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New front against TNF

By Lauren Martz, Staff Writer

New York University School of Medicine researchers have designed a molecule based on the growth factor progranulin that could help treat rheumatoid arthritis and other autoimmune diseases.[1] The team has formed a company, **ATreaon**, to develop the compound and related analogs.

Previous work has suggested roles for progranulin (PGRN) in cancer,[2] inflammation,[3] host defense,[4] cartilage development and degeneration[5] and neurological functions.[6,7] However, using or targeting the molecule has been difficult because its receptors remained unknown.

Now, Chuan-ju Liu and colleagues at NYU have found that PGRN binds tumor necrosis factor receptors (TNFRs) and blocks their interactions with tumor necrosis factor-α (TNF-α), thus halting inflammatory signaling.

Liu is an associate professor at the NYU School of Medicine.

In a yeast two-hybrid screen using PGRN as bait, the team identified tumor necrosis factor receptor 1 (TNFRSF1A; TNFR1; CD120a) and TNFR2 as the main binding proteins for PGRN. The group confirmed the association through coimmunoprecipitation experiments in human chondrocytes.

In a mouse model of collagen-induced arthritis, knocking out *Pgrn* caused the development of more severe arthritis with bone and joint destruction, more rapid disease onset, greater disease incidence and higher levels of bone-resorbing osteoclasts than those in wild-type littermate controls.

The group also showed that administration of recombinant human PGRN (rhPGRN) to the knockouts blocked disease progression and prevented symptoms of inflammatory arthritis including synovitis, pannus formation, tissue destruction and loss of cartilage compared with administration of saline.

The findings were replicated in a mouse model of inflammatory arthritis induced by transgenic expression of TNF-α.

With the help of **Cytovance Biologics LLC**, a contract biologics manufacturer, the NYU team developed a molecule called Atsttrin (Antagonist of TNF/TNFR Signaling via Targeting to TNF Receptors), which includes parts of three granulin (GRN) domains from progranulin as well as three of the protein's linker regions. Despite its smaller size, Atsttrin retains the functionality of PGRN on TNF receptors.

Compared with the parent molecule, Atsttrin also was more selective for the two TNFRs than for other closely related receptors.

Atsttrin also had higher affinity for TNFR2 than TNFR1—a finding that Martin Bachmann, CSO and EVP at **Cytos Biotechnology AG**,

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said needs to be further probed. "The fact that the molecule has a higher affinity for TNFR2 than TNFR1 may change its therapeutic properties compared with mAbs against TNF," he said. "This may or may not be beneficial."

Cytos' CYT020-TNFQb, a vaccine that binds TNF-α and was developed with the company's Immunodrug platform, is in preclinical testing to treat inflammation.

In the collagen-induced arthritis mouse model, Atsttrin decreased disease severity and delayed onset and progression better than rhPGRN; in a collagen antibody–induced arthritis mouse model, Atsttrin was more effective at treating inflammation than both rhPGRN and Enbrel etanercept, a soluble TNF receptor marketed by **Amgen Inc.**, **Pfizer Inc.** and **Takeda Pharmaceutical Co. Ltd.** for RA and a variety of other autoimmune indications.

> **"The unique anti-inflammatory mechanism of action of Atsttrin [means it] may be effective for those patients who do not respond to current TNF inhibitor treatments."**
> ***—Jeffrey Su, Cytovance Biologics LLC***

Atsttrin was well absorbed via intraperitoneal administration and had high stability and a half-life of about five days.

The findings were published in *Science*. The paper also included researchers from **Shandong University School of Medicine**, **Weill Cornell Medical College**, **Yale School of Medicine**, **Nankai University** and **Texas A&M Health Science Center**.

In the fall of 2010, Jeffrey Su and colleagues formed ATreaon to develop Atsttrin and related compounds.

Su is CSO at Cytovance, which has not invested in the new compound but is a potential service provider to make the molecule.

ATreaon has raised an undisclosed amount of seed money and used the funds to license Atsttrin from the university and to develop analogs. The company hopes to put its lead compound into the clinic in the next 12 months for an autoimmune indication and is in talks with VCs and private equity investors to secure funding for IND-enabling studies, GMP manufacturing and clinical studies.

Liu told *SciBX* that Atsttrin could be developed for multiple TNF-associated conditions and pathologies including systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), ankylosing spondylitis, plaque psoriasis and psoriatic arthritis.

Room in the sandbox

Although the market for TNF modulators is crowded—there are five marketed biologics that block TNF—ATreaon thinks its product initially could be used behind those drugs or in the about 50% of RA patients who do not respond to them.

"The unique anti-inflammatory mechanism of action of Atsttrin [means it] may be effective for those patients who do not respond to current TNF inhibitor treatments," said Su.

"It will also be quite interesting to find out whether this strategy can be used as an early intervention to prevent progression of symptoms or whether it works as an agent to use once other options have failed. I could imagine Atsttrin having both uses," said Andrew Bateman, a professor in the Department of Medicine at **McGill University**. "It will also be interesting to find out whether Atsttrin can be used along with

conventional agents in combination therapy."

Bateman's research on the role of PGRN in wound healing showed that the protein promotes repair and regeneration of damaged tissues. "One could imagine that progranulin or an analog could repair the tissue damaged during the course of disease once the inflammation is under control," he said. "TNF has a lot of effects on immune responses and is a major switch for inflammation. TNF is not a bad thing, but it is a problem when it gets out of control and can be very dangerous. Rather than squishing it completely and blocking its beneficial functions, the goal is to be able to bring it back to a healthy range. It will be interesting to see if progranulin or related analogs can bring it back down to appropriate levels. This will take a lot of tuning to get the conditions right."

"It will also be interesting to find out whether Atsttrin can be used along with conventional agents in combination therapy."
—Andrew Bateman, McGill University

In terms of safety, Aihao Ding, professor in the Department of Microbiology and Immunology at Weill Cornell, thinks Atsttrin could enjoy an advantage over anti-TNF antibodies.

"One assumes Atsttrin would have fewer side effects because this is a small protein and not an antibody," she said. "Antibodies can have more side effects because they can form new complexes in the blood stream" that can either lead to unwanted activation of cytokines or to immune suppression that increases susceptibility to serious infections.

Liu added that Atsttrin should not induce unwanted immune reactions because it is derived from a natural protein.

Bachmann, however, thinks that Atsttrin has been so heavily modified that it could be more immunogenic than mAbs. He also noted that "there is really no reason to believe that the elevated risk of infection associated with other autoimmune disease treatments will be reduced by Atsttrin because, at the end of the day, you still block TNF."

Koh Ono, associate professor in the Department of Cardiovascular Medicine at **Kyoto University**, noted that "progranulin was first identified as a tumor growth factor. Therefore, Atsttrin or progranulin need to be carefully given to RA patients with cancer."

"There is a worry that progranulin is a growth factor, and the question of whether it can cause cancer or not has not been tested," Ding agreed. "But Atsttrin is a truncated form with the C terminal that is responsible for the growth factor effect removed, so the risk probably shouldn't be there anymore."

A final advantage that Atsttrin could have over the anti-TNF biologics is in cost of manufacturing. Liu told *SciBX* that Atsttrin is produced in bacteria, which he said should be cheaper than antibodies.

Su told *SciBX* that the currently available TNF blockers are complex molecules produced by mammalian cell culture via recombinant DNA technologies, which cost hundreds to thousands of dollars per gram of product to manufacture. He said that the manufacturing cost of Atsttrin-related compounds can be as low as 10%–20% of the cost of TNF blockers produced in animal cells.

According to Laurent Galibert, head of inflammation and metabolic disorders at **Addex Pharmaceuticals Ltd.**, a key consequence of the high cost of production, and thus the high price tag for anti-TNF antibodies, is that the drugs "are not used as a first-line therapy even though from a purely scientific standpoint they should be."

Addex has a small molecule TNFR1 negative allosteric modulator in the discovery stage to treat Alzheimer's disease (AD), multiple sclerosis (MS), RA, psoriasis and depression.

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Texas A&M Health Science Center, Houston, Texas
Weill Cornell Medical College, New York., N.Y.
Yale School of Medicine, New Haven, Conn.

Receptor strategy for brain ischemia

By Lev Osherovich, Senior Writer

A U.S. team has devised a way to prevent neurological damage caused by ischemia by agonizing nicotinic acetylcholine receptors.[1] The findings open a new indication for at least two biotechs, **Targacept Inc.** and **EnVivo Pharmaceuticals Inc.**, which along with **Roche** have agonists of those receptors in clinical development for cognitive disorders.

Cerebral ischemia typically occurs when cardiac arrest cuts off the blood supply to the brain. Even if the heart is restarted through cardiopulmonary resuscitation or defibrillation, a brief episode of cerebral ischemia "sets off a cascade of proinflammatory markers and cytokines that lead to permanent damage to brain cells," said Patrick Lippiello, senior principal scientist at Targacept.

Recent studies have suggested that signaling by nicotinic acetylcholine receptor α_7 (CHRNA7) counteracts inflammation in systemic cardiovascular conditions like hypovolemic or septic shock.[2] Now, researchers at **The Ohio State University** and **The Feinstein Institute for Medical Research** have made a case that the receptor also exerts its effects in the brain, showing that agonizing CHRNA7 protects against ischemia-induced neuronal loss in mice.

A team led by A. Courtney DeVries, associate professor of psychology at Ohio State, suspected that acetylcholine signaling may contribute to brain damage after cardiac arrest. To find out, the researchers looked at gene expression in the brains of mice that had undergone a surgical procedure that temporarily cuts off the brain's blood supply.

> **"The news in this paper is that delayed treatment can still yield improvement."**
> ***—Gerhard Koenig, EnVivo Pharmaceuticals Inc.***

"We wanted to see whether cerebral ischemia caused changes in the cholinergic system and what would be the effect of intervention in the cholinergic system," said Greg Norman, the study's corresponding author. Norman is now a postdoctoral fellow in the Department of Psychology at **The University of Chicago**.

The team found that although levels of inflammatory markers increased in ischemic mice, levels of enzymes involved in cholinergic signaling decreased compared with those in control mice that did not undergo cerebral ischemia. Histological studies showed that the hippocampuses of ischemic mice had fewer neurons than those of controls, presumably as a result of neuronal death.

To demonstrate the beneficial effect of cholinergic signaling, the team gave the mice a CHRNA7 agonist 24 hours after cardiac arrest. Intraperitoneal injections of the agonist led to fewer inflammatory markers and greater neuron survival than injection of vehicle.

Data were published in *The Journal of Neuroscience*.

Calming nerves

Precisely how and where activation of CHRNA7 dampens neuroinflammation remains unclear. Norman told *SciBX* that identifying the specific cells that mediate the receptor's anti-inflammatory effects is the Ohio team's next step.

He suspects that the effects of CHRNA7 agonists are mediated by the interplay between the innate immune response and the autonomic nervous system in the periphery.

Norman cited prior evidence from the laboratory of Kevin Tracey that showed "the autonomic nervous system has a large effect on peripheral immune response." Tracey, who is president of the Laboratory of Biomedical Sciences at the Feinstein Institute, was part of the study team.

Targacept's Lippiello thinks CHRNA7 agonists likely prevent neuroinflammation by counteracting the downregulation of cholinergic signaling caused by ischemia.

"As a result of this insult, the brain starts shutting down acetylcholine production and you lose the natural ability to intervene against inflammation," he said.

Targacept's CHRNA7 agonist, TC6987, is in Phase II trials for asthma and type 2 diabetes.

EnVivo CMO and SVP of clinical development Dana Hilt said CHRNA7 is traditionally considered to be a neuronal target but actually is expressed in a variety of cell types, including microglia in the brain and macrophages in the periphery.

Hilt suspects that in the Ohio team's study, CHRNA7 is acting in the periphery. He said Tracey's group previously used surgical techniques to demonstrate that the anti-neuroinflammatory effects of CHRNA7 agonists required an intact vagus nerve connected to the spleen, which houses many innate immune cells including macrophages.

"Clipping the vagus nerve branch at the very end near the spleen can abolish the effect" of cholinergic stimulation on neuroinflammation, said Hilt. "This implies that you would have to give a drug to patients that would have some effect in the spleen."

EnVivo's EVP-6125 CHRNA7 agonist is in Phase II trials for cognitive impairment associated with schizophrenia and for Alzheimer's disease (AD).

Hilt said EVP-6125 acts predominantly in the brain but has not been tested in cerebral ischemia.

"The $64,000 question is if you're treating someone for ischemia and inflammation, would you want a compound that has more of a peripheral distribution" than centrally acting CHRNA7 agonists like EVP-6125, said Hilt.

In addition to the Targacept and EnVivo compounds, the only other disclosed CHRNA7 agonist in the clinic is Roche's MEM 3454, which is in Phase II trials for AD and schizophrenia.

Window of opportunity

Norman said previous studies have implicated CHRNA7 as a guardian against neuroinflammation in mouse models of acute brain hemorrhage and injury, but the new findings suggest CHRNA7 agonists could be used for the more global cerebral ischemia that accompanies cardiac arrest.

Preventing brain damage caused by cardiac arrest is a wide-open market without a current standard of care. Previous efforts at neuroprotection have failed because of difficulties in administering brain-penetrant therapies at the right time.

Norman noted that CHRNA7 agonists could be useful during a wide window of time after cardiac arrest and resuscitation. "We didn't give

the drug until 24 hours after the event" and still observed a protective effect, he noted.

According to EnVivo CSO and SVP of research Gerhard Koenig, the peripheral effect and relatively wide time window for agonizing CHRNA7 are potentially game-changing advantages for this target.

"The news in this paper is that delayed treatment can still yield improvement," said Koenig.

Lippiello suggested the team "should look at even longer windows" to test the time limit for intervention.

Another question is whether dosing animals with CHRNA7 agonists for longer than two days can further improve neuronal survival.

Lippiello and Hilt both said that their respective company's compounds could in principle be ready for clinical testing to prevent brain damage after cardiac arrest, although the indication is not a primary focus for either biotech.

The Ohio State findings are not patented.

Lippiello did say that Targacept previously licensed IP covering the use of nicotinic acetylcholine receptor agonists for inflammatory indications from Critical Therapeutics, a company cofounded by Tracey that merged with **Cornerstone Therapeutics Inc.** in 2008.

Targacept's lead candidate is a broad-spectrum nicotinic acetylcholine receptor (nAchR) antagonist, TC-5214, which is in Phase III testing as an adjunct treatment for major depressive disorder (MDD). It is partnered with **AstraZeneca plc**.

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COMPANIES AND INSTITUTIONS MENTIONED

AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K.
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EnVivo Pharmaceuticals Inc., Watertown, Mass.
The Feinstein Institute for Medical Research, Manhassett, N.Y.
The Ohio State University, Columbus, Ohio
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
Targacept Inc. (NASDAQ:TRGT), Winston-Salem, N.C.
The University of Chicago, Chicago, Ill.

Hypoxic homing in prostate cancer

By Tracey Baas, Senior Editor

A U.K. team has engineered an oncolytic virus with multiple regulatory elements that target it specifically to hypoxic prostate cancer cells.[1] Delivery of these viruses was effective in mice with human prostate tumors, although it remains unclear whether relying on hypoxic regulation as the only homing determinant will be sufficient in metastatic tumors, which are much smaller than solid tumors and not overtly hypoxic.

The group's delivery vehicles of choice for the oncolytic virus were macrophages, which naturally home to hypoxic areas and respond to low oxygen levels by upregulating hypoxia-inducible transcription factors.

Hypoxic areas are not exclusive to tumors and also occur in wounds, arthritic joints and atherosclerotic plaques. Thus, the researchers constructed an oncolytic adenovirus with a hypoxic promoter element that activates viral replication in the presence of hypoxia-inducible transcription factors and a recombinant prostate tumor regulatory sequence that activates replication in the presence of prostate-specific proteins (*see* **Figure 1, "Oncolytic control"**).

In immune-compromised mice with human prostate tumors, transduced murine macrophages migrated into the hypoxic tumor regions and released large quantities of oncolytic virus, which then killed tumor cells and increased survival.

The transduced macrophages did not promote the formation of new blood vessels, and tumors in the treated mice were less vascularized than tumors that received nontransduced, control macrophages.

Results were published in *Cancer Research*, and the team was co-led by Norman Maitland and Claire Lewis. Maitland is a professor of molecular biology at **The University of York**, and Lewis is a professor of molecular and cellular pathology at **The University of Sheffield**.

The team also included researchers from the **University of Oxford**, **University of Liverpool**, **University of Kent**, **Sheffield Hallam University**, **University of Leicester**, **Mount Vernon Hospital** and **Uppsala University**.

Lewis noted that the macrophage-adenoviral system could potentially deliver therapeutic genes to other types of tumors or diseased tissues that contain hypoxic sites, like arthritic joints, myocardial infarcts and atherosclerotic plaques.

For other types of tumors, the recombinant prostate tumor regulatory sequence could be replaced by an appropriate tumor-specific regulatory sequence, she said. For nonmalignant diseases, the oncolytic virus would be replaced by a replication-deficient adenovirus in which a therapeutic gene was placed under the control of a tissue-specific regulatory sequence.

Nancy Boudreau, professor of surgery at the **University of California, San Francisco**, also thinks other regulatory sequences could be explored but said the first focus should be on using something other than hypoxia to amplify the virus in macrophages.

"Not all tumors may be overtly hypoxic, particularly smaller but potentially aggressive metastatic tumors, so relying on hypoxia to improve specificity and activation of the virus may be limiting," she said. "Other factors that contribute to homing of macrophages to tumors could be exploited. One example is secretion of specific breast cancer chemokines that attract macrophages to the breast tumors. They could modify their system to allow a chemokine or some other secreted protein to induce viral replication in the macrophage."

(Continues on p. 7)

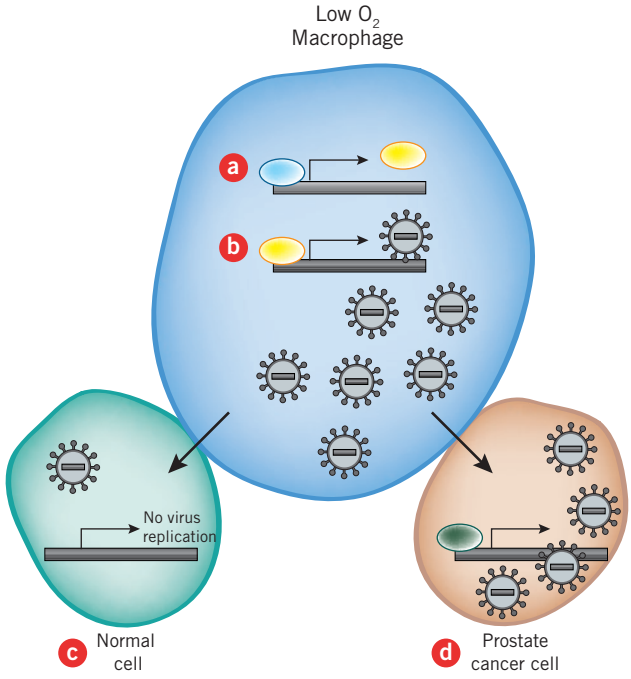

Figure 1. Oncolytic control. Macrophages are first transfected with a vector (light grey rectangle) in which the gene encoding the adenovirus small early region 1A (E1A) protein (yellow oval) is under the control of a hypoxic response element (HRE). They are then co-transduced with a conditionally competent, oncolytic adenovirus (Ad; dark grey rectangle)—the replication of which can be regulated by either E1A protein or a regulatory sequence called PPT. PPT is a composite of promoter enhancers from three genes expressed in prostate tumor cells: *TCR-γ alternate reading frame protein* (*TARP*), *prostate-specific antigen* (*KLK3*; *PSA*) and *prostate-specific membrane antigen* (*PSMA*; *FOLH1*; *GCPII*).
In regions of low oxygen, macrophages upregulate a transcription factor called hypoxia-inducible factor 1 (HIF1; light blue oval) which binds the HRE to produce E1A protein [**a**]. Production of E1A (yellow oval) then initiates adenovirus replication in the macrophage, leading to virus production [**b**].

The virus is then released and can enter surrounding cells. When the virus enters normal cells, lack of either E1A or the prostate-specific factors that stimulate the PPT sequence prevents further viral replication [**c**]. When the virus enters a prostate cancer cell, the PPT sequence is activated (dark green oval), leading to a further round of replication of the oncolytic virus and then cell death [**d**].

In regions of normal oxygen, macrophages do not upregulate HIFs. As a result, E1A and adenovirus production do not occur.

Aspiring cancer diagnostic

By Michael J. Haas, Senior Writer

Massachusetts researchers have developed portable NMR technology that uses fine needle aspirates to help scientists diagnose cancer more quickly and accurately than is possible with conventional tumor biopsies.[1] Although the technology could confirm the results of a biopsy or provide preliminary evidence that a biopsy is warranted, it is unlikely to replace histological analysis of biopsies as the diagnostic standard because it does not involve visual inspection of the sample to confirm the presence of cancer cells.

Biopsies rely on histological analysis and microscopic inspection of a sample of suspect tissue. The tissue sample is taken percutaneously with a large-gauge needle in core biopsy procedures or with a fine-gauge needle in a less invasive procedure called fine needle aspiration. The latter has a lower risk of complications, such as excessive bleeding, but yields a smaller amount of tissue that limits the number and total amount of markers available for histological analysis.

In addition, fine needle aspirates have inconclusive or false-negative results in up to 25% of cases. Furthermore, methods of analyzing core biopsies or fine needle aspirates can take days to complete and thus cannot be performed at the point of care.

To overcome these limitations, a team led by Ralph Weissleder and Cesar Castro sought to develop technology that could use fine needle aspirates to diagnose cancer rapidly and accurately in the clinic.

Weissleder is a professor of systems biology and radiology at **Harvard Medical School** and director of the Center for Systems Biology (CSB) at **Massachusetts General Hospital** (MGH). Castro is a physician at Massachusetts General Hospital Cancer Center and a member of Weissleder's CSB lab.

The group's technology involves incubating fine needle aspirates with magnetic nanoparticles covalently linked to antibodies[2] to tag selected marker proteins in the tissue sample. Next, the tagged sample is put into a portable NMR (microNMR) analyzer for quantitative detection of the markers. The 10 cm by 10 cm analyzer weighs about as much as a laptop and can be controlled with a smartphone.

In 2008, the team described a prototype of the microNMR technology that distinguished breast cancer cell lines expressing epidermal growth factor receptor 1 (EGFR1; HER1; ERBB1) and HER2 (EGFR2; ERBB2; neu) from normal fibroblasts.[3] Further refinements of the technology allowed detection of up to three cancer markers in fine needle aspirates from mice with xenograft breast or prostate tumors.[4]

In a new paper published in *Science Translational Medicine*, the team showed that a third generation of the technology could detect multiple markers in fine needle aspirates to diagnose cancer in humans.

The team used microNMR to detect 11 cancer markers in 50 patients who had suspected breast, lung, pancreatic and other abdominal tumors and determined which combination of markers gave the most accurate diagnoses. A 4-protein signature consisting of mucin 1 (MUC1; CD227), EGFR1, HER2 and epithelial cell adhesion molecule (EpCAM) diagnosed patients with 96% accuracy and a turnaround time of about 1 hour per

(Continues on p. 8)

(Continued from **"Hypoxic homing in prostate cancer,"** p. 6)

Look before you leap

The authors acknowledged that there are limitations to using immune-compromised mouse models because the host immune system can affect tumor progression. Thus, the researchers plan to adapt their system to replace adenovirus with viruses that infect mice, like lentivirus or vaccinia virus, and to use normal, immune-competent mice that express human genes.

Simon Barry, head of the vascular modulation group at **AstraZeneca plc**, wanted to see how delivery differs in immune-competent mice and also was interested in how tightly controlled the viral regulation is in nonhypoxic tissues or in noncancerous prostate tissues.

Because prostate cancer tends to occur in older patients, there often are comorbidities like arthritis with hypoxic tissues in the joints or atherosclerosis with hypoxic tissues in the vascular system. Thus, said Barry, it would be good "to see studies done in mouse or rat models of atherosclerosis or lung fibrosis—to get a glimpse of situations where there are comorbidities."

Lewis doesn't think effects in off-target hypoxic tissue will be an issue. She noted that viral replication remains in the macrophage until the cells are in the presence of prostate-specific proteins.

Stuart Naylor, CSO of therapeutic vaccine company **Oxford BioMedica plc**, thinks the approach's requirement of *ex vivo* manipulation of macrophages may prove cumbersome. "The requirement to both transfect macrophages with a vector and then transduce them with an adenovirus may be challenging to validate prior to clinical evaluation," he said.

Barry agreed. "To routinely transfect macrophages with a high probability of success and maintain viral expression would be a significant hurdle," he told *SciBX*. "To use this therapy in the clinic, you would also have to be in a position to generate the 'killer' macrophages for each individual patient."

The work is not patented and not available for licensing.

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University of Leicester, Leicester, U.K.
University of Liverpool, Liverpool, U.K.
University of Oxford, Oxford, U.K.
The University of Sheffield, Sheffield, U.K.
The University of York, York, U.K.
Uppsala University, Uppsala, Sweden

patient. By comparison, core biopsies in the same patients had 84% accuracy and a mean turnaround of 3 days.

The team, which included researchers from the **Harvard School of Public Health** and **Massachusetts Institute of Technology**, validated its findings by using the 4-protein signature to diagnose an independent cohort of 20 patients with 100% accuracy.

"We're excited that the third iteration of the device maintained the same level of accuracy and speed that we found in cell lines and mouse cancer models," Weissleder told *SciBX*.

"I like the underlying concept of the technology—combining an ELISA-like assay with analysis of multiple markers—and it has some interesting potential uses in the clinic," said David Rimm, professor of pathology, director of medical studies and director of pathology tissue services at **Yale School of Medicine**.

"Ultimately this is ultrasensitive protein detection technology" that works with small tumor samples, said Douglas Clark, professor of pathology and oncology at **The Johns Hopkins University School of Medicine**. The ability to get information from small samples is important because "imaging technology lets us detect lesions when they are early and small, and we don't want tumors to grow too large before we can sample them," he said.

Snap decisions

Rimm thinks the microNMR technology could be used "on top of the standard histological and morphological evaluation to provide added confidence in the diagnosis."

Clark, who is also founder and CSO of **BioMarker Strategies LLC**, added that the technology could be used for triage in point-of-care settings.

"For example, if a patient comes into the emergency room with a lump, you would want to know whether it's a tumor or an abscess," he said. "The microNMR technology would have enough accuracy in that setting to help you decide whether to schedule a core biopsy or begin antibiotic therapy."

Clark said he was also interested to know whether the technology would work in conjunction with BioMarker's SnapPath platform. SnapPath utilizes live tumor cells from fine needle aspirates to identify the dominant signaling pathways in an individual tumor and thus predict which targeted therapy will be most effective in that tumor.

The microNMR technology could serve as an ultrasensitive detector of the phosphoproteins that SnapPath uses as a readout of signaling pathway activity, he said. BioMarker plans to begin a pilot study of SnapPath in patients with solid tumors later this year.

But Rimm said the variability inherent in fine needle aspiration would make it challenging to develop the microNMR technology as a primary cancer diagnostic.

"Aspirates essentially use a needle to scrape some sample from the suspect site and you hope you're getting tumor cells," he said. "But you can only confirm whether you have tumor cells or normal cells by examining part of the sample under a microscope" during histological analysis—which the Weissleder-Castro team did not do.

"They seem to be suggesting that they can use this technology to make the primary diagnosis without ever seeing the cells," which would present a huge barrier to clinical development, he said.

Rimm also said that although the small patient cohort the team used to evaluate the markers and select the four-protein signature was acceptable, the number of patients in the team's validation study was too small for the results to be meaningful.

"The validation group should be at least twice the size of the training group—preferably three or four times larger," he said. "Instead, their validation group was half the size of the training group," which made it difficult to compare their technology with conventional methods.

Clark also pointed out that the four proteins in the signature "are not cancer-specific molecules but instead epithelium-specific molecules" that are indicative of cancer when they occur out of place—such as in the abdominal cavity or liver. But because the four proteins also occur in normal tissue, he cautioned against "assuming their signature is a litmus test for cancer."

Future aspirations

Castro expects microNMR to complement rather than replace biopsy.

For instance, in the earliest stages of diagnosis—such as when imaging shows a suspicious result—the technology could help determine whether performing a core biopsy by taking a larger tissue sample with a more invasive procedure is warranted, he said.

The technology could also confirm the results of a core biopsy, Castro said.

Additionally, "we envision using this device to interrogate how relevant cancer markers change over the course of treatment or to steer patients toward clinical trials of therapies that target a marker that may be elevated in their tumors," he said.

The Weissleder-Castro team plans to begin testing the microNMR technology in a larger patient population this year. "We will work with our statisticians to arrive at an ideal study size based on our previous findings," said Castro.

Weissleder added that the group is also working on "customization of the technology and selected markers to query specific subsets of cancer such as ovarian cancer."

MGH has patented the technology. That IP is unlicensed, and Weissleder said the team has sufficient funding to proceed with future testing.

In addition to developing the microNMR technology as a diagnostic, the team is investigating undisclosed applications of the magnetic nanoparticle–antibody affinity ligands[2] that the microNMR uses to detect protein markers, Castro said.

Haas, M.J. *SciBX* 4(12); doi:10.1038/scibx.2011.331
Published online March 24, 2011

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   e-mail: cmcastro@partners.org
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COMPANIES AND INSTITUTIONS MENTIONED

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This week in therapeutics

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

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

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Autoimmune disease				
Rheumatoid arthritis (RA)	Progranulin (PGRN); tumor necrosis factor-α (TNF-α); tumor necrosis factor receptor 1 (TNFRSF1A; TNFR1; CD120a); TNFR2	*In vitro* and mouse studies identified a peptide derived from PGRN that could help treat RA. *In vitro*, PGRN bound TNFR1 and TNFR2 and blocked proinflammatory TNF-α signaling compared with no treatment. In two mouse models of RA, recombinant PGRN or Atsttrin (Antagonist of TNF/TNFR Signaling via Targeting to TNF Receptors), a peptide composed of three PGRN fragments, decreased disease severity and delayed onset compared with vehicle control. Next steps include preclinical studies in undisclosed animal models. At least 12 companies have therapies blocking TNF-α signaling in development stages from preclinical to marketed for RA (*see* **New front against TNF, page 1**). ***SciBX* 4(12); doi:10.1038/scibx.2011.332** **Published online March 24, 2011**	Patent applications filed covering atsttrin and analogs; licensed to ATreaon; available for licensing for some indications or co-development arrangements	Tang, W. *et al. Science*; published online March 10, 2011; doi:10.1126/science.1199214 **Contact:** Chuan-ju Liu, New York University School of Medicine, New York, N.Y. e-mail: chuanju.liu@med.nyu.edu
Cancer				
Acute lymphoblastic leukemia (ALL); B cell lymphoma	CREB binding protein (CREBBP; CBP); histone deacetylase (HDAC)	Two genomic studies identified loss-of-function mutations in the histone acetyltransferase CREBBP in ALL and B cell lymphomas that could lead to new therapeutics. In one study of patient tumor tissue, deletions or somatic mutations of the *CREBBP* gene were associated with 29% of diffuse large B cell lymphoma and 41% of follicular lymphoma samples. In a second study of tumor tissue from ALL patients, mutations in *CREBBP* that decreased acetyltransferase activity were identified in 18% of relapsed cases compared with none of nonrelapsed cases. Next steps include testing the effects of HDAC inhibitors in preclinical models of cancers with CREBBP mutations. ***SciBX* 4(12); doi:10.1038/scibx.2011.333** **Published online March 24, 2011**	Patent and licensing status for findings in first study unavailable Findings in second study unpatented; unavailable for licensing	Pasqualucci, L. *et al. Nature*; published online March 9, 2011; doi:10.1038/nature09730 **Contact:** Riccardo Dalla-Favera, Columbia University, New York, N.Y. e-mail: rd10@Columbia.edu Mullighan, C.G. *et al. Nature*; published online March 9, 2011; doi:10.1038/nature09727 **Contact:** Charles G. Mullighan, St. Jude Children's Research Hospital, Memphis, Tenn. e-mail: charles.mullighan@stjude.org
Breast cancer	HER2 (EGFR2; ERBB2; neu); epidermal growth factor receptor 3 (EGFR3; HER3; ERBB3)	Mouse and patient tissue studies suggest that inhibiting HER3 could improve the efficacy of anti-HER2 therapeutics in breast cancers. In a mouse xenograft model of HER2-amplified breast cancer, the anti-HER3 antibody AMG-888 plus Tykerb lapatinib decreased tumor volume compared with either drug alone. Next steps could include testing the combination in additional models of breast cancer. Daiichi Sankyo Co. Ltd. and Amgen Inc. have AMG-888 in Phase I testing to treat cancer. GlaxoSmithKline plc markets Tykerb, an anti-HER2 mAb, to treat breast cancer. At least five other companies have anti-HER3 therapeutics in clinical and preclinical testing to treat cancers. ***SciBX* 4(12); doi:10.1038/scibx.2011.334** **Published online March 24, 2011**	Patent and licensing status unavailable	Garrett, J.T. *et al. Proc. Natl. Acad. Sci. USA*; published online March 7, 2011; doi:10.1073/pnas.1016140108 **Contact:** Carlos L. Arteaga, Vanderbilt University School of Medicine, Nashville, Tenn. e-mail: carlos.arteaga@vanderbilt.edu

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Cancer	CD40; FK506 binding protein 1A 12 kDa (FKBP1A); myeloid differentiation primary response gene 88 (MYD88)	A study in mice suggests that a fusion protein called DC-CAR could help boost the efficacy of cancer vaccines. DC-CAR is a fusion protein composed of MYD88, the cytoplasmic region of CD40 and two ligand-binding FKBP1A domains. In mouse models of melanoma and lymphoma, a dendritic cell–based vaccine plus DC-CAR decreased tumor progression and increased survival compared with vaccine plus saline control ($p<0.001$). Next steps include running IND-enabling studies with clinical-grade versions of the compounds. Bellicum Pharmaceuticals Inc.'s DC-CAR and AP1903 combination is in preclinical development for cancer. Bellicum has nonexclusively licensed AP1903, a homodimerizing compound that activates genetically engineered receptors on cell therapies, from Ariad Pharmaceuticals Inc. ***SciBX* 4(12); doi:10.1038/scibx.2011.335** **Published online March 24, 2011**	Patent pending; unavailable for licensing	Narayanan, P. *et al. J. Clin. Invest.*; published online March 7, 2011; doi:10.1172/JCI44327 **Contact:** David M. Spencer, Baylor College of Medicine, Houston, Texas e-mail: dspencer@bcm.tmc.edu
Cancer	Src	*In vitro* and mouse studies suggest that Src inhibitors could decrease breast cancer resistance to Herceptin trastuzumab. In five Herceptin-resistant human breast cancer cell lines, the small molecule Src inhibitor saracatinib (AZD0530) increased sensitivity to Herceptin compared with vehicle. In a mouse model of Herceptin-resistant human breast cancer, Herceptin plus small hairpin RNA–mediated Src knockdown or saracatinib resulted in lower tumor volumes than Herceptin alone. Next steps could include developing a dosing protocol to evaluate Herceptin and saracatinib in patients with Herceptin-resistant cancers. Roche's Genentech Inc. unit markets Herceptin to treat breast and gastric cancers. AstraZeneca plc's saracatinib is in Phase II testing to treat breast and prostate cancer in patients with metastatic bone disease and to treat advanced ovarian cancer and recurrent osteosarcoma localized to the lung. At least six other companies have therapeutics targeting Src in development stages ranging from preclinical to marketed to treat cancer. ***SciBX* 4(12); doi:10.1038/scibx.2011.336** **Published online March 24, 2011**	Patent and licensing status unavailable	Zhang, S. *et al. Nat. Med.*; published online March 13, 2011; doi:10.1038/nm.2309 **Contact:** Dihua Yu, The University of Texas M.D. Anderson Cancer Center, Houston, Texas e-mail: dyu@mdanderson.org
Pancreatic cancer	Not applicable	*In vitro* and mouse studies suggest that inhibiting autophagy could help treat pancreatic cancer. In human pancreatic cancer cell lines, the autophagy inhibitor chloroquine decreased proliferation and growth compared with phosphate buffered saline. In four mouse models of pancreatic cancer, chloroquine lowered tumor growth and increased survival compared with phosphate buffered saline. Ongoing work includes Phase II testing of hydroxychloroquine in patients with previously treated metastatic pancreatic cancer. Chloroquine is a generic drug marketed to prevent or treat malaria. Hydroxychloroquine, a generic analog of chloroquine, is marketed to treat malaria, rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). ***SciBX* 4(12); doi:10.1038/scibx.2011.337** **Published online March 24, 2011**	Unpatented; available for licensing or partnering	Yang, S. *et al. Genes Dev.*; published online March 15, 2011; doi:10.1101/gad.2016111 **Contact:** Alec C. Kimmelman, Harvard Medical School, Boston, Mass. e-mail: alec_kimmelman@dfci.harvard.edu

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Hepatic disease				
Liver disease	Neurocan (NCAN); glucokinase hexokinase 4 regulator (GCKR); lysophospholipase-like 1 (LYPLAL1); patatin-like phospholipase domain containing 3 (PNPLA3)	Genomewide association studies identified markers that could help predict risk of nonalcoholic fatty liver disease (NAFLD). A meta-analysis of genomewide studies of over 9,000 subjects identified SNPs in *NCAN*, *GCKR*, *LYPLAL1* and *PNPLA3* that were significantly associated with NAFLD ($p<5\times10^{-5}$ for all). Meta-analyses of NAFLD patients also identified associations between the *NCAN* and *GCKR* SNPs and serum levels of triglycerides, low-density lipoprotein (LDL) cholesterol and/or other serum components ($p \leq 4.4\times10^{-4}$). Future studies could include elucidating the functions of the identified SNPs in NAFLD. ***SciBX* 4(12); doi:10.1038/scibx.2011.338** **Published online March 24, 2011**	Patent and licensing status unavailable	Speliotes, E.K. *et al. PLoS Genet.*; published online March 10, 2011; doi:10.1371/journal.pgen.1001324 **Contact:** Ingrid B. Borecki, Washington University in St. Louis, St. Louis, Mo. e-mail: iborecki@wustl.edu **Contact:** Elizabeth K. Speliotes, University of Michigan, Ann Arbor, Mich. e-mail: espeliot@med.umich.edu
Infectious disease				
Pneumococcus	Not applicable	*In vitro* and mouse studies identified *Streptococcus pneumoniae* antigens that could be used in T helper type 17 (Th17) cell–based vaccines for pneumococcal infections. In an *S. pneumoniae* protein library, antigens were identified that induced a proinflammatory IL-17 (IL-17A) response in T cells from mice immune to pneumococcus. In mice, immunization with the antigens plus cholera toxin adjuvant decreased bacterial burden following intranasal *S. pneumoniae* challenge compared with immunization using a nonspecific protein antigen. Ongoing studies are finalizing the composition of a vaccine based on the identified antigens. Next steps include testing the finalized version in animals. Genocea Biosciences Inc. collaborated with Harvard Medical School on the paper. ***SciBX* 4(12); doi:10.1038/scibx.2011.339** **Published online March 24, 2011**	Patent application filed for the most promising T cell antigens; Genocea Biosciences is considering partnership opportunities	Moffitt, K.L. *et al. Cell Host Microbe*; published online Feb. 17, 2011; doi:10.1016/j.chom.2011.01.007 **Contact:** Richard Malley, Harvard Medical School, Boston, Mass. e-mail: richard.malley@childrens.harvard.edu
Viral infection	Sterol pathway	Cell culture and mouse studies suggest that statins and other antagonists of sterol biosynthesis could improve the efficacy of antivirals. In mouse cytomegalovirus (mCMV)-infected cell culture, the generic statin simvastatin decreased viral replication compared with vehicle control. In mice challenged with mCMV, pretreatment with simvastatin led to less viral replication than pretreatment with vehicle controls. Ongoing studies are evaluating a range of sterol pathway–targeting inhibitors to increase protection against infection. Simvastatin is marketed to treat several metabolic and cardiovascular indications. Samaritan Pharmaceuticals Inc.'s SP-01A, an adjunct, oral viral-entry inhibitor that targets the sterol biosynthetic enzyme HMG-CoA reductase, is in Phase II/III testing for HIV/AIDS. ***SciBX* 4(12); doi:10.1038/scibx.2011.340** **Published online March 24, 2011**	Unpatented; licensing status not applicable	Blanc, M. *et al. PLoS Biol.*; published online March 8, 2011; doi:10.1371/journal.pbio.1000598 **Contact:** Peter Ghazal, The University of Edinburgh, Edinburgh, U.K. e-mail: p.ghazal@ed.ac.uk

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Inflammation				
Inflammation	Inducible nitric oxide synthase 2 (NOS2; iNOS); nitric oxide (NO); prostaglandin E_2 (PGE_2)	A study in rodents and in cell culture identified a thiazolidine-2,4-dione analog that could help treat inflammation. In a mouse macrophage cell line, the analog decreased iNOS activity and lowered proinflammatory NO and PGE_2 production compared with the generic NSAID indomethacin. In mouse models of acute inflammation and a rat model of adjuvant-induced arthritis, the analog resulted in dose-dependent decreases in disease symptoms compared with vehicle. Next steps could include improving the efficacy and pharmacokinetics of thiazolidine-2,4-dione. ***SciBX* 4(12); doi:10.1038/scibx.2011.341** **Published online March 24, 2011**	Patent and licensing status unavailable	Ma, L. *et al. J. Med. Chem.*; published online March 7, 2011; doi:10.1021/jm1011534 **Contact:** Lijuan Chen, Sichuan University, Chengdu, China e-mail: lijuan17@hotmail.com **Contact:** Mingli Xiang, same affiliation as above e-mail: tmkxiang@gmail.com
Musculoskeletal disease				
Spinal muscular atrophy (SMA)	*Survival of motor neuron 2 centromeric* (*SMN2*; *SMNC*)	Studies in mice suggest that targeting *SMN2* with antisense oligonucleotides could help treat SMA. In a mouse model of severe SMA, a single intrathecal injection of the *SMN2* RNA–binding oligonucleotide ISIS-SMNRx increased SMN protein levels, which are decreased in SMA, improved motor physiology and function and increased survival compared with injection of a control oligonucleotide. In nonhuman primates, intrathecal infusion of ISIS-SMNRx led to therapeutic concentrations of the oligonucleotide in all regions of the spinal cord. Next steps include testing ISIS-SMNRx in IND-enabling toxicology studies. Isis Pharmaceuticals Inc.'s ISIS-SMNRx, an antisense oligonucleotide modulating the splicing of SMN2, is in preclinical development to treat SMA. In 2008, Isis granted Genzyme Corp. right of first negotiation to ISIS-SMNrx, which Genzyme gave up in 2011 for undisclosed reasons. ***SciBX* 4(12); doi:10.1038/scibx.2011.342** **Published online March 24, 2011**	Patent application filed by Isis; available for partnering	Passini, M.A. *et al. Sci. Transl. Med.*; published online March 2, 2011; doi:10.1126/scitranslmed.3001777 **Contact:** Marco A. Passini, Genzyme Corp., Framingham, Mass. e-mail: marco.passini@genzyme.com
Neurology				
Alzheimer's disease (AD)	Unknown	A study in mice suggests that peripheral administration of Gleevec imatinib could be useful for treating AD. In wild-type mice, intraperitoneal injection of Gleevec lowered levels of β-amyloid (Aβ) in the brain and plasma compared with injection of vehicle control. Next steps include testing Gleevec in AD mouse models. Novartis AG markets the multikinase inhibitor Gleevec to treat chronic myelogenous leukemia (CML) and gastrointestinal stromal tumors (GIST). The study's authors have founded ModGene LLC, a company focused on discovering disease-related genes in neurological indications. ***SciBX* 4(12); doi:10.1038/scibx.2011.343** **Published online March 24, 2011**	Patented; available for licensing or partnering from ModGene	Sutcliffe, J.G. *et al. J. Neurosci. Res.*; published online March 3, 2011; doi:10.1002/jnr.22603 **Contact:** J. Gregor Sutcliffe, The Scripps Research Institute, La Jolla, Calif. e-mail: gregorsutcliffe@aol.com

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Alzheimer's disease (AD); Parkinson's disease (PD)	Caspase-3 (CASP3; CPP32); CASP7 (MCH3); CASP8 (FLICE)	Studies in rats and in human brain tissue suggest that antagonizing CASP3, CASP7 or CASP8 could help treat AD or PD. In immunostaining studies of brain samples, AD and PD patients had higher levels of microglia with activated CASP3 and CASP8 than healthy controls. In rat models of neuroinflammation, small interfering RNA knockdown or pharmacological inhibition of Casp3, Casp7 or Casp8 decreased inflammatory cytokine production by microglia compared with that seen using vector or vehicle controls. Next steps include identifying brain-penetrant caspase inhibitors and testing their effects in animal models of AD and PD. Roche's Genentech Inc. unit has a discovery stage program targeting caspases to treat AD. ***SciBX* 4(12); doi:10.1038/scibx.2011.344** **Published online March 24, 2011**	Unpatented; licensing status not applