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# Bulking up immunity with instant Abs

By Michael J. Haas, Senior Writer

When **Pfizer Inc.** bought CovX Pharmaceuticals Inc. in 2007, the driver of the deal was the biotech's CovX-Body technology, which used a single antibody as a scaffold on which to build multiple product candidates that could be given via infusion. Pfizer may earn bonus miles from its acquisition, as CovX's cofounder at **The Scripps Research Institute** has now devised a way to produce the antibody therapeutics entirely *in vivo*, potentially obviating the need for infusions.

The technology, which is already licensed to Pfizer, uses a vaccine to induce the antibody scaffold, then a chemical agent to modify and direct the antibody against a specific disease target, thereby providing what the Scripps team has termed "instant immunity."

The group has shown proof of principle in mouse models of cancer and thinks the technology for chemically programmed antibodies could work against infectious diseases.

Unlike most antibodies, which bind their targets noncovalently, the antibody scaffolds used by Pfizer and Scripps are capable of binding their targets covalently, so that antibody and target fuse into a single molecule. Such antibodies were first reported in 1995 by a team led by Carlos Barbas III, chair of molecular biology at Scripps. The group found that mice injected with a small molecule (1,3-diketone) always developed antibodies that could covalently bind that molecule.<sup>1</sup>

According to team member Richard Lerner, now president at Scripps as well as a professor of chemistry and immunochemistry, this led to the hypothesis that the antibodies could be programmed against disease targets by linking a target-specific molecule to the antibody-inducing diketone.

Lerner and Barbas formed CovX in 2002 to commercialize these antibodies.

## Abs training

The first-generation therapeutics are produced *ex vivo* and must be delivered by infusion. The latest Scripps work, also led by Barbas, investigated whether therapeutic antibodies could be produced and programmed entirely *in vivo*.

First, the team ascertained whether the anti-diketone antibody scaffold could find and bind a programming agent *in vivo*. To do this, they inoculated healthy mice with a vaccine based on a 1,3-diketone. Sixty-five days later they injected the mice with a programming agent composed of a diketone linked to an inhibitor of two antiangiogenic integrins: integrin  $\alpha_v\beta_3$  and integrin  $\alpha_v\beta_5$ .

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Experiments on serum pooled from the treated mice confirmed that the antibodies and programming agent had indeed found one another *in vivo* and fused into programmed antibodies (see **Figure 1**, “**Production of chemically programmed antibodies *in vivo***”).

The team repeated the treatment with the vaccine and programming agent in mouse models of colon cancer and melanoma and observed decreases in tumor growth of more than 75% compared with that seen in controls.

The findings were published in the *Proceedings of the National Academy of Sciences*.<sup>2</sup>

In the paper, the team also suggested that programmed antibodies could induce immunity against infectious diseases such as HIV, malaria and pandemic flu.

To do so, Lerner told SciBX that humans could be inoculated with the diketone at any time to induce the programmable antibodies. “You could then give a chemical programming agent as needed to activate this reservoir of antibodies” against an emerging disease or even a chemical threat such as nerve gas to confer immunity almost instantaneously, he said. Lerner added that chemical programming agents could be taken orally.

Barbas noted that the approach would have lower production and prescription costs than infused antibody therapies.

**Abs vantage points**

Other researchers agreed that the technology is ready to test in cancer and potentially autoimmune disease, but they said direct evidence for its effectiveness against infectious disease is lacking.

Fons Uytdehaag, senior director of R&D strategy development at vaccine company **Crucell N.V.**, said the Scripps approach has a big advantage over immunization with recombinant or vectored vaccines because it induces a universal immune response and memory, then rapidly directs that response against a disease target with the chemical programming agent.

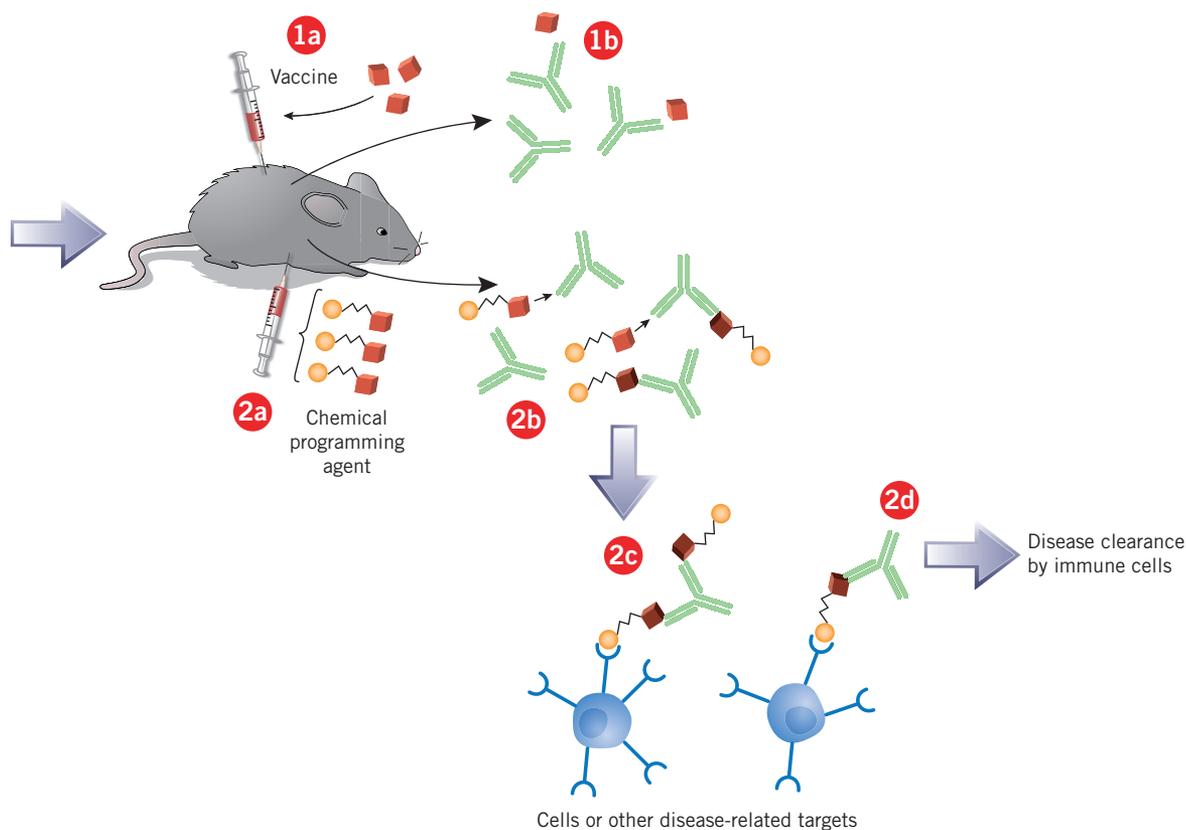
Eric Guenzi, associate director of immunology research at cancer and autoimmune disease company **MediGene AG**, agreed that the instant immunity conferred by programmed antibodies offers a major selling point over conventional vaccines or infused antibody therapy.

“You could use this approach to re-create and reprogram therapeutic agents—which previously would have to be injected—by inducing instant immunity through vaccination with reactive compounds,” he said. “With this system, your body does the job.”

Guenzi said the results in cancer were promising, but he wanted to see animal studies showing that programmed antibodies could induce regression in established tumors and prevent metastasis. “It would be highly relevant to check the efficacy of the reprogrammed antibodies after the tumor has been established” for 2–3 weeks instead of beginning treatment before increasing tumor volume or tumor growth were measurable, as the Barbas collaborators did in their study, he said.

Guenzi also wanted to see experiments against more established cancer targets. “To my knowledge, the efficacy of inhibitors of  $\alpha_v\beta_3$  and  $\alpha_v\beta_5$  integrins has not been established in the clinic,” he said.

Nevertheless, Guenzi noted that past approaches to treating cancer with therapeutic antibodies required adjuvant therapy. “Here they showed inhibition of tumor growth without recourse to adjuvant therapy, which is a clear advantage,” he said.



**Figure 1. Production of chemically programmed antibodies *in vivo*.** In a paper in the *Proceedings of the National Academy of Sciences*, Popkov *et al.* showed a process for generating chemically programmed antibodies in mice:

**[1a]** In the first stage of the process, mice are inoculated with a vaccine consisting of a specific kind of small molecule, a 1,3-diketone (brown cube).

**[1b]** As a result, mice generate an antibody response against the diketone molecule.

**[2a]** In the second stage, the immunized mice are injected with a chemical programming agent composed of the diketone linked to a therapeutic moiety (yellow circle), designed to bind a disease target.

**[2b]** The diketone moiety of the programming agent re-elicits the antibody response triggered in the first stage and covalently binds to the anti-diketone moiety of the generated antibodies.

**[2c]** The antibodies are now programmed to bind to the disease target via the therapeutic moiety.

**[2d]** The target-programmed antibody complex is cleared by the immune system following binding to the programmed antibody's Fc region.

Guenzi said the Barbas team's approach also allowed control over the immune response to self-antigens, which would avoid long-term safety issues that could arise when vaccinating against self-antigens.

"This is the first time I've read about something that combines an immunization approach with a short, intense reaction that controls the immune response and the memory of immune response," he said. "If you stop taking the programming agent, you stop the reactions, making the immune response controllable and reversible. This is a very important point for both cancer and autoimmune conditions."

Robert Rickert, associate professor of inflammatory diseases at the **Burnham Institute for Medical Research**, agreed that the technology provides a broad platform that could apply to multiple diseases. "The key will be to find appropriate therapeutic molecules or peptides that can be combined with the diketone" to make programming agents that are as effective as those used in the *PNAS* study, he said.

Barbas said his group has not encountered any significant difficulties in synthesizing programming agents. "Usually there is a site on a therapeutic peptide or small molecule that can be used for linkage" to the diketone, he said.

#### Ab extensions

There was less consensus about whether the technology could extend to infectious diseases.

Rickert said the technology's effectiveness against infection needs to be demonstrated, "but it is a perfectly valid extrapolation to make from these findings. The challenge with targeting pathogens will be that they are constantly evolving and mutating."

Thus, he said a programming agent should direct antibodies against a conserved site on a pathogen. Otherwise, the agent would be useless once the pathogen mutates—for example, as seasonal flu does.

MediGene's Guenzi was more cautious. "There is no evidence in the paper that this system could be used for non-self-antigens," he said.

Crucell's Uytdehaag agreed that preventing infection with programmed antibodies was a long way off. "For vaccination against viral diseases, it remains to be demonstrated whether programmed antibodies can neutralize—not just bind—a virus," he said.

Uytdehaag said that success in treating malaria, HIV and flu would depend on developing chemical programming agents with high affinity for the pathogens. He agreed with Rickert that such agents should target highly conserved epitopes to prevent escape mutations.

Uytdehaag also said there would be logistical issues in using the programmable antibodies for many infectious diseases.

"The broad and universal applicability of the technology to create instant immunity in the event of, for example, a flu pandemic, would require a pre-existing immunity to the [diketone] in the general population," he said. "Mass immunization early in life to generate a long-lived memory B cell response to the diketone is theoretically possible, but there may be ethical and regulatory issues involved with such an approach."

