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Beta-O2 Technologies and an international team of academic collaborators have shown that the company's bioartificial pancreas normalizes blood glucose levels in rat models of diabetes for up to three months. The team hopes to start a trial of the implant in a single patient this year.

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Merck is investing up to \$90 million over the next seven years to fund the California Institute for Biomedical Research. The pharma is hoping the wide spectrum of translational research to be covered by the institute will yield first access to drugs against new targets that might not yet be on the company's radar.

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NoNO has become the first company to show that macaque models could bridge the rodent-human gap to potentially derisk clinical testing of new stroke therapies. The company reported that its neuroprotective peptide NA-1 was effective both in macaque models and in a Phase II trial for the indication.

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By Kai-Jye Lou, Staff Writer

Beta-O2 Technologies Ltd. and an international team of academic collaborators have shown that the company's bioartificial pancreas can house donor islets, supply them with oxygen and protect them from the host immune system *in vivo* for at least three months.¹ They also demonstrated that the minimally invasive implant could normalize blood glucose levels and improve glycemic control in rat models of diabetes. The team hopes to start a trial of the implant in a single patient this year.

Islet transplantation for type 1 diabetes has seen limited use in the clinic due to the short supply of donor tissue and because islet cells have high oxygen demands that make them particularly intolerant of the hypoxic conditions encountered during isolation and transplantation.

In addition, islet transplant recipients require immunosuppressive drugs to prevent graft rejection. These drugs not only carry the risk of serious infections and malignancies but also can impair the revascularization and function of grafted islets.^{2,3}

Finally, standard islet transplantation procedures involve using a catheter to infuse islets into the portal vein of the liver. This procedure, while minimally invasive, carries the risk of portal vein thrombosis and intraperitoneal bleeding.

For three years, Beta-O2 and their collaborators have been developing a bioartificial pancreas to address the shortcomings of islet transplantation and have now published the first data showing how the system works.

The subcutaneous implant consists of two chambers separated by an oxygen-permeable membrane, with one module to house and protect an alginate slab that contains the islets and a gas module to supply the islets with oxygen (*see Figure 1, "Beta-O2's bioartificial pancreas system"*).

In a rat model of streptozotocin-induced diabetes, implantation of a device containing rat islets normalized blood glucose levels until the implant was removed at day 90. The implant site had prominent vascularization and showed no signs of compatibility issues such as inflammation or fibrosis.

The researchers then examined the implant itself to confirm the absence of inflammatory reactions and showed that the islets housed within the alginate slab remained intact.

To tackle the problem of a limited supply of donor islets, the group looked to a 2010 paper that showed the synthetic growth hormone-releasing hormone (GHRH) agonist JI-36 could promote the survival and proliferation of pancreatic islets and also improve their ability to restore blood glucose levels and glycemic control in diabetic mice.⁴

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PO Box 1246
San Carlos, CA 94070-1246
T: +1 650 595 5333Chadds Ford
223 Wilmington-West Chester Pike
Chadds Ford, PA 19317
T: +1 610 558 1873Chicago
20 N. Wacker Drive, Suite 1465
Chicago, IL 60606-2902
T: +1 312 755 0798Oxford
287 Banbury Road
Oxford OX4 7JA
United Kingdom
T: +44 (0)18 6551 2184Washington, DC
2008 Q Street, NW, Suite 100
Washington, DC 20009
T: +1 202 462 9582**Nature Publishing Group**New York
75 Varick Street, 9th Floor
New York, NY 10013-1917
T: +1 212 726 9200London
The Macmillan Building
4 Crinan Street
London N1 9XW
United Kingdom
T: +44 (0)20 7833 4000Tokyo
Chiyoda Building 6F
2-37 Ichigayatamachi
Shinjuku-ku, Tokyo 162-0843
Japan
T: +81 3 3267 8751

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Indeed, when the researchers pretreated islets with JI-36, the total number of islets needed in the implant to achieve normal blood glucose levels in diabetic rats was reduced by about 50%. Rats receiving the pretreated islets also showed better glycemic control than those that received untreated islets.

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

Stefan Bornstein said patients with type 1 diabetes usually need about 500,000 islets to achieve insulin independence but pointed out the current bioartificial pancreas system only houses around half that amount.

“This is why we sought to use GHRH agonists to improve the function of the transplanted islets, though 250,000 islets should be sufficient to achieve insulin independence in lean patients,” said Bornstein, a coauthor of the paper who is chair of medicine and director of the **University Hospital of Carl Gustav Carus** and the **Dresden University of Technology**. “GHRH agonists could help reduce the

“We will be ready to test our system in human trials very soon, and we will most likely start by using our system to deliver human islets.”

**—Stefan Bornstein,
Dresden University of Technology**

number of islets needed, and we didn’t want to make our system too big as it would complicate the implantation process.”

Bornstein added that the implant’s subcutaneous delivery route should pose fewer safety risks than standard islet transplantation and simplifies the process of implanting and extracting the device from the patient.

O₂ delivery

“The nice thing about their system is that they incorporate an oxygen delivery system to support the transplanted islets before the graft is vascularized,” said Emmanuel Opara, co-director of the islet transplantation program and a professor at the Institute for Regenerative Medicine and the Center for Diabetes Research at the **Wake Forest School of Medicine**. “It takes about 7–10 days for new vasculature to form around a graft, and during this time a lot of the implanted islet cells could otherwise die.”

“For me, the most interesting aspect of the current study is the use of the GHRH agonist,” said **ViaCyte Inc.** CSO Kevin D’Amour. “An adjunctive therapy like this has the potential to improve islet delivery.”

ViaCyte’s lead program is Pro-Islet, a preclinical, subcutaneously delivered cell therapy that provides replacement islet cells for patients with diabetes.

D’Amour said ViaCyte’s strategy for addressing the oxygen supply problem is to transplant encapsulated pancreatic progenitors, which have much lower oxygen requirements than mature islet cells.

“The cells we deliver differentiate and mature into highly functional insulin-producing cells in the weeks and months after delivery, when the graft has become fully vascularized,” he told *SciBX*.

Merck KGaA already markets the GHRH agonist Egrifta tesamorelin to help reduce excess abdominal fat in HIV-infected patients with lipodystrophy. The pharma acquired U.S. rights to the drug from

