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## Cystic fibrosis two-step

By *Chris Cain, Staff Writer*

A Canadian and a U.S. team have independently shown that restoring normal function to mutant CFTR requires correcting two distinct folding steps.<sup>1,2</sup> The findings could provide a road map to guide the rational development of more effective therapies to treat cystic fibrosis.

CF is caused by genetic mutations in the cystic fibrosis transmembrane conductance regulator (CFTR), an ion channel that helps keep the lung epithelium hydrated and prevents mucous buildup that leads to airway obstruction and infection.

Last month, the FDA approved the first disease-modifying treatment for CF—Kalydeco ivacaftor from **Vertex Pharmaceuticals Inc.** Kalydeco is a small molecule CFTR potentiator that increases ion transport through the channel. The drug is indicated for CF patients with the G551D CFTR mutation, which decreases ion transport through the channel but does not impair its localization to the cell surface. This mutation occurs in about 4% of patients with CF.

About two-thirds of patients with CF, however, inherit two copies of a different mutation, the  $\Delta F508$  CFTR allele, which generates a misfolded version of the protein that is rapidly degraded and does not reach the surface of the cell in the first place. Because Kalydeco can only improve the function of CFTR that reaches the cell surface, distinct corrector compounds are needed to repair the folding defect caused by the  $\Delta F508$  mutation.

The only corrector in clinical development is VX-809, a small molecule from Vertex that is in Phase II testing in combination with Kalydeco in patients with  $\Delta F508$  CFTR. Data are expected this year. *In vitro* studies have suggested that Kalydeco and VX-809 can together restore up to about 25% of CFTR function, leaving open the question of whether further correction of CFTR folding could lead to additional improvement in  $\Delta F508$  function.<sup>3</sup>

To answer this question, separate groups at **The University of Texas Southwestern Medical Center** and **McGill University** set out to use biophysical, computational and cell-based experiments to determine the exact mechanisms underlying  $\Delta F508$  CFTR misfolding.

The teams built upon work published by their labs in 2005 that suggested the  $\Delta F508$  mutation disrupts two distinct steps in CFTR maturation—the folding of CFTR's nucleotide binding domain 1 (NBD1), where F508 is located, and the additional domain-domain interactions between NBD1 and distinct structural regions within CFTR.<sup>4,5</sup>

“For the last 20 years or so, the dogma was that the predominant defect of  $\Delta F508$  was caused by the destabilization of the NBD1 domain,”

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said Gergely Lukacs, professor of physiology at McGill. “When the crystal structure came out about seven years ago for  $\Delta$ F508 NBD1, some doubt was cast on this theory.”

Indeed, the structure suggested that the F508 residue may not play a central role in stabilizing NBD1 functionality, but rather that its location on an exposed surface of NBD1 may potentially affect NBD1’s intramolecular interactions with other regions of the protein.<sup>6</sup>

Lukacs said that subsequent homology modeling of CFTR structure provided additional evidence that intramolecular interactions likely played a role in CFTR maturation.<sup>7,8</sup>

**Correcting by suppressing**

The unanswered question was whether it is possible to simultaneously correct both defects—the intramolecular destabilization and the compromised folding of the binding domain—and if so whether this would lead to a more substantial improvement in CFTR activity than stabilizing NBD1 alone.

Both teams independently sought to identify amino acid residues that interact at a structural level with the  $\Delta$ F508 position and could therefore provide a path toward correcting the two defects and restoring CFTR folding.

The UT Southwestern team, led by professor of physiology Philip Thomas, performed a computational analysis of 493 CFTR-related gene sequences to identify amino acid residues whose variation was coupled to variation at the F508 position. This approach identified 16 residues that affected the folding of  $\Delta$ F508 CFTR *in vitro*.

Mapping the residues to the NBD1 crystal structure suggested a critical interaction between NBD1 and the fourth intracellular loop (ICL4) located in membrane spanning domain 2 (MSD2).

Lukacs’ McGill group performed *in vitro* biophysical studies and reported that mutations that increased NBD1 stability in the  $\Delta$ F508 background did not lead to a proportional increase in CFTR maturation. This confirmed that an additional folding step must be altered in  $\Delta$ F508 CFTR. Additional mutational analysis led them to pinpoint disruption of the NBD1-ICL4 interface as the likely second step.

Both teams tested suppressor mutations that either stabilized NBD1 folding or stabilized the NBD1-ICL4 interface and saw about a 20% increase in  $\Delta$ F508 CFTR maturation. However, when they combined the two suppressor mutations,  $\Delta$ F508 CFTR maturation and function were restored to near wild-type levels *in vitro*.

Results from both studies were published in *Cell*.

“This work significantly moves the field forward—there was a huge amount of work in the papers. It really nails down the two-step hypotheses,” said David Thomas, professor and chair of the Department of Biochemistry at McGill. “Because the previous crystal structures revealed very little difference between wild-type NBD1 and  $\Delta$ F508 NBD1, they didn’t lead us very far. Looking at the dynamic state of CFTR folding was key.” Thomas was not involved in the studies.

**“This work significantly moves the field forward—there was a huge amount of work in the papers. It really nails down the two-step hypotheses.”**

**—David Thomas, McGill University**

“When we correct both steps together, instead of an additive effect, we see a synergistic effect,” said Philip Thomas. “This suggests it would be desirable to correct both steps. The open question is whether there is a single small molecule out there, or one that could even exist, that is capable of doing that, because they are steps that are temporally isolated from each other.”

### Searching for function

Philip Thomas said the assays and mutations outlined in the two studies could provide a road map to identify how existing small molecule correctors function. “The use of mutations we identify will allow a better understanding of how they’re acting, and that is one of the important features of this work. It provides an operations manual for determining the mechanism of action of extant correctors.”

Almost all existing small molecule CFTR correctors have been identified through cell-based assays that screen for improvements in CFTR maturation and function but do not reveal detailed mechanisms of action.

“Our approach has been to do cell-based screens using chloride transport in cells as an endpoint, then to narrow them down using different criteria to select scaffolds for lead optimization,” said Fred Van Goor, head of biology for Vertex’s CF research program. “Phenotypic assays don’t make any assumption on what folding state the compounds need to work on; they are just looking at the effect of compounds on CFTR cell surface localization and function.”

VX-809 has been shown to be additive *in vitro* when combined with small molecule correctors identified by academics, but its molecular target and the CFTR folding step at which it functions have not been determined.<sup>3</sup>

David Thomas agreed that cell-based screens are the workhorse for discovery. “A lot of us are trying to come up with a rational way to look for synergy, but the brute force screening approach is being done too, and in some ways it is a lot easier to take that approach,” he said.

In January 2011, David Thomas entered into a two-year collaboration with **GlaxoSmithKline plc** to screen for CFTR-correcting compounds. Also that year, his lab found a small molecule corrector of CFTR that directly bound to and stabilized mouse NBD1.<sup>9</sup>

Philip Thomas said the findings in the two studies could help researchers design more targeted screens. “For example, you could go to a cell-based assay and use the mutations we have identified here to screen for compounds that selectively correct step one and then look for compounds that could selectively fix step two. It informs a way to look for compounds that act at specific steps,” he said.

Lukacs agreed and said his team’s next steps include determining the mechanism of existing correctors and designing screening assays to identify correctors that act at each folding step.

“We can speculate that perhaps the drugs that have been developed so far predominantly target only one of these folding defects, because despite extensive efforts the maximum improvement seen in CFTR folding is around 15%,” said Lukacs.

Philip Thomas said he next plans to investigate the molecular pathology of additional CF mutations. He is also a cofounder of **Reata Pharmaceuticals Inc.**, which has licensed the *in vitro* screening assay that was used in his paper.

Chris Wigley, VP of research at Reata, would not disclose the company’s plans for the screening platform. “The work described by these two independent labs suggests an elegant resolution to the so-called efficacy ceiling observed for corrector molecules that have been studied to date. Together, results of these studies support the potential of combination therapies that target the two defects in  $\Delta F508$  CFTR maturation. It is attractive to speculate that with this information in hand, single agents can be designed that achieve similar functional correction.”

Van Goor said that for patients with CF, full correction may not be necessary for clinical benefit. “What is clear from natural history studies of CF patients is that you don’t need full amounts of CF function to have a difference in the clinical phenotype of disease progression. As little as 10% of normal function is present in individuals with much less severe CF disease.”