Rickert disagreed, noting that the diketone used by the Barbas team was inert, did not accumulate in the body and had no known human toxicity.

Lerner concurred with Rickert, adding that the compounds used

**"If you stop taking the programming agent, you stop the reactions, making the immune response controllable and reversible. This is a very important point for both cancer and autoimmune conditions."**

**—Eric Guenzi, MediGene AG**

by CovX and Pfizer to induce the antibody scaffolds have long-standing safety records in humans. Thus, he didn't anticipate significant ethical or regulatory hurdles to generating pre-existing, programmable immunity in the general population.

Barbas said his group has developed a variety of different antibodies that are also suitable for chemical programming and just as versatile as the anti-diketone antibodies. He added that his group is working to advance the technology described in *PNAS* to treat HIV, influenza and cancer.

Lerner said Scripps holds all of the IP related to chemically programmed antibodies and Pfizer has licensed the rights.

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# Hitting Hsp90 where it hurts

By Kai-Jye Lou, Staff Writer

Researchers at the **University of Massachusetts Medical School** have synthesized a class of targeted molecules called gamitrinibs that selectively inhibit Hsp90 in tumor mitochondria, the organelle where Hsp90 exerts many of its cancer-promoting effects. The compounds could have an advantage over the plethora of Hsp90 inhibitors in the clinic that exert their effects in the cytosol.<sup>1</sup>

Heat shock protein 90 (HSP90AA1; Hsp90) is a chaperone that facilitates proper protein folding in multiple signaling pathways, including those that drive tumor development and progression. In tumor cell mitochondria, the protein can preserve organelle integrity and prevent the initiation of cell death.<sup>2</sup> By contrast, in most normal cells, Hsp90 is expressed in the cytosol, where it protects the cells from environmental stressors like heat and hypoxia.

Because tumor cells can exploit the protective properties of mitochondrial Hsp90, Dario Altieri and collaborators set out to synthesize therapeutics targeted to subcellular compartments—specifically, mitochondria. “We coupled a known Hsp90 inhibitor backbone from 17-AAG with molecules that are known to target cargo to mitochondria,” he told *SciBX*. Altieri is chair of the Department of Cancer Biology at UMass Medical.

The resulting compounds, published in *The Journal of Clinical Investigation*, were geldanamycin mitochondrial matrix inhibitors (gamitrinibs). The compounds were synthesized by linking a 17-(allylamino)-17-demethoxygeldanamycin (17-AAG)-derived benzoquinone ansamycin backbone to a mitochondrial-targeting moiety. Molecular dynamic simulation studies suggested that the 17-AAG portion of gamitrinibs antagonize the ATPase pocket on Hsp90.

17-AAG from **Bristol-Myers Squibb Co.** is an ansamycin-based Hsp90 inhibitor known as tanespimycin. It is in Phase III testing for multiple myeloma (MM).

In xenograft mouse models of human leukemia, breast cancer and

lung cancer, a gamitrinib analog lowered tumor proliferation, whereas 17-AAG did not. The gamitrinib also showed activity across a panel of 12 cancer cell lines with a mean IC<sub>50</sub> of 10.9 μM. In contrast, 17-AAG showed lower efficacy in each cell line and had IC<sub>50</sub> values greater than 200 μM in 8 of 12 cell lines.

Concentrations of the gamitrinibs that killed tumor cells did not induce cell death in a panel of normal cells, and organs isolated from gamitrinib-treated mice were histologically similar to those from vehicle-treated controls.

Indeed, gamitrinibs selectively accumulated in tumor cell mitochondria, disrupted their integrity and caused cell death by mitochondria-induced apoptosis. The compounds showed negligible activity against cytosolic Hsp90.

“The most significant potential benefit of the gamitrinibs would be an improvement in the therapeutic index over the currently available ansamycins” like 17-AAG, said Luke Whitesell, a senior research scientist at the **Whitehead Institute for Biomedical Research**.

**“The gamitrinibs are cytotoxic. Rather than taking two days, the gamitrinibs kill tumor cells in one hour.”**

—Dario Altieri,  
University of Massachusetts  
Medical School

### The targeted advantage

At least eight Hsp90 inhibitors are in clinical development to treat cancer (see **Table 1**, “**Hsp90 pipeline**”). By comparison, Altieri thinks gamitrinibs have the potential for increased activity and lower toxicity.

“What we have seen is that the pool of Hsp90 in mitochondria escapes inhibition by conventional small molecule Hsp90 antagonists,” he told *SciBX*. “What we wanted to do was show that the mitochondrial pool of Hsp90 is very important for tumor cell survival.”

Data in the *JCI* article showed that the non-organelle-targeted Hsp90 inhibitors 17-AAG, IPI-504, BIIB021 and NVP-AUY922 primarily lowered cytosolic Hsp90 activity and did not disrupt mitochondrial integrity.

Altieri noted that such inhibitors typically induce a cytostatic phenotype in tumor cells. “These cells are not dead—they simply stop dividing for a while and only start to die after about two to three days,” he said. “The gamitrinibs are cytotoxic. Rather than taking two days, the gamitrinibs kill tumor cells in one hour. They eliminate a very important mechanism for maintaining mitochondrial integrity in cancer cells.”

IPI-504 from **Infinity Pharmaceuticals Inc.**, an ansamycin also known as retaspimycin, is in Phase III testing to treat gastrointestinal

**Table 1. Hsp90 pipeline.** At least eight inhibitors of heat shock protein 90 (HSP90AA1; Hsp90) are in clinical development for various cancers.

Company	Product	Indication	Status
Bristol-Myers Squibb Co. (NYSE:BMJ)	Tanespimycin	Multiple myeloma (MM) and other cancers	Phase III (MM)
Infinity Pharmaceuticals Inc. (NASDAQ:INFI)	Retaspimycin	Gastrointestinal stromal tumors (GIST) and other cancers	Phase III (GIST)
Biogen Idec Inc. (NASDAQ:BIIB)	BIIB021	GIST	Phase II
Vernalis plc (LSE:VER)/Novartis AG (NYSE:NVS; SIX:NOVN)	AUY922	Cancer	Phase I/II
Astex Therapeutics Ltd.	AT13387	Cancer	Phase I
Infinity	IPI-493	Cancer	Phase I
Kyowa Hakko Kirin Co. Ltd. (Tokyo:4151)	KW-2478	Cancer	Phase I
Synta Pharmaceuticals Corp. (NASDAQ:SNTA)	STA-9090	Cancer	Phase I

Source: BCIQ: BioCentury Online Intelligence

stromal tumors (GIST). BIIB021, a purine-based analog from **Biogen Idec Inc.**, is in Phase II testing to treat GIST. NVP-AUY922, a resorcinol-based Hsp90 inhibitor from **Vernalis plc** and **Novartis AG**, is in Phase I testing to treat solid tumors and hematological malignancies. All of the companies offered no comments about the UMass research.

Neil Thompson, SVP of biology at **Astex Therapeutics Ltd.**, which is also developing an Hsp90 product, also noted that the Hsp90 inhibitors in the clinic prompt tumor cells to induce the action of Hsp70 (HSPA4), which can counter the inhibitor's activity. "All such compounds that I am aware of elicit this compensatory mechanism," he told *SciBX*. Like Hsp90, Hsp70 is a chaperone protein that promotes cell survival and is associated with resistance to cancer drugs.<sup>3,4</sup>

Gamitrinib-treated tumor cells did not show a compensatory increase in Hsp70.

"The work opens up a new dimension to the Hsp90 field and gives us insights on how to target some diseases and cancers that have not responded to conventional Hsp90 inhibitors," said Thompson. "However, I don't think it takes anything away from current Hsp90 inhibitors that are already in the clinic."

Astex's AT13387, a non-ansamycin inhibitor of Hsp90, is in Phase I testing to treat solid tumors. The company also has an Hsp70 inhibitor program in preclinical development for cancer.

## Formal demonstrations desired

Despite the potential advantages that gamitrinibs offer over conventional Hsp90 inhibitors, researchers contacted by *SciBX* wanted to see data clearly demonstrating mitochondria-specific Hsp90 inhibition and a series of pharmacokinetic and toxicology studies.

"What they have done is to link an Hsp90 inhibitor backbone to a mitochondrial targeting moiety and assumed that it would target mitochondrial Hsp90," Thompson told *SciBX*. "But definitive evidence that these compounds are affecting mitochondrial Hsp90 is lacking."

Thompson also said that gamitrinibs are larger than other Hsp90 inhibitors and have charged chemical groups. Those features, he said, "generally come with a number of liabilities including formulation and distribution difficulties that would make it difficult for the molecule to be used as a drug."

Whitesell agreed, adding that gamitrinibs are "apparently still poorly water soluble and had to be formulated in DMSO/Cremophor for administration to animals."

The use of dimethyl sulfoxide (DMSO) in formulating 17-AAG has been implicated as a source of off-target toxicities in clinical trials.<sup>5</sup> Cremophor-based drug formulations require corticosteroid premedi-

**"Definitive evidence that these compounds are affecting mitochondrial Hsp90 is lacking."**

—Neil Thompson,  
*Astex Therapeutics Ltd.*

cation and have been associated with anaphylaxis, hyperlipidemia, abnormal lipoprotein patterns and neurotoxicity.<sup>6</sup>

Whitesell also wanted to know whether gamitrinibs could have the potential for some mitochondrial toxicity in normal tissues, which may manifest in skeletal muscle or the heart. "Full toxicology across a range

of doses and schedules will be essential," he told *SciBX*. "In addition, considerably more work needs to be done in terms of ADME characterization before one of the compounds described in this manuscript could be advanced as a true clinical candidate."

Finally, he wanted to see a pharmacokinetic study evaluating how stable the linkage between the mitochondrial-targeting and Hsp90-inhibiting moieties of the gamitrinibs are *in vivo*. "17-AAG is rapidly and extensively metabolized by the liver and something similar could happen to the gamitrinibs," he told *SciBX*. "If such metabolism occurs, the targeted parent compound would disappear very rapidly from the plasma."

Altieri said he is discussing taking the gamitrinibs into clinical development with the **National Cancer Institute**. His next steps are to conduct long-term efficacy and safety studies in animals.

He said multiple patent applications have been filed covering the structure and biology of the gamitrinibs. The compounds are available for licensing from University of Massachusetts Commercial Ventures and Intellectual Property.

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# Ganging up on TB

By Lauren Martz, Staff Writer

Work by researchers at **Albert Einstein College of Medicine of Yeshiva University** suggests that two FDA-approved antibiotics—meropenem and clavulanate—could be used in combination to overcome drug-resistant *Mycobacterium tuberculosis*.<sup>1</sup> Although the fact that meropenem must be given through i.v. could restrict use, researchers think the prevalence of drug-resistant disease makes testing the combination worthwhile.

