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Truly boronic

By Michael J. Haas, Senior Writer

Researchers at **Tufts University** have shown that peptide boronic acid inhibitors of dipeptidyl peptidase-4 could provide effective, low-toxicity treatments for diabetes.¹ The findings challenge the long-held assumption that boronic acids are too toxic for therapeutic use. **Arisaph Pharmaceuticals Inc.** has already in-licensed the related IP and has ARI-2243, a boronic acid inhibitor of dipeptidyl peptidase-4, in Phase I testing to treat diabetes.

Other companies contacted by *SciBX* said the findings make the case for taking another look at boronic acids as therapeutics, but they noted that the high potency makes selectivity a key issue, because that potency increases the likelihood of off-target effects at therapeutic doses.

Boronic acid redux

Dipeptidyl peptidase-4 (DPP-4) is expressed in many mammalian cells and tissues and plays a role in glucose metabolism. The serine protease degrades glucagon-like peptide 1 (GLP-1) and gastric inhibitory peptide (GIP), two gastrointestinal hormones secreted in response to the intake of food and involved in regulating insulin and glucose production.

Two non-boronic acid DPP-4 inhibitors are already approved for type 2 diabetes: Januvia sitagliptin, a selective DPP-4 inhibitor from **Merck & Co. Inc.**, and Galvus vildagliptin, a nonselective DPP-4 inhibitor from **Novartis AG**. Two other non-boronic acid DPP-4 inhibitors are in registration for the indication: Onglyza saxagliptin from partners **Bristol-Myers Squibb Co.**, **AstraZeneca plc** and **Otsuka Pharmaceutical Co. Ltd.** and alogliptin from **Takeda Pharmaceutical Co. Ltd.**

However, dipeptide boronic acids were among the first—and are still among the most potent—inhibitors of DPP-4, according to William Bachovchin, leader of the Tufts team and CSO of Arisaph. In 1991, he and colleagues at Tufts reported the discovery of dipeptide boronic acids with binding affinities for DPP-4 that extended into the picomolar range.² But he said that long-held—though unproven—assumptions about the intrinsic toxicity of boronic acids have largely precluded their commercial development.

Indeed, the only marketed boronic acid drug is Velcade bortezomib, a proteasome inhibitor from **Millennium Pharmaceuticals Inc.** that is approved to treat multiple myeloma (MM) and mantle cell lymphoma. Millennium, a unit of Takeda, markets Velcade in the U.S., whereas **Johnson & Johnson** markets the drug elsewhere.

In a paper in the *Journal of Medicinal Chemistry*, the Tufts team compared DPP-4 inhibitors to test whether boronic acids were indeed more toxic than other classes of molecules.



Science-Business eXchange

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 For inquiries, contact editorial@scibx.com
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Associate Publishers: Melanie Brazil, Ph.D.; Eric Pierce

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OFFICES
BioCentury Publications, Inc.

 San Francisco
 PO Box 1246
 San Carlos, CA 94070-1246
 T: +1 650 595 5333

 Chadds Ford
 223 Wilmington-West Chester Pike
 Chadds Ford, PA 19317
 T: +1 610 558 1873

 Chicago
 20 N. Wacker Drive, Suite 1465
 Chicago, IL 60606-2902
 T: +1 312 755 0798

 Oxford
 287 Banbury Road
 Oxford OX4 7JA
 United Kingdom
 T: +44 (0)18 6551 2184

 Washington, 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 9200

 London
 The Macmillan Building
 4 Crinan Street
 London N1 9XW
 United Kingdom
 T: +44 (0)20 7833 4000

 Tokyo
 Chiyoda Building 6F
 2-37 Ichigayatamachi
 Shinjuku-ku, Tokyo 162-0843
 Japan
 T: +81 3 3267 8751

SciBX is produced by BioCentury Publications, Inc. and Nature Publishing Group Joint Steering Committee: Karen Bernstein, Ph.D., Chairman & Editor-in-Chief, BioCentury; David Flores, President & CEO, BioCentury; Bennet Weintraub, Finance Director, BioCentury; Steven Inchcoombe, Managing Director, Nature Publishing Group; Peter Collins, Ph.D., Publishing Director, NPG; Richard Hartgill, Chief Financial Officer, NPG.

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The group chose three dipeptide boronic acid inhibitors of DPP-4: Val-boroPro talabostat, Ala-boroPro and Glu-boroAla. Talabostat and Ala-boroPro were potent but nonselective. The molecules had low picomolar binding affinities for DPP-4 and low nanomolar binding affinities for DPP-8 and DPP-9. Talabostat also inhibits fibroblast activation protein (FAP).

The third compound, Glu-boroAla, was more selective, with a low nanomolar binding affinity for DPP-4 but micromolar binding affinities for DPP-8 and DPP-9.

Talabostat was being developed by Point Therapeutics Inc., but a Phase III trial was halted last year when the talabostat arm showed lower overall survival than the control arm. Point reverse merged with **DARA BioSciences Inc.** later that year.

All three compounds lowered blood glucose in mice and rats at least as well as two non-boronic acid DPP-4 inhibitors—one selective, the other nonselective—examined in an earlier study at Merck Research Laboratories.³

The Tufts team also found that the maximum tolerated dose for Glu-boroAla in rats was comparable to the two non-boronic acid DPP-4 inhibitors.

The university team concluded that dipeptide boronic acids can be potent inhibitors of DPP-4 and are not intrinsically more toxic than non-boronic acid inhibitors of DPP-4.

Bachovchin told SciBX that in his team's unpublished experiments in animal models, dipeptide boronic acids showed greater efficacy than sitagliptin, as measured by lower levels of glucose and hemoglobin A1c.

"It is always encouraging to see science push the conventional boundaries and challenge perceptions of what is achievable," said Chris Claiborne, senior director of medicinal chemistry at Millennium. Boronic

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acids do not have any intrinsic limitations as potential therapeutics, and “this publication will enhance interest in the use of boronic acid derivatives to selectively target proteases for therapeutic areas outside oncology,” he said.

Dispelling a bad rap

Other companies and academics contacted by *SciBX* agreed that the *JMC* report is a major step forward in dispelling the misconceptions about boronic acid toxicity. The consensus is that the data could revive therapeutic interest in the class, if off-target activity against other serine proteases can be curbed.

Historically, boronic acid has not been considered a likely pharmacophore, due in part to numerous reports in the 1950s and 1960s of infants who died as a result of accidental ingestion of boric acid.^{4,5}

In the 1980s and 1990s, **E.I. du Pont de Nemours and Co.** held patents on boronic acids as inhibitors of elastase, thrombin and other proteolytic enzymes, but “people assumed that they must be toxic because du Pont didn’t do anything with them,” Bachovchin said.

However, Charles Kettner, who co-discovered du Pont’s boronic acid elastase inhibitors in the 1980s, told *SciBX* that the compounds exhibited no obvious adverse effects in animals or in cell culture. du Pont was not interested in developing the compounds, he said, because the company did not have the appropriate biological resources at the time. Indeed, du Pont did not shy away from developing boronic acids when the company expanded its focus in the late 1980s to include pharmaceuticals.

Kettner was a research fellow when he retired from Bristol-Myers Squibb in 2003.

“du Pont was ahead of its time with its work,” said John Kozarich, chairman and president of **ActivX Biosciences Inc.**, a subsidiary of **Kyorin Pharmaceutical Co. Ltd.** “It was done before human genome studies revealed how broad the class of serine proteases is and how many thrombin homologs there are.”

He estimated that there are 300 serine proteases or serine hydrolases—another indication that selectivity is the main issue for boronic acids.