Vertex is combining VX-809 with Kalydeco but does not currently plan to test corrector compound combinations. The company expects to begin a Phase II trial of VX-661, a second CFTR corrector, this quarter.

“Vertex is committed to several ongoing collaborations with the **Cystic Fibrosis Foundation** and their folding and structural consortium to understand the basic science underlying how VX-809 functions. We are continuing to work with the community to understand how these correctors work, which could lead to insights on how to improve correctors,” he added.

The Cystic Fibrosis Foundation partially funded both studies, and the results are unpatented.

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### COMPANIES AND INSTITUTIONS MENTIONED

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**GlaxoSmithKline plc** (LSE:GSK; NYSE:GSK), London, U.K.  
**McGill University**, Montreal, Quebec, Canada  
**Reata Pharmaceuticals Inc.**, Irving, Texas  
**The University of Texas Southwestern Medical Center**, Dallas, Texas  
**Vertex Pharmaceuticals Inc.** (NASDAQ:VRTX), Cambridge, Mass.

# Broadening TDO's base

By Kai-Iye Lou, Staff Writer

A team at the **Ludwig Institute for Cancer Research Ltd. Brussels Branch** and the **University of Namur** has shown in mice that a small molecule inhibitor of tryptophan 2,3-dioxygenase promotes immune rejection of tumors without signs of toxicity.<sup>1</sup> The group plans to run high throughput screens to identify a more stable inhibitor that could be advanced into clinical testing, and the institute is in discussions to spin out a company this half.

Tryptophan 2,3-dioxygenase (TDO2; TDO) catalyzes tryptophan to generate kynurenine, a metabolite that inhibits the antitumor immune response.<sup>2</sup> Last October, a group in Germany reported in *Nature* that glioblastomas could exploit the immunoregulatory properties of TDO-generated kynurenine to dampen the antitumor immune response and promote growth.<sup>3</sup>

However, Michael Platten, corresponding author on the October *Nature* paper, chose to pursue targets downstream of TDO, as there were concerns on whether inhibiting the enzyme itself would have adverse effects because normal liver and brain cells also express TDO.<sup>4</sup> Platten is a professor in the Department of Neurooncology at **Heidelberg University Hospital** and head of the Experimental Neuroimmunology Unit at the **German Cancer Research Center**.

To find out, a group led by Benoît Van den Eynde, director of the LICR Brussels Branch and a professor at the **Université Catholique de Louvain**, set out to determine how widespread TDO activity is across tumors and whether inhibiting the enzyme's function would have adverse effects.

The team first showed that TDO is not just a target in glioblastoma. His team assayed a range of tumor types from 144 patient samples for TDO expression and found all 7 hepatocarcinoma samples, 10 of 20 melanoma samples and 9 of 22 bladder carcinoma samples tested to be TDO-positive.

Van den Eynde's group then addressed the toxicity concerns by treating mice injected with *Tdo*-expressing murine mastocytoma tumor cells with a small molecule TDO inhibitor. In treated mice, the inhibitor, a tetrazolyl-vinyl substituted (fluoro)indole scaffold dubbed LM10, promoted immune rejection of the cells compared with no treatment.

Animals receiving the inhibitor for more than 100 days did not show signs of toxicity, and liver enzyme levels in plasma remained within normal ranges.

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

"Our work shows that TDO could be a relevant new therapeutic target in many cancers and provides pharmacological proof of concept that the enzyme could be blocked with a small molecule," said Van den Eynde.

"The preliminary toxicity studies in the mouse model strongly suggest that TDO inhibition would not cause liver damage," added Vincenzo Cerundolo, director of the MCR Human Immunology Unit at **The Weatherall Institute of Molecular Medicine at University of Oxford** and a professor of immunology at the **University of Oxford**.

"The current findings suggest that tryptophan degradation is a mechanism employed by a broad range of tumors to suppress the antitumor immune response," said Platten.

Cerundolo agreed. "The study raises the possibility that tryptophan degradation could be a general strategy that tumors employ to hamper the immune system," he told *SciBX*. "The findings suggest that an effective therapeutic strategy would be to combine an agent that amplifies the specific antitumor response with one that abolishes the immunosuppressive mechanisms employed by the tumor itself."

## Being a good host

Whereas Platten's work suggests that TDO's tumor growth-increasing effect in glioblastomas primarily stems from kynurenine-mediated effects on the tumor cells themselves, the current findings in a different tumor model suggest that the antitumor effect of TDO inhibition is primarily mediated by the host immune system (*see Figure 1, "Dependency of TDO inhibition on the host immune system"*).

Indeed, Van den Eynde's team found that LM10 decreased tumor growth in immunocompetent mice injected with *Tdo*-expressing mastocytoma cell lines but had no effect on tumor growth in immunodeficient mice injected with the same cell lines, suggesting that the immune system is the key regulator of tumor growth in this case.

"The current paper not only is confirmatory of the *Nature* publication, but also further raises an interesting issue as to whether the underlying mechanism promoting tumorigenicity by TDO is dependent on, or independent of, the host's immune system," said Ursula Grohmann, a professor of pharmacology in the Department of Experimental Medicine and Biochemical Sciences at the **University of Perugia**.

She said Van den Eynde's findings open up the possibility of developing antitumor strategies that enhance or reinforce host immune surveillance.

## Complementing immunotherapy

The ability of the TDO inhibitor to reverse tumor immune resistance and the molecule's safety profile suggest it could complement existing cancer immunotherapies.

"Because of the main mechanism of action, we would recommend testing TDO inhibitors in therapeutic settings where one wants to induce a strong immune response to attack the tumor, such as in combination with a cancer vaccine," Van den Eynde told *SciBX*. "Our data suggest that specific tumor types where a TDO inhibitor could be useful are melanomas, bladder carcinomas and liver carcinomas."

In addition, targeting TDO also could complement current efforts to develop inhibitors of indoleamine 2,3-dioxygenase (INDO; IDO), another tryptophan metabolism-related enzyme that also generates kynurenine. The discovery of a link between tryptophan metabolism

**"The findings suggest that an effective therapeutic strategy would be to combine an agent that amplifies the specific antitumor response with one that abolishes the immunosuppressive mechanisms employed by the tumor itself."**

— Vincenzo Cerundolo,  
University of Oxford

and immunosuppression in a variety of diseases, including cancer, was first established through IDO.<sup>2</sup>

“This work is particularly interesting because the authors show that most human tumors will express either TDO, IDO or a combination of both,” said Grohmann. “IDO is another major enzyme that catalyzes the same reaction as TDO, which points to the striking finding that aberrant tryptophan catabolism is a hallmark of most human tumors.”

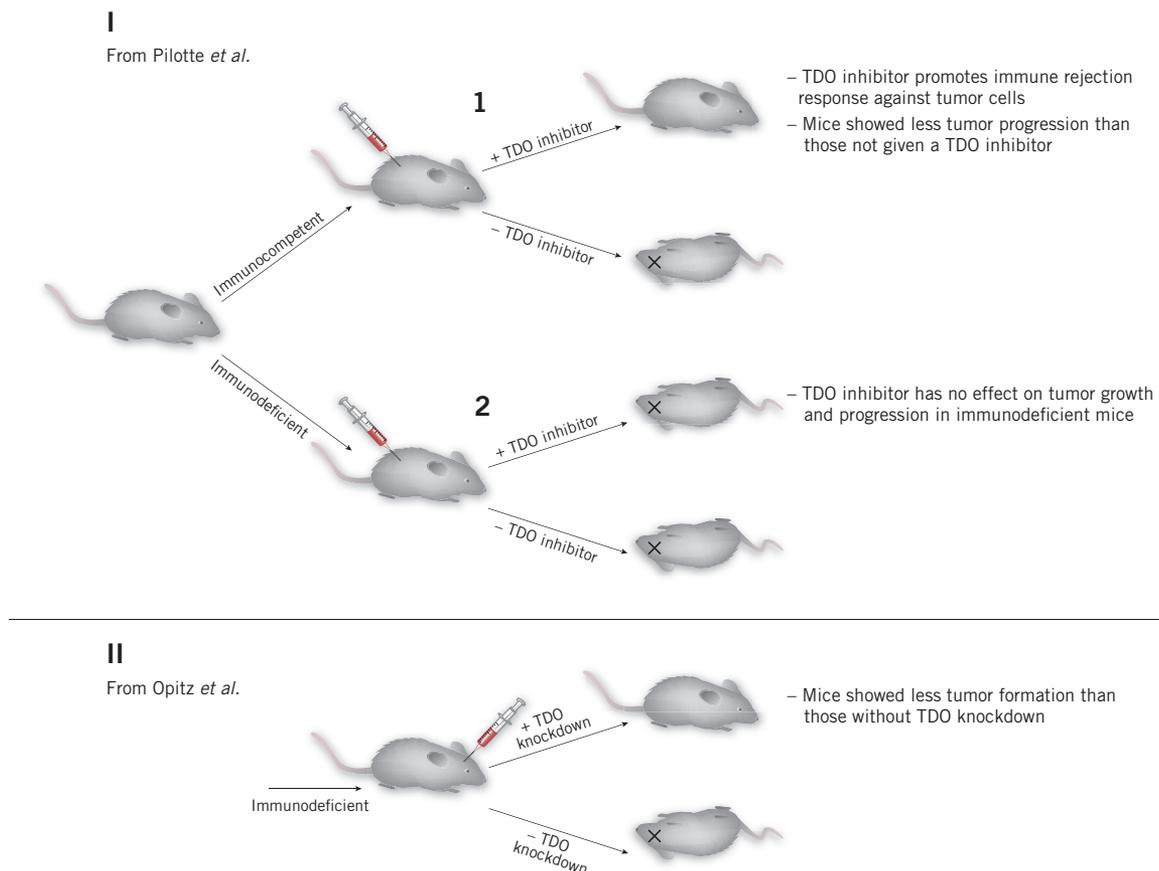
In the *PNAS* paper, Van den Eynde’s team found that out of a panel of 104 human tumor cell lines analyzed, 20 expressed only TDO, 17 expressed only IDO and 16 expressed both. The researchers did not