Meropenem, marketed as Merrem by **AstraZeneca plc**, is a member of the carbapenem class of  $\beta$ -lactam antibiotics.  $\beta$ -lactam antibiotics have had little effect against tuberculosis infection because they are hydrolyzed by *M. tuberculosis*'  $\beta$ -lactamase (BLAC).<sup>2</sup>

To circumvent this problem, previous efforts have combined  $\beta$ -lactams such as amoxicillin with the BLAC inhibitor clavulanate.<sup>3</sup> Clavulanate is not marketed alone, but it is available in combination with amoxicillin as Augmentin from **GlaxoSmithKline plc**.

In a paper published in *Science*, professor of biochemistry John Blanchard and colleagues at Albert Einstein suggest that combining clavulanate with meropenem could control the infection in areas that other  $\beta$ -lactams have failed. That is because meropenem is not as readily hydrolyzed by BLAC as other  $\beta$ -lactam antibiotics, because it is a relatively poor substrate for the enzyme.

*In vitro*, clavulanate significantly increased the minimum inhibitory concentration (MIC) of meropenem and other carbapenems. The BLAC inhibitor had little effect on the MIC of other classes of  $\beta$ -lactams such as penicillins.

Under aerobic conditions, meropenem plus clavulanate decreased the number of colony-forming units and eventually killed a strain of drug-sensitive *M. tuberculosis* over 9–12 days.

The combination also inhibited bacteria grown under anaerobic conditions, which is reflective of the persistent, nonreplicative state that is often resistant to antibiotic treatment.

Finally, meropenem plus clavulanate showed efficacy against 13 clinical isolates of drug-resistant TB strains with efficacy comparable to that seen in sensitive strains.

## Straight to the clinic

Because both drugs used in the study are FDA approved, the Albert Einstein group thinks the combination is ready for clinical trials.

Brian Currie, assistant dean for clinical research and professor of clinical medicine and clinical epidemiology and population health at Albert Einstein, told *SciBX* that a study is being planned to test the combination of meropenem and Augmentin. The short-term African trial is expected to start mid-year.

Currie said the objective of the study is to show efficacy. “The drugs are FDA approved and relatively free of side effects. There shouldn't be any issues of toxicity or interactions between the two compounds,” he said. Patients will receive the combination therapy for five to seven days.

Zhenkun Ma, CSO of the **Global Alliance for TB Drug Development**, concurred. “Human pharmacokinetic and metabolism information as well as short-term safety data are already available for both meropenem and clavulanate,” he noted. “This is an advantage and could potentially translate into a quicker approval process for the meropenem-clavulanate combination than for a novel clinical entity.”

Jose Garcia-Bustos, director of molecular drug discovery at GSK's Diseases of the Developing World Discovery Performance Unit, told *SciBX* that “clavulanate has been used for a large number of years with an excellent record of efficacy and safety, with the caveat that it was not developed for continuous use over such a long period.”

Ma also noted that longer-term trials would be important. “Meropenem and clavulanate have only been tested for and are currently only approved for short-term use,” he said. “Since TB requires many months of therapy, especially for drug-resistant disease, the long-term safety of these two agents must be investigated. New side effects could emerge with long-term administration.”

John Rex, VP of clinical infection at AstraZeneca, was also cautious. “We have no safety data on the combination or on pharmacological interactions between the two compounds,” he said. “Furthermore, meropenem does not have an indication for tuberculosis.”

**“At best, meropenem/  
clavulanate treatment  
would relieve the  
symptoms. It would never  
cure the disease.”**

—**Kenneth Coleman, Novoxel S.A.**

## Elusive pathogen

Kenneth Coleman, CSO of **Novoxel S.A.**, also thinks there are a few reasons why the *in vitro* data might not translate into the clinic. “Most infecting bacteria exist within the body of the

patient but outside of host cells. These are easily treated by a broad range of antibiotic classes. But *M. tuberculosis* exists both within and outside host cells,” which is a problem because  $\beta$ -lactams do not penetrate mammalian cells.

As a result, said Coleman, a  $\beta$ -lactam “could reduce the bacterial burden by removing the extracellular *M. tuberculosis* but can never completely eliminate the organism. Bacteria can continue to grow and multiply inside cells and eventually break out. At best, meropenem/clavulanate treatment would relieve the symptoms. It would never cure the disease.”

Novoxel's NX1104, a BLAC inhibitor, is in Phase II testing to treat Gram-negative bacterial infections.

Ma said the adaptability *M. tuberculosis* could further complicate treatment. “The bacterium is a somewhat challenging organism that can adopt various noninheritable, drug-persistent forms in patients, which are not yet fully understood,” he said. “Additionally, *Mycobacterium tuberculosis* can also quickly develop inheritable mono- and multidrug resistance.”

An additional challenge, said Coleman, is the bacterium's dormant phase. “When it is dormant, it is often not killed by treatments, so they can only be effective when the pathogen has come out of dormancy,” which is why it needs to be treated for so long.

## Drug delivery

Even if the meropenem and clavulanate combination produces strong clinical data, there remain logistical issues that could hamper use of the cocktail.

(Continues on p. 8)

# New osteoporosis strategies

By Brian Moy, Staff Writer

A study by Japanese researchers suggests a pair of new strategies for treating osteoporosis: using iron chelation therapy and antagonizing PGC-1 $\beta$ . Both approaches are geared at targeting regulators of mitochondrial biogenesis, an energy-generating process that osteoclasts use to fuel their bone-resorptive effects. In both cases, the challenge will be to specifically target only the activity of osteoclasts and not the bone-forming activity of osteoblasts.

Osteoporosis is caused by an imbalance in the activity of osteoclasts and osteoblasts.<sup>1</sup> In a *Nature Medicine* paper, researchers led by principal investigator Kyoji Ikeda at the **National Center for Geriatrics and Gerontology** reported that mitochondrial biogenesis is regulated during osteoclast development by PGC-1 $\beta$  and iron uptake through the transferrin receptor (TFRC; TFR1).

The team found that knockdown of peroxisome proliferation-activated receptor- $\gamma$ , coactivator 1 $\beta$  (PPARGC1B; PGC-1 $\beta$ ) in bone marrow macrophages inhibited osteoclast differentiation compared with that seen in untreated control cells. In mice, knockdown of Pgc-1 $\beta$  led to greater bone mass than that seen in wild-type mice.

These findings, they wrote, “may provide a platform for the development of therapeutic strategies against various bone diseases with

“Our findings also show that PGC-1 $\beta$  deficiency is manifest most prominently in osteoclasts.”

—Kyoji Ikeda,  
National Center for  
Geriatrics and Gerontology

accelerated osteoclastic bone resorption,” including osteoporosis.

Ikeda, head of the Department of Bone and Joint Disease at the National Center for Geriatrics and Gerontology, told *SciBX*, “Our findings also show that PGC-1 $\beta$  deficiency is manifest most prominently in osteoclasts.” Thus, he said, “PGC-1 $\beta$  antagonism seems to be a rational approach to combat bone diseases without having serious side effects in other energy-requiring organs that are dependent upon mitochondrial oxidative energy metabolism.”

Ikeda and colleagues are now screening for compounds that inhibit PGC-1 $\beta$  production or activity in osteoclasts.

The study also showed that iron uptake through TFRC promoted osteoclast differentiation and bone-resorbing activity. In ovariectomized estrogen-deficient mice, the iron chelator desferrioxamine inhibited tfrc-mediated bone resorption by mature osteoclasts and prevented bone loss compared with what was seen in vehicle-treated controls.<sup>2</sup>

Thus, the authors said, “our data suggest a new explanation that iron overload leads to increased production and function of osteoclasts and may underlie the accelerated bone resorption observed in thalassemia patients.”

Ikeda said iron chelators, such as Exjade, could be useful for the management of skeletal complications in thalassemia patients who have undergone repeated blood transfusions, which often result in iron overload.

Exjade deferasirox, an oral iron chelator from **Novartis AG**, is approved in the U.S. and EU to treat chronic iron overload due to blood transfusions.

(Continues on p. 9)

(Continued from “Ganging up on TB,” p. 7)

The main issue is that meropenem is only available in i.v. formulations. As a result, said Ma, “its potential for widespread use may be limited, especially in resource-limited settings.”

Coleman agreed, noting that i.v. delivery “increases the cost of therapy enormously compared to oral agents and requires the patient to either stay in a hospital or report to a clinic two to three times daily for dose administration. Since TB is predominantly a Third World disease, the cost of such therapy would be prohibitive,” he said.

Setting aside the issue of cost, Coleman told *SciBX* that the months of i.v. therapy “would most likely need an in-dwelling i.v. catheter, which would put a large portion of patients at risk for secondary infection by other bacteria.”

The challenges are worth tackling, said Martin Pan, manager of discovery medicine at GSK’s Diseases of the Developing World unit. Although a lack of oral formulations restricts meropenem to the hospital setting, “this would be enough to save the lives of many patients with drug-resistant TB who are already hospitalized,” he said.

The GlaxoSmithKline researchers told *SciBX* that the Diseases of the Developing World unit is working with the authors of the paper to

help the progress of this potential new treatment option.

David Schoenhaut, assistant director of the office of biotechnology at Albert Einstein, told *SciBX* that a U.S. provisional patent application has been filed, and the IP is available for licensing.

Martz, L. *SciBX* 2(10); doi:10.1038/scibx.2009.390  
Published online March 12, 2009

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## COMPANIES AND INSTITUTIONS MENTIONED

**Albert Einstein College of Medicine of Yeshiva University**, Bronx, N.Y.  
**AstraZeneca plc** (LSE:AZN; NYSE:AZN), London, U.K.  
**GlaxoSmithKline plc** (LSE:GSK; NYSE:GSK), London, U.K.  
**Global Alliance for TB Drug Development**, New York, N.Y.  
**Novexel S.A.**, Romainville, France

## Target specificity

Although the findings clearly point to new ways to treat osteoporosis, a key issue is whether PGC-1 $\beta$  and iron uptake play roles in the function of osteoblasts.

“We certainly don’t want to inhibit bone formation by antagonizing PGC-1 $\beta$ ,” said Clifford Rosen, senior scientist at the **Maine Medical Center Research Institute**. “While the strategies identified in the *Nature Medicine* paper are certainly promising, we need to further investigate exactly why bone formation was suppressed in these mice and further elucidate the role of PGC-1 $\beta$  in osteoblast function.”

The authors of the *Nature Medicine* article suggested that the impaired bone formation seen in mice lacking Pgc-1 $\beta$  partly reflects the lack of functional Pgc-1 $\beta$  in osteoblasts.

Robert Brommage, associate director of metabolism research at **Lexicon Pharmaceuticals Inc.**, was less convinced about the therapeutic potential of the strategies and suggested that both iron metabolism and PGC-1 $\beta$  “may have some pitfalls as drug targets for osteoporosis.”

Brommage thinks modulating iron metabolism will have effects throughout the entire body, rather than only on osteoclasts. Regarding PGC-1 $\beta$ , he said bone “may not be the only tissue affected by inhibition of PGC-1 $\beta$ .” Indeed, PGC-1 $\beta$  is highly expressed in several tissues characterized by high oxidative metabolism, including brown adipose tissue and skeletal and cardiac muscle.<sup>3</sup>

Through its large-scale knockout mouse program, Lexicon has identified an anti-resorptive target that “has a much stronger bone phenotype than PGC-1 $\beta$ ,” according to Brommage. The company

would not disclose the target or development plans.