“In reality, du Pont’s compounds just weren’t selective enough,” Kozarich said. “There is a lot of potential in using boronic acids. They have many possible targets—serine proteases and serine hydrolases—that play roles in many diseases, such as diabetes, atherosclerosis, cancer and others.”

The key question, he said, is whether boronic acids can be both selective and safe enough for chronic use. “Emerging evidence like this paper says yes,” Kozarich concluded.

In August, **ActivX** completed a Phase IIa trial of KRP-104, a selective non-boronic acid DPP-4 inhibitor, to treat type 2 diabetes. The company has not disclosed a timeline for additional studies of the compound.

“It would be hard to find a better pharmacophore for protease inhibitors than boronic acid,” said David Campbell, VP of drug discovery and preclinical sciences at **Phenomix Corp.** “But because it’s so good, you have to devote a lot of time to selectivity” to avoid off-target effects on structurally related serine proteases.

For example, a drug candidate with nanomolar activity should typically have binding affinities for other molecules (off-target selectivity) that are 10–100 times lower than its affinity for the intended target, he said. But with a picomolar drug, off-target binding that is 100-fold lower

“This publication will enhance interest in the use of boronic acid derivatives to selectively target proteases for therapeutic areas outside oncology.”

—Chris Claiborne,
Millennium Pharmaceuticals Inc.

puts such activity in the nanomolar range—still in the preferred range for drugs—making off-target effects likely even at therapeutic doses.

Thus, the off-target selectivity of a picomolar-active compound needs to be several orders of magnitude lower than the compound’s binding affinity for its target.

“It really comes down to what the off-target proteins are and what the selectivity index for the compound is,” Campbell said. “These are the same issues you have with any compound, but it

arises more often with boronic acids because they are often so potent.”

Earlier this year, **Phenomix** completed a Phase IIb study of its non-boronic acid DPP-4 inhibitor, dutogliptin (formerly PHX1149). Phase III testing is expected to start this year.

Making a comeback

Although selectivity is usually essential for drugs, off-target effects are not always toxic or unwelcome. A case in point is the boronic acid that **Arisaph** has in the clinic.

“ARI-2243’s effect goes beyond DPP-4 inhibition,” said Bachovchin. “It lowers blood glucose even in DPP-4 knockout animals. So, we are looking for the second mechanism that explains this enhanced efficacy.”

Bachovchin said ARI-2243, which was not studied in the *JMC* paper, is not a dipeptide boronic acid but rather a new class of boronic acid. He declined to describe the structure.

“We are also looking at the selectivity and mechanisms of interactions between boronic acids and other enzymes such as DPP-2, FAP, DPP-8, DPP-9 and prolyl endopeptidase,” Bachovchin said. These studies will be the subject of future papers.

Arisaph has other boronic acids in preclinical development to treat cancer and atherosclerosis.

Tufts holds international patents for the use of boronic acids to treat diabetes, cancer and atherosclerosis and has out-licensed them to **Arisaph**.

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COMPANIES AND INSTITUTIONS MENTIONED

Arisaph Pharmaceuticals Inc., Boston, Mass.
AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K.
Bristol-Myers Squibb Co. (NYSE:BMJ), New York, N.Y.
DARA BioSciences Inc., Raleigh, N.C.
E.I. du Pont de Nemours and Co. (NYSE:DD), Wilmington, Del.
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Kyorin Pharmaceutical Co. Ltd. (Tokyo:4560), Tokyo, Japan
Merck & Co. Inc. (NYSE:MRK), Whitehouse Station, N.J.
Millennium Pharmaceuticals Inc. (NASDAQ:MLNM), Cambridge, Mass.
Novartis AG (NYSE:NVS; SWX:NOVN), Basel, Switzerland
Otsuka Pharmaceutical Co. Ltd. (Tokyo:4768), Tokyo, Japan
Phenomix Corp., San Diego, Calif.
Takeda Pharmaceutical Co. Ltd. (Tokyo:4502), Osaka, Japan
Tufts University, Boston, Mass.

Moving upstream in Huntington's

By Lauren Martz, Staff Writer

Researchers at **Harvard Medical School** and **The Scripps Research Institute** each have published new strategies to treat Huntington's disease, a condition for which there is only one approved drug (see **Table 1, Attacking Huntington's disease**).^{1,2} The Harvard group showed that inhibiting cytochrome C release from the mitochondria might effectively combat the disease. The Scripps team described a more upstream approach—using histone deacetylase (HDAC) inhibitors to curb transcriptional dysregulation.

Companies and academics interviewed by *SciBX* had safety concerns about both approaches, but they think that if these issues are addressed, the strategies could be used together.

Huntington's disease (HD) is a neurodegenerative disorder caused by CAG repeats in the *huntingtin* (*HTT*) gene that manifest as a range of motor and cognitive defects. *HTT* is a 3,144 amino acid–long protein involved in many protein-protein interaction networks.³

Although HD is a monogenic disorder, the therapeutic challenge is posed by the myriad phenotypic effects that can culminate in neurodegeneration. Moreover, the exact route of pathogenesis is still ill defined. Known contributors—and thus potential points of therapeutic intervention—include transcriptional dysregulation, mitochondrial dysfunction,

aberrant protein aggregation, excitotoxicity and disruptions in cellular trafficking.⁴

Stop the apoptosis

In a paper published in the *Journal of Neuroscience*, Robert Friedlander and colleagues at Harvard showed that intervention at the stage of mitochondrial dysregulation might provide neuroprotection. Friedlander is vice chairman of the Department of Neurosurgery and associate director of cerebrovascular surgery at **Brigham and Women's Hospital**.

Friedlander's team screened 1,040 neurological compounds on the market and in development by testing them on purified mitochondria. They identified 21 compounds that potently inhibited cytochrome C release. Of those, 16 also lowered cytochrome C release from mitochondria and lowered cell death in ST14A cells with mutated *HTT*.

The researchers chose one of the most potent compounds, methazolamide, for further analysis. Methazolamide is a generic approved to treat glaucoma.

In HD cell lines, the drug inhibited release of both cytochrome C and the proapoptotic mitochondrial protein Smac/Diablo. In a mouse model of HD, methazolamide delayed disease onset, extended lifespan and lowered both cytochrome C release and neuronal death compared with the effects of saline controls.

"The release of cytochrome C occurs fairly early in the cell death process, so it is a good step to target," Friedlander told *SciBX*.

He added that many of the compounds addressed by the group's screening approach are already on the market for other indications.

Table 1. Attacking Huntington's disease. A number of companies are attempting to treat Huntington's disease (HD) by using different mechanisms. Some are targeting the disease by repairing the mutated protein responsible for the disease or eliminating its aggregation, whereas others are working further downstream at the points of mitochondria dysfunction, oxidative stress or excessive apoptosis, which all cause neuronal damage. Still other companies have compounds that protect or repair the neurons from the effects of the mutated protein. Selected compounds in development and on the market for HD are listed below.

Category	Company	Product	Description	Status
Aberrant apoptosis	Neurologix Inc. (OTCBB:NRGX)	dXIAP	Mutated form of the gene <i>X-linked inhibitor of apoptosis (XIAP)</i> delivered by adeno-associated virus (AAV) vector	Preclinical
Neuroprotection	Ovation Pharmaceuticals Inc./ Biovail Corp. (NYSE:BVF; TSX:BVF)/ Cambridge Laboratories Ltd.	Xenazine tetraabenazine	Selective inhibitor of vesicular monoamine transporter 2 (VMAT2)	Marketed
	NeuroSearch A/S (CSE:NEUR)	ACR16	Dopamine stabilizer	Phase III
	ReNeuron Group plc (LSE:RENE)	ReN005	Neuronal stem cell transplantation	Preclinical
Mitochondrial dysfunction	Amarin Corp. plc (NASDAQ:AMRN)/ Scil Group	Miraxion (AMR-101)	Eicosapentaenoic acid derivative that inhibits phospholipase A ₂ (PLA ₂) and caspases	Phase III
	Medivation Inc. (NASDAQ:MDVN)/ Pfizer Inc. (NYSE:PFE)	Dimebon	Small molecule that blocks an undisclosed target involving mitochondrial pores	Phase II
Mutated protein	Alnylam Pharmaceuticals Inc. (NASDAQ:ALNY)/ Medtronic Inc. (NYSE:MDT)	ALN-HTT	Small interfering RNA (siRNA) against the <i>huntingtin (HTT)</i> gene delivered by Medtronic's implantable infusion pump	Preclinical
	Targeted Genetics Corp. (NASDAQ:TGEN)/ Merck & Co. Inc. (NYSE:MRK)	siRNA/AAV1	AAV vector delivering siRNA targeting <i>HTT</i>	Preclinical
Neuronal repair	Ceregene Inc.	CERE-120	AAV Type 2 vector encoding <i>neurturin (NTN)</i> gene	Preclinical
Oxidative stress	Avicena Group Inc. (Pink:AVCE)	HD-02	Therapeutic that incorporates a clinical form of creatine	Phase II
Protein aggregation	Prana Biotechnology Ltd. (ASX:PBT; NASDAQ:PRAN)	PBT2	Metal protein-attenuating compound (MPAC)	Phase I

“These are FDA-approved drugs. We already know that methazolamide is safe and can cross the blood-brain barrier,” Friedlander said.

“In theory, this is a shorter pathway to an approved compound for Huntington’s disease treatment” compared with the discovery of new compounds, said Robert Pacifici, CSO of the **CHDI Foundation Inc.** “But it is important to look out for pitfalls. For example, minocycline, which is an approved antibiotic that was identified in the screen, was used in clinical testing for amyloid lateral sclerosis and the trials were halted because the compound was actually making people worse.”

CHDI is a not-for-profit organization that supports the discovery and development of HD therapeutics.

Pacifici was also concerned that the compounds in the *Journal of Neuroscience* article might have effects on processes other than cytochrome C release. He noted that methazolamide is primarily a carbonic anhydrase inhibitor, so it has at least one other function.

Other researchers were concerned about the long-term effects of shutting off apoptosis in HD patients.

“There is concern that apoptosis is necessary to prevent cancer.

Therefore, an increased risk of cancer could be an adverse effect” of an apoptosis inhibitor, said Ashley Bush, Australian Research Council Federation Fellow at the **Mental Health Research Institute of Victoria** and a founding scientist of **Prana Biotechnology Ltd.**

Prana’s PBT2 is a metal protein-attenuating agent that blocks generation of reactive oxygen species and subsequent apoptosis. The compound has completed Phase I testing to treat HD.

David Rubinsztein, a professor of molecular neurogenetics at the **University of Cambridge**, agreed that cancer is a potential issue. “There is a chance that inhibiting apoptosis could increase the risk of cancer, and, with Huntington’s disease, a long-term treatment is necessary, which could increase that risk,” he said.

Potential safety issues aside, Pacifici questioned whether inhibiting apoptosis is the most efficacious way to treat HD. “You are preventing the neurons from dying, but it is not clear whether having a sick neuron is actually better than having a dead neuron,” he said.

Friedlander’s team showed that methazolamide delayed disease onset and extended lifespan by up to 27% and 20%, respectively, in mice. He said the most important next step for his group is testing their findings in the clinic.

Belinda Tsao-Nivaggioli, chairman and CEO at **Avicena Group Inc.**, agreed that clinical trials are the logical next step. “In Huntington’s disease, if a therapeutic shows activity of increasing life by about 17–20% in preclinical models, it is usually worth moving forward into clinical testing,” she said.

Avicena’s HD-02, a therapeutic that incorporates a clinical form of creatine, has completed Phase II testing in HD.

Brigham and Women’s Hospital of the Harvard Medical School has filed a patent application for the inhibitors of cytochrome C release. The compounds are available for licensing worldwide, said Friedlander.

Transcription prescription

In a paper in the *Proceedings of the National Academy of Sciences*, Elizabeth Thomas and colleagues at Scripps used a new HDAC inhibitor,

HDACi 4b, to correct the transcriptional dysregulation associated with HD.

Her team showed that HDACi 4b was not cytotoxic *in vitro*, and it caused a twofold increase in acetylation of H4, which opens the chromatin structure to facilitate transcription. In a mouse model of HD, the compound improved motor performance and coat appearance compared with the effects of vehicle controls.

Compared with the control group, mice receiving HDACi 4b also lost less body and brain weight.

Thomas, assistant professor in the Department of Molecular Biology at Scripps, told *SciBX* that transcriptional dysregulation is one of the earliest pathological mechanisms in HD. Even though the exact pathway of disease pathology has not been confirmed, she said it is thought that the defects in gene expression precede mitochondrial dysfunction and therefore inhibition of HDAC might act upstream of inhibitors of cytochrome C release.

“Because transcriptional dysregulation is very likely a core pathogenic mechanism of disease, our compounds should also help relieve the downstream pathologies,” said Thomas.

“We’ve looked at the effects of the compounds at the beginning of symptoms and are now looking at the effects of administration before symptom onset. If we find that it works better before symptoms occur, genetic screening and early treatment could be more effective ways to treat the disease,” she noted.

Thomas also said her lab is working to resolve toxicity issues associated with HDAC inhibitors. The first marketed HDAC inhibitor, Zolinza vorinostat (suberoylanilide hydroxamic acid) from **Merck & Co. Inc.**, is associated with side effects including nausea, vomiting and diarrhea, tiredness, upper respiratory infection, deep vein thrombosis and pulmonary embolus. The pan-HDAC inhibitor is approved to treat cutaneous T cell lymphoma (CTCL).

“The toxicity profile would be unacceptable” in HD patients, said Pacifici. “Pan inhibitors are not the way to go.”

Thomas said that Scripps has filed a patent for HDACi 4b and other similar compounds. **Repligen Corp.** holds rights to the patent and is conducting preclinical work to determine ideal doses and metabolic effects of the compounds.

“More than a dozen HDAC enzymes have been identified, and we are targeting members of class 1,” said Repligen president and CEO Walter Herlihy. “The compounds have high inhibitory potential for HDAC3 specifically.”

He added that “we are analyzing toxicity and pharmacology, which includes bioavailability and the ability of the compounds to cross the blood-brain barrier.”

Herlihy told *SciBX* that Repligen hopes to identify a pharmaceutical candidate by the end of this year and to start Phase I testing in 2009, pursuing the initial indication of Friedreich’s ataxia (FA).

Combinations

Although the treatment strategies presented by the Harvard and Scripps teams are different, they are not necessarily competing approaches. Indeed, companies and institutions contacted by *SciBX* hope both strategies could fit into the treatment space. (Continues on p. 6)

“In theory, this is a shorter pathway to an approved compound for Huntington’s disease treatment.”

**—Robert Pacifici,
CHDI Foundation Inc.**

Autoimmunity gets Mincle and dimed

By Kai-Jye Lou, Staff Writer

Researchers at the **RIKEN Research Center for Allergy and Immunology** have identified MINCLE as a receptor that triggers neutrophil recruitment and secretion of proinflammatory cytokines in response to necrotic cells derived from injured tissue.¹ Companies next want to see data in animals demonstrating the link between the receptor and autoimmune diseases. If the mechanistic link is confirmed, the receptor could be a more specific and selective target than the targets of currently marketed drugs.