detect expression of either enzyme in the other 51 tumor cell lines.

“TDO inhibition would be very complementary to IDO inhibition,” Van den Eynde told *SciBX*. “For example, a TDO inhibitor could be used when a tumor develops resistance to an IDO inhibitor by upregulating TDO. One could also consider inhibiting both TDO and IDO simultaneously, which could increase the proportion of tumors that become responsive to an immunotherapy.”

At least two biotechs—**Incyte Corp.** and **NewLink Genetics Corp.**—have IDO inhibitors in the clinic. Both programs are in Phase I testing to treat solid tumors.

(Continues on p. 6)



**Figure 1. Dependency of TDO inhibition on the host immune system.** Tumors can exploit the immunoregulatory properties of tryptophan 2,3-dioxygenase (TDO2; TDO) to dampen the antitumor immune response and promote their own growth. As reported by Pilotte *et al.*, a small molecule TDO inhibitor could reverse the immune-dampening effects of TDO.

In immunocompetent mice, a small molecule TDO inhibitor promoted a rejection response against injected *Tdo*-expressing murine mastocytoma cells and decreased tumor progression compared with no inhibitor (I.1). In contrast, the TDO inhibitor had no effect on tumor growth in immunodeficient mice (I.2), suggesting TDO’s tumor-promoting activity depends primarily on the enzyme’s effects on the host immune system.

The results in the mastocytoma model differ from those in a study by Opitz *et al.*, which suggest TDO’s tumor-promoting activity in glioblastoma hinges on the enzyme’s effects in the tumor cells themselves. In that study, immunodeficient mice were transplanted with human glioblastoma cells with and without small hairpin RNA-mediated TDO knockdown.

Despite being immunodeficient, only one of six mice receiving the glioblastoma cells with TDO knockdown developed tumors compared with five of six for those receiving cells without TDO knockdown (II).

The differences between these two studies may stem from the different tumor types analyzed, but taken together, the results provide two distinct mechanistic rationales for targeting TDO in cancer.

# Rebuilding a better bone

By Tracey Baas, Senior Editor

A team from the **University of California, Davis Medical Center** has designed a chimeric molecule that could treat osteoporosis by increasing the homing of transplanted mesenchymal stem cells to bone surfaces in mice.<sup>1</sup> The next step is showing the method works in large animal models of bone diseases.

Mesenchymal stem cells (MSCs) occur in a variety of adult tissues including bone marrow, in which they help regenerate bone by differentiating into osteoblasts. The number of endogenous MSCs decreases with age, leading to a decreased ability to regenerate bone and increased potential for developing osteoporosis and other bone diseases.

A potential solution for age-related bone disorders is MSC transplantation, but in preclinical studies the cells do not home to bone surfaces and show limited long-term engraftment unless the cells are first genetically modified<sup>2-5</sup> or delivered after bone injury.<sup>3,6,7</sup>

The UC Davis Medical Center team addressed some of those limitations by designing a chimeric molecule that binds integrin  $\alpha_4\beta_1$  (CD49D/CD29), which is highly expressed by MSCs undergoing osteoblast differentiation, and brings the MSCs to the bone surface to increase bone mass.

One portion of the chimeric molecule is LLP2A, a peptidomimetic ligand that binds integrin  $\alpha_4\beta_1$ . The other portion is Ale, better known as Fosamax alendronate, an osteoporosis drug that has intrinsic bone-seeking properties.

**Merck & Co. Inc.** markets Fosamax to treat and prevent osteoporosis and to treat Paget's disease. Merck declined to comment on the work.

The researchers characterized LLP2A-Ale in three different mouse models of bone disease.

(Continued from "Broadening TDO's base," p. 5)

Van den Eynde said his group now is looking to validate the effects of TDO inhibition in other preclinical tumor models. The team also is trying to develop a more stable small molecule TDO inhibitor that could be advanced into the clinic, which will include medicinal chemistry studies to optimize LM10 and high throughput screening efforts to identify new inhibitors.

"I envision that the first clinical trials for such an inhibitor would be in the form of combination therapy for patients receiving a cancer vaccine," he said.

LICR has filed multiple patent applications to cover the findings described in *PNAS*. LICR's planned spinoff will focus on immunomodulatory therapies for cancer, including the TDO inhibitor program. The institute said the spinoff already has an undisclosed amount of committed financing.

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In immunodeficient mice, a single i.v. injection of LLP2A-Ale plus human MSCs resulted in MSCs at bone surfaces at 24 hours postinjection. Those MSCs differentiated into osteoblasts and became embedded within the bone matrix at three weeks postinjection.

For the second model, the researchers looked at whether LLP2A-Ale could direct endogenous MSCs to the bone surface and thus increase bone mass in the absence of MSC transplants.

In mice with age-related bone loss, i.v. injection of LLP2A-Ale alone increased bone mass, vertebral maximum load and maximum bone stress compared with injection of LLP2A or Ale alone. Also in the mice, a single i.v. injection of LLP2A-Ale significantly prevented age-related bone loss for up to eight weeks compared with saline injection ( $p < 0.05$ ).

In an acute estrogen-deficient mouse model of osteopenia, which is less severe than osteoporosis, i.v. injection of LLP2A-Ale two weeks after ovariectomy prevented bone mass loss and increased bone formation compared with LLP2A or Ale injection alone. The chimeric molecule injection had effects similar to those of a four-week treatment with the anabolic agent parathyroid hormone (PTH).

Results were published in *Nature Medicine*.

## Breaking barriers

Wei Yao, corresponding author on the paper and an assistant professor at the **UC Davis Center for Healthy Aging**, hopes to start toxicity studies beginning August 2012 and Phase I and II trials of LLP2A-Ale as early as 2014 in osteoporosis patients ages 50 and higher.

Yao's group is part of a larger Osteoporosis Disease Team, which recently received \$110,000 from the **California Institute for Regenerative Medicine** (CIRM). The larger disease team will use the seeding money to put together an IND application to the FDA, a critical component needed to apply for a larger Disease Team Therapy Development Award from CIRM, worth up to \$20 million. That money would be used to fund future clinical trials.

Other key members of the Osteoporosis Disease Team are Nancy Lane, director of the UC Davis Center for Healthy Aging; Jan Nolte,

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## COMPANIES AND INSTITUTIONS MENTIONED

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**Université Catholique de Louvain**, Brussels, Belgium  
**University of Namur**, Namur, Belgium  
**University of Oxford**, Oxford, U.K.  
**University of Perugia**, Perugia, Italy  
**The Weatherall Institute of Molecular Medicine at University of Oxford**, Oxford, U.K.

# The TAU of PD

By Lev Osherovich, Senior Writer

An Australian team has shown that loss of microtubule-associated protein- $\tau$  leads to accumulation of toxic intracellular iron, a shared feature of Parkinson's disease and Alzheimer's disease.<sup>1</sup> The findings could mean that companies developing AD therapies that target the aggregated protein will need to be mindful of iron levels.

Microtubule-associated protein- $\tau$  (MAPT; TAU; FTDP-17) is a structural component of the cytoskeleton that helps

(Continued from "Rebuilding a better bone," p. 6)

director of the Stem Cell Program and Institute for Regenerative Cures at the **University of California, Davis School of Medicine**; and Kit Lam, chair of the Department of Biochemistry and Molecular Medicine at the UC Davis Medical Center.

"The next steps needed are to show how this regeneration is occurring, especially in the situation where LLP2A-Ale is delivered on its own," said Anna Spagnoli, associate professor of pediatrics at **The University of North Carolina at Chapel Hill**. "It is interesting to speculate that the compound is acting upon endogenous MSCs, but that possibility has not yet been proven by experiment. The experiments that will need to be done to show those specific mechanisms will be quite challenging."

**"The next steps needed are to show how this regeneration is occurring, especially in the situation where LLP2A-Ale is delivered on its own."**

—Anna Spagnoli,  
The University of North Carolina  
at Chapel Hill

Those challenges have to do with the technical limitations of tracking endogenous MSCs without affecting the characteristics of stem cells or the subsequent osteoblasts.

David Scadden wanted "to see more long-term studies that show details of the magnitude and durability of repair these cells [MSCs] are capable of, especially in disease models" that are not immunodeficient.

Scadden is professor of medicine at **Harvard University**, director of the **Massachusetts General Hospital Center for Regenerative Medicine and Technology** and co-director of the **Harvard Stem Cell Institute**.

"We have already done additional experiments with the combination therapy in an aged mouse model of osteoporosis and have extended our characterization of bone mass formation out to three months. The work will be published in the near future," Yao told *SciBX*.

Instead of osteoporosis, Scadden thinks orthopedic indications or osteogenesis imperfecta could be a better initial indication for LLP2A-Ale plus MSC transplants. Osteogenesis imperfecta—brittle bone disease—has no cure and is caused by a mutation in the *collagen* gene.

"Mouse models of osteogenesis imperfecta are available, so it would be possible to see how the method translates. Ultimately, one could envision MSCs being harvested from the patient, genetically corrected for the

neurons move proteins to distant synapses. In AD, TAU becomes hyperphosphorylated and forms large aggregates called neurofibrillary tangles that are thought to hasten the destruction of neurons.

Recent findings have suggested that TAU aggregates are present in PD as well, but exactly how TAU contributes to the disease has been unclear.<sup>2</sup>

Now, a team led by Ashley Bush, professor of pathology at **The University of Melbourne**, has found that the soluble form of TAU normally functions in a pathway that helps to export excess iron and that this process goes awry in the brains of PD patients and in mice lacking Tau.

(Continues on p. 8)

collagen mutation, and then directed back toward the bone," said Scadden.

Spagnoli wanted to see the approach tried in nonunion fractures. These nonhealing fractures are treated mostly with bone autografts harvested from the back of the pelvis. A small number of pilot clinical studies have shown positive results for MSC transplants.<sup>8-11</sup>

"If the MSCs that the team delivered are truly acting as osteoblasts and integrate to promote healing in a fracture nonunion model, that would be a most interesting situation," she said.

The work described in the paper is patented by the **University of California** and is available for licensing. Yao said her team has had "some informal discussions with two big pharmas that really want to see large animal and toxicology studies before they're ready to hold discussions with us."

Baas, T. *SciBX* 5(8); doi:10.1038/scibx.2012.194  
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e-mail: [wei.yao@ucdmc.ucdavis.edu](mailto:wei.yao@ucdmc.ucdavis.edu)
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## COMPANIES AND INSTITUTIONS MENTIONED

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**Harvard University**, Cambridge, Mass.

**Harvard Stem Cell Institute**, Boston, Mass.

**Massachusetts General Hospital Center for Regenerative Medicine and Technology**, Boston, Mass.

**Merck & Co. Inc.** (NYSE:MRK), Whitehouse Station, N.J.

**UC Davis Center for Healthy Aging**, Davis, Calif.

**University of California**, Oakland, Calif.

**University of California, Davis Medical Center**, Sacramento, Calif.

**University of California, Davis School of Medicine**,

Sacramento, Calif.

**The University of North Carolina at Chapel Hill**, Chapel Hill, N.C.

“The findings pertain as much to Alzheimer’s disease as Parkinson’s disease,” said Bush. Indeed, he expects TAU aids the normal function of amyloid precursor protein (APP), a key AD player that his team has previously shown to aid the detoxification of iron.<sup>3</sup>

The findings add support for **Prana Biotechnology Ltd.**’s strategy of treating AD, PD and other neurodegenerative diseases by trapping excess metals.

### Metal health

The team’s first clue that TAU deficiency could play a role in PD came from studying the postmortem brains of patients with PD. The group found that the substantia nigra—the dopaminergic brain region most affected by PD—had higher levels of iron and lower levels of soluble TAU than the same region in healthy controls.

The team also examined the brains of aged Tau knockout mice and saw increased iron levels and degeneration of the substantia nigra as well as PD-like motor difficulties compared with what was seen in wild-type control brains.

“TAU knockouts don’t develop much of a phenotype prior to seven months,” so in previous studies of these mice the PD-like phenotype had been overlooked, said Bush.

He hypothesized that other mouse models of PD also would show Tau abnormalities. Indeed, mice with a chemically induced form of the disease had excess iron accumulation and a shortage of soluble Tau compared with untreated controls.

Bush thinks that one of TAU’s normal functions may be to help APP travel to the cell surface, which is where APP facilitates the transport of iron out of the neuron. In primary cortical neurons from Tau knockout mice, iron accumulation was higher and cell surface levels of App were lower than those in wild-type controls.

Finally, Bush’s team showed that pretreatment with clioquinol, an iron-chelating compound, protected Tau knockout mice from degeneration of the substantia nigra and cortex compared with no treatment.

Results were reported in *Nature Medicine*.

Bush’s findings are in line with the hypothesis that metal accumulation is a central feature of several neurodegenerative diseases, said James Connor, professor and vice-chair of neurosurgery research at **Pennsylvania State University**.

“The idea that some disruption in APP’s function [in iron transport] is involved in AD has been around for a while,” said Connor. “The argument is that if you disrupt this function of APP or prevent it from reaching the cell surface, there is an accumulation of iron in the neurons.”

It is unclear why Tau knockouts initially develop PD-like symptoms rather than AD symptoms. Connor suspects the substantia nigra may be especially sensitive to decreases in the iron-detoxifying activity of APP and thus is the first brain region to show signs of pathology.

The neurons of the substantia nigra use an iron-requiring enzyme to make dopamine, and thus “have a high turnover of iron,” said Connor. “These cells may be more vulnerable to deficiency of APP, since they are in an iron-rich area to begin with.”

Bush agreed and said older Tau knockouts go on to develop AD-like pathology, including cortical atrophy, increased ventricular area and decreased cognitive functioning compared with wild-type controls.

### Iron it out

Study coauthor Robert Cherny, head of research at Prana and an associate professor at the University of Melbourne, said the paper shows that Prana’s “approach of re-establishing metal homeostasis is applicable across a range of neurodegenerative disorders.”

Prana’s lead compound is PBT2, a metal protein–attenuating compound that is in Phase II testing for AD and Huntington’s disease.

Prana also is developing PBT434, a metal-binding compound that is in preclinical development for PD in a project sponsored by **The Michael J. Fox Foundation for Parkinson’s Research**.

Cherny said Prana’s compounds work by performing APP’s metal-transporting functions, “taking metals from places of excess to areas where they are in deficit, restoring homeostasis.”

Bush, who cofounded Prana and is the company’s former CSO, said his next steps are identifying metal-binding compounds that have high specificity for iron and testing them in animal models of PD.

His findings could serve as a caution for companies developing AD therapeutics that lower levels of aggregated TAU—either directly or indirectly.

In the former group is **TauRx Pharmaceuticals Ltd.** Its rember methylthioninium chloride, a dye that binds to TAU aggregates, has completed Phase II testing to treat AD. The company is planning to advance a related compound called LMTX into Phase III testing. TauRx did not respond to queries by *SciBX*.

Among the companies with compounds that indirectly affect TAU is **reMYND N.V.**, a spinout of the **Catholic University Leuven** that has preclinical compounds that reduce the toxicity of TAU aggregates in cell culture models of AD.

CSO of drug discovery Gerard Griffioen said reMYND’s compounds likely work by modulating vesicular trafficking and, in addition to decreasing levels of TAU aggregates, may also offset the toxic effect of TAU deficiency seen by Bush.

Bush’s study shows “that in addition to TAU having a gain of toxic function in neurodegenerative disease, the soluble form has an important function itself,” said Griffioen. “Many people, including us, are focused on TAU aggregation and the toxic process around that. But here they show that TAU function is important for iron export. This holds lessons for the field. If you are thinking about degrading or removing TAU as a therapeutic approach, you have to be careful because you might affect other things, such as iron export.”

**“Many people, including us, are focused on TAU aggregation and the toxic process around that. But here they show that TAU function is important for iron export. This holds lessons for the field. If you are thinking about degrading or removing TAU as a therapeutic approach, you have to be careful because you might affect other things, such as iron export.”**

—Gerard Griffioen,  
reMYND N.V.

Griffioen said that a potential solution is to focus on preventing TAU from aggregating in the first place rather than on eliminating TAU aggregates that have already formed.

The findings reported in *Nature Medicine* are unpatented.

Osherovich, L. *SciBX* 5(8); doi:10.1038/scibx.2012.195

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**Catholic University Leuven**, Leuven, Belgium

**The Michael J. Fox Foundation for Parkinson's Research**, New York, N.Y.

**Pennsylvania State University**, University Park, Pa.

**Prana Biotechnology Ltd.** (ASX:PBT; NASDAQ:PRAN), Melbourne, Victoria, Australia

**reMYND N.V.**, Leuven, Belgium

**TauRx Pharmaceuticals Ltd.**, Singapore

**The University of Melbourne**, Melbourne, Victoria, Australia



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## This week in therapeutics