Ikeda agreed that there might be some problems regarding the sensitivity of osteoclasts compared with that of osteoblasts to the inhibition of PGC-1 $\beta$ . However, with additional research into the role of PGC-1 $\beta$  in osteoblasts, he thinks it will still be possible to develop drugs that inhibit the target satisfactorily in osteoclasts without exhibiting deleterious effects in osteoblasts.

Ikeda added that adverse effects due to iron chelation on osteoblasts are likely to be of little concern due to the fact that osteoblasts express very little TFRC.

The Japanese researchers have filed a patent application in Japan covering PGC-1 $\beta$  and iron uptake through TFRC as methods for regulating osteoclastic bone resorption. The patent is available for licensing.

Moy, B. *SciBX* 2(10); doi:10.1038/scibx.2009.391

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## COMPANIES AND INSTITUTIONS MENTIONED

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**Novartis AG** (NYSE:NVS; SIX:NOVN), Basel, Switzerland



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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>				
Celiac disease	Phospholipase A <sub>2</sub> , group IVA (cytosolic, calcium-dependent) (PLA <sub>2</sub> G4A); killer cell lectin-like receptor subfamily K member 1 (KLRK1; CD314; NKG2D)	A study in human cell culture and tissues suggests that antagonizing PLA <sub>2</sub> G4A could help treat celiac disease. In cell culture, small molecule inhibition or small interfering RNA knockdown of PLA <sub>2</sub> G4A lowered proinflammatory cytotoxic T lymphocyte activity triggered by NKG2D activation compared with that seen in mock-treated controls. Intestinal biopsy tissues from patients with active celiac disease had higher levels of active PLA <sub>2</sub> G4A compared with healthy controls. Next steps include identifying the specific lipid mediator that is produced by NKG2D-mediated PLA <sub>2</sub> G4A activation and starting clinical trials of PLA <sub>2</sub> G4A inhibitors for celiac disease. Wyeth's PLA <sub>2</sub> G4A inhibitors efipladib and WAY-196025 are in preclinical development for undisclosed indications.  <b>SciBX 2(10); doi:10.1038/scibx.2009.392</b> <b>Published online March 12, 2009</b>	Unpatented; licensing status not applicable; modulating NKG2D to treat autoimmune disease patented by the University of California; licensing status undisclosed	Tang, F. <i>et al. J. Exp. Med.</i> ; published online Feb. 23, 2009; doi:10.1084/jem.20071887 <b>Contact:</b> Bana Jabri, University of Chicago, Chicago, Ill. e-mail: <a href="mailto:bjabri@bsd.uchicago.edu">bjabri@bsd.uchicago.edu</a>
<b>Cancer</b>				
Acute lymphoblastic leukemia (ALL)	Notch homolog 1 translocation-associated (Drosophila) (NOTCH1); mammalian target of rapamycin (mTOR; FRAP; RAFT1); $\gamma$ -secretase	Studies <i>in vitro</i> and in mice suggest that inhibiting both NOTCH1 and the mTOR pathway could help treat T cell ALL. In mouse T cell ALL (T-ALL) cells and <i>ex vivo</i> tumors, the notch pathway inhibitor MRK-003 increased apoptosis compared with that seen in controls. In leukemic mice, MRK-003 increased tumor cell apoptosis and survival while repressing NOTCH1 activity. In human and mouse T-ALL cell lines as well as in mice with subcutaneous human T-ALL tumors, a combination of MRK-003 and rapamycin inhibited tumor progression and increased survival compared with what was seen using either compound alone. Next steps include exploring the potential for this therapeutic strategy in mouse xenograft models of additional T-ALL cell lines.  At least eight companies have compounds targeting mTOR in clinical and preclinical testing to treat cancer.  At least five companies have compounds in development targeting the Notch signaling pathway, including $\gamma$ -secretase inhibitors.  <b>SciBX 2(10); doi:10.1038/scibx.2009.393</b> <b>Published online March 12, 2009</b>	Combination therapy unpatented; licensing status not applicable	Cullion, K. <i>et al. Blood</i> ; published online Feb. 26, 2009; doi:10.1182/blood-2008-02-136762 <b>Contact:</b> Michelle A. Kelliher, University of Massachusetts Medical School, Worcester, Mass. e-mail: <a href="mailto:michelle.kelliher@umassmed.edu">michelle.kelliher@umassmed.edu</a>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Cancer	Heat shock protein 90 (HSP90AA1; Hsp90)	<p>A study in mice and in cell culture identified a non-benzoquinone ansamycin Hsp90 inhibitor that may be useful for treating cancer. In six human cancer cell lines, the compound inhibited proliferation with IC<sub>50</sub> values in the 55–190 nM range. In a human colorectal adenocarcinoma mouse xenograft model, 15 mg/kg of the Hsp90 inhibitor prevented tumor proliferation with efficacy comparable to treatment with 90 mg/kg of tanespimycin. Next steps include identifying additional non-benzoquinone ansamycin-based analogs that inhibit Hsp90.</p> <p>Tanespimycin (17-(allylamino)-17-demethoxygeldanamycin (17-AAG)), an Hsp90 inhibitor from Bristol-Myers Squibb Co., is in Phase III testing to treat multiple myeloma (MM).</p> <p>At least 11 other companies have Hsp90 inhibitors in Phase II or earlier to treat cancer.</p> <p><b>SciBX 2(10); doi:10.1038/scibx.2009.394</b> Published online March 12, 2009</p>	Patent application filed covering use in multiple cancers; licensed to Bristol-Myers Squibb	<p>Menzella, H.G. <i>et al. J. Med. Chem.</i>; published online Feb. 20, 2009; doi:10.1021/jm900012a</p> <p><b>Contact:</b> Hugo G. Menzella, National University of Rosario, Rosario, Argentina e-mail: <a href="mailto:menzella@ibr.gov.ar">menzella@ibr.gov.ar</a></p>
Cancer	Heat shock protein 90 (HSP90AA1; Hsp90)	<p>Studies in mice and cell culture suggest that gamitrinibs may be useful for treating cancer. Gamitrinibs consist of a 17-(allylamino)-17-demethoxygeldanamycin (17-AAG)-derived scaffold linked to a mitochondrial targeting moiety. In human leukemia, breast cancer and lung cancer xenograft mouse models, a gamitrinib analog decreased tumor proliferation compared with that seen using vehicle or 17-AAG. In cancer cell lines, gamitrinibs entered mitochondria, inhibited Hsp90 activity and induced cell death via mitochondrial apoptosis. Gamitrinibs also had broad-spectrum activity across a panel of 12 cancer cell lines, whereas 17-AAG did not. Next steps include evaluating gamitrinibs in long-term studies in animals.</p> <p>Tanespimycin (17-AAG), an Hsp90 inhibitor from Bristol-Myers Squibb Co., is in Phase III testing to treat multiple myeloma (MM).</p> <p>At least 11 other companies have Hsp90 inhibitors in Phase II or earlier to treat cancer (see <b>Hitting Hsp90 where it hurts</b>, page 5).</p> <p><b>SciBX 2(10); doi:10.1038/scibx.2009.395</b> Published online March 12, 2009</p>	<p>Multiple patent applications filed covering structure and biology of the compounds; available for licensing from the University of Massachusetts Commercial Ventures and Intellectual Property</p> <p><b>Contact:</b> James McNamara, University of Massachusetts Medical School, Worcester, Mass. phone: 508-856-4390 e-mail: <a href="mailto:james.mcnamara@umassmed.edu">james.mcnamara@umassmed.edu</a></p>	<p>Kang, B.H. <i>et al. J. Clin. Invest.</i>; published online Feb. 23, 2009; doi:10.1172/JCI37613</p> <p><b>Contact:</b> Dario C. Altieri, University of Massachusetts Medical School, Worcester, Mass. e-mail: <a href="mailto:dario.altieri@umassmed.edu">dario.altieri@umassmed.edu</a></p>
Cancer	Retinoblastoma 1 (RB1; pRB)	<p><i>In vitro</i> and mouse studies suggest that RB1 could help treat cancer by improving responses to chemotherapy. In p53-defective human glioblastoma cells, RB1 bound the transcription factor E2F1 and induced formation of a proapoptotic RB1-E2F1 complex in response to doxorubicin or other DNA-damaging agents. Formation of the complex led to activation of proapoptotic genes and repression of cell cycle-regulating genes. Next steps could include studying RB1-dependent apoptosis in other cancer cell lines and xenograft mouse models.</p> <p><b>SciBX 2(10); doi:10.1038/scibx.2009.396</b> Published online March 12, 2009</p>	Patent and licensing status unavailable	<p>Ianari, A. <i>et al. Cell</i>; published online March 2, 2009; doi:10.1016/j.ccr.2009.01.026</p> <p><b>Contact:</b> Jacqueline A. Lees, David H. Koch Institute for Integrative Cancer Research at MIT, Cambridge, Mass. e-mail: <a href="mailto:jalees@mit.edu">jalees@mit.edu</a></p> <p><b>Contact:</b> Alberto Gulino, La Sapienza University of Rome, Rome, Italy e-mail: <a href="mailto:alberto.gulino@uniroma1.it">alberto.gulino@uniroma1.it</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Cancer	Syndecan-1 (SDC1); integrin $\alpha_v\beta_3$ ; integrin $\alpha_v\beta_5$	<p>Studies in human cells and in mice suggest that synstatin, a peptide derived from the cell-surface receptor SDC1, could treat cancer by inhibiting angiogenesis. In human vascular cells, synstatin disrupted interactions between SDC1 and integrins <math>\alpha_v\beta_3</math> and <math>\alpha_v\beta_5</math>, which play known roles in angiogenesis. Synstatin also disrupted those interactions in mouse aortic tissue and prevented vascular growth, which decreased tumor growth, in a mouse model of mammary carcinoma. Ongoing work includes development of better synstatin mimetics. Merck KGaA's cilengitide, an inhibitor of integrins <math>\alpha_v\beta_3</math> and <math>\alpha_v\beta_5</math>, is in Phase III testing to treat glioblastoma. At least four other companies have compounds targeting integrin <math>\alpha_v\beta_3</math>, <math>\alpha_v</math> integrins or unspecific integrins in preclinical to early-stage clinical testing to treat various cancers.</p> <p><b>SciBX 2(10); doi:10.1038/scibx.2009.397</b> Published online March 12, 2009</p>	Patented; available for licensing	<p>Beauvais, D. <i>et al. J. Exp. Med.</i>; published online March 2, 2009; doi:10.1084/jem.20081278 <b>Contact:</b> Alan C. Rapraeger, University of Wisconsin–Madison, Madison, Wis. e-mail: <a href="mailto:acrabrae@wisc.edu">acrabrae@wisc.edu</a></p>
Cancer	Vascular endothelial growth factor receptor (VEGFR); platelet-derived growth factor receptor (PDGFR)	<p>Studies in mice suggest that marketed VEGFR tyrosine kinase inhibitors may need further evaluation of optimal dose, treatment schedule, adjuvant therapy and combination therapy to improve safety and efficacy. In a mouse model of human breast cancer cell metastasis, short-term treatment with Sutent sunitinib accelerated metastasis and lowered mean survival compared with what was seen with vehicle controls. Similar results were seen with the VEGF inhibitors Nexavar sorafenib and SU10944. In xenograft mice with primary breast cancer tumors, sunitinib decreased growth of the primary tumor but also led to increased metastatic burden. Next steps could include evaluating combination therapies of angiogenesis inhibitors with compounds that block tumor metastasis or cell invasion. Pfizer Inc. markets Sutent, an inhibitor of VEGFR and PDGFR, to treat renal and gastrointestinal cancers. Onyx Pharmaceuticals Inc. and Bayer AG market Nexavar to treat renal cancer.</p> <p><b>SciBX 2(10); doi:10.1038/scibx.2009.398</b> Published online March 12, 2009</p>	Patent cooperation treaty application filed in 2001 covering use of antiangiogenic therapies in combination with chemotherapeutic agents; available for licensing	<p>Ebos, J. <i>et al. Cell</i>; published online March 2, 2009; doi:10.1016/j.ccr.2009.01.021 <b>Contact:</b> Robert S. Kerbel, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada e-mail: <a href="mailto:robert.kerbel@sunnybrook.ca">robert.kerbel@sunnybrook.ca</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Multiple myeloma (MM)	Insulin-like growth factor 1 (IGF1); IGF1 receptor (IGF1R); IL-6; IL-6 receptor (IL-6R)	<p>Studies in patient samples and in cell culture suggest that co-inhibiting IGF1R and IL-6 activity may help treat myeloma patients with IGF1R expression in cancer cells. In a panel of human myeloma cell lines, IL-6 or IGF1 significantly increased cell proliferation compared with that seen using no treatment (<math>p &lt; 0.05</math>). An IL-6-targeting mAb or an IGF1R inhibitor prevented IL-6-induced and IGF1-induced proliferation. Next steps could include evaluating co-inhibition of IGF1R and IL-6 in preclinical models of MM.</p> <p>AVE1642, a nonconjugated antibody binding to IGF1R from ImmunoGen Inc. and sanofi-aventis Group, is in Phase I testing to treat MM. APG 206, an IGF1R antagonist from Allosteria Pharma, is in preclinical testing for MM.</p> <p><b>SciBX 2(10); doi:10.1038/scibx.2009.399</b> Published online March 12, 2009</p>	Patent and licensing status unavailable	<p>Sprynski, A.C. <i>et al. Blood</i>; published online Feb. 18, 2009; doi:10.1182/blood-2008-07-170464 <b>Contact:</b> Bernard Klein, Institut National de la Santé et de la Recherche Médicale (INSERM), Montpellier, France e-mail: <a href="mailto:bernard.klein@inserm.fr">bernard.klein@inserm.fr</a></p>
Renal cell carcinoma (RCC); clear cell RCC	Speckle-type POZ protein (SPOP); c-jun N-terminal kinase (MAPK8; JNK)	<p>Studies in human cell culture and in tissue samples suggest that SPOP is a biomarker and a potential target for treating clear cell RCC. In human embryonic kidney cells, overexpression of SPOP increased JNK signaling pathway activity compared with that seen in controls. In human tissue samples, SPOP was highly expressed in 77% of human RCC specimens but not in normal kidney tissue or other organs. SPOP was also highly expressed in 99% of clear cell RCC samples and in 97% of RCC metastases. Ongoing work includes identifying SPOP's substrate and determining whether it will be a viable target for RCC.</p> <p>Eight companies have compounds marketed or approved to treat RCC.</p> <p>At least 11 companies have therapies in Phase III testing to treat RCC.</p> <p>At least 30 companies have therapies in preclinical to early-stage clinical testing to treat RCC.</p> <p><b>SciBX 2(10); doi:10.1038/scibx.2009.400</b> Published online March 12, 2009</p>	Patented; licensed to LifeX Pharmaceuticals Inc.	<p>Liu, J. <i>et al. Science</i>; published online Feb. 27, 2009; doi:10.1126/science.1157669 <b>Contact:</b> Kevin P. White, University of Chicago, Chicago, Ill. e-mail: <a href="mailto:kpwhite@uchicago.edu">kpwhite@uchicago.edu</a></p>