C-type lectin domain family 4, member e (MINCLE) falls into the class of c-type lectin receptors, which are involved in autoimmune responses. An earlier analysis of patient samples identified a correlation between MINCLE expression and rheumatoid arthritis (RA), although a causal link was not established.² In that study, nearly half of the bone marrow-derived mononuclear cell samples from RA patients had a 5- to 50-fold increase in expression of MINCLE compared with that seen in samples from healthy controls.

(Continued from "Moving upstream in Huntington's," p. 5)

"I think a cocktail-type approach will be the best answer for this disease, as it is for cancer and HIV," said Friedlander.

Tsao-Nivaggioli agreed. "Probably in the end it will be combination treatment. We will still need to rely on some symptomatic treatments and some to slow disease progression," she said.

In addition to symptomatic treatments, the HDAC- and cytochrome C-inhibiting approaches could be coupled with therapies that aim to fix the source of the disease: the mutated protein.

Rubinsztein said exclusively targeting downstream effects such as neuron damage might not address all of the pathogenic mechanisms of the disease, and patients might see little efficacy. "It would be more appealing to remove the toxic protein itself," he said.

Ideally, an HD therapy would correct the mutant gene. However, said Rubinsztein, "one would have to chop out the extra repeats and would have to do it in a high enough proportion of relevant cells in the brain. There might be a way to do it in a limited number of cells, but this poses quite a challenge."

He concluded: "The next best thing would be to remove the toxic protein."

Rubinsztein's lab is currently trying to enhance degradation of the mutated protein.

The CHDI foundation and **Isis Pharmaceuticals Inc.** are trying to lower mutant HTT protein expression with antisense oligonucleotides under an agreement that was expanded last year.

"One important thing to consider is that rodent studies have proven that htt is an essential protein and its knockdown is embry-

In the current study, now published in *Nature Immunology*, the RIKEN RCAI group, led by Takashi Saito, deputy director of the center and group director of the laboratory for cell signaling, showed that an antibody against Mincle significantly lowered neutrophil infiltration in mice injected with dead melanoma or 2B4 (CD244) cells compared with what was seen in mice that received a nontargeting antibody ($p < 0.05$). 2B4 cells are members of the signaling lymphocytic activation molecule-related receptors (SRRs) that modulate NK cell activity.

The antibody against Mincle also significantly lowered neutrophil recruitment in a mouse model of radiation-induced cell death compared with what was seen in untreated or mock-treated mice ($p < 0.05$). The antibody also decreased the expression of proinflammatory cytokines secreted in response to necrotic cells, including tumor necrosis factor (TNF), IL-2 and chemokine (CXC motif) ligand 2 (CXCL2; MIP-2).¹

Defining a role

Saito told *SciBX* that although *Mincle* is part of a class of genes associated with autoimmunity, research covering *Mincle*-related disease associations is still in the very early stages.

Indeed, Gordon Brown, associate professor in the Institute of Infectious Disease and Molecular Medicine at the **University of Cape Town**,

(Continues on p. 7)

onically lethal. We now need to determine how much can be knocked down for therapeutic benefit and how much would be detrimental," Pacifici said.

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e-mail: rfriedlander@rics.bwh.harvard.edu
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e-mail: bthomas@scripps.edu
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COMPANIES AND INSTITUTIONS MENTIONED

Avicena Group Inc. (OTCBB:AVGO), Palo Alto, Calif.
Brigham and Women's Hospital, Boston, Mass.
CHDI Foundation Inc., New York, N.Y.
Harvard Medical School, Boston, Mass.
Isis Pharmaceuticals Inc. (NASDAQ:ISIS), Carlsbad, Calif.
Mental Health Research Institute of Victoria, Melbourne, Australia
Merck & Co. Inc. (NYSE:MRK), Whitehouse Station, N.J.
Prana Biotechnology Ltd. (ASX:PBT; NASDAQ:PRAN), Melbourne, Australia
Repligen Corp. (NASDAQ:RGEN), Waltham, Mass.
The Scripps Research Institute, La Jolla, Calif.
University of Cambridge, Cambridge, U.K.

ALDH2 for the heart

By Brian Moy, Staff Writer

Researchers at **Stanford University School of Medicine** and **Indiana University School of Medicine** have shown that activation of the mitochondrial aldehyde dehydrogenase 2 enzyme correlates with less ischemic heart damage following myocardial infarction. The group also has identified a small molecule activator of the enzyme that could be useful for limiting ischemia-induced cardiac damage that occurs in MI and coronary artery bypass graft surgery.¹

According to university and industry researchers polled by *SciBX*, therapeutic application of these findings will hinge on timing, dosage and potential side effects of such aldehyde dehydrogenase 2 (ALDH2) activators, as well as identifying the most appropriate patient populations for treatment.

(Continues on p. 8)



(Continued from "Autoimmunity gets Mincle and dimed," p. 6)

said that "the identification of a receptor triggering inflammatory responses to necrotic cells is of great importance, and the receptor may well be involved in the development of autoimmune diseases. However, there is as yet no evidence to suggest that this receptor is involved in the development of these diseases, so speculating on its role as a potential therapeutic target is premature."

Tomas Mustelin, VP of research for inflammation at **Amgen Inc.**, agreed. "Much work remains to be done to illuminate the possible role of MINCLE in inflammatory disease processes," he said.

Amgen markets several drugs for autoimmune diseases, including Enbrel etanercept, a soluble TNF receptor.

Basil Dahiyat, president and CEO of **Xencor Inc.**, thinks future work on associations between MINCLE and autoimmune disease could pay off, as the receptor's profile makes it a promising target.

"An interesting aspect of MINCLE is that it is only expressed transiently on macrophages, and expression appears to happen when the cell detects stresses like cell death," he said. "The inducible and highly regulated expression is interesting because it could be a very selective and specific target for immune modulation and not have some of the side effects seen with agents targeting more broadly expressed targets."

The downside of that transient expression, said Dahiyat, is that "the role of MINCLE might be more limited than expected."

Regardless, Dahiyat said, it is interesting and worth further study to determine the direct roles that MINCLE plays in disease processes such as RA, where Xencor's XPro 1595 TNF- α inhibitor is in preclinical testing.

"The etiology of cell death and tissue damage in rheumatoid arthritis is not clear, though neutrophils definitely play a role, so MINCLE is a plausible target based on the work in the paper," he said.

Brown told *SciBX* that compounds targeting MINCLE will need to be highly specific. "C-type lectins are relatively conserved in sequence and structure and the intracellular signaling pathways are used by

As published in *Science*, Daria Mochly-Rosen, professor in the Department of Chemical and Systems Biology at the Stanford medical school, and colleagues from both universities used a proteomic approach to identify proteins whose phosphorylation correlated with less cardiac damage from ischemia. In ischemic rat hearts, they found that increased phosphorylation of ALDH2 was consistently associated with cardioprotection from ischemia.

Additionally, a high throughput screen for activators of ALDH2 identified Alda-1, a small molecule substituted dichlorobenzamide. In a rat model of acute MI, administration of Alda-1 into the left ventricle five minutes before an ischemic event lowered infarct size by 60% compared with that seen in vehicle-treated controls ($p < 0.01$).

Mochly-Rosen told *SciBX* that "the importance of Alda-1 is not only that the compound activates basal activity of ALDH2, but it also prevents inactivation of the enzyme by its substrate," an aldehyde called 4-hydroxynonenal (4HNE).

many other receptors, so the therapeutic would have to specifically target MINCLE itself," he said.

Next steps

Going forward, Saito said his group plans to create and use a Mincle knockout mouse in models of autoimmune disease. The RCAI group also plans to analyze samples from patients with autoimmune diseases.

Saito also noted that his group is developing antibodies against the human version of MINCLE.