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

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

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
<b>Cancer</b>				
Brain cancer	Insulin-like growth factor binding protein 2 (IGFBP2); integrin $\alpha_5$ (CD49e); integrin $\beta_1$ (CD29); integrin-linked kinase (ILK); NF- $\kappa$ B	<p>Patient sample and mouse studies suggest inhibiting the integrin/ILK/NF-<math>\kappa</math>B pathway could help treat IGFBP2-driven gliomas.</p> <p>In patient samples, increased expression of integrin <math>\alpha_5</math>, integrin <math>\beta_1</math> and ILK all correlated with decreased survival. In a mouse model of IGFBP2-driven glioma, inhibiting Ilk or Nf-<math>\kappa</math>b signaling lowered the incidence of high-grade gliomas compared with no inhibition. Next steps could include evaluating integrin, ILK and NF-<math>\kappa</math>B inhibitors in additional mouse models of IGFBP2-driven gliomas.</p> <p>At least three companies have compounds that inhibit NF-<math>\kappa</math>B signaling in Phase II or earlier testing to treat cancer.</p> <p><b>SciBX 5(8); doi:10.1038/scibx.2012.196</b> Published online Feb. 23, 2012</p>	Unpatented; licensing status not applicable	<p>Holmes, K.M. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Feb. 15, 2012; doi:10.1073/pnas.1120375109</p> <p><b>Contact:</b> Wei Zhang, The University of Texas MD Anderson Cancer Center, Houston, Texas e-mail: <a href="mailto:wzhang@mdanderson.org">wzhang@mdanderson.org</a></p>
Breast cancer	IL-4 receptor (CD124)	<p>A study in mice identified an aptamer targeting CD124 that depleted tumor-promoting myeloid-derived suppressor cells (MDSCs) and could help treat breast cancer.</p> <p>In mouse models of breast cancer, the aptamer increased MDSC apoptosis and decreased both tumor growth and lung metastases compared with a control aptamer. Next steps include confirming the effects of the aptamer in human tissue samples and coupling the aptamer to a chemotherapeutic.</p> <p><b>SciBX 5(8); doi:10.1038/scibx.2012.197</b> Published online Feb. 23, 2012</p>	Patent and licensing status unavailable	<p>Roth, F. <i>et al. Cancer Res.</i>; published online Jan. 26, 2012; doi:10.1158/0008-5472.CAN-11-2772</p> <p><b>Contact:</b> Paolo Serafini, University of Miami, Miami, Fla. e-mail: <a href="mailto:pserafini@med.miami.edu">pserafini@med.miami.edu</a></p>
Chronic lymphocytic leukemia (CLL)	Solute carrier family 7 member 11 cysteine glutamate transporter (SLC7A11; xCT)	<p><i>In vitro</i> and mouse studies suggest the xCT inhibitor sulfasalazine could be repurposed to help treat CLL. In cocultures of primary CLL cells and human bone marrow stromal cell lines, compared with CLL cells cultured alone, xCT-mediated cystine uptake and subsequent cysteine secretion by stromal cells increased CLL cell viability. In the same coculture, sulfasalazine and chemotherapy increased CLL apoptosis compared with chemotherapy alone. In mouse models of CLL, sulfasalazine decreased leukemia burden compared with pretreatment burden in the same animal. Ongoing work includes testing additional therapies that block stromal cell protection of CLL cells <i>in vitro</i> and in animals. Generic sulfasalazine is approved to treat rheumatoid arthritis (RA) and inflammatory bowel disease (IBD).</p> <p><b>SciBX 5(8); doi:10.1038/scibx.2012.198</b> Published online Feb. 23, 2012</p>	Patent status undisclosed; available for licensing or partnering	<p>Zhang, W. <i>et al. Nat. Cell Biol.</i>; published online Feb. 19, 2012; doi:10.1038/ncb2432</p> <p><b>Contact:</b> Peng Huang, The University of Texas MD Anderson Cancer Center, Houston, Texas e-mail: <a href="mailto:p Huang@mdanderson.org">p Huang@mdanderson.org</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Gastric cancer	$\alpha$ -1,4- <i>N</i> -acetylglucosaminyltransferase (A4GNT)	<p>Patient sample and mouse studies suggest increasing A4GNT signaling could help prevent gastric cancer. <i>A4gnt</i> knockout mice developed gastric adenocarcinomas, whereas wild-type mice did not. In patient gastric adenoma and adenocarcinoma samples, <i>A4GNT</i> expression was lower than that in non-neoplastic gastric mucosa. Next steps could include developing and evaluating compounds that increase A4GNT expression.</p> <p><b>SciBX 5(8); doi:10.1038/scibx.2012.199</b>  <b>Published online Feb. 23, 2012</b></p>	Patent and licensing status unavailable	<p>Karasawa, F. <i>et al. J. Clin. Invest.</i>; published online Feb. 6, 2012; doi:10.1172/JCI59087</p> <p><b>Contact:</b> Jun Nakayama, Shinshu University Graduate School of Medicine, Matsumoto, Japan  e-mail: <a href="mailto:jnaka@shinshu-u.ac.jp">jnaka@shinshu-u.ac.jp</a></p>
Liposarcoma	Peroxisome proliferation-activated receptor- $\gamma$ (PPARG; PPAR $\gamma$ )	<p>Studies in mice suggest combining Yondelis trabectedin and PPAR<math>\gamma</math> agonists could help treat p53-mutant round cell liposarcoma. Mutations in <i>p53</i> previously have been found in some patients with round cell liposarcoma and have been associated with poor prognosis. In a mouse model of round cell liposarcoma with p53 deficiency, Yondelis induced the expression of Ppar<math>\gamma</math> compared with no treatment. Also in the mice, Yondelis plus the PPAR<math>\gamma</math> agonist Avandia rosiglitazone prolonged survival compared with Yondelis alone. Next steps could include testing the approach in additional mouse models of the disease.</p> <p>Yondelis, a cytotoxic alkaloid from the PharmaMar S.A. unit of Zeltia S.A., is approved outside the U.S. to treat advanced soft tissue sarcoma and advanced ovarian cancer.</p> <p>Avandia, from GlaxoSmithKline plc, is marketed to treat type 2 diabetes.</p> <p><b>SciBX 5(8); doi:10.1038/scibx.2012.200</b>  <b>Published online Feb. 23, 2012</b></p>	Patent and licensing status unavailable	<p>Charytonowicz, E. <i>et al. J. Clin. Invest.</i>; published online Feb. 1, 2012; doi:10.1172/JCI60015</p> <p><b>Contact:</b> Igor Matushansky, Columbia University, New York, N.Y.  e-mail: <a href="mailto:im17@columbia.edu">im17@columbia.edu</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Non-small cell lung cancer (NSCLC)	Ret proto-oncogene (RET); KIF5B-RET oncogenic fusion protein	<p>Three separate studies in patient samples and in cell culture identified KIF5B-RET translocation proteins that could be targeted by approved NSCLC drugs. In cohorts of NSCLC samples representing more than 2,000 patients, transcriptome sequencing, fluorescent <i>in situ</i> hybridization, RT-PCR and immunohistochemistry identified a KIF5B-RET translocation protein expressed in 1%–2% of samples. In cell culture, expression of KIF5B-RET induced oncogenic cell growth. In cells expressing the <i>KIF5B-RET</i> gene, the RET kinase inhibitors Caprelsa vandetanib, Nexavar sorafenib or Sutent sunitinib inhibited growth compared with kinase inhibitors that do not block RET activity. Next steps include developing clinical diagnostics for KIF5B-RET and testing RET inhibitors in this patient population.</p> <p>Pfizer Inc. markets the receptor tyrosine kinase (RTK) inhibitor Sutent to treat renal and gastrointestinal cancers.</p> <p>Bayer AG and Onyx Pharmaceuticals Inc. market the RTK inhibitor Nexavar to treat renal and liver cancer.</p> <p>AstraZeneca plc markets the RTK inhibitor Caprelsa to treat thyroid cancer.</p> <p><b>SciBX 5(8); doi:10.1038/scibx.2012.201</b> Published online Feb. 23, 2012</p>	<p>Patent and licensing status undisclosed for findings in the first study</p> <p>Patent application filed for findings in the second study; available for licensing from the National Cancer Center Research Institute</p> <p>Patent application filed by Foundation Medicine Inc. for findings in the third study; licensing status undisclosed</p>	<p>Takeuchi, K. <i>et al. Nat. Med.</i>; published online Feb. 12, 2012; doi:10.1038/nm.2658 <b>Contact:</b> Kengo Takeuchi, Japanese Foundation for Cancer Research, Tokyo, Japan e-mail: <a href="mailto:kentakouchi-ty@umin.net">kentakouchi-ty@umin.net</a></p> <p>Kohno, T. <i>et al. Nat. Med.</i>; published online Feb. 12, 2012; doi:10.1038/nm.2644 <b>Contact:</b> Takashi Kohno, National Cancer Center Research Institute, Tokyo, Japan e-mail: <a href="mailto:tkkohno@ncc.go.jp">tkkohno@ncc.go.jp</a></p> <p>Lipson, D. <i>et al. Nat. Med.</i>; published online Feb. 12, 2012; doi:10.1038/nm.2673 <b>Contact:</b> Philip J. Stephens, Foundation Medicine Inc., Cambridge, Mass. e-mail: <a href="mailto:pstephens@foundationmedicine.com">pstephens@foundationmedicine.com</a> <b>Contact:</b> Maureen T. Cronin, same affiliation as above e-mail: <a href="mailto:mcronin@foundationmedicine.com">mcronin@foundationmedicine.com</a> <b>Contact:</b> Pasi A. Jänne, Dana-Farber Cancer Institute, Lowe Center for Thoracic Oncology, Boston, Mass. e-mail: <a href="mailto:pjanne@partners.org">pjanne@partners.org</a></p>
Ovarian cancer	MicroRNA-155 (miR-155)	<p>Studies in mice suggest anti-CD40 antibodies plus nanoparticles carrying pre-miR-155 could be used to treat ovarian cancer. In mice bearing ovarian tumors, anti-CD40 antibodies plus nanoparticles carrying pre-miR-155 led to increased tumor antigen-specific T cell responses and overall survival compared with anti-CD40 antibodies plus nanoparticles carrying control miR-155. Next steps include moving the strategy into clinical trials with ovarian cancer patients.</p> <p><b>SciBX 5(8); doi:10.1038/scibx.2012.202</b> Published online Feb. 23, 2012</p>	Unpatented; licensing status not applicable	<p>Cubillos-Ruiz, J.R. <i>et al. Cancer Res.</i>; published online Feb. 3, 2012; doi:10.1158/0008-5472.CAN-11-3160 <b>Contact:</b> Jose R. Conejo-Garcia, The Wistar Institute, Philadelphia, Pa. e-mail: <a href="mailto:jrconejo@wistar.org">jrconejo@wistar.org</a></p>
<b>Endocrine/metabolic disease</b>				
Diabetes	Taste receptor, type 1, member 2 (TAS1R2; T1R2)	<p><i>In vitro</i> and mouse studies suggest activation of T1R2 by fructose could increase glucose-stimulated insulin secretion. In mouse pancreatic islets, fructose dose-dependently activated T1r2 and increased glucose-mediated insulin release compared with no fructose treatment. In mice, fructose injection increased plasma insulin levels, but the effect was absent in <i>T1r2</i><sup>-/-</sup> mice. Next steps include determining whether this pathway translates to humans.</p> <p><b>SciBX 5(8); doi:10.1038/scibx.2012.203</b> Published online Feb. 23, 2012</p>	Findings unpatented; available for strategic partnerships with the option to license	<p>Kyriazis, G.A. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Feb. 6, 2012; doi:10.1073/pnas.1115183109 <b>Contact:</b> Björn Tyrberg, Sanford-Burnham Medical Research Institute, Orlando, Fla. e-mail: <a href="mailto:bjtyrberg@sanfordburnham.org">bjtyrberg@sanfordburnham.org</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Diabetes; obesity	Family with sequence similarity 132 member A (FAM132A; CTRP12)	A study in mice suggests CTRP12 could help treat obesity and type 2 diabetes. Insulin-resistant obese mice had less Ctrp12 expression in fat pads and lower levels of Ctrp12 in serum than lean mice. In genetic and diet-induced models of obesity, adenoviral-mediated expression of Ctrp12 decreased blood glucose levels and increased insulin sensitivity compared with those seen using a control adenoviral vector. Next steps could include identifying the mechanism involved in CTRP12-mediated improvements in metabolism.  <b>SciBX 5(8); doi:10.1038/scibx.2012.204</b> <b>Published online Feb. 23, 2012</b>	Patent and licensing status unavailable	Wei, Z. <i>et al. J. Biol. Chem.</i> ; published online Jan. 24, 2012; doi:10.1074/jbc.M111.303651 <b>Contact:</b> G. William Wong, The Johns Hopkins University School of Medicine, Baltimore, Md. e-mail: <a href="mailto:gwwong@jhmi.edu">gwwong@jhmi.edu</a>
Obesity	Natriuretic peptide precursor A (NPPA; ANP); B-type natriuretic peptide (BNP; NPPB)	A study in mice suggests ANP or BNP might increase energy expenditure to help treat obesity. In mice, animals with cold-induced activation of brown fat had greater transcription of <i>Anp</i> and <i>Bnp</i> in the heart and higher levels of Bnp in the plasma than mice at room temperature. Also in mice, infusion of Bnp increased both expression of brown adipocyte markers in adipose tissue and energy expenditure compared with saline infusion. Next steps could include testing the effects of BNP infusion on brown fat levels and energy expenditure in humans. Johnson & Johnson markets Natrecor nesiritide, a recombinant BNP, for heart failure. Palatin Technologies Inc.'s PL-3994, a long-acting ANP receptor agonist, is in Phase II testing for congestive heart failure and hypertension.  <b>SciBX 5(8); doi:10.1038/scibx.2012.205</b> <b>Published online Feb. 23, 2012</b>	Patent application filed; available for licensing	Bordicchia, M. <i>et al. J. Clin. Invest.</i> ; published online Feb. 6, 2012; doi:10.1172/JCI59701 <b>Contact:</b> Sheila Collins, Sanford-Burnham Medical Research Institute, Orlando, Fla. e-mail: <a href="mailto:scollins@sanfordburnham.org">scollins@sanfordburnham.org</a>
<b>Infectious disease</b>				
Streptococcus	Streptokinase	<i>In vitro</i> and mouse studies identified inhibitors of <i>streptokinase</i> gene expression that could help treat group A streptococcus infection. <i>In vitro</i> , a screen of 55,000 compounds identified inhibitors of <i>streptokinase</i> gene expression. In a mouse model of streptococcus infection, a lead inhibitor prolonged survival compared with vehicle control. Next steps could include identifying the mechanism by which the lead compound blocks streptokinase gene expression.  <b>SciBX 5(8); doi:10.1038/scibx.2012.206</b> <b>Published online Feb. 23, 2012</b>	Patent and licensing status undisclosed	Sun, H. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Feb. 13, 2012; doi:10.1073/pnas.1201031109 <b>Contact:</b> David Ginsburg, University of Michigan, Ann Arbor, Mich. e-mail: <a href="mailto:ginsburg@umich.edu">ginsburg@umich.edu</a>