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## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Cardiovascular disease</b>				
Atherosclerosis	Cholesteryl ester transfer protein (CETP)	<i>In vitro</i> and <i>in vivo</i> studies identified a CETP inhibitor that could help treat atherosclerosis. Chemical modifications to a CETP inhibitor from Pharmacia Corp. (now part of Pfizer Inc.) led to a compound with an IC <sub>50</sub> of 39 nM <i>in vitro</i> , an IC <sub>50</sub> of 0.2 μM in an assay using human plasma, and good pharmacokinetics in rats, dogs and cynomolgus monkeys. In high fat-fed hamsters, human CETP transgenic mice and male cynomolgus monkeys, the inhibitor caused dose-dependent increases in high-density lipoprotein cholesterol that were comparable to those seen using torcetrapib, a discontinued CETP inhibitor from Pfizer. Next steps could include testing the inhibitor in animal models of atherosclerosis. At least five companies have CETP inhibitors in clinical and preclinical testing to treat dyslipidemia, hyperlipidemia or atherosclerosis.  <b>SciBX 2(10); doi:10.1038/scibx.2009.401</b> <b>Published online March 12, 2009</b>	Patent and licensing status unavailable	Kuo, G. <i>et al. J. Med. Chem.</i> ; published online Feb. 24, 2009; doi:10.1021/jm801319d <b>Contact:</b> Margery A. Connelly, Johnson & Johnson Pharmaceutical Research and Development, Cranbury, N.J. e-mail: <a href="mailto:mconnell@its.jnj.com">mconnell@its.jnj.com</a> <b>Contact:</b> Gee-Hong Kuo, same affiliation as above e-mail: <a href="mailto:gkuo@its.jnj.com">gkuo@its.jnj.com</a>
Thrombosis	Protein tyrosine phosphatase, receptor type, J (PTPRTJ; CD148); glycoprotein VI (platelet) (GP6; GPVI)	A study in mice suggests that inhibiting CD148 may be useful for preventing thrombosis. Platelets isolated from CD148-deficient mice showed less GP6-mediated aggregation and ATP secretion than platelets from wild-type controls. CD148 knockout mice showed significantly more bleeding and time to vessel occlusion than wild-type controls ( $p < 0.03$ and $p < 0.001$ , respectively). Thrombus formation in CD148-deficient mice was also delayed. Next steps could include developing small molecule inhibitors of CD148.  <b>SciBX 2(10); doi:10.1038/scibx.2009.402</b> <b>Published online March 12, 2009</b>	Patent and licensing status undisclosed	Senis, Y.A. <i>et al. Blood</i> ; published online Feb. 25, 2009; doi:10.1182/blood-2008-08-174318 <b>Contact:</b> Yotis A. Senis, University of Birmingham, Birmingham, U.K. e-mail: <a href="mailto:y.senis@bham.ac.uk">y.senis@bham.ac.uk</a>
<b>Endocrine disease</b>				
Obesity	Orexin 2 receptor (HCRTR2; OX2R)	A study in mice suggests that agonizing OX2R could help treat obesity. Mice overexpressing the neuropeptide hormone orexin had less weight gain on a high-fat diet than wild-type controls. Deletion of OX2R, which is one of two orexin receptors, reversed the protective effects of orexin overexpression against weight gain compared with what was seen in controls. A small molecule OX2R agonist boosted metabolic turnover and lowered weight gain compared with that seen in untreated controls. Next steps include designing efficient OX2R agonists for use in humans.  <b>SciBX 2(10); doi:10.1038/scibx.2009.403</b> <b>Published online March 12, 2009</b>	Patent pending on a small molecule agonist of OX2R; available for licensing	Funato, H. <i>et al. Cell Metabol.</i> ; published online Jan. 6, 2009; doi:10.1016/j.cmet.2008.10.010 <b>Contact:</b> Masashi Yanagisawa, University of Texas Southwestern Medical Center, Dallas, Texas e-mail: <a href="mailto:masashi.yanagisawa@utsouthwestern.edu">masashi.yanagisawa@utsouthwestern.edu</a>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Gastrointestinal disease</b>				
Diarrhea (infectious)	<i>Clostridium difficile</i> toxin B	<p>Studies in hamsters suggest that targeting the toxin B virulence factor of <i>C. difficile</i> could be useful for treating <i>C. difficile</i>-associated diarrhea (CDAD). Previous studies have shown that purified toxin A induces most of the pathology observed upon infection with <i>C. difficile</i>. In hamsters, challenge with toxin B mutants of a virulent strain of <i>C. difficile</i> led to higher survival than that seen in wild-type and toxin A mutant-infected hamsters, suggesting that toxin B is essential for virulence. Next steps include developing vaccines that protect against <i>C. difficile</i> toxin B.</p> <p>Medarex Inc. is developing MDX-066 and MDX-1388, mAbs against <i>C. difficile</i> toxin A and B, respectively, as a combination treatment that is in Phase II testing to treat CDAD and prevent relapse.</p> <p><b>SciBX 2(10); doi:10.1038/scibx.2009.404</b> Published online March 12, 2009</p>	Unpatented; unlicensed	<p>Lyras, D. <i>et al. Nature</i>; published online March 1, 2009; doi:10.1038/nature07822</p> <p><b>Contact:</b> Julian Rood, Monash University, Clayton, Australia e-mail: <a href="mailto:julian.rood@med.monash.edu.au">julian.rood@med.monash.edu.au</a></p>
<b>Genitourinary disease</b>				
Erectile dysfunction (ED)	Cystathionine $\beta$ -synthase (CBS); cystathionase (cystathionine $\gamma$ -lyase) (CTH)	<p>Studies in cell culture and in rats suggest that intracavernous administration of hydrogen sulfide (<math>H_2S</math>) or L-cysteine could be useful for treating ED. Analysis of human corpus cavernosum tissue showed that CBS and CTH, enzymes responsible for metabolizing L-cysteine to produce <math>H_2S</math>, are localized in the smooth-muscle component of the penile artery. Exogenous administration of <math>H_2S</math> or L-cysteine relaxed strips of human corpus cavernosum in a concentration-dependent manner. In rats, intracavernous administration of <math>H_2S</math> or L-cysteine promoted erections. Next steps include developing <math>H_2S</math> donor compounds and investigating their use in treating ED.</p> <p><b>SciBX 2(10); doi:10.1038/scibx.2009.405</b> Published online March 12, 2009</p>	Unpatented; licensing status undisclosed	<p>Bianca, R. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online March 2, 2009; doi:10.1073/pnas.0807974105</p> <p><b>Contact:</b> Giuseppe Cirino, University of Naples Federico II, Napoli, Italy e-mail: <a href="mailto:cirino@cds.unina.it">cirino@cds.unina.it</a></p>
<b>Infectious disease</b>				
HIV/AIDS	Chemokine (CC motif) ligand 20 (CCL20; MIP-3 $\alpha$ ); IL-8	<p>A study in cell culture and in rhesus macaques suggests that glycerol monolaurate (GML) could be useful in preventing HIV transmission. In cultured HIV-infected human vaginal epithelial cells, GML inhibited the induction of proinflammatory factors CCL20 and IL-8 compared with that seen in mock-treated controls. These inflammatory factors provide the stimulus to recruit new T cell targets, which leads to the expansion of HIV infection. Four of five macaques treated intravaginally with a 5% solution of GML in gel did not develop systemic SIV infection after repeated high-dose challenge, unlike mock-treated controls. Next steps include scaling up further macaque trials of GML to optimize delivery and efficacy and launching clinical trials to prevent HIV transmission.</p> <p><b>SciBX 2(10); doi:10.1038/scibx.2009.406</b> Published online March 12, 2009</p>	Use of GML as an anti- inflammatory covered by previous patents; licensing information undisclosed	<p>Li, Q. <i>et al. Nature</i>; published online March 5, 2009; doi:10.1038/nature07831</p> <p><b>Contact:</b> Ashley Haase, University of Minnesota, Minneapolis, Minn. e-mail: <a href="mailto:haase001@umn.edu">haase001@umn.edu</a></p> <p><b>Contact:</b> Pat Schlievert, same affiliation as above e-mail: <a href="mailto:schli001@umn.edu">schli001@umn.edu</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Infectious	Ring finger protein 128 (RNF128; GRAIL)	<p>Mouse and <i>ex vivo</i> studies suggest that targeting GRAIL could help treat schistosomiasis and other chronic infections associated with T helper type 2 (Th2) cell hyporesponsiveness. In <i>Schistosoma mansoni</i>-infected mice, the percentage of proliferating Th2 cells increased early in infection but then decreased despite persistent infection. In Th2 cells from the mice, gene expression analysis showed that the E3 ubiquitin ligase GRAIL was upregulated during the hyporesponsive state, and small interfering RNA against GRAIL prevented development of Th2 hyporesponsiveness induced by repeated <i>Schistosoma</i> antigen stimulation. Next steps could include additional studies to determine the relationship between GRAIL expression and cytokine production in Th2 hypoproliferation.</p> <p><b>SciBX 2(10); doi:10.1038/scibx.2009.407</b> Published online March 12, 2009</p>	Patent and licensing status unavailable	<p>Taylor, J. <i>et al. J. Clin. Invest.</i>; published online March 2, 2009; doi:10.1172/JCI36534 <b>Contact:</b> Edward J. Pearce, University of Pennsylvania, Philadelphia, Pa. e-mail: <a href="mailto:ejpearce@mail.med.upenn.edu">ejpearce@mail.med.upenn.edu</a></p>
Influenza virus	Tumor necrosis factor (TNF) and nitric oxide synthase 2 (inducible) (NOS2; iNOS)-producing dendritic cells (tipDCs)	<p>Studies in mice suggest that diminishing, but not eliminating, tipDC recruitment to the lungs could be useful for treating influenza. In mice, infection with lethal influenza A viruses led to increased selective accumulation of tipDCs in the airways. In infected mice, the peroxisome proliferation-activated receptor-<math>\gamma</math> (PPARG; PPAR-<math>\gamma</math>) agonist pioglitazone lowered tipDC migration and protected the mice from lethal influenza challenge compared with what was seen using saline control. Next steps include further investigating how tipDCs are regulated and how they induce damage to the host. Takeda Pharmaceutical Co. Ltd. and Eli Lilly and Co. market Actos pioglitazone to treat type 2 diabetes.</p> <p><b>SciBX 2(10); doi:10.1038/scibx.2009.408</b> Published online March 12, 2009</p>	Patent application filed by St. Jude Children's Research Hospital; available for licensing	<p>Aldridge, J. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online March 9, 2009; doi:10.1073/pnas.0900655106 <b>Contact:</b> Robert G. Webster, St. Jude Children's Research Hospital, Memphis, Tenn. e-mail: <a href="mailto:robert.webster@stjude.org">robert.webster@stjude.org</a></p>
Malaria	<i>Plasmodium falciparum</i> protein farnesyl transferase (PFT)	<p>An SAR study identified a series of PFT inhibitors based on an ethylenediamine scaffold that could be useful for treating malaria. <i>In vitro</i>, three of the compounds inhibited PFT with nanomolar IC<sub>50</sub> values. Two of the three compounds had &gt;1,000-fold selectivity for PFT over human farnesyl transferase. Next steps could include testing the inhibitors in animal models of malaria.</p> <p><b>SciBX 2(10); doi:10.1038/scibx.2009.409</b> Published online March 12, 2009</p>	Patent and licensing status unavailable	<p>Hast, M. <i>et al. Chem. Biol.</i>; published online Feb. 26, 2009; doi:10.1016/j.chembiol.2009.01.014 <b>Contact:</b> Lorena S. Beese, Duke University Medical Center, Durham, N.C. e-mail: <a href="mailto:lsb@biochem.duke.edu">lsb@biochem.duke.edu</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Sepsis	Integrin $\alpha_3\beta_1$ (VLA-3); integrin $\alpha_5\beta_1$ ; integrin $\alpha_5\beta_3$	A study in mice and in cell culture suggests that inhibiting integrin-mediated neutrophil migration may help treat sepsis. Protein-binding and cellular-migration assays showed that recombinant human activated protein C (rhAPC) decreased neutrophil migration by inducing conformational changes in neutrophil-specific integrin $\alpha_3\beta_1$ , integrin $\alpha_5\beta_1$ and integrin $\alpha_5\beta_3$ . The Arg-Gly-Asp (RGD) motif of rhAPC was required for the integrin interaction. In a mouse model of sepsis, the RGD peptide significantly decreased mortality compared with that seen using a control peptide ( $p < 0.05$ ). Next steps include identifying specific sepsis-relevant neutrophil integrins that bind to rhAPC and evaluating blockers of the integrins in preclinical sepsis models. Xigris drotrecogin alfa, a rhAPC from Eli Lilly and Co., is marketed to treat sepsis. At least 13 other companies have compounds in clinical and preclinical testing for the indication.  <b>SciBX 2(10); doi:10.1038/scibx.2009.410</b> <b>Published online March 12, 2009</b>	Patent application filed; available for licensing from the University of Rochester Office of Technology Transfer <b>Contact:</b> Harl Tolbert, University of Rochester, Rochester, N.Y. phone: 585-784-8862 e-mail: <a href="mailto:Harl_Tolbert@URMC.Rochester.edu">Harl_Tolbert@URMC.Rochester.edu</a>	Elphick, G.F. <i>et al. Blood</i> ; published online Feb. 24, 2009; doi:10.1182/blood-2008-09-180968 <b>Contact:</b> Minsoo Kim, University of Rochester, Rochester, N.Y. e-mail: <a href="mailto:minsoo_kim@urmc.rochester.edu">minsoo_kim@urmc.rochester.edu</a>
Tuberculosis (TB)	$\beta$ -lactamase (BLAC)	<i>In vitro</i> studies suggest that a combination of meropenem and clavulanate could help treat drug-resistant strains of tuberculosis. $\beta$ -lactam antibiotics like meropenem have been ineffective against <i>Mycobacterium tuberculosis</i> because the bacteria transcribe a BLAC that hydrolyzes the antibiotics. In aerobically grown Erdman <i>M. tuberculosis</i> cultures, meropenem plus the BLAC inhibitor clavulanate decreased bacterial growth and completely sterilized the bacterial culture in 9–12 days. The combination was also effective against aerobically grown cultures, which represent a persistent state, and against 13 drug-resistant isolates. Next steps include clinical testing of the combination. AstraZeneca plc markets Merrem meropenem to treat bacterial infection. GlaxoSmithKline plc and Ranbaxy Laboratories Ltd. each market amoxicillin-clavulanate combinations to treat infections ( <i>see Ganging up on TB, page 7</i> ).  <b>SciBX 2(10); doi:10.1038/scibx.2009.411</b> <b>Published online March 12, 2009</b>	U.S. provisional patent application filed; available for licensing	Hugonnet, J. <i>et al. Science</i> ; published online Feb. 23, 2009; doi:10.1126/science.1167498 <b>Contact:</b> John S. Blanchard, Albert Einstein College of Medicine of Yeshiva University, Bronx, N.Y. e-mail: <a href="mailto:blanchar@aecom.yu.edu">blanchar@aecom.yu.edu</a>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Tuberculosis (TB)	Not available	<i>In vitro</i> and mouse studies suggest that inducing autophagy could increase the efficacy of TB vaccines. In macrophages treated with the vaccine bacillus Calmette-Guérin (BCG), induction of autophagy by rapamycin triggered increased presentation of the main BCG antigen, Ag85B, compared with that seen in controls. In mice, subcutaneous immunization with rapamycin-treated dendritic cells (DCs) carrying BCG increased antigen presentation and improved response to aerosol TB challenge compared with what was seen in mice immunized with untreated DCs. Next steps could include developing Ag85B- or other antigen-overexpressing BCG variants as well as exploring similar antigen-enhancement techniques for other vaccines. At least six companies have TB vaccines in clinical and preclinical development.  <b>SciBX 2(10); doi:10.1038/scibx.2009.412</b> <b>Published online March 12, 2009</b>	Patent and licensing status unavailable	Jagannath, C. <i>et al. Nat. Med.</i> ; published online March 1, 2009; doi:10.1038/nm.1928 <b>Contact:</b> Chinnaswamy Jagannath, University of Texas Health Sciences Center, Houston, Texas e-mail: <a href="mailto:Chinnaswamy.Jagannath@uth.tmc.edu">Chinnaswamy.Jagannath@uth.tmc.edu</a>