According to Dahiyat, "the next step is to examine Mincle inhibition in rodent models of arthritis as well as in other models of inflammation and autoimmunity. Perhaps most critical is verifying similar activities of human MINCLE in human cell-based assay systems, as all of the current work is being done in mice. There are often differences between human and mouse immune biology and those differences need to be carefully examined to see if human MINCLE behaves similarly."

A patent application covering the use of antibodies targeting MINCLE and its epitopes to treat autoimmune diseases has been filed. The antibodies are available for licensing on a nonexclusive basis from the Center for Intellectual Property Strategies at RIKEN.

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Contact: Takashi Saito, RIKEN Research Center for Allergy and Immunology, Yokohama City, Japan
e-mail: saito@rcai.riken.jp
2. Nakamura, N. *et al. DNA Res.* **13**, 169-183 (2006)

COMPANIES AND INSTITUTIONS MENTIONED

Amgen Inc. (NASDAQ:AMGN), Thousand Oaks, Calif.
RIKEN Research Center for Allergy and Immunology, Yokohama City, Japan
University of Cape Town, Cape Town, South Africa
Xencor Inc., Monrovia, Calif.

4HNE is a toxin that accumulates during cardiac ischemia.² It induces rapid inactivation of ALDH2 by forming protein adducts within the enzyme.

In vitro, Alda-1 blocked 4HNE-induced inactivation of ALDH2. Thus, the authors wrote that the molecular basis for Alda-1-induced ALDH2 protection “is probably due to prevention of 4HNE adduct formation on ALDH2.”

Alda-1 also is able to restore the activity of ALDH2*2, an inactive mutant form of ALDH2 found in about 40% of East Asian populations. “It is rare to find a small molecule that can specifically rescue a mutation in humans,” the researchers wrote.

According to Gregory Bell, SVP of development and CMO at **KAI Pharmaceuticals Inc.**, another potential use of Alda-1 is to mimic ischemic preconditioning of the heart or other organs, such as the brain, kidneys or liver.

Preconditioning is a protective mechanism in which short periods of low or no oxygen to the heart or other organs can confer resistance to longer periods of ischemia and therefore limit the amount of damage that occurs to the organ following ischemia. “A treatment that mimics ischemic preconditioning is something that researchers have been trying to develop for years,” said Bell.

Furthermore, said Mochly-Rosen, Alda-1 may be useful in conjunction with nitroglycerin treatment. Nitroglycerin is often administered chronically to patients with unstable angina, acute MI and acute coronary syndrome (ACS); the drug confers cardiac protection when it is metabolized by ALDH2 and generates the vasodilator nitric oxide (NO).

But prolonged treatment with nitroglycerin decreases ALDH2 activity,³ so individuals with an ALDH2*2 mutation might benefit more from Alda-1 than carriers of wild-type ALDH2.

“Patients with ALDH2*2 are expected to have already reduced natural protection from ischemic injury, and treatment with nitroglycerin may reduce this protection even further,” said Mochly-Rosen. Thus, Alda-1, which inhibits nitroglycerin tolerance and increases bioconversion of nitroglycerin to NO, may be more beneficial in those with an ALDH2*2 mutation, she said.

Mochly-Rosen also noted that ALDH2 is located in mitochondria, which are permeable to small molecules, suggesting that a compound such as Alda-1 should be highly effective in activating the enzyme.

Optimal activation

Junichi Sadoshima, vice chairman of the Department of Cell Biology and Molecular Medicine at **New Jersey Medical School**, said that “because cardiac ischemia is one of the leading causes of death, a small molecule that can greatly reduce myocardial injury would have a significant impact.”

However, he thinks it is too early to talk about the use of Alda-1 in the clinic. “It is not clear how the compound would be delivered or what the side effects and pharmacokinetic properties of the compound are,” he said.

In addition, it is not clear what sort of patient population would benefit most from a compound that activates ALDH2.

“A treatment that mimics ischemic preconditioning is something that researchers have been trying to develop for years.”

— Gregory Bell,
KAI Pharmaceuticals Inc.

Indeed, patients do not know when an MI will occur, so a molecule that activates ALDH2 would need to be chronically administered to be effective in lowering infarct size during an MI.

“You would have to deliver the drug immediately before the ischemic event occurs,” which is difficult in patients presenting with MI, noted Elizabeth McNally, a professor in the Department of Medicine and director of the

Institute for Cardiovascular Research at the **University of Chicago**.

“A small molecule activator of ALDH2 would be most useful in an acute, short-term setting in patients who are at high risk for ischemic injuries during planned surgeries, such as coronary artery bypass graft surgery or other major vascular surgery,” said Bell.

KAI is developing KAI-1455, a protein kinase C_ε (PKC_ε) activator in Phase I testing to treat ischemia-induced reperfusion injury. Mochly-Rosen, who is also the founder of KAI, and colleagues previously showed that ethanol and selective activation of PKC_ε mimic ischemic preconditioning and lower infarct size.⁴

In contrast to Bell, Kai Pinkernell, head of research at **Cytori Therapeutics Inc.**, thinks Alda-1 could be well suited to longer-term use. “Chronic administration of an ALDH2 activator could be useful for treating patients at high risk for MI, such as those with angina or chronic ischemic heart disease,” he said.

Cytori’s adipose tissue-derived stem and regenerative cell therapy device is in feasibility testing to repair heart muscle damaged from heart attacks or chronic ischemic heart disease.

Ongoing studies by Mochly-Rosen and colleagues are aimed at improving the pharmacokinetics of Alda-1, investigating the benefits of administering the compound following ischemic damage and determining the effects of chronic treatment.

Additionally, the researchers are investigating whether Alda-1 has utility in other diseases associated with higher accumulation of 4HNE and lower ALDH2 activity, as well as diseases that occur more frequently in individuals carrying an ALDH2*2 mutation. These include chronic conditions such as Alzheimer’s disease (AD) and Parkinson’s disease (PD).

The findings of the *Science* paper, as well as Alda-1 and its derivatives, are patented by Stanford and available for licensing.

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COMPANIES AND INSTITUTIONS MENTIONED

Cytori Therapeutics Inc. (NASDAQ:CYTX; Xetra:XMPA), San Diego, Calif.
Indiana University School of Medicine, Indianapolis, Ind.
KAI Pharmaceuticals Inc., South San Francisco, Calif.
New Jersey Medical School, Newark, N.J.
Stanford University School of Medicine, Stanford, Calif.
University of Chicago, Chicago, Ill.

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
Autoimmune disease				
Autoimmune	Sugar moiety of IgG	Studies in mice suggest that glycoside hydrolase enzyme therapy could be useful for treating autoimmune disease. In healthy mice, i.v. administration of recombinant endoglycosidase S (EndoS) from <i>Streptococcus pyogenes</i> increased hydrolysis of IgG-associated carbohydrates in serum at 45 minutes compared with baseline. In a murine model of spontaneous lupus-like disease, EndoS treatment lowered serum IgG autoantibody levels and increased survival compared with what was seen in untreated controls. Further preclinical studies in other animal models of autoimmune disease are ongoing to determine the indications that should first be targeted in clinical testing.	EndoS treatment of conditions involving IgG autoantibodies patented by Hansa Medical AB; available for licensing in the U.S. and Europe	Albert, H. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Sept. 22, 2008; doi:10.1073/pnas.0808248105 Contact: Falk Nimmerjahn, University of Erlangen-Nuremberg, Erlangen, Germany e-mail: fnimmerj@molmed.uni-erlangen.de Contact: Jeffrey V. Ravetch, The Rockefeller University, New York, N.Y. e-mail: ravetch@rockefeller.edu
Rheumatoid arthritis (RA)	Tumor necrosis factor (ligand) superfamily, member 13b (TNFSF13B; BLYS; BAFF)	Studies in mice suggest that antagonizing BAFF in local joint tissue could be useful for treating RA. In a mouse model of collagen-induced arthritis, intra-articular injection of a lentivirus vector expressing small hairpin RNA for BAFF lowered the incidence and clinical severity of arthritis compared with what was seen using saline buffer or a lentiviral control vector expressing β -actin shRNA. Compared with those controls, shRNA BAFF knockdown improved ankle synovitis, cartilage degradation and joint erosion. Next steps include further investigating the safety of the lentivirus vector. AMG 623, a peptide fusion protein that antagonizes BAFF from Amgen Inc. and Anthera Pharmaceuticals Inc., is in Phase I testing to treat lupus. Belimumab (LymphotoStat-B), a human anti-BAFF mAb from Human Genome Sciences Inc. and GlaxoSmithKline plc, is in Phase III testing to treat lupus and Phase II testing to treat RA.	Not patented; licensing status unknown	Lam, Q. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Sept. 15, 2008; doi:10.1073/pnas.0806044105 Contact: Liwei Lu, University of Hong Kong, Hong Kong, China e-mail: liweilu@hkucc.hku.hk
Cancer				
Brain cancer	Isocitrate dehydrogenase 1 (NADP ⁺), soluble (IDH1)	A genome-wide association study suggests that IDH1 may be a therapeutic target for slowing the progression of glioblastoma multiforme (GBM). In GBM patients with mutations in IDH1, median survival was 3.8 years compared with 1.1 years in patients with wild-type IDH1 ($p < 0.001$). The identified R132H substitution in IDH1 was conserved across the mutant population of 5 of 22 GBM tumors. Next steps include categorizing subgroups of brain cancer patients based on IDH1 and using biochemical and molecular analysis to characterize how the R132H mutation affects IDH1 activity.	Patent pending; Beckman Coulter Inc. assessing exclusive option for certain aspects of this technology	Parsons, D.W. <i>et al. Science</i> ; published online Sept. 4, 2008; doi:10.1126/science.1164382 Contact: Kenneth W. Kinzler, Johns Hopkins University, Baltimore, Md. e-mail: kinzke@welch.jhu.edu Contact: Victor E. Velculescu, same affiliation as above e-mail: velculescu@jhmi.edu Contact: Bert Vogelstein, same affiliation as above e-mail: bertvog@gmail.com

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cancer	Mammalian target of rapamycin (mTOR; FRAP; RAFT1)	Studies in cell culture and in mice suggest that mTOR inhibitors like Rapamune rapamycin may be useful for treating SF2/ASF-overexpressing cancers. The splicing factor SF2/ASF is an oncoprotein that is upregulated in some lung, colon and breast cancers. In cultured human 3T3 cells, mTOR activity was required for SF2/ASF-mediated oncogenic transformation. In nude mice that received implants of 3T3 cells, rapamycin lowered tumor volume compared with that seen in mice that received vehicle control. Further studies in cancer cell lines are necessary to establish and confirm the links between overexpression of SF2/ASF, malignant transformation and rapamycin sensitivity. At least six companies have mTOR inhibitors in development stages ranging from preclinical to marketed to treat various cancers. Wyeth markets Rapamune to prevent graft rejection.	Findings not patented; unavailable for licensing	Karni, R. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Sept. 22, 2008; doi:10.1073/pnas.0801376105 Contact: Adrian R. Krainer, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y. e-mail: krainer@cshl.edu Contact: Rotem Karni, The Hebrew University–Hadassah Medical School, Jerusalem, Israel e-mail: rotemka@ekmd.huji.ac.il
Cancer	Spliceosome	An SAR study suggests that Judemycin C—an analog of the spliceosome inhibitor FR901464—could be useful for treating cancer. <i>In vitro</i> , Judemycin C had IC ₅₀ values of 4.65, 2.29, 1.98, 2.12 and 2.03 μM against the A549, MCF-7, OVCAR-3, PC-3 and WiDr cancer cell lines, respectively. FR901464 is a natural product isolated from a species of <i>Pseudomonas</i> that inhibits mRNA splicing and induces cell-cycle arrest at the G1 and G2/M phases. Ongoing studies are aimed at optimizing Judemycin C and its analogs.	Provisional U.S. patent application filed covering Judemycin C, its analogs and their use in inhibiting cell replication to treat various forms of cancer; unlicensed	Lagiseti, C. <i>et al. J. Med. Chem.</i> ; published online Sept. 13, 2008; doi:10.1021/jm8006195 Contact: Thomas R. Webb, St. Jude Children's Research Hospital, Memphis, Tenn. e-mail: thomas.webb@stjude.org
Squamous cell carcinoma (SCC)	Toll-like receptor 7 (TLR7)	Studies in cell culture suggest that TLR7 agonists could be useful for treating SCC. In cultured SCC tumor cells, the TLR7 agonist imiquimod increased expression of E-selectin on tumor vessels, lowered recruitment of immunosuppressive T regulatory cells and increased tumor regression compared with what was seen in untreated SCC tumor cells. Next steps could include clinical testing of imiquimod to treat SCC. Meda AB markets Aldara imiquimod to treat superficial basal cell carcinoma (sBCC). ANA773, a prodrug of a TLR7 agonist from Anadys Pharmaceuticals Inc., is in Phase I testing to treat cancer and chronic HCV.	Invention disclosures filed; unlicensed	Clark, R. <i>et al. J. Exp. Med.</i> ; published online Sept. 15, 2008; doi:10.1084/jem.20071190 Contact: Rachael A. Clark, Brigham and Women's Hospital, Boston, Mass. e-mail: rclark1@partners.org
Cardiovascular disease				
Ischemia; reperfusion injury	Not applicable	Studies in mice suggest that intracranial implantation of exogenous mesenchymal stromal (MS) cells could help protect against neuronal death following ischemia. In a mouse model of global ischemia, injection of human MS cells one day after transient common carotid artery occlusion improved neurological function and decreased neuronal cell death compared with injection of saline control ($p < 0.05$). Microarray readouts showed that the MS cells lowered expression of more than 10% of the 586 mouse genes that were induced during ischemia and that these downregulated genes were primarily involved in inflammatory and immune responses. The MS cells persisted for less than seven days, suggesting that their modulation of inflammatory and immune responses is responsible for affecting neuronal cell survival. Further toxicity and efficacy studies in mice and larger animals are necessary before the therapy can be tested in humans. Almost 13 companies have stem cell–based therapies to treat cardiovascular and neurological conditions in preclinical and clinical testing.	MS cells and their therapeutic use are patented; licensing status unavailable	Ohtaki, H. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Sept. 15, 2008; doi:10.1073/pnas.0803670105 Contact: Darwin Prockop, Tulane University Health Sciences Center, New Orleans, La. e-mail: dprocko@tulane.edu

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Endocrine disease				
Diabetes	Insulin receptor tyrosine kinase (INSR tyrosine kinase)	<i>In vitro</i> and <i>in vivo</i> studies suggest that a class of phenylamine derivatives are INSR tyrosine kinase activators that might help treat diabetes. In a murine model of streptozotocin-induced diabetes, intraperitoneal or oral delivery of one of the derivatives lowered blood glucose levels compared with the effects of saline control. In cultured mouse adipocytes, the compound plus insulin increased glucose transport activity compared with the effect of insulin alone. Next steps include advancing INSR tyrosine kinase activators into Phase Ib/IIa trials.	Patented for treating type 2 diabetes; licensed to ReceptorBio Inc.	Lum, R.T. <i>et al. J. Med. Chem.</i> ; published online Sept. 13, 2008; doi:10.1021/jm800600v Contact: Joseph L. Evans, ReceptorBio Inc., Foster City, Calif. e-mail: jevansphd@earthlink.net
Infectious disease				
HIV	Cofilin 1 (non-muscle) (CFL1)	Studies in cell culture suggest that inhibiting CFL1 could be useful for preventing latent HIV infection. In cultured CD4 T cells, interaction between the HIV envelope and the cell surface chemokine (CXC motif) receptor 4 (CXCR4) led to activation of intracellular CFL1 and consequent actin-mediated localization of the HIV viral replication complex to the nucleus. In resting CD4 T cells, 120 nM of jasplakinolide, a small molecule F-actin-stabilizing agent, inhibited latent HIV infection by directly blocking actin dynamics. Next steps include mapping the HIV-triggered signaling pathways that can lead to CFL1 activation.	Patent application filed by George Mason University; unlicensed	Yoder, A. <i>et al. Cell</i> ; published online Sept. 4, 2008; doi:10.1016/j.cell.2008.06.036 Contact: Yuntao Wu, George Mason University, Manassas, Va. e-mail: ywu8@gmu.edu Contact: Jon W. Marsh, National Institute of Mental Health, Bethesda, Md. e-mail: marshj@mail.nih.gov
Staphylococcus	FtsZ	Studies in cell culture and in mice identified methoxybenzamide analogs as FtsZ inhibitors that could be useful for treating <i>Staphylococcus aureus</i> infections. FtsZ is a bacterial cell-division protein that is distantly related to mammalian β -tubulin. In a bacterial survival assay, one of the analogs—PC190723—showed potent growth inhibitory activity in methicillin- and multidrug-resistant <i>S. aureus</i> strains. In a murine septicemia model of staphylococcal infection, 100% of mice receiving subcutaneous or i.v. PC190723 survived a lethal challenge of <i>S. aureus</i> compared with 0% of untreated mice. Further preclinical optimization of the compounds is ongoing. Almost 12 companies have therapeutics to treat <i>S. aureus</i> infections in clinical and preclinical development.	Patent application filed covering the antibacterial agents; available for licensing	Haydon, D. <i>et al. Science</i> ; published online Sept. 18, 2008; doi:10.1126/science.1159961 Contact: Neil Stokes, Prolysis Ltd., Oxfordshire, U.K. e-mail: neil.stokes@prolysis.com
Neurology				
Alzheimer's disease (AD)	Cyclophilin D (CYPD; peptidylprolyl isomerase D; PPID)	Studies <i>in vitro</i> and in mice suggest that inhibiting CYPD could help treat AD. CYPD is a component of the mitochondrial permeability transition pore. In mice overexpressing human amyloid precursor protein (APP), <i>CypD</i> knockout improved spatial learning and memory compared with what was seen in APP transgenic mice that expressed <i>CypD</i> . The next step is to develop an inhibitor of CypD for further testing. Medivation Inc.'s Dimebon, a small molecule that blocks an undisclosed target in the mitochondrial pore, is in Phase III testing to treat AD. The compound is partnered with Pfizer Inc.	Findings patented; available for licensing	Du, H. <i>et al. Nat. Med.</i> ; published online Sept. 21, 2008; doi:10.1038/nm.1868 Contact: Shi Du Yan, Columbia University, New York, N.Y. e-mail: sdyl1@columbia.edu

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Huntington's disease (HD)	Cytochrome C	<i>In vitro</i> and <i>in vivo</i> studies suggest that inhibition of cytochrome C could help treat HD. A screen of 1,040 compounds identified 16 molecules that inhibited cytochrome C release from the mitochondrion and lowered rates of cell death in striatal cells that expressed a mutated huntingtin (htt) protein. Methazolamide, one of the most potent compounds in the cellular assay, inhibited release of cytochrome C and the proapoptotic mitochondrial protein Smac/Diablo in the HD cells. In a mouse model of HD, 40 mg/kg of daily methazolamide delayed disease onset and extended lifespan by 20% compared with the effects of saline controls ($p < 0.05$), and it lowered both cytochrome C release and loss of immunoreactive striatal neurons. The next step is to test the series of inhibitors identified by the screens in clinical trials (<i>see Moving upstream in Huntington's</i> , page 4).	Patent application filed for the cytochrome c release inhibitors; available for licensing worldwide	Wang, X. <i>et al. J. Neurosci.</i> ; published online Sept. 17, 2008; doi:10.1523/JNEUROSCI.1867-08.2008 Contact: Robert M. Friedlander, Harvard Medical School, Boston, Mass. e-mail: rfriedlander@rics.bwh.harvard.edu
Huntington's disease (HD)	Histone deacetylase (HDAC)	Studies in cell culture and in mice suggest that benzamide-based HDAC inhibitors could help treat HD. In cultured human lymphoblasts, lead HDAC inhibitor HDACi 4b had lower cytotoxicity than global HDAC inhibitors, including suberoylanilide hydroxamic acid, a marketed HDAC inhibitor that is structurally similar to the benzamide-based HDAC inhibitors. In a mouse model of HD, injection of HDACi 4b improved motor performance as well as body and brain weight. In addition, a subset of genes induced by HD protein showed reversal of gene expression after HDACi 4b treatment, suggesting these genes might be potential biomarkers that could be used to clinically assess drug treatment. Further preclinical studies with related compounds are necessary to determine whether this lead HDAC inhibitor has optimal specificity and potency to treat HD. Almost 17 companies have therapeutics to treat HD in development stages ranging from preclinical to marketed (<i>see Moving upstream in Huntington's</i> , page 4).	The Scripps Research Institute patented the class of HDAC inhibitors for neurodegenerative disorders; Repligen Corp. has in-licensed the compounds and owns the patents; unavailable for licensing	Thomas, E. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Sept. 15, 2008; doi:10.1073/pnas.0804249105 Contact: Elizabeth A. Thomas, The Scripps Research Institute, La Jolla, Calif. e-mail: bthomas@scripps.edu
Pain	NADPH oxidase 1 (NOX1)	Studies in mice suggest that antagonizing NOX1 could help treat inflammatory pain. In a mouse model of carrageenan-induced inflammatory pain, knockout of the NOX1 catalytic subunit led to less local edema and less pain withdrawal behavior than was seen in wild-type mice. The next step is to develop a specific inhibitor of NOX1. GenKyoTex S.A. has isoform-specific NOX inhibitors in preclinical development for cardiovascular, metabolic and neurodegenerative diseases.	Findings not patented; licensing status unavailable	Ibi, M. <i>et al. J. Neurosci.</i> ; published online Sept. 17, 2008; doi:10.1523/JNEUROSCI.1857-08.2008 Contact: Chihiro Yabe-Nishimura, Kyoto Prefectural University of Medicine, Kyoto, Japan e-mail: nchihiro@koto.kpu-m.ac.jp

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Pulmonary disease				
Acute lung injury	Adenosine A2B receptor (ADORA2B; A2BAR)	<p>Studies in mice suggest that increasing A2BAR expression may be useful for treating acute lung injury. Wild-type mice with ventilator-induced lung injury (VILI) that were treated with the A2BAR antagonist PSB1115 had significantly shorter survival times on a ventilator than vehicle-treated mice ($p<0.001$). Conversely, wild-type mice with VILI that were treated with the A2BAR agonist BAY 60-6583 had substantially longer survival times on a ventilator than vehicle-treated controls ($p<0.001$). Next steps include evaluating A2BAR agonists in patient samples and large animal models of acute lung injury and identifying the specific pulmonary tissues that express the receptor.</p> <p>BAY 60-6583, a nonpurine-selective A2BAR agonist from Bayer AG, is in preclinical testing for acute lung injury.</p> <p>CVT-6883, an A2BAR antagonist from CV Therapeutics Inc., is in Phase I testing to treat pulmonary diseases.</p> <p>At least two other companies have A2BAR antagonists in preclinical testing to treat pulmonary diseases.</p>	Bayer's Bayer HealthCare AG subsidiary has patented BAY 60-6583 for use in multiple indications; licensing status undisclosed	Eckle, H. <i>et al. J. Clin. Invest.</i> ; published online Sept. 11, 2008; doi:10.1172/JCI34203 Contact: Holger K. Eltzschig, University of Colorado Health Sciences Center, Denver, Colo. e-mail: holger.eltzschig@uchsc.edu
Transplantation				
Graft-versus-host disease (GvHD)	CD28 receptor	<p>Studies in cell culture and in mice suggest that antagonizing the B7 binding site of CD28 may be useful for preventing GvHD. In cultured mouse thymocytes, the anti-mouse CD28 antibody E18 blocked binding of B7 ligands to CD28 expressed on the cell surface. In a mouse model of acute GvHD, E18 significantly increased survival compared with that of mice receiving a control antibody ($p=0.02$). The E18-treated acute GvHD mice also had lower mean clinical disease scores than controls ($p<0.03$). Next steps include identifying and evaluating human anti-CD28 mAbs in animal models.</p> <p>Amotosalen, a plasma pathogen inactivation system using a psoralen S-59 light-activated compound from Cerus Corp., is marketed to treat GvHD.</p> <p>Thymoglobulin, a rabbit anti-thymocyte Ig from Genzyme Corp., is marketed for the same indication.</p> <p>At least 10 other companies have compounds in Phase III or earlier development for the indication.</p>	Not patented; E18 mAb commercially available from MorphoSys AG's AbD Serotec subsidiary	Beyersdorf, N. <i>et al. Blood</i> ; published online Sept. 9, 2008; doi:10.1182/blood-2008-03-146662 Contact: Niklas Beyersdorf, University of Wurzburg, Wurzburg, Germany e-mail: niklas.beyersdorf@vim.uni-wuerzburg.de

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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
Carbon nanotubes for cancer phototherapy	Studies <i>in vitro</i> and in mice suggest that carbon nanotubes could be used to create a multimodal form of phototherapy to treat cancer. The nanotubes, functionalized with the photodynamic therapy (PDT) agent zinc phthalocyanine, provide both PDT and photothermal therapy (PHT) using a single laser. In xenograft mice, tumors injected with nanotubes disappeared over time after daily 15-minute single-wavelength laser irradiation. Tumors continued to grow in mice that received saline buffer or nanotube treatment without laser irradiation. Further studies are necessary to examine long-term toxicity and to use chemical modifications to ensure construct has high efficiency in tumor targeting.	Method patented; available for licensing	Zhang, M. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Sept. 22, 2008; doi:10.1073/pnas.0801343105 Contact: Masako Yudasaka, Advanced Industrial Science and Technology, Ibaraki, Japan e-mail: m-yudasaka@aist.go.jp Contact: Minfang Zhang, affiliation same as above e-mail: m-zhang@aist.go.jp
Computational model for designing inhibitors of solute carrier family 22 organic cation transporter member 1 (SLC22A1; OCT1)	A computational model could be useful for identifying OCT1 inhibitors to treat diabetes and cancer. A high throughput OCT1 inhibition screen identified 47 new OCT1 inhibitors out of 191 structurally diverse compounds. The results of the screen then guided the development of a qualitative predictive model of OCT1 inhibition, which correctly predicted 82% of OCT1 inhibitors and 88% of noninhibitors in a proof-of-concept test set. Researchers said they are not planning to commercialize the model but can make it available to interested parties upon request.	Not patented; unlicensed	Ahlin, G. <i>et al. J. Med. Chem.</i> ; published online Sept. 13, 2008; doi:10.1021/jm8003152 Contact: Per Artursson, Uppsala University, Uppsala, Sweden e-mail: Per.Artursson@farmaci.uu.se
Electron-vibration-vibration (EVV) two-dimensional coherent infrared (2DIR) spectroscopy for proteomics analysis	<i>In vitro</i> studies suggest that EVV 2DIR spectroscopy could be useful for identifying new biomarkers and developing diagnostics. The method identified individual proteins in a heterogeneous mixture within 4–5 minutes based on the vibrational signatures of amino acid side chains. Further studies are necessary to increase the precision and accuracy of the method by raising the number of amino acids detected per protein.	Four families of patent applications covering 2DIR spectroscopy filed; technology not available for licensing in its current state of development	Fournier, F. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Sept. 22, 2008; doi:10.1073/pnas.0805127105 Contact: David R. Klug, Imperial College London, London, U.K. e-mail: d.klug@imperial.ac.uk
Helper-dependent adenoviral vectors (HDAdVs) for gene transfer in embryonic stem (ES) cells	Cell-culture studies suggest that gene transfer using HDAdVs in cynomolgus monkey ES cells could provide a useful ES cell resource for biological and preclinical research before the clinical use of human ES cells. HDAdVs resemble conventional adenoviral gene therapy vectors but lack viral replication genes that cause cytotoxicity. In cynomolgus monkey and human ES cells, transient gene transfer efficacy using HDAdV transfection was about 98% and did not interfere with cell pluripotency. Next steps include modifying the HDAdV vectors to improve the speed of gene transfer. Microbix Biosystems Inc. markets Helper Dependent Adenovirus Vector Kit K as a research and drug delivery tool.	Not patented; unavailable for licensing	Suzuki, K. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Aug. 25, 2008; doi:10.1073/pnas.0806976105 Contact: Kohnosuke Mitani, Saitama Medical University, Hidaka, Saitama, Japan e-mail: mitani@saitama-med.ac.jp
Spleen-targeted antigen delivery to improve the efficacy of therapeutic vaccines	A study in mice suggests that targeted antigen delivery to the periarteriolar lymphoid sheath (PALS) of the spleen may be useful for increasing host immune response to vaccine antigens. <i>In situ</i> fluorescence microscopy studies of <i>Listeria</i> -infected mice revealed that splenic dendritic cells (DCs) delivered bacterial antigens to the PALS to initiate CD8 ⁺ T cell responses. In the same murine infection models, pretreatment with pertussis toxin to prevent DC migration to the PALS significantly lowered survival compared with that of untreated infected controls ($p < 0.0001$). Next steps include identifying the molecular requirements for antigen delivery to the PALS and studying antigen transport during infection using other pathogens to see if the observed results can be generalized to other infectious agents.	Not patented; available for licensing through the Washington University Office of Technology Management	Aoshi, A. <i>et al. Immunity</i> ; published online Sept. 18, 2008; doi:10.1016/j.immuni.2008.06.013 Contact: Mark J. Miller, Washington University School of Medicine, St. Louis, Mo. e-mail: miller@pathology.wustl.edu

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Targeting core signaling pathways in pancreatic cancer	A genome-wide association study suggests that targeting core signaling pathways, as opposed to individual genes, may be a more viable strategy for treating pancreatic cancer. An analysis of 24 advanced pancreatic adenocarcinomas identified 1,562 disease-associated somatic mutations from a set of 20,661 genes. Many of the mutated genes play roles in 12 partially overlapping core signaling pathways. Next steps include identifying compounds that target key mediators in the core signaling pathways.	Patent pending; Beckman Coulter Inc. assessing exclusive option for certain aspects of the technology	Jones, S. <i>et al. Science</i> ; published online Sept. 4, 2008; doi:10.1126/science.1164368 Contact: Kenneth W. Kinzler, Johns Hopkins University, Baltimore, Md. e-mail: kinzlike@welch.jhu.edu Contact: Victor E. Velculescu, same affiliation as above e-mail: velculescu@jhmi.edu Contact: Bert Vogelstein, same affiliation as above e-mail: bertvog@gmail.com

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