## This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
<b>Musculoskeletal disease</b>				
Osteoporosis; bone repair	Integrin $\alpha_4\beta_1$ (CD49D/CD29)	<p>Mouse studies suggest LLP2A-Ale alone or in combination with mesenchymal stem cells (MSCs) could help treat osteoporosis and bone fractures. LLP2A-Ale is a peptidomimetic ligand targeting CD49D/CD29 (LLP2A) linked to the bone-targeting bisphosphonate alendronate (Ale). In immunodeficient mice, injection of human MSCs plus LLP2A-Ale increased numbers of MSCs embedded within the bone matrix compared with injection of MSCs alone. In mice with age-related or ovariectomy-related osteopenia, LLP2A-Ale prevented bone mass loss compared with LLP2A or Ale alone. Next steps include toxicology studies in rats. Merck &amp; Co. Inc. markets Fosamax alendronate to treat osteoporosis. EffRx Pharmaceuticals S.A. has a formulation of alendronate approved to treat osteoporosis. Merrion Pharmaceuticals plc has a formulation of alendronate in Phase II trials to treat osteoporosis (<i>see Rebuilding a better bone, page 6</i>).</p> <p><b>SciBX 5(8); doi:10.1038/scibx.2012.207</b> Published online Feb. 23, 2012</p>	Patented; available for licensing	<p>Guan, M. <i>et al. Nat. Med.</i>: published online Feb. 5, 2012; doi:10.1038/nm.2665</p> <p><b>Contact:</b> Wei Yao, University of California, Davis Medical Center, Sacramento, Calif. e-mail: <a href="mailto:wei.yao@ucdmc.ucdavis.edu">wei.yao@ucdmc.ucdavis.edu</a></p>
<b>Neurology</b>				
Neurology	DNA-damage-inducible transcript 3 (DDIT3; CHOP10; CHOP; GADD153); x-box binding protein 1 (XBP1)	<p>Mouse studies suggest inhibiting CHOP or activating XBP1 could help treat neurodegenerative diseases. In mice, an optic nerve crush model that causes root ganglion cell (RGC) destruction led to sustained upregulation of Chop and transient upregulation of Xbp1 compared with what was seen in uninjured controls. In this model, <i>Chop</i> knockout or adenoviral-mediated <i>Xbp1</i> overexpression promoted RGC survival compared with normal expression of both. Next steps could include identifying CHOP inhibitors or XBP1 activators.</p> <p><b>SciBX 5(8); doi:10.1038/scibx.2012.208</b> Published online Feb. 23, 2012</p>	Patent and licensing status unavailable	<p>Hu, Y. <i>et al. Neuron</i>: published online Feb. 9, 2012; doi:10.1016/j.neuron.2011.11.026</p> <p><b>Contact:</b> Zhigang He, Children's Hospital Boston and Harvard Medical School, Boston, Mass. e-mail: <a href="mailto:zhigang.he@childrens.harvard.edu">zhigang.he@childrens.harvard.edu</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Schizophrenia	Dopamine D2 receptor; dopamine D3 receptor	<p>Studies in cell culture suggest antagonizing heterodimers of D2 and D3 receptors could help treat schizophrenia. In cell culture, fluorescently labeled D2 and D3 receptors physically interacted at the cell surface. In cells expressing both D2 and D3 receptors, dopamine treatment led to more potent activation of downstream signaling pathways than that seen in cells expressing only the D2 receptor. Next steps include identifying selective antagonists of D2/D3 receptor heterodimers and testing them in mouse models of schizophrenia.</p> <p>At least 12 companies have D2 receptor antagonists in development and on the market for schizophrenia and other neurological indications.</p> <p>GlaxoSmithKline plc has the D3 receptor antagonist GSK618334 in Phase I testing for addiction.</p> <p><b>SciBX 5(8); doi:10.1038/scibx.2012.209</b> Published online Feb. 23, 2012</p>	Unpatented; licensing status not applicable	<p>Pou, C. <i>et al. J. Biol. Chem.</i>; published online Jan. 30, 2012; doi:10.1074/jbc.M111.326678</p> <p><b>Contact:</b> Graeme Milligan, University of Glasgow, Glasgow, U.K. e-mail: <a href="mailto:graeme.milligan@glasgow.ac.uk">graeme.milligan@glasgow.ac.uk</a></p>
<b>Ophthalmic disease</b>				
Retinitis	Neurotrophic tyrosine kinase receptor 2 (NTRK2; TrkB)	<p>Mouse studies identified an <i>N</i>-acetyl serotonin (NAS) derivative that could help treat retinal degeneration. In a mouse model of light-induced retinal degeneration, injection of the NAS derivative <i>N</i>-[2-(5-hydroxy-1H-indol-3-yl)ethyl]-2-oxopiperidine-3-carboxamide (HIOC) decreased loss of visual function and photoreceptors by activating TrkB compared with injection of vehicle control. In mouse serum and liver microsomes, HIOC had greater stability and a better half-life than NAS. Next steps include optimizing the compound's activity and increasing its <i>in vivo</i> half-life.</p> <p><b>SciBX 5(8); doi:10.1038/scibx.2012.210</b> Published online Feb. 23, 2012</p>	Patent application filed for neuroprotective indications including retinal degradation; available for licensing	<p>Shen, J. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Feb. 13, 2012; doi:10.1073/pnas.1119201109</p> <p><b>Contact:</b> Keqiang Ye, Emory University School of Medicine, Atlanta, Ga. e-mail: <a href="mailto:kye@emory.edu">kye@emory.edu</a></p> <p><b>Contact:</b> Xuebing Cao, same affiliation as above e-mail: <a href="mailto:caoxuebing@126.com">caoxuebing@126.com</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
<b>Renal disease</b>				
Renal damage	MicroRNA-21 (miR-21)	<p>Studies in humans and mice suggest inhibiting miR-21 could help prevent or treat fibrosis caused by renal damage. miR-21 was upregulated in patients with acute kidney injury or chronic allograft nephropathy compared with normal controls. In two mouse models of renal damage, kidney fibrosis was greater in wild-type mice than <i>mir-21</i> knockout mice. In both models, an miR-21 antagomir decreased kidney fibrosis when administered before or after the occurrence of injury-induced fibrosis compared with a control antagomir. Ongoing work by Regulus Therapeutics Inc. includes optimizing and testing the miR-21 antagomir in additional models of renal fibrosis.</p> <p>Regulus' antagomir-21, an antisense oligonucleotide targeting miR-21, is in preclinical development to treat cardiac fibrosis.</p> <p><b>SciBX 5(8); doi:10.1038/scibx.2012.211</b>  <b>Published online Feb. 23, 2012</b></p>	Patented by Regulus; antifibrotic applications of anti-miR-21 antagomirs licensed to Sanofi	<p>Chau, B.N. <i>et al. Sci. Transl. Med.</i>; published online Feb. 15, 2012; doi:10.1126/scitranslmed.3003205</p> <p><b>Contact:</b> Jeremy S. Duffield, University of Washington, Seattle, Wash.  e-mail: <a href="mailto:jeremysd@u.washington.edu">jeremysd@u.washington.edu</a></p> <p><b>Contact:</b> B. Nelson Chau, Regulus Therapeutics Inc., San Diego, Calif.  e-mail: <a href="mailto:nchau@regulusrx.com">nchau@regulusrx.com</a></p>
Renal damage	Solute carrier family 29 nucleoside transporter member 1 (SLC29A1; ENT1)	<p>Studies in mice suggest antagonizing ENT1 could help prevent acute kidney injury. In a mouse model of ischemic acute kidney injury, <i>Ent1</i> knockout mice or wild-type mice treated with the nonselective ENT1 antagonist dipyrindamole had less ischemic damage and greater renal function than wild-type or vehicle-treated controls, respectively. Next steps include identifying and testing selective ENT1 antagonists in mouse models of kidney transplant-associated renal injury.</p> <p><b>SciBX 5(8); doi:10.1038/scibx.2012.212</b>  <b>Published online Feb. 23, 2012</b></p>	Unpatented; licensing status not applicable	<p>Grenz, A. <i>et al. J. Clin. Invest.</i>; published online Jan. 24, 2012; doi:10.1172/JCI60214</p> <p><b>Contact:</b> Holger K. Eltzschig, University of Colorado Denver, Aurora, Colo.  e-mail: <a href="mailto:holger.eltzschig@ucdenver.edu">holger.eltzschig@ucdenver.edu</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>Assays &amp; screens</b>			
Next-generation sequencing for diagnosis of infantile mitochondrial disease	Next-generation sequencing of mitochondrial DNA and nuclear genes encoding mitochondrial proteins could help diagnose infantile mitochondrial disease. In 42 infants with clinical and biochemical features of mitochondrial disease, next-generation sequencing of the entire mitochondrial DNA and about 1,000 nuclear genes encoding mitochondrial proteins identified 1 infant with a large mitochondrial DNA deletion, 10 infants with mutations in known disease-related genes and 12 infants with candidate disease-causing mutations in nuclear genes not previously linked to disease. The nuclear genes included <i>acylglycerol kinase (AGK)</i> and <i>NADH dehydrogenase (ubiquinone) 1<math>\beta</math> subcomplex 3 (NDUFB3)</i> . Next steps include incorporating other approaches, such as whole-exome sequencing.	Unpatented; licensing status not applicable	Calvo, S.E. <i>et al. Sci. Transl. Med.</i> ; published online Jan. 25, 2012; doi:10.1126/scitranslmed.3003310 <b>Contact:</b> David R. Thorburn, The Royal Children's Hospital, Parkville, Victoria, Australia e-mail: <a href="mailto:david.thorburn@mcri.edu.au">david.thorburn@mcri.edu.au</a> <b>Contact:</b> Vamsi K. Mootha, Massachusetts General Hospital, Boston, Mass. e-mail: <a href="mailto:vamsi@hms.harvard.edu">vamsi@hms.harvard.edu</a> <b>Contact:</b> Sarah E. Calvo, same affiliation as above e-mail: <a href="mailto:scalvo@broadinstitute.org">scalvo@broadinstitute.org</a>
<b>Disease models</b>			
<i>Microtubule-associated protein-<math>\tau</math> (MAPT; TAU; FTDP-17)</i> knockout model of Parkinson's disease (PD)	Studies in mice suggest that loss of function of TAU could contribute to PD. Previous studies suggested that TAU forms aggregates in PD. Aged Tau knockout mice showed signs of PD including nigrostriatal iron accumulation, degeneration of dopaminergic neurons and decreased motor function compared with wild-type controls. Next steps include devising ways to increase levels of soluble TAU and decrease intracellular iron accumulation in PD. Prana Biotechnology Ltd. has the iron-sequestering agent PBT434 in preclinical development for PD. reMYND N.V. has ReS19-T, a small molecule that prevents TAU neurotoxicity, in preclinical development to treat Alzheimer's disease (AD). TauRx Pharmaceuticals Ltd.'s rember methylthioninium chloride, a TAU aggregation inhibitor, has completed Phase II trials to treat AD (see <i>The TAU of PD</i> , page 7).	Unpatented; licensing status undisclosed	Lei, P. <i>et al. Nat. Med.</i> ; published online Jan. 29, 2012; doi:10.1038/nm.2613 <b>Contact:</b> Ashley I. Bush, The University of Melbourne, Melbourne, Victoria, Australia e-mail: <a href="mailto:ashleyib@unimelb.edu.au">ashleyib@unimelb.edu.au</a>
<b>Drug delivery</b>			
DNA nanorobots for programmable and targeted drug delivery	<i>In vitro</i> studies suggest DNA nanorobots could be used for targeted drug delivery. DNA nanorobots were designed with DNA aptamer-based locks that allow release of payloads upon binding specific cell surface proteins. In cultured leukemia cells, DNA nanorobots with locks targeting leukemia cell surfaces discriminated between cancer cells and healthy cells. In cell culture, nanorobots loaded with human anti-CD33 antibodies and human sialic acid binding Ig-like lectin 7 (SIGLEC7; CDw328) Fab fragments inhibited leukemia cell growth compared with unloaded nanorobots. Next steps include rodent studies.	Patent application filed; available for licensing	Douglas, S.M. <i>et al. Science</i> ; published online Feb. 17, 2012; doi:10.1126/science.1214081 <b>Contact:</b> Shawn M. Douglas, Harvard Medical School, Boston, Mass. e-mail: <a href="mailto:shawn.douglas@wyss.harvard.edu">shawn.douglas@wyss.harvard.edu</a> <b>Contact:</b> George M. Church, same affiliation as above e-mail: <a href="mailto:gmc@harvard.edu">gmc@harvard.edu</a>