<b>Musculoskeletal disease</b>				
Osteoporosis; sarcopenia	Thyrotropin-releasing hormone receptor (TRHR); SNP rs16892496; SNP rs7832552	A genomewide association study identified two SNPs within <i>TRHR</i> that could be useful biomarkers for predicting susceptibility to diseases associated with low lean body mass, including osteoporosis and sarcopenia. A meta-analysis of data from the scan and three replication datasets revealed that the rs16892496 and rs7832552 SNPs were significantly associated with lean body mass ( $p=5.53 \times 10^{-9}$ and $p=3.88 \times 10^{-10}$ , respectively). Next steps include further investigating how polymorphisms in <i>TRHR</i> contribute to lean body mass variation.  <b>SciBX 2(10); doi:10.1038/scibx.2009.413</b> <b>Published online March 12, 2009</b>	Unpatented; unlicensed	Liu, X. <i>et al. Am. J. Hum. Genet.</i> ; published online March 5, 2009; doi:10.1016/j.ajhg.2009.02.004 <b>Contact:</b> Hong-Wen Deng, University of Missouri–Kansas City, Kansas City, Mo. e-mail: <a href="mailto:dengh@umkc.edu">dengh@umkc.edu</a>
<b>Neurology</b>				
Alzheimer's disease (AD)	$\beta$ -amyloid (A $\beta$ )	A study in mice suggests that intracerebroventricular (ICV) perfusion of antibodies against A $\beta$ could be useful for treating AD. In a mouse model of AD, both ICV and systemic delivery of A $\beta$ antibodies lowered brain plaque area and cognitive dysfunction compared with that seen in mock-treated controls. However, ICV also decreased signs of cerebral amyloid angiopathy such as deposition of plaques in the cortical and hippocampal vasculature compared with what was seen in mock-treated or systemically-treated controls. Next steps could include optimizing long-term ICV delivery regimens and testing the effect of ICV therapeutic delivery in animal models of other neurodegenerative disorders. Medtronic Inc. and Alnylam Pharmaceuticals Inc. have a joint preclinical program to develop Huntington's disease (HD) and Parkinson's disease (PD) therapeutics and delivery methods.  <b>SciBX 2(10); doi:10.1038/scibx.2009.414</b> <b>Published online March 12, 2009</b>	Patent and licensing status undisclosed	Thakker, D.R. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Feb. 25, 2009; doi:10.1073/pnas.0813404106 <b>Contact:</b> Lisa L. Shafer, Medtronic Inc., Minneapolis, Minn. e-mail: <a href="mailto:lisa.l.shafer@medtronic.com">lisa.l.shafer@medtronic.com</a>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Alzheimer's disease (AD)	Prion protein (PRNP; PrP <sup>c</sup> )	A cell culture and mouse brain tissue study suggests that PrP <sup>c</sup> could be targeted to treat AD. Cultured monkey fibroblasts that expressed murine PrP <sup>c</sup> could bind AD-associated $\beta$ -amyloid (A $\beta$ ) oligomers, unlike mock-transfected controls. Cultured murine hippocampal slices from PrP <sup>c</sup> knockout mice had lower A $\beta$ oligomer-induced toxicity than wild-type controls. Next steps include identifying antibodies and small molecules that modulate PrP <sup>c</sup> interactions with A $\beta$ oligomers and testing their effects in animal models of AD.  <b>SciBX 2(10); doi:10.1038/scibx.2009.415</b> <b>Published online March 12, 2009</b>	Patents pending; available for licensing from Yale University <b>Contact:</b> John Puziss, Yale University Office of Cooperative Research, New Haven, Conn. e-mail: <a href="mailto:john.puziss@yale.edu">john.puziss@yale.edu</a>	Laurén, J. <i>et al. Nature</i> ; published online Feb. 26, 2009; doi:10.1038/nature07761 <b>Contact:</b> Stephen Strittmatter, Yale University School of Medicine, New Haven, Conn. e-mail: <a href="mailto:stephen.strittmatter@yale.edu">stephen.strittmatter@yale.edu</a>
Amyotrophic lateral sclerosis (ALS)	Fusion (involved in t(12;16) in malignant liposarcoma) (FUS; TLS)	Gene mapping of human CNS tissue and a cell culture study suggests that FUS could be targeted to treat ALS. In CNS tissues, 13 mutations in the <i>FUS</i> gene were linked to a rare familial form of ALS. In CNS tissues from a patient with one ALS-linked <i>FUS</i> mutation, FUS protein showed cytoplasmic localization, whereas healthy controls showed nuclear localization. Cultured neuroblastoma cells expressing FUS proteins with one of two ALS-linked mutations formed cytoplasmic aggregates, whereas wild-type protein was soluble and nuclear. Next steps include studying FUS mislocalization in animal models of ALS and examining how FUS might interact with TAR DNA-binding protein 43 (TDP-43) and superoxide dismutase 1 (SOD1), two other genes associated with familial ALS.  <b>SciBX 2(10); doi:10.1038/scibx.2009.416</b> <b>Published online March 12, 2009</b>	Patent pending; available for licensing from Massachusetts General Hospital	Kwiatkowski, T.J. <i>et al. Science</i> ; published online Feb. 27, 2009; doi:10.1126/science.1166066 <b>Contact:</b> T.J. Kwiatkowski, Jr., Massachusetts General Hospital, Charlestown, Mass. e-mail: <a href="mailto:tjkwiatkowski@partners.org">tjkwiatkowski@partners.org</a> <b>Contact:</b> R.H. Brown, Jr., University of Massachusetts, Worcester, Mass. e-mail: <a href="mailto:robert.brown@umassmed.edu">robert.brown@umassmed.edu</a>
Amyotrophic lateral sclerosis (ALS)	Fusion (involved in t(12;16) in malignant liposarcoma) (FUS; TLS)	Gene mapping of human CNS tissue and cell and rat neuronal culture studies suggests that FUS could be targeted to treat ALS. In CNS tissues, three mutations in the <i>FUS</i> gene were linked to a familial form of ALS. In CNS tissues from three patients with ALS-linked <i>FUS</i> mutations, FUS protein showed cytoplasmic localization, which was absent in normal controls, <i>superoxide dismutase 1 (SOD1)</i> mutant ALS patients and patients with sporadic ALS. Cultured cells or rat cortical neurons expressing FUS proteins bearing ALS-linked mutations formed cytoplasmic aggregates, whereas wild-type protein was soluble and nuclear. Next steps include studying FUS mislocalization in animal models for ALS and examining how FUS might interact with TAR DNA-binding protein 43 (TDP-43) and SOD1, two other genes associated with familial ALS.  <b>SciBX 2(10); doi:10.1038/scibx.2009.417</b> <b>Published online March 12, 2009</b>	Unpatented; licensing status not applicable	Vance, C. <i>et al. Science</i> ; published online Feb. 27, 2009; doi:10.1126/science.1165942 <b>Contact:</b> Christopher E. Shaw, King's College London, London, U.K. e-mail: <a href="mailto:shaw@iop.kcl.ac.uk">shaw@iop.kcl.ac.uk</a>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Amyotrophic lateral sclerosis (ALS)	Superoxide dismutase 1 (SOD1)	Studies in mice suggest that preventing the inhibition of dismutase active mutant SOD1 in Schwann cells may slow ALS progression. In ALS mice with a Schwann cell-specific knockout of dismutase active mutant SOD1, disease progression was significantly faster than that seen in controls without the tissue-specific knockout ( $p=0.0003$ ). In sciatic nerves from the mice with accelerated ALS progression, insulin-like growth factor 1 (IGF1) levels were lower than those seen in controls. IGF1 protects motor neurons in ALS mice. Next steps could include developing strategies to prevent SOD1 inhibition in Schwann cells.  <b>SciBX 2(10); doi:10.1038/scibx.2009.418</b> <b>Published online March 12, 2009</b>	Patent and licensing status unavailable	Lobsiger, C.S. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Feb. 23, 2009; doi:10.1073/pnas.0813339106 <b>Contact:</b> Don W. Cleveland, University of California, San Diego, La Jolla, Calif. e-mail: <a href="mailto:dccleveland@ucsd.edu">dccleveland@ucsd.edu</a>
Huntington's disease (HD)	$\alpha$ -Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid glutamate receptor (GRIA; AMPAR); brain-derived neurotrophic factor (BDNF)	A study in mice suggests that AMPAR agonists that stimulate BDNF production could be useful for treating HD. In a mouse model of HD, injection of the AMPAR agonist CX929 raised BDNF levels and increased cognitive performance and locomotor activity compared with what was seen in mock-treated controls. Next steps include testing AMPAR agonists in other cell culture and mouse models of HD and starting clinical trials of lead compounds. Cortex Pharmaceuticals Inc. has analogs of CX929 in preclinical development to treat HD.  <b>SciBX 2(10); doi:10.1038/scibx.2009.419</b> <b>Published online March 12, 2009</b>	Use of CX929 and related compounds to treat cognitive disorders and increase growth factor production patented by Cortex Pharmaceuticals; licensing status undisclosed <b>Contact:</b> Mark Varney, Cortex Pharmaceuticals Inc., Irvine, Calif. e-mail: <a href="mailto:mvarney@cortexpharm.com">mvarney@cortexpharm.com</a>	Simmons, D.A. <i>Proc. Natl. Acad. Sci. USA</i> ; published online March 2, 2009; doi:10.1073/pnas.0811228106 <b>Contact:</b> Danielle A. Simmons, University of California, Irvine, Calif. e-mail: <a href="mailto:danielle.a.simmons@gmail.com">danielle.a.simmons@gmail.com</a> <b>Contact:</b> Gary Lynch, same affiliation as above e-mail: <a href="mailto:glynch@uci.edu">glynch@uci.edu</a>
<b>Pulmonary disease</b>				
Cystic fibrosis (CF)	Interferon-related developmental regulator 1 (IFRD1; PC4)	Genomics analyses, cellular assays and mouse studies suggest that targeting IFRD1 could help treat CF. A genome-wide analysis of SNPs revealed an association between <i>IFRD1</i> polymorphisms and lung function variation in CF patients. <i>Ifrd1</i> <sup>-/-</sup> mice challenged with bacteria showed less weight loss and less airway and systemic inflammation than wild-type controls. Ongoing <i>in vitro</i> studies are investigating IFRD1's precise mechanism of action in the differentiation of immune cells like neutrophils. Novartis AG markets TOBI tobramycin inhalation solution to treat CF. Genentech Inc.'s Pulmozyme is approved to treat CF. Compounds in Phase III for CF include Inspire Pharmaceuticals Inc.'s denufosol, Pharmaxis Ltd.'s bronchitol as well as PTC124 from partners PTC Therapeutics Inc. and Genzyme Corp. At least 17 companies have therapies in preclinical to early stage clinical testing to treat CF.  <b>SciBX 2(10); doi:10.1038/scibx.2009.420</b> <b>Published online March 12, 2009</b>	Patented; available for licensing	Gu, Y. <i>et al. Nature</i> ; published online Feb. 25, 2009; doi:10.1038/nature07811 <b>Contact:</b> Christopher L. Karp, Cincinnati Children's Hospital Research Foundation, Cincinnati, Ohio e-mail: <a href="mailto:chris.karp@chmcc.org">chris.karp@chmcc.org</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>Assays &amp; screens</b>			
Conditional transposon-based genetic screening system for identification of cancer-associated genes (Sleeping Beauty Transposon system)	<p>The Sleeping Beauty transposon system may be a useful genetic screen in mice to identify new cancer-associated genes. The system can be used to induce traceable oncogenic mutations in a tissue of interest. In two proof-of-concept studies, researchers used transgenic mice either with Sleeping Beauty transposition to the liver to induce hepatocellular carcinoma (HCC) or with Sleeping Beauty transposition to the gastrointestinal tract epithelium to induce colorectal cancer. The studies identified known HCC and colorectal cancer-associated genes and implicated additional genes for each disease. Next steps include using the system to identify genes associated with other cancers.</p> <p><b>SciBX 2(10); doi:10.1038/scibx.2009.421</b> Published online March 12, 2009</p>	<p>Patent pending covering use of Sleeping Beauty transposon system to identify cancer genes in laboratory animals using a forward genetics approach; available for licensing from the University of Minnesota Office for Technology Commercialization</p>	<p>Keng, V.W. <i>et al. Nat. Biotechnol.</i>; published online Feb. 22, 2009; doi:10.1038/nbt.1526 <b>Contact:</b> David Largaespa, University of Minnesota, Minneapolis, Minn. e-mail: <a href="mailto:larga002@umn.edu">larga002@umn.edu</a></p> <p>Starr, T.K. <i>et al. Science</i>; published online Feb. 26, 2009; doi:10.1126/science.1163040 <b>Contact:</b> David Largaespa, University of Minnesota, Minneapolis, Minn. e-mail: <a href="mailto:larga002@umn.edu">larga002@umn.edu</a> <b>Contact:</b> Timothy K. Starr, same affiliation as above e-mail: <a href="mailto:star0044@umn.edu">star0044@umn.edu</a></p>
piggyBac transposon-mediated reprogramming of somatic cells into induced pluripotent stem (iPS) cells	<p>The piggyBac transposon may be useful for reprogramming somatic cells into iPS cells without using viral vectors. In mouse and human embryonic fibroblasts, a piggyBac transposon vector containing four genes needed to reprogram somatic cells was inserted into the host cell genome with high efficiency, leading to reprogrammed cells expressing pluripotency markers. The mouse iPS cells differentiated into multiple cell types, and individual piggyBac insertions could be removed. Next steps include a functional evaluation of pluripotency and evaluating the necessity of the four genes in the reprogrammed human cells.</p> <p><b>SciBX 2(10); doi:10.1038/scibx.2009.422</b> Published online March 12, 2009</p>	<p>Multiple patent applications filed covering piggyBac transposon system and key vector features; available for licensing <b>Contact:</b> Office of Technology Transfer and Industrial Liaison, Mount Sinai Hospital, Toronto, Ontario, Canada phone: 416-586-4800 x3117 <b>Contact:</b> Shona Cunningham, The University of Edinburgh, Edinburgh, U.K. phone: +44 (0)131-650-9090 e-mail: <a href="mailto:scunnin1@staffmail.ed.ac.uk">scunnin1@staffmail.ed.ac.uk</a></p>	<p>Woltjen, K. <i>et al. Nature</i>; published online March 1, 2009; doi:10.1038/nature07863 <b>Contact:</b> Andras Nagy, Mount Sinai Hospital, Toronto, Ontario, Canada e-mail: <a href="mailto:nagy@mshri.on.ca">nagy@mshri.on.ca</a></p> <p>Kaji, K. <i>et al. Nature</i>; published online March 1, 2009; doi:10.1038/nature07864 <b>Contact:</b> Keisuke Kaji, The University of Edinburgh, Edinburgh, U.K. e-mail: <a href="mailto:keisuke.kaji@ed.ac.uk">keisuke.kaji@ed.ac.uk</a></p>
<b>Chemistry</b>			
Biosynthetic pathway for the production of thiopeptide antibiotics	<p>A biosynthetic pathway for thiopeptides could be used to produce thiocillin I antibiotics and could be modified to generate new classes of antibiotics. In two strains of bacteria, the cloning, sequencing and characterization of two biosynthetic gene clusters—thiostrepton and siomycin—identified a biosynthetic pathway for thiopeptide formation. In <i>Bacillus cereus</i> ATCC 14579, a bacterial strain previously unknown to synthesize thiopeptides, genome mining confirmed that the pathway is used to produce thiocillin I. Next steps include genome mining to identify new members of the thiopeptide family with biological activity and using combinatorial biosynthesis to generate analogs that overcome solubility and bioavailability problems.</p> <p><b>SciBX 2(10); doi:10.1038/scibx.2009.423</b> Published online March 12, 2009</p>	<p>Patent applications filed for the biosynthetic gene clusters of thiostrepton and siomycin and their potential uses; unavailable for licensing</p>	<p>Liao, R. <i>et al. Cell</i>; published online Feb. 26, 2009; doi:10.1016/j.chembiol.2009.01.007 <b>Contact:</b> Wen Liu, Shanghai Institute of Organic Chemistry, Shanghai, China e-mail: <a href="mailto:wliu@mail.sioc.ac.cn">wliu@mail.sioc.ac.cn</a> <b>Contact:</b> Yi Yu, same affiliation as above e-mail: <a href="mailto:yuyi19@hotmail.com">yuyi19@hotmail.com</a></p>

