 1 18  
 Der p 2 5  
 DMT1 14  
 DNMT1L 17  
 Doxorubicin 13,20  
 DPC4 10  
 DRP1 17  
 Dynamin 1-like 17  
 Dystrophin 7

**E**

E5564 4  
 Emetine 1  
 EN 20  
 EndoTAG-1 6  
 EPAS1 14  
 EPX-102216 6  
 Eritoran 4  
 ETO9a 20

**F**

FAM129B 12  
 Family with sequence similarity 129, member B 12  
 FGF-2 18  
 FGF2 18  
 Fibroblast growth factor 2 18  
 Follistatin 7  
 Fosdium 14  
 FRK 10  
 Fyn-related kinase 10

**G**

Gleevec 11  
 Glutathione S-transferase P1-1 13

Glutathione S-transferase  $\omega$ 1 1  
 GMI-1070 19  
 GPR109A 17  
 G protein-coupled receptor 109A 17  
 Griffithsin 21  
 GSTO1 1  
 GSTP1 13  
 GST P1-1 13  
 Guaifenesin 7  
 Guaifenesin dinitrate 7

**H**

HA 17  
 Harmol 13  
 HCV nonstructural protein 5B 15  
 HDAC1 11,16  
 HDAC6 11  
 Heparin 21  
 HIF2A 14  
 Histone deacetylase 1 11  
 HIV-1 Gag protein 15  
 HM74A 17  
 Hydroxamate 11  
 Hydroxyapatite 17  
 Hypoxia-inducible factor 2 $\alpha$  14

**I**

IgE 5  
 IL-10 9  
 IL-12 15  
 IL-13 5  
 IL-1 $\beta$  14  
 IL-2 21  
 IL-28B 15  
 IL-4 5  
 IMA 18  
 Imatinib 11  
 INCB1902 17  
 INOmax inhaled nitric oxide 7  
 Integrin  $\alpha_5\beta_1$  13  
 Isosorbide dinitrate 7

**J**

JWH-015 19

**K**

Kahalalide F 15

**L**

LacZ 17  
 Leukemia inhibitory factor 10  
 LIF 10  
 Lipopolysaccharide 4  
 LPS 4

**M**

Macrophage scavenger receptor 1 11  
 MADH4 10  
 MCH2 18  
 MCP-1 5  
 MDR1 20  
 Mdr65 20  
 Melittin 21  
 Methocarbamol 7  
 MGST1 13  
 Microsomal glutathione S-transferase 1 13  
 MINERVA 12

MIP3A	5	<b>P</b>	PTEN	10	<b>T</b>	TAK-242	4
Miraxion	18	P selectin	19	Pyridylbenzo[b]thiophene-2-	10	Tamatinib	14
MLL	20	p53	20	carboxamide	10	TCP	17
MLN4294	11	Paclitaxel	6	Pyrvinium	13	TEP1	10
MMAC1	10	Pamoate	13	<b>Q</b>		TGFβ	10
Monocyte chemoattractant protein-1	5	PDGFB	13	Quinoline	16	TGFB1	10
Monophosphoryl lipid A	11	PDGFR	11	Quinuclidine	18	TGFβ1	10
MSR1	11	PEG	21	<b>R</b>		Tiotropium	18
Multidrug resistance	20	Peroxisome proliferator-activated receptor-γ	14	R1479	15	TLK286	13
Multiple drug resistance 65	20	PFI1260c	16	R1626	15	TLR4	4,11
Muscarinic M3 receptor	18	PhGa1	12	RAK	10	Toll-like receptor 4	4,11
<b>N</b>		Phosphatase and tensin homolog deleted on chromosome ten	10	RBBP9	1	Transforming growth factor-β	10
N <sup>6</sup> -benzyl adenosine	11	Phosphoinositide 3-kinase	19	Retinoblastoma binding protein 9	1	Tri-Ca phosphate	17
NAE	11	PI3K	19	<b>S</b>		<b>U</b>	
NALP3	14	PKB	19	SELP	19	Unc-5 homolog A	12
NEDD8 activating enzyme	11	PKC	12	SLC11A2	14	UNC5A	12
Netrin 1	12	<i>Plasmodium falciparum</i> histone deacetylase 1	16	SMAD4	10	UNC5C	12
NI-0101	4	Platelet derived growth factor B chain	13	SMAD family member 4	10	UNC5D	12
Nicotinic acid	17	Platelet derived growth factor receptor	11	Solute carrier family 11 (proton-coupled divalent metal ion transporters), member 2	14	UNC5H1	12
Nitric oxide	7	PLL	21	Spiriva	18	UNC5H3	12
NLR family pyrin domain containing 3	14	Polyethylene glycol	21	SR-A	11	UNC5H4	12
NLRP3	14	Polylysine	21	Sulfonamide isatin Michael acceptor	18	<b>V</b>	
NO	7	PPARα	14	SYK	14	Vinblastine	20
NOD2	9	PPARG	14	Syk tyrosine kinase	14	Vorinostat	16
Norepinephrine	12	PPARγ	14			<b>W</b>	
NS5B	15	Prostaglandin D <sub>2</sub>	17			Wnt	17
NTN1	12	Protein kinase B	19			<b>X</b>	
<b>O</b>		Protein kinase C	12			Xolair	5
Omalizumab	5					<b>Z</b>	
Ovalbumin	11					Zolinza	16