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Poly( $\epsilon$ -caprolactone) (PCL)-based nanoparticles for targeted delivery of antibiotics	PCL-containing nanoparticles could be useful for delivering antibiotics to cells infected by lipase-secreting bacteria such as <i>Staphylococcus aureus</i> . In <i>S. aureus</i> -infected mouse macrophage and human endothelial cell lines, vancomycin-loaded PCL nanoparticles decreased levels of intracellular bacteria compared with free vancomycin. The nanoparticles did not affect cell viability. Future studies could include testing the stability and efficacy of the nanoparticles in animal models of bacterial infection.  <b>SciBX 5(8); doi:10.1038/scibx.2012.216</b> <b>Published online Feb. 23, 2012</b>	Patent and licensing status unavailable	Xiong, M.-H. <i>et al. J. Am. Chem. Soc.</i> ; published online Feb. 3, 2012; doi:10.1021/ja211279u <b>Contact:</b> Jun Wang, University of Science and Technology of China, Hefei, China e-mail: <a href="mailto:jwang699@ustc.edu.cn">jwang699@ustc.edu.cn</a> <b>Contact:</b> Bao-Lin Sun, same affiliation as above e-mail: <a href="mailto:sunb@ustc.edu.cn">sunb@ustc.edu.cn</a>
Targeted delivery of chemotherapeutics with an EPHA2 (EPHA2)-targeting peptide	Conjugates of a chemotherapeutic and an EPHA2-targeting peptide could help treat cancer more effectively and safely than unconjugated chemotherapy. In a human prostate cancer cell line, paclitaxel conjugated to an EPHA2-targeting peptide induced more cell death than paclitaxel conjugated to a scrambled control peptide. In mice with xenograft prostate tumors, the paclitaxel-peptide conjugate was safe and decreased tumor growth compared with unconjugated paclitaxel. Ongoing work includes conjugating EPHA2-targeting peptides to other chemotherapies.  <b>SciBX 5(8); doi:10.1038/scibx.2012.217</b> <b>Published online Feb. 23, 2012</b>	Patented by the Sanford-Burnham Medical Research Institute; available for licensing or partnering	Wang, S. <i>et al. J. Med. Chem.</i> ; published online Feb. 13, 2012; doi:10.1021/jm201743s <b>Contact:</b> Maurizio Pellecchia, Sanford-Burnham Medical Research Institute, La Jolla, Calif. e-mail: <a href="mailto:mpellecchia@sanfordburnham.org">mpellecchia@sanfordburnham.org</a>

Drug platforms

Binding scaffolds based on variable lymphocyte receptors (VLRs)	<i>In vitro</i> studies suggest VLR-based binding scaffolds could be an alternative to immunoglobulin-based antibody scaffolds, which are large, expensive to produce in mammalian cells and difficult to design. A binding scaffold based on VLRs from jawless vertebrates was designed to target lymphocyte antigen 96 (LY96; MD2) and was produced in a bacterial expression system. In a cell-based assay, the MD2-targeting VLR scaffold decreased a lipopolysaccharide (LPS)-induced immune response compared with no treatment. Ongoing studies suggest the VLR-based binding scaffolds have greater binding efficacy than mAbs. Next steps include testing the scaffold proteins in animal disease models.  <b>SciBX 5(8); doi:10.1038/scibx.2012.218</b> <b>Published online Feb. 23, 2012</b>	Findings patented; available for licensing for therapeutic and diagnostic applications	Lee, S.-C. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Feb. 10, 2012; doi:10.1073/pnas.1113193109 <b>Contact:</b> Hak-Sung Kim, Korea Advanced Institute of Science and Technology, Daejeon, South Korea e-mail: <a href="mailto:hskim76@kaist.ac.kr">hskim76@kaist.ac.kr</a>
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