## This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Single-molecule nanopore DNA sequencing	A single-molecule nanopore combined with an exonuclease DNA processing system (exonuclease I) could be useful for high-speed, low-cost DNA sequencing without the need for fluorescent labeling. A protein nanopore with a covalently attached adapter molecule was able to continuously identify unlabeled nucleosides with 99.8% accuracy. Next steps include integrating the base-detecting nanopore into a more efficient exonuclease sequencing system with better salt tolerance, digestion rate and stability.  <b>SciBX 2(10); doi:10.1038/scibx.2009.424</b> Published online March 12, 2009	Oxford Nanopore Technologies Ltd. has patent protection for its technologies; the first-generation nanopore sequencing technology will be exclusively commercialized by Illumina Inc.	Clarke, J. <i>et al. Nat. Nanotechnol.</i> ; published online Feb. 22, 2009; doi:10.1038/NNANO.2009.12 <b>Contact:</b> Hagan Bayley, University of Oxford, Oxford, U.K. e-mail: <a href="mailto:hagan.bayley@chem.ox.ac.uk">hagan.bayley@chem.ox.ac.uk</a>
<b>Computational models</b>			
High-speed, parallel DNA sequence assembly	A high-speed DNA sequence assembly algorithm, Assembly by Short Sequences (ABYSS), could offer a quick and cost-effective way to identify disease-associated genetic mutations and polymorphisms. ABYSS lowers the time needed to assemble large sets of gene sequence reads by distributing the task across a network of computers. The algorithm assembled about 3.5 billion paired-end reads from a sample human genome with 98.8% accuracy. The <i>Escherichia coli</i> K12 genome was also assembled with an accuracy comparable to that of other assembly algorithms. Next steps include increasing the accuracy of ABYSS and adapting it for transcriptome analysis.  <b>SciBX 2(10); doi:10.1038/scibx.2009.425</b> Published online March 12, 2009	Software is unpatented; freely available at <a href="http://www.bcgsc.ca/platform/bioinfo/software/abyss">http://www.bcgsc.ca/platform/bioinfo/software/abyss</a>	Simpson, J.T. <i>et al. Genome Res.</i> ; published online Feb. 27, 2009; doi:10.1101/gr.089532.108 <b>Contact:</b> Inanc Birol, British Columbia Cancer Agency, Vancouver, British Columbia, Canada e-mail: <a href="mailto:ibirol@bcgsc.ca">ibirol@bcgsc.ca</a>
<b>Disease models</b>			
Mouse model of $\beta$ -thalassemia major	A humanized mouse model could help guide the development of new transfusion, iron-chelation or genetic therapies for $\beta$ -thalassemia major. Transgenic mice that switched from producing human fetal to human adult hemoglobin after being born developed severe anemia, which led to death. Similar to human patients, the severe anemia brought on by the switch to adult hemoglobin production was corrected by regular blood transfusion but led to iron overload, which causes other pathologies. According to the researchers, the mouse model is ready to be used.  <b>SciBX 2(10); doi:10.1038/scibx.2009.426</b> Published online March 12, 2009	Unpatented; mice available to be licensed from the University of Alabama at Birmingham for use as a research tool	Huo, Y. <i>et al. Blood</i> ; published online March 3, 2009; doi:10.1182/blood-2008-12-197012 <b>Contact:</b> Thomas M. Ryan, University of Alabama at Birmingham, Birmingham, Ala. e-mail: <a href="mailto:tryan@uab.edu">tryan@uab.edu</a>
<b>Drug delivery</b>			
Chemically programmable antibodies	Chemically programmable antibodies may provide a versatile vaccination platform for a variety of diseases. Immunization with a diketone hapten vaccine elicited diketone-specific antibodies, which in turn could covalently attach to adaptors carrying a diketone tag and a disease target-specific binder. The resulting antibodies were thus programmed to neutralize the corresponding disease agent. In proof-of-concept experiments, mouse models of colon cancer and melanoma were inoculated with the diketone hapten vaccine. Weeks later, an injection of an adaptor that targeted tumor-specific integrins resulted in a >75% decrease in tumor volume compared with that seen in controls. Next steps should include exploring whether these programmable antibodies can be targeted against pathogens such as HIV, malaria and influenza virus (see <b>Bulking up immunity with instant Abs</b> , page 1).  <b>SciBX 2(10); doi:10.1038/scibx.2009.427</b> Published online March 12, 2009	Patented; licensed to Pfizer Inc.	Popkov, M. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online March 2, 2009; doi:10.1073/pnas.0900147106 <b>Contact:</b> Carlos F. Barbas III, The Scripps Research Institute, La Jolla, Calif. e-mail: <a href="mailto:carlos@scripps.edu">carlos@scripps.edu</a>

## This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
<b>Instrumentation</b>			
Multidimensional, in-cell NMR analysis of proteins	An NMR method can determine protein conformations, functions and interactions in living human cells at atomic resolutions, which could be useful for drug screening programs. Cell-penetrating peptides delivered isotope-labeled human ubiquitin to human HeLa cells, which enabled in-cell, 2D NMR spectrum acquisition that was consistent with previous results in <i>Xenopus</i> oocytes. The same was done with an immunosuppressant target, FKBP12. In addition, after the administration of immunosuppressant FK506 or rapamycin, both the in-cell FKBP12-FK506 complex spectrum and the FKBP12-rapamycin complex spectrum were acquired. Future studies will extend the NMR method to other human cell types and disease-related proteins.  <b>SciBX 2(10); doi:10.1038/scibx.2009.428</b> <b>Published online March 12, 2009</b>	Unpatented; unlicensed	Inomata, K. <i>et al. Nature</i> ; published online March 4, 2009; doi:10.1038/nature07839 <b>Contact:</b> Masahiro Shirakawa Kyoto University, Kyoto, Japan e-mail: <a href="mailto:shirakawa@moleng.kyoto-u.ac.jp">shirakawa@moleng.kyoto-u.ac.jp</a> <b>Contact:</b> Hidehito Tochio, same affiliation as above e-mail: <a href="mailto:tochio@moleng.kyoto-u.ac.jp">tochio@moleng.kyoto-u.ac.jp</a>
Protein structure determination in cells by multidimensional NMR	An NMR method determined protein structures in living cells at atomic resolutions and could help detect protein conformation changes in response to cellular events. To prevent instability and low sensitivity of living cell samples, NMR data collection used a nonlinear data acquisition method to cut NMR scan times. The in-cell strategy determined the structure of rat calmodulin protein overexpressed in <i>Escherichia coli</i> . Future experiments will apply this method to larger proteins of therapeutic interest.  <b>SciBX 2(10); doi:10.1038/scibx.2009.429</b> <b>Published online March 12, 2009</b>	Unpatented; unlicensed	Sakakibara, D. <i>et al. Nature</i> ; published online March 4, 2009; doi:10.1038/nature07814 <b>Contact:</b> Yutaka Ito, Tokyo Metropolitan University, Tokyo, Japan e-mail: <a href="mailto:ito-yutaka@tmu.ac.jp">ito-yutaka@tmu.ac.jp</a>

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