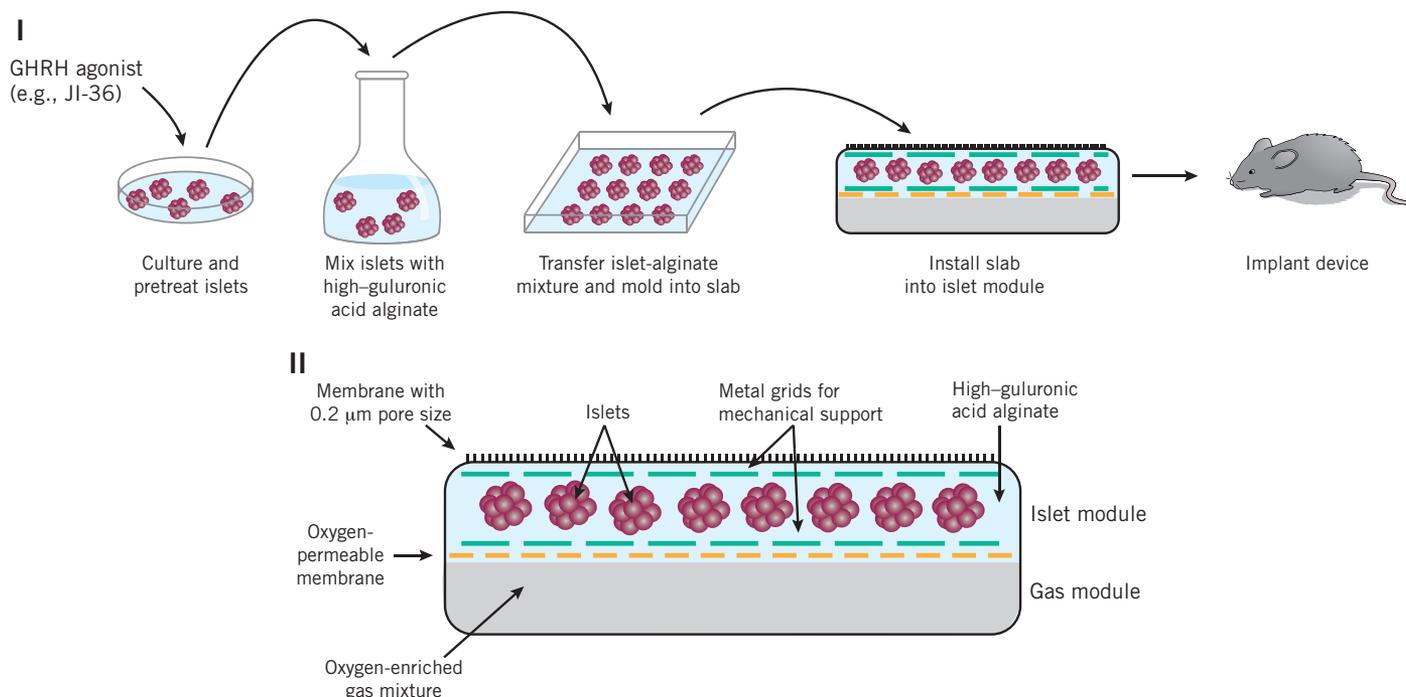


Figure 1. Beta-O2's bioartificial pancreas system. As reported by Ludwig *et al.*, the bioartificial pancreas system from **Beta-O2 Technologies Ltd.** and collaborators restores normal blood glucose levels and improves glycemic control in rat models of diabetes.

Isolated islets are cultured in a medium containing the growth hormone–releasing hormone (GHRH) agonist JI-36 (I). Islets are collected, mixed with a solution of high-guluronic acid alginate and transferred into a mold to create an islet-containing alginate slab. Next, the slab is installed into the islet module of the bioartificial pancreas and implanted into the host.

The porous outer membrane of the islet module and the alginate create an immune barrier to protect the islets from the host immune system while still allowing secreted factors such as insulin to pass through (II). The gas module supplies the islets with oxygen through the oxygen-permeable membrane. The metal grid in the islet module provides mechanical support for the implant. (Figure based on Figure 1 in ref. 1.)

Theratechnologies Inc.

Akela Pharma Inc. has a GHRH analog in Phase II testing to treat malnutrition in patients with stage IV chronic renal failure.

Duration of effect

Although the data reported in the paper demonstrate the implant's effect in rats for 90 days, the researchers still need to test the implant's long-term durability and its ability to restore glycemic control in additional animal models.

"The reported findings are mechanistically interesting, and this group has made some advances in supplying the transplanted islets with oxygen," said Matthias von Herrath, director of the Center for Type 1 Diabetes Research at the **La Jolla Institute for Allergy & Immunology** and VP at the **Novo Nordisk A/S** type 1 diabetes R&D center. "However, they will need to run additional studies to evaluate the implant's duration of effect. They will need to show that the implant remains functional for a year or longer for such a system to be considered viable for use in humans."

Avi Rotem, CTO of Beta-O2, said the team has run implantation experiments in rats out to 250 days.

"Upon retrieval of the device the blood glucose was returned to the

disease state, like all other studies, and the islet functionality remained similar to islets at time zero," he told *SciBX*. "These results suggest long-term viability and functionality of the islets within Beta-O2's device is due to its built-in oxygen supply and immune protection."

ViaCyte's D'Amour wanted to see studies showing that the system can deliver human islets—the researchers used rat islets. "The researchers also suggest that their bioartificial pancreas system provides xenoprotection, so I think it would be a good idea for them to test whether their system could deliver porcine islets into immunocompetent rodents," he added.

Opara said the system should be tested in an autoimmune model of type 1 diabetes in which the animal displays other features of the disease such as autoantibodies that target islet β cells. "One of the things I was curious about is whether the membrane surrounding the islets, which has pore size of 200 nanometers, will be able to block some of the molecules that could attack the implanted islets, such as antibodies," he told *SciBX*.

Bornstein acknowledged that the bioartificial pancreas may need further optimization, such as increasing the amount of oxygen the system delivers to the islets.

Rotem said the group is now testing the bioartificial pancreas in a

diabetic pig model.

“We will be ready to test our system in human trials very soon, and we will most likely start by using our system to deliver human islets,” added Bornstein. “However, I do see the potential to use this system

“They will need to show that the implant remains functional for a year or longer for such a system to be considered viable for use in humans.”

—*Matthias von Herrath,
La Jolla Institute for
Allergy & Immunology*

Andrew Schally, corresponding author on the *PNAS* paper, said his group has developed more potent GHRH analogs than JI-36 and plans to evaluate the effects of these newer analogs on islet function in future studies.

Schally is a medical research scientist of the **U.S. Department of Veterans Affairs** and head of the Endocrine, Polypeptide and Cancer Institute at the **Miami VA Healthcare System**. He also is a professor in the department of medicine at the **University of Miami Miller School of Medicine**.

The **University of Miami** and the U.S. Department of Veterans Affairs have filed a patent covering GHRH agonists for promoting the survival and growth of pancreatic islets. The patent is available for

to deliver porcine islets in future trials. Currently, we hope to start a single-patient trial later this year and then, depending on the results of these trials, start a larger clinical trial in the next two to three years.”

licensing. Rotem said Beta-O2 has filed multiple patents covering its bioartificial pancreas and said the company is interested in finding a partner to help develop the system.

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e-mail: andrew.schally@va.gov
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COMPANIES AND INSTITUTIONS MENTIONED

Akela Pharma Inc. (TSX:AKL), Austin, Texas
Beta-O2 Technologies Ltd., Petah Tikva, Israel
Dresden University of Technology, Dresden, Germany
La Jolla Institute for Allergy & Immunology, La Jolla, Calif.
Merck KGaA (Xetra:MRK), Darmstadt, Germany
Miami VA Healthcare System, Miami, Fla.
Novo Nordisk A/S (CSE:NVO; NYSE:NVO), Bagsvaerd, Denmark
Theratechnologies Inc. (TSX:TH; NASDAQ:THER), Montreal, Quebec, Canada
University Hospital of Carl Gustav Carus, Dresden, Germany
University of Miami, Miami, Fla.
University of Miami Miller School of Medicine, Miami, Fla.
U.S. Department of Veterans Affairs, Washington, D.C.
ViaCyte Inc., San Diego, Calif.
Wake Forest School of Medicine, Winston-Salem, N.C.

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Merck's reCalibration

By Chris Cain, Staff Writer

Merck & Co. Inc. has traditionally formed external academic partnerships with labs working on projects in areas of the pharma's direct interest. Now, Merck is expanding its early stage academic outreach by investing up to \$90 million over seven years to found the not-for-profit **California Institute for Biomedical Research**, which is focused on the translation of basic research into new medicines.

By doing so, the pharma is creating a halfway house between academia and pharma with the expertise to develop academic discoveries to the point at which they would be of commercial interest.

The California Institute for Biomedical Research (Calibr) is located in San Diego and hopes to begin collaborating with academics on 5–10 projects within the next year. It is the largest academic partnering initiative ever launched by Merck.

The institute plans to eventually employ 100–150 people and have 20 projects ongoing at any given time.

In return for Merck's investment, it has the first option to exclusively license work at preclinical proof of concept, which is defined as evidence of efficacy in a relevant preclinical disease model.

Calibr's founding director Peter Schultz told *SciBX*, "I started talking with Peter Kim about how to build this several years ago, but it gained momentum one to one-and-a-half years ago. We both agreed that academics do discovery well and pharma develops drugs well, and so we sought a better way to interface industry with academia. It has become increasingly hard for the two worlds to connect."

Kim is president of Merck's R&D division, Merck Research Labs, and is a member of Calibr's scientific advisory board.

Schultz, who will remain a professor in the Department of Chemistry at **The Scripps Research Institute**, said Calibr was set up as a not-for-profit institute outside of Merck so that academics will view it as an equal partner that can provide valuable early stage drug development expertise that complements an academic's own discovery efforts.

Calibr does not plan to start its own internal drug discovery programs. Instead the institute will choose projects from applications submitted by outside researchers seeking to discover and develop small molecules and biologics against new targets. Schultz said the development process at Calibr will include screening, medicinal chemistry, informatics, imaging and pharmacology.

He said those capabilities will set Calibr apart from academic institutes that have initiated drug discovery efforts in recent years.^{1,2}

"At Scripps we built a lot of screening systems for the academic drug discovery operation, but running a screen based on an idea is very different from getting a molecule where you understand its mechanism and behavior in animal models. The point of Calibr is not just to run screens but to develop an understanding of the biology of a drug. This is what the simple screening centers are missing, and it requires hiring people with expertise in early stage drug discovery," said Schultz.

Thus, Schultz will hire medicinal chemists, pharmacologists

and informatics experts, about half of whom will be postdoctoral researchers. In addition to its own staff, Schultz expects Calibr to host visiting postdoctoral and clinical fellows to ensure close ties between the institute and its academic collaborators.

The institute will solicit applications for projects, which will be selected by a steering committee made up of Schultz, Kim and Christopher Walsh, professor of biochemistry and pharmacology at **Harvard Medical School**. Walsh is chair of the institute's scientific advisory board.

In addition to the scientific advisory board, Calibr will be managed by an external board of directors chaired by John Diekman, founder and a managing director of **5AM Ventures**.

"Schultz is good at picking projects. He has founded seven or eight companies, and he understands what it takes for a project to go from early stage to the clinic. He is incredibly impatient and practical. In the discovery phase things will move fast—or he will kill them," said Diekman.

5AM will not have rights to the projects; Diekman said he views the role of the board as opening doors and offering strategic advice, and he does not intend to micromanage the institute. He also is chairman of **Ambrix Inc.**, which Schultz founded in 2003 with funding from 5AM.

James Schaeffer, executive director for external scientific affairs at Merck, said Calibr already is talking to other San Diego institutions about possible collaborations, but

he emphasized that the institute is agnostic to location. This sets Calibr apart from **Pfizer Inc.**'s Global Centers for Therapeutic Innovation, which are performing similar collaborative drug discovery and development activities specifically tied to institutions in their immediate vicinity.³ Pfizer's centers also act as a direct arm of the pharma, in contrast to Calibr's relative independence from Merck.

The independent, not-for-profit status and exclusive focus on outside collaboration further distinguishes Calibr from the drug discovery mission of the **Genomics Institute of the Novartis Research Foundation (GNF)**, where Schultz was director from its founding in 1999 until 2010. GNF has a broad mandate to develop and apply new technologies to discover medicines in areas of unmet medical need, and although the institute also engages in outside collaborations, it pursues a number of its own in-house basic discovery programs alongside its translational efforts.

Schaeffer told *SciBX* Calibr is a departure from Merck's early stage academic partnerships. "Our existing major, early stage collaborations with academics have been focused on very intense, very cherry-picked high-quality labs working in areas we are interested in. The purpose of this institute is to cast a wider net."

Greg Wiederrecht, VP and head of external scientific affairs at Merck, told *SciBX* that 35% of major licensing deals executed by Merck each year are with academic institutions, and the company does 50 such deals each year. However, he added that in 2011 the company did 277 unannounced, smaller, IP-generating research collaborations "that span the gamut from no-cost risk share to less than \$500,000" in costs to Merck.

"Our existing major, early stage collaborations with academics have been focused on very intense, very cherry-picked high-quality labs working in areas we are interested in. The purpose of this institute is to cast a wider net."

—James Schaeffer, Merck & Co. Inc.

He added that if other transactions including fee-for-service work or those done by other Merck divisions are included, “overall, our interactions with academia number in the thousands each year.”

Schaeffer emphasized that although Merck has the first option to license findings from Calibr, it is not interested in restricting the institute’s

“The point of Calibr is not just to run screens but to develop an understanding of the biology of a drug.”

—Peter Schultz,
California Institute for
Biomedical Research

development efforts in any therapeutic areas. “We want to use this institute to look at new and innovative early stage projects. If Merck is not interested in licensing a project when it reaches

preclinical proof of concept, it may become interesting to venture capitalists, and perhaps even Merck’s venture fund, and we would be in a position to follow the work closely as it progresses.”

Last September, Merck launched its Merck Research Ventures Fund with \$250 million.

Schaeffer added that projects at Calibr are expected to predominantly originate in academic labs, although there may also be instances of

interactions between the institute and small biotechs.

Schultz said that for the time being Calibr is dependent on Merck funding, but the institute will later consider seeking outside funding from federal and state grants and from disease foundations.

He added that the institute is in lease negotiations and has purchased equipment that is ready for move in, and he noted that Calibr has already received inquiries for partnerships through its website.

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COMPANIES AND INSTITUTIONS MENTIONED

5AM Ventures, Menlo Park, Calif.

Ambix Inc., La Jolla, Calif.

California Institute for Biomedical Research, San Diego, Calif.

Genomics Institute of the Novartis Research Foundation, San Diego, Calif.

Harvard Medical School, Boston, Mass.

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

Pfizer Inc. (NYSE:PFE), New York, N.Y.

The Scripps Research Institute, La Jolla, Calif.

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Gleevec for pain

By Lauren Martz, Staff Writer

Researchers at **The University of Texas MD Anderson Cancer Center** have found a potential new use for **Novartis AG's** Gleevec imatinib cancer drug—reducing tolerance to opioid analgesics.¹ Gleevec prevented and reversed morphine tolerance in rats, but it is still unclear whether the molecule's safety profile would be suitable for the pain indication.

Novartis is not pursuing the new indication, but the academics are pressing forward and plan to submit an IND for a reformulated version of the drug within the next year.

Opioid analgesics, including morphine, lose potency over time as patients become tolerant to the analgesic effects, resulting in the need for higher doses. This may contribute to addiction and exacerbate side effects such as respiratory depression, constipation and cognitive changes including depression and sedation.

There has been no shortage of research on ways to block tolerance. For example, protein kinase A (PKA), PKC and NMDAR have been identified as potential contributors to the development of opioid tolerance.²⁻⁴ What has been lacking is small molecule inhibitors against those targets.

Now, a group led by Howard Gutstein, associate professor of anesthesiology and biochemistry at MD Anderson, has added platelet derived growth factor receptor B (PDGFRB; PDGFR1; CD140B) to the list of potential targets for opioid tolerance and has used Gleevec to test the effects of inhibiting the target.

Gleevec is a BCR-ABL tyrosine kinase inhibitor that nonselectively targets PDGFRB. It is approved to treat chronic myelogenous leukemia (CML) and gastrointestinal stromal tumors.

His group had hints about PDGFRB's role in tolerance from a pair of studies from a **University of Minnesota Medical School** team led by Kalpna Gupta, associate professor of hematology, oncology and transplantation.

In 2006, the Minnesota team showed that morphine activates PDGFRB, as well as other receptor tyrosine kinases, in endothelial cells.⁵ Six years later, the researchers found that morphine also activated the receptor in vascular pericytes *in vitro* and in mice.⁶

In rats, Gutstein and colleagues showed that intrathecal morphine increased PDGFRB activation by 47%. That effect was blocked by the team's reformulated version of imatinib, which has better blood brain barrier penetration than the parent compound.

Intrathecal or subcutaneous doses of the drug also prevented or reversed morphine tolerance, whereas vehicle control had no effect. Gleevec alone did not cause or prevent analgesia.

Moreover, Gleevec did not prevent tolerance to the nonopioid analgesic clonidine, suggesting its effect is specific to opioid therapeutics.

Because Gleevec hits multiple targets, the researchers wanted to be sure its activity on PDGFRB was causing the observed effects. Thus,

the team treated rats with morphine plus an antibody against PDGFRB. The molecule produced a reversal of morphine tolerance similar to that seen using Gleevec.

Finally, Gutstein's group showed that activating PDGFRB with its ligand, platelet derived growth factor BB (PDGFBB), reversed the effects of PDGFRB inhibition by Gleevec and restored and further induced tolerance. These findings suggest that morphine-induced increases in PDGFRB signaling contribute to opioid tolerance and that inhibiting the signaling could prevent tolerance.

Data were published in *Nature Medicine*.

"A number of other targets have shown similar promise in reducing opioid tolerance, including PKA and several PKC isoforms, as well as a number of different G protein-coupled receptors," said John Violin, head of biology at **Trevena Inc.** "This study adds PDGFRB and imatinib to that list, and also nicely illustrates the mechanism whereby that target is engaged. This discovery may help the field better understand the molecular mechanisms of tolerance."

Therapeutic strategy

Gutstein told *SciBX* his team has performed pharmacokinetic and pharmacodynamic studies of the reformulated Gleevec and hopes to submit an IND within the next year.

"To be used therapeutically, one would need to combine a PDGFR antagonist with the analgesic. This introduces significant complexities classically associated with combination therapies such as determining the correct dose for both agents and formulating both agents to allow them to be used together," said Violin. "There is also the potential for new or augmented side effects due to combination therapy."

Trevena's TRV130, a G protein-based μ -opioid receptor (OPRM1; MOR) ligand, is in Phase I testing to treat postoperative pain. TRV130 is designed to stimulate the G protein-coupling mechanism that induces analgesia without stimulating the arrestin- β -coupling mechanism that causes respiratory and GI side effects.

Violin said a key question is whether "blocking tolerance will increase the incidence of adverse events more than it will increase analgesia." He said the researchers also need to consider Gleevec's known side effects, which include edema and fluid retention.

He said that instead of using Gleevec, a better approach to reducing opioid tolerance could be to start from scratch and design a specific inhibitor of PDGFRB.

Gutstein, however, doesn't think this will be necessary. "Imatinib is well-tolerated in patients, so I think it would not be necessary to develop a more specific antagonist," he said.

Gupta thinks Gleevec would be an ideal therapeutic for cancer patients with breakthrough pain. These patients, who are already being treated with imatinib, could experience the added benefit of reduced morphine tolerance.

"A number of other targets have shown similar promise in reducing opioid tolerance, including PKA and several PKC isoforms, as well as a number of different G protein-coupled receptors. This study adds PDGFRB and imatinib to that list, and also nicely illustrates the mechanism whereby that target is engaged. This discovery may help the field better understand the molecular mechanisms of tolerance."

—John Violin, *Trevena Inc.*

Javier Garzón, head of neuropharmacology at the **Cajal Institute**, which is affiliated with the **Spanish National Research Council**, thinks PDGFRB is unlikely to be the ideal target in the path of morphine tolerance. He said the process of morphine tolerance

“Imatinib is well-tolerated in patients, so I think it would not be necessary to develop a more specific antagonist.”

**—Howard Gutstein,
The University of Texas MD
Anderson Cancer Center**

can be manipulated at many points, and that the team should identify the target that is furthest upstream in the pathway.

Novartis spokesperson Julie Masow said the company is “aware of the report in *Nature Medicine* that a reformulation of Gleevec imatinib may improve the effectiveness of narcotic medications. Novartis was not involved in this research and has no plans to conduct studies of Gleevec in this setting.”

Gutstein said MD Anderson has filed for a patent covering the work. The IP is available for licensing.

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COMPANIES AND INSTITUTIONS MENTIONED

Cajal Institute, Madrid, Spain
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Spanish National Research Council, Madrid, Spain
Trevena Inc., King of Prussia, Pa.
University of Minnesota Medical School, Minneapolis, Minn.
The University of Texas MD Anderson Cancer Center, Houston, Texas

Monkeys bridge the stroke gap

By Michael J. Haas, Senior Writer

Toronto-based **NoNO Inc.** has become the first company to show that macaque models have the potential to derisk clinical testing of new stroke therapies, which typically have gone right from rat or rabbit models into humans. In February, the company reported that its neuroprotective peptide NA-1 was effective both in macaque models of stroke¹ and in a Phase II trial to treat ruptured brain aneurysms.

The only drug in the U.S. to treat ischemic stroke is the clot buster Activase alteplase from **Roche's Genentech Inc.** unit and **Boehringer Ingelheim GmbH**, which was approved in 1996. Since then, numerous neuroprotective therapies have shown efficacy in standard rat models of stroke, but all have failed in the clinic.

In 1999, the Stroke Academic Industry Roundtable (STAIR) recommended testing neuroprotective agents in nonhuman primate models of stroke because their brains are anatomically and biologically similar to humans, and they can be given neurological and behavioral tests similar to those used to measure outcomes in clinical trials.²

But the specialized facilities, expertise and costs associated with such models have largely precluded their use, said Michael Tymianski, cofounder, president and CEO of NoNO. He is also assistant professor of surgery and physiology at the **University of Toronto**, staff neurosurgeon at **Toronto Western Hospital** and senior scientist at the hospital's **Toronto Western Research Institute**.

Previous Tymianski-led teams showed the neuroprotective effects of NoNO's NA-1 (Tat-NR2B9c) in rat models of ischemic stroke.^{3,4} The compound inhibits discs large homolog 4 (DLG4; PSD95). NA-1 is a 20-mer peptide composed of the 9 C-terminal amino acids of NMDA receptor NR2B subtype (GRIN2B; NR2B) linked to an 11-mer HIV Tat peptide that allows NA-1 to cross the blood brain barrier.

In its latest study, Tymianski's team developed two macaque models of surgery-induced stroke and tested NA-1 in the animals. The models involved clamping off the middle cerebral artery to induce ischemia, administering NA-1 and then removing the clamp to allow reperfusion of the ischemic zone.

The two models differed in the placement of the clip to induce either rapid-onset strokes that are more severe than those usually seen in humans or slowly evolving strokes that resemble those frequently presented by patients. The team reasoned that showing a therapeutic effect for NA-1 in both models would increase the chance of eventual success in the clinic, Tymianski said.

Macaque models given NA-1 1 hour after the onset of severe stroke and up to 3 hours after the onset of slow-evolving stroke had smaller infarct sizes 48 hours after reperfusion than animals given placebo. The treated animals also had better neurobehavioral and sensorimotor

performance on day 14 than untreated animals. Data were reported in *Nature*.¹

Also last month, at the International Stroke Conference, NoNO presented results from a Phase II trial of NA-1 to treat subarachnoid hemorrhage (ruptured brain aneurysm) showing that NA-1 lowered ischemic brain damage and led to better neurological scores on day 30 than placebo.

"NA-1 is the first neuroprotective agent for stroke that, after testing in macaque models, went on to show benefit in a Phase II trial," Tymianski said. "By showing preclinical proof of concept in macaques, we potentially derisked the human experiment" and made a case for wider use of macaque models in preclinical testing of such therapies. "Without the macaque data, we would have been making the leap from rodents to humans—a leap that has failed with every previous therapy."

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"The data presented in the *Nature* study and the data from NoNO's Phase II trial represent a significant and much-needed step forward" in stroke research, said Thomas Sager, head of the Department of Neurodegeneration at **H. Lundbeck A/S**. "NoNO's approach bridged the gap between preclinical and clinic studies, thereby increasing the likelihood of seeing a therapeutic effect in humans. We need more experiences and papers like this to put new energy into the field of stroke and stimulate a new way of thinking about how to treat it."

Lundbeck has two stroke therapies in clinical development. Desmoteplase (DP5A), a genetically engineered salivary plasminogen activator from the vampire bat *Desmodus rotundus*, is in Phase III testing. Lu AA24493, a carbamylated form of human erythropoietin (EPO), is in Phase I testing. Lundbeck is co-developing the therapies with **Bayer AG** and **Warren Pharmaceuticals Inc.**, respectively.

Lundbeck obtained desmoteplase in 2005 from **Paion AG**, which in turn in-licensed the compound from Schering AG, now part of Bayer.

Victor Gurewich, cofounder and scientific director of **Thrombolytic Science International LLC**, agreed with Sager. "This is an impressive paper that should interest all of us in the stroke community because it is one of the few studies showing success for neuroprotection in monkeys," he said.

Gurewich is also professor of medicine at **Harvard Medical School** and director of **Beth Israel Deaconess Medical Center's** Vascular Research Laboratory.

Thrombolytic Science's TS01, a combination of a recombinant form of pro-urokinase with one amino acid mutation administered with a plasma complement 1 esterase inhibitor, is in preclinical development to treat stroke. The company expects to begin Phase I testing this year.

Segment segue

Sager said NoNO's preclinical data also point to the need to segment stroke populations.

"Stroke is a complex disease that occurs in a heterogeneous population with many factors of comorbidity," Sager said. "There are many preclinical models of stroke, but at best, only a few reflect the real-life aspects of the disease and none mimics what happens to stroke

patients at large.”

He added that NoNO circumvented this problem by “testing its therapy in animals that model the clinical situation of one well-defined segment of the stroke population—patients undergoing endovascular repair of intracranial aneurysms.” Then, instead of attempting to translate those findings to the general stroke population, the company translated them into

a small segment of stroke patients who have an experience very similar to the macaque models, he said. “I think this approach of segmenting the stroke population and developing models of those segments—whether in rats or macaques—points to a new standard for preclinical studies.”

The upshot, said Sager, is that the stroke field likely requires a “matrix of complementary stroke models that represent different aspects of the disease and subgroups of stroke patients.”

Indeed, there was no clear consensus on whether NoNO’s macaque models could have broader applications in the development of stroke therapies.

Gurewich suggested using the team’s macaque models to test neuroprotective agents that previously succeeded in rat models but failed in humans. “If those therapies also failed in the macaques, that would further strengthen the argument for using macaques as a bridge between rat models and clinical trials,” he said.

Tymianski agreed that testing failed neuroprotective therapies in the macaque models could “clinch the notion that macaques may be an essential translational step” for such therapies. However, he noted, “It is our view that primates should be used for translational studies only if there is a clear commitment to take a successful candidate into human testing.”

Sager added: “We also have to be careful not to think about these macaques as models of stroke in general, and instead keep in mind which segment of the patient population this model best represents.” Thus, testing therapies that failed to treat a general stroke population in NoNO’s macaque models would probably not be meaningful, he said.

Sager said he wants to see macaques and/or other stroke models extended to include aged animals, because “the human stroke population consists largely of older people with diabetes, hypertension and other comorbidities. While it would not be easy to do, age is the simplest aspect of this population to model.”

Gurewich was interested in the development of a macaque model of thrombus-induced stroke—in addition to the surgery-induced one NoNO developed.

“For the purpose of demonstrating preclinical proof of concept for NA-1, it doesn’t matter whether ischemia occurs as a result of a clamp or a clot,” he said. But in a model of thrombus-induced stroke, “you could test the combination of a thrombolytic agent, such as our TS01, and a

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— Thomas Sager, H. Lundbeck A/S

neuroprotective agent such as NA-1” in a way that reflected how those agents would be used in the clinic.

Tymianski said his team does not plan to develop a macaque model of thrombus-induced stroke. “We have attempted this already, but the variability in infarct size from one animal to the next with this model was too large,” he said. “Consequently, the experiments

would require population sizes that are not realistic” for nonhuman primate research.

He declined to disclose details about the Phase II trial of NA-1 because the results will be released in a forthcoming publication. He said NoNO also plans to conduct additional clinical trials of NA-1 to treat subarachnoid hemorrhage and acute ischemic stroke.

NoNO’s IP portfolio includes more than 50 patent applications or issued patents covering NA-1 and its use to treat stroke, traumatic brain injury, epilepsy, pain, anxiety and other indications, Tymianski said.

The company has also filed patent applications covering several macaque models of stroke for drug screening purposes. Those models are available for licensing or partnering, Tymianski said.

NA-1 has Fast Track designation from the FDA to reduce procedurally induced stroke and cognitive impairment in patients undergoing endovascular repair of brain aneurysms.

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e-mail: mike.tymianski@uhn.ca
2. Fisher, M. *et al. Stroke* **40**, 2244–2250 (2009)
3. Aarts, M. *et al. Science* **298**, 846–850 (2002)
4. Brätane, B.T. *et al. Stroke* **42**, 3265–3270 (2011)

COMPANIES AND INSTITUTIONS MENTIONED

Bayer AG (Xetra:BAYN), Leverkusen, Germany
Beth Israel Deaconess Medical Center, Boston, Mass.
Boehringer Ingelheim GmbH, Ingelheim, Germany
Genentech Inc., South San Francisco, Calif.
Harvard Medical School, Boston, Mass.
H. Lundbeck A/S (CSE:LUN), Copenhagen, Denmark
NoNO Inc., Toronto, Ontario, Canada
Paion AG (Xetra:PA8), Aachen, Germany
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
Thrombolytic Science International LLC, Cambridge, Mass.
Toronto Western Hospital, Toronto, Ontario, Canada
Toronto Western Research Institute, Toronto, Ontario, Canada
University of Toronto, Toronto, Ontario, Canada
Warren Pharmaceuticals Inc., Westchester, N.Y.

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
Cancer				
Acute myelogenous leukemia (AML)	Lysine-specific histone demethylase 1 (KDM1A; LSD1)	Cell culture and mouse studies suggest inhibition of LSD1 in combination with all- <i>trans</i> retinoic acid (ATRA) could help treat AML. In a xenograft mouse model of AML, ATRA plus tranylcypromine, a nonspecific inhibitor of LSD1 and other monoamine oxidases, decreased tumor engraftment compared with ATRA alone. In an AML cell line that mimics leukemia-initiating cells, tranylcypromine plus ATRA induced differentiation and subsequent apoptosis, whereas ATRA alone did not. Ongoing studies include Phase II testing of tranylcypromine plus ATRA in AML patients. Tranylcypromine is a generic monoamine oxidase inhibitor (MAOI) marketed to treat depression. Oryzon Genomics and Epi Pharmaceuticals Inc. have specific LSD1 inhibitors in preclinical development for cancer. Salaris Pharmaceuticals LLC's SP-2528, a selective LSD1 inhibitor, is in preclinical development for cancer.	Unpatented; licensing status not applicable	Schenk, T. <i>et al. Nat. Med.</i> ; published online March 11, 2012; doi:10.1038/nm.2661 Contact: Arthur Zelent, The Institute of Cancer Research, Sutton, U.K. e-mail: arthur.zelent@icr.ac.uk
Cancer	Proliferating cell nuclear antigen (PCNA)	<i>In vitro</i> studies suggest the triiodothyronine T3 derivative PCNA inhibitor T2AA could help treat cancer. <i>In vitro</i> , T2AA inhibited PCNA protein-protein interactions with an IC ₅₀ of about 1 μM. In human cancer cell lines, T2AA inhibited proliferation and increased cisplatin-induced DNA damage compared with no treatment. Next steps could include optimizing T2AA to generate lead compounds with higher PCNA affinity.	Patent and licensing status unavailable	Punchihewa, C. <i>et al. J. Biol. Chem.</i> ; published online March 1, 2012; doi:10.1074/jbc.M112.353201 Contact: Naoaki Fujii, St. Jude Children's Research Hospital, Memphis, Tenn. e-mail: naoaki.fujii@stjude.org
Hematologic malignancies	Myeloid leukemia cell differentiation protein (MCL1)	<i>In vitro</i> and cell culture studies suggest marinopyrrole A could help treat hematological malignancies. <i>In vitro</i> , marinopyrrole A (maritoclax) decreased MCL1 activity compared with vehicle control but did not affect the activity of the related protein B cell lymphoma 2 (BCL-2; BCL2). In cultured MCL1-driven human myeloid leukemia cells, maratoclax induced degradation of MCL1 and promoted apoptosis, whereas vehicle did not. In BCL2 inhibitor-resistant leukemia cells, maratoclax restored sensitivity to BCL2 inhibition. Next steps include further optimization and preclinical testing of maratoclax as an adjunct to BCL2 inhibitors in hematological malignancies. At least nine BCL2-family inhibitors are in development stages ranging from preclinical to Phase II trials to treat cancer.	Patent pending; licensing status undisclosed	Doi, K. <i>et al. J. Biol. Chem.</i> ; published online Feb. 6, 2012; doi:10.1074/jbc.M111.334532 Contact: Hong-Gang Wang, Pennsylvania State University Hershey College of Medicine, Hershey, Pa. e-mail: huw11@psu.edu

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Liver cancer	Transcription factor CP2 (TFCP2; LSF)	<i>In vitro</i> and mouse studies identified a small molecule inhibitor of the transcription factor LSF that could help treat hepatocellular carcinoma (HCC). In assays, factor quinoline inhibitor 1 (FQI1) inhibited the DNA-binding activity of LSF and transcriptional stimulation of LSF-dependent reporter constructs. In an aggressive HCC cell line that overexpressed LSF, FQI1 decreased viability and proliferation compared with vehicle control. In mice with human HCC xenografts, FQI1 lowered tumor growth and vasculature compared with vehicle control and did not show toxicity. Next steps include additional pharmacokinetic testing.	Patent application filed; available for licensing	Grant, T.J. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online March 5, 2012; doi:10.1073/pnas.1121601109 Contact: Ulla Hansen, Boston University, Boston, Mass. e-mail: uhansen@bu.edu
		SciBX 5(12); doi:10.1038/scibx.2012.305 Published online March 22, 2012		
Pancreatic cancer	Cytidine deaminase (CDA)	Mouse studies suggest inhibiting CDA with Abraxane nab-paclitaxel could help improve the efficacy of gemcitabine by reducing its breakdown in tumor cells. In a mouse model of pancreatic cancer, gemcitabine plus Abraxane decreased Cda protein stability and increased intratumoral gemcitabine concentrations compared with gemcitabine alone. The combination also slowed tumor growth, lowered metastasis and increased survival compared with gemcitabine alone. Next steps could include assessing whether the mechanism occurs in humans in an ongoing Phase III trial of Abraxane plus gemcitabine in patients with metastatic pancreatic cancer. Celgene Corp. and Otsuka Pharmaceutical Co. Ltd. market Abraxane to treat breast cancer.	Patent and licensing status unavailable	Frese, K.K. <i>et al. Cancer Discov.</i> ; published online Feb. 28, 2012; doi:10.1158/2159-8290.CD-11-0242 Contact: David A. Tuveson, Cancer Research UK, Cambridge, U.K. e-mail: david.tuveson@cancer.org.uk
		SciBX 5(12); doi:10.1038/scibx.2012.306 Published online March 22, 2012		
Cardiovascular disease				
Cardiovascular disease	Hypoxia-inducible factor 1 α (HIF1A; HIF1 α); transforming growth factor- β 1 (TGFB1)	Mouse studies suggest inhibiting TGFB1 could help protect against heart failure. Mice with inducible <i>Hif1a</i> knockout in endothelial cells and cardiomyocytes had greater myocardial hypertrophy, cell death and <i>Tgfb1</i> signaling from cardiac pressure overload than wild-type mice. In the mice with inducible <i>Hif1a</i> knockout, an anti-TGFB1 antibody protected against some of the pathological effects of cardiac pressure overload, whereas vehicle did not. Next steps could include testing TGFB1 inhibition in additional models. At least six companies have TGFB1 inhibitors in clinical and preclinical testing to treat cancer.	Patent and licensing status unavailable	Wei, H. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online March 8, 2012; doi:10.1073/pnas.1202081109 Contact: Gregg L. Semenza, The Johns Hopkins University School of Medicine, Baltimore, Md. e-mail: gsemenza@jhmi.edu
		SciBX 5(12); doi:10.1038/scibx.2012.307 Published online March 22, 2012		
Endocrine/metabolic disease				
Diabetes	Adenosine kinase	Cell culture and rodent studies identified adenosine kinase inhibitors that could help treat diabetes. An <i>in vitro</i> small molecule screen identified adenosine kinase inhibitors that promoted replication of cultured mouse, rat and pig primary β cells. In rodents, intraperitoneal injection of an adenosine kinase inhibitor increased β cell proliferation compared with vehicle. Next steps include additional screens of small molecule libraries.	Patented; available for licensing from Evotec AG	Annes, J.P. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Feb. 15, 2012; doi:10.1073/pnas.1201149109 Contact: Douglas A. Melton, Harvard Medical School, Boston, Mass. e-mail: dmelton@harvard.edu
		SciBX 5(12); doi:10.1038/scibx.2012.308 Published online March 22, 2012		

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Infectious disease				
Ebola	v-abl Abelson murine leukemia viral oncogene homolog 1 (ABL1)	<p>Cell culture studies suggest ABL1 inhibitors could help treat Ebola infection. In cells cultured with Ebola virus-like particles, either Gleevec imatinib or Tasigna nilotinib, which inhibit ABL1 and the oncogenic BCR-ABL tyrosine kinase fusion, produced dose-dependent decreases in the release of virus-like particles from the cells compared with vehicle. In cells cultured with the Ebola virus Zaire strain, nilotinib lowered virus production compared with vehicle. Next steps include pilot pharmacokinetic studies in nonhuman primates.</p> <p>Novartis AG markets Gleevec to treat chronic myelogenous leukemia (CML) and gastrointestinal stromal tumors, and the company markets Tasigna to treat CML.</p> <p>SciBX 5(12); doi:10.1038/scibx.2012.309 Published online March 22, 2012</p>	Patent application filed; available for licensing	<p>Garcia, M. <i>et al. Sci. Transl. Med.</i>; published online Feb. 29, 2012; doi:10.1126/scitranslmed.3003500</p> <p>Contact: Gary J. Nabel, National Institutes of Health, Bethesda, Md. e-mail: glabel@nih.gov</p>
Malaria	Not applicable	<p><i>In vitro</i> studies suggest hybrid macrolide antibiotic-quinoline compounds could help treat malaria. Chemical synthesis and <i>in vitro</i> testing of erythromycin analogs linked to 4-aminoquinoline structures identified several lead compounds that inhibited the growth of chloroquine-sensitive and chloroquine-resistant <i>Plasmodium falciparum</i> strains in human red blood cells with low nanomolar IC₅₀ values. These analogs showed no antibacterial activity against three <i>Streptococcus</i> species. Future studies could include testing the lead compounds in animal models of malaria.</p> <p>The generic chloroquine is marketed to treat malaria.</p> <p>SciBX 5(12); doi:10.1038/scibx.2012.310 Published online March 22, 2012</p>	Patented by GlaxoSmithKline plc; licensing status unavailable	<p>Pešić, D. <i>et al. J. Med. Chem.</i>; published online March 1, 2012; doi:10.1021/jm201676t</p> <p>Contact: Mihaela Perić, University of Zagreb School of Medicine, Zagreb, Croatia e-mail: mihaela.peric@mef.hr</p>
Musculoskeletal disease				
Muscular dystrophy	Dystrophia myotonica-protein kinase (DMPK; DM1); RNaseH	<p>Mouse and cell culture studies identified modified antisense oligonucleotides that could help treat myotonic dystrophy type 1, which is caused by nuclear accumulation of mutant DMPK mRNA with expanded CUG repeats. In nonhuman primate fibroblast cell lines expressing DMPK mRNA, an oligonucleotide with CAG repeat sequences and an RNaseH recruitment site promoted degradation of DMPK with expanded CUG repeats and had no effect on the degradation of DMPK with normal CUG repeats. In a mouse model of myotonic dystrophy type 1, a different CAG repeat oligonucleotide decreased levels of mutant DMPK compared with a control oligonucleotide. Next steps could include developing a method to safely and peripherally deliver a CAG repeat antisense oligonucleotide.</p> <p>SciBX 5(12); doi:10.1038/scibx.2012.311 Published online March 22, 2012</p>	Patented by Isis Pharmaceuticals Inc.; licensing status unavailable	<p>Lee, J.E. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Feb. 27, 2012; doi:10.1073/pnas.1117019109</p> <p>Contact: Thomas A. Cooper, Baylor College of Medicine, Houston, Texas e-mail: tcooper@bcm.edu</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Neurology				
Alzheimer's disease (AD); cognitive dysfunction	Microtubule-associated protein- τ (MAPT; TAU; FTDP-17)	<p>Transgenic mouse studies suggest microtubule-stabilizing compounds that penetrate the blood brain barrier could help treat AD. In transgenic mice with Tau-mediated neurodegenerative disease, the microtubule stabilizer epothilone D decreased axonal degeneration and Tau pathology and improved memory and spatial learning compared with vehicle. Planned work by the authors includes testing epothilone D in additional transgenic mouse models of AD, and planned work by Bristol-Myers Squibb Co. includes a Phase Ib trial of epothilone D to treat AD.</p> <p>Epothilone D (KOS-862; R1492) was evaluated in Phase II trials for multiple cancers, but Kosan Biosciences Inc. (now part of Bristol-Myers) and Roche discontinued its development in 2007.</p> <p>Bristol-Myers and Otsuka Pharmaceutical Co. Ltd. market Ixempra ixabepilone, a tubulin-binding agent derived from epothilone B, to treat breast cancer.</p> <p>Davunetide (AL 108), an eight-amino-acid, activity-dependent neuroprotective protein targeting tubulin from Allon Therapeutics Inc., has completed Phase II testing to treat AD and cognitive dysfunction and is in Phase II/III testing to treat progressive supranuclear palsy (PSP).</p> <p>SciBX 5(12); doi:10.1038/scibx.2012.312 Published online March 22, 2012</p>	Use of epothilone D to treat AD and other TAU-associated diseases patented by Bristol-Myers; licensing status unavailable	<p>Zhang, B. <i>et al. J. Neurosci.</i>; published online March 14, 2012; doi:10.1523/JNEUROSCI.4922-11.2012</p> <p>Contact: Kurt R. Brunden, Center for Neurodegenerative Disease Research, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pa. e-mail: kbrunden@upenn.edu</p>
Multiple sclerosis (MS)	Neurotrophic tyrosine kinase receptor 2 (NTRK2; TrkB)	<p>Patient sample and mouse studies suggest inhibiting TrkB on astrocytes could help treat MS. In a mouse model of experimental autoimmune encephalitis (EAE), conditional astrocyte-specific knockout of TrkB decreased disease severity compared with wild-type TrkB expression. In patient brain tissue samples, MS lesions had greater expression of a truncated TrkB isoform than normal control brain tissue. Next steps include studies to determine what level of TrkB inhibition would be needed for therapeutic effects.</p> <p>SciBX 5(12); doi:10.1038/scibx.2012.313 Published online March 22, 2012</p>	Unpatented; licensing status not applicable	<p>Colombo, E. <i>et al. J. Exp. Med.</i>; published online March 5, 2012; doi:10.1084/jem.20110698</p> <p>Contact: Cinthia Farina, San Raffaele Scientific Institute, Milan, Italy e-mail: farina.cinthia@hsr.it</p>
Nerve damage	Chondroitin sulfate proteoglycan (CSPG); chondroitin sulphate E (CS-E)	<p><i>In vitro</i> and mouse studies suggest inhibiting the CSPG disaccharide subunit CS-E could help treat CNS damage. In <i>ex vivo</i> chick dorsal root ganglia neurons and rat cerebellar granule neurons, CS-E blocked neurite outgrowth, whereas other CSPG subunits did not. In mouse models of optic nerve injury, local application of an anti-CS-E antibody increased axonal regrowth compared with application of a control antibody. Ongoing work includes testing the anti-CS-E antibody in animal models of spinal cord injury (SCI).</p> <p>SciBX 5(12); doi:10.1038/scibx.2012.314 Published online March 22, 2012</p>	Patented by the California Institute of Technology and the Howard Hughes Medical Institute; available for licensing or partnering	<p>Brown, J.M. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online March 12, 2012; doi:10.1073/pnas.1121318109</p> <p>Contact: Linda C. Hsieh-Wilson, California Institute of Technology, Pasadena, Calif. e-mail: lhw@caltech.edu</p>
Pain	Transient receptor potential cation channel subfamily M member 2 (TRPM2)	<p>Studies in mice suggest inhibiting TRPM2 could help treat inflammatory and neuropathic pain. In mouse models of mechanical, thermal and neuropathic pain, <i>Trpm2</i> knockout decreased inflammation and sensitivity to pain compared with wild-type <i>Trpm2</i> expression. Next steps could include studying whether TRPM2 inhibition increases susceptibility to infection.</p> <p>SciBX 5(12); doi:10.1038/scibx.2012.315 Published online March 22, 2012</p>	Patent and licensing status unavailable	<p>Haraguchi, K. <i>et al. J. Neurosci.</i>; published online March 14, 2012; doi:10.1523/JNEUROSCI.4703-11.2012</p> <p>Contact: Takayuki Nakagawa, Kyoto University, Kyoto, Japan e-mail: tnakaga@pharm.kyoto-u.ac.jp</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Renal disease				
Renal damage	Homeodomain interacting protein kinase 2 (HIPK2)	<p>Patient tissue and mouse studies suggest inhibiting HIPK2 could help prevent or treat kidney fibrosis. In kidneys from patients with diabetic neuropathy, HIV-associated nephropathy and focal segmental glomerulosclerosis, HIPK2 expression was greater than that in kidneys from healthy volunteers. In a mouse model of HIV-associated nephropathy, mice lacking Hipk2 had less kidney fibrosis and better renal function than wild-type mice. Next steps include screening for HIPK2 inhibitors and testing them in mice.</p> <p><i>SciBX</i> 5(12); doi:10.1038/scibx.2012.316 Published online March 22, 2012</p>	Unpatented; available for licensing	<p>Jin, Y. <i>et al. Nat. Med.</i>; published online March 11, 2012; doi:10.1038/nm.2685 Contact: John Cijiang He, Mount Sinai School of Medicine, New York, N.Y. e-mail: cijiang.he@mssm.edu Contact: Avi Ma'ayan, same affiliation as above e-mail: avi.maayan@mssm.edu</p>

This week in techniques

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

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

Approach	Summary	Licensing status	Publication and contact information
Chemistry			
Hydrogen bond acceptor-donor pairs to increase peptide membrane permeability	Engineering hydrogen bond acceptor-donor pairs into peptide-based drugs could help increase membrane permeability and improve efficacy. Peptides were synthesized with modified amino acids that contained hydrogen bond acceptor atoms. In cell culture, the peptides had better membrane permeability than analogs synthesized using unmodified amino acids. Next steps include evaluating permeability, solubility and target binding of larger engineered peptides. SciBX 5(12); doi:10.1038/scibx.2012.317 Published online March 22, 2012	Unpatented; available for licensing	Rafi, S.B. <i>et al. J. Med. Chem.</i> ; published online March 6, 2012; doi:10.1021/jm201634q Contact: Adam R. Renslo, University of California, San Francisco, Calif. e-mail: adam.renslo@ucsf.edu Contact: Matthew P. Jacobson, same affiliation as above e-mail: matt.jacobson@ucsf.edu
Drug platforms			
Implantable, bioartificial pancreas for type 1 diabetes	An implantable, bioartificial pancreas system could help treat type 1 diabetes. The two-chamber device consists of a module that houses islet cells in an alginate slab and a module that supplies the islets with oxygen. In a rat model of type 1 diabetes, the device restored normal blood glucose levels until the implant was removed at day 90. Rats that received implants containing islet cells pretreated with the growth hormone-releasing hormone (GHRH) agonist JI-36 had better glycemic control and required fewer islets than rats with implants containing untreated islets. Beta-O2 Technologies Ltd. is developing the bioartificial pancreas system and has ongoing studies evaluating the implant in large animal models of type 1 diabetes (<i>see Bioartificial pancreas beta test, page 1</i>). SciBX 5(12); doi:10.1038/scibx.2012.318 Published online March 22, 2012	Use of GHRH agonists in diabetes applications patented by the University of Miami; bioartificial pancreas system patented by Beta-O2 Technologies; both available for licensing	Ludwig, B. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online March 5, 2012; doi:10.1073/pnas.1201868109 Contact: Andrew V. Schally, University of Miami Miller School of Medicine, Miami, Fla. e-mail: andrew.schally@va.gov
Skin-delivered vaccines	Mouse studies suggest that vaccines designed to generate virus-specific memory T cells in the skin might provide better viral protection than vaccines that generate memory T cells in circulation. Most marketed vaccines are delivered intramuscularly and do not generate memory T cells in the skin. Mice immunized with a vaccinia virus by local skin infection generated virus-specific memory T cells in the skin and had lower levels of viral replication and more rapid viral clearance after challenge than mice immunized by intraperitoneal injection, which induced virus-specific circulating memory T cells. Next steps include extending the vaccine strategy to test protection against other viruses, intracellular bacteria and cancer. SciBX 5(12); doi:10.1038/scibx.2012.319 Published online March 22, 2012	Patented; Trem Rx Inc. has licensed the vaccine-relevant IP, which may be available for licensing for some indications	Jiang, X. <i>et al. Nature</i> ; published online Feb. 29, 2012; doi:10.1038/nature10851 Contact: Thomas S. Kupper, Brigham and Women's Hospital, Boston, Mass. e-mail: tkupper@partners.org
Targeted RNA import to correct diseases caused by mitochondrial mutations	A sequence that targets RNA molecules to mitochondria could help generate compounds to treat mitochondrial diseases. Disease-causing mutations in the mitochondrial genome are difficult to correct by gene therapy because many mitochondrial RNAs are not properly imported into the mitochondria from the nucleus. To solve this problem, extra sequences were engineered into mitochondrial RNAs, allowing them to enter mitochondria. In two model cell lines of diseases caused by mutations in mitochondrial tRNAs, transfection of mitochondrial tRNAs expressing the extra sequences rescued mitochondrial tRNA function. Next steps include testing the approach in an animal model of mitochondrial disease. SciBX 5(12); doi:10.1038/scibx.2012.320 Published online March 22, 2012	Patent application filed; available for licensing	Wang, G. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online March 12, 2012; doi:10.1073/pnas.1116792109 Contact: Carla M. Koehler, University of California, Los Angeles, Calif. e-mail: koehlerc@chem.ucla.edu Contact: Michael A. Teitell, same affiliation as above e-mail: mteitell@mednet.ucla.edu

This week in techniques

Approach	Summary	Licensing status	Publication and contact information
Imaging			
<i>In vivo</i> synthetic chemistry for generating tumor-specific fluorescence and PET imaging agents	An <i>in vivo</i> method for conducting selective chemical reactions in organisms could efficiently generate tumor-specific fluorescence and PET imaging agents. Testing in normal mice identified a polymer-modified tetrazine (PMT10) that reacted with a <i>trans</i> -cyclooctene compound. In mice with xenograft tumors that overexpressed glycoprotein A33 transmembrane (GPA33; A33), an anti-A33 antibody linked to the <i>trans</i> -cyclooctene compound reacted with A33 on tumors and with fluorophore- or ¹⁸ F-tagged PMT10 to selectively label tissue for fluorescence and PET imaging, respectively. Future studies could include using the method to label other disease-relevant targets <i>in vivo</i> for PET imaging. SciBX 5(12); doi:10.1038/scibx.2012.321 Published online March 22, 2012	Patent and licensing status unavailable	Devaraj, N.K. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online March 12, 2012; doi:10.1073/pnas.1113466109 Contact: Ralph Weissleder, Harvard Medical School, Boston, Mass. e-mail: rweissleder@mgh.harvard.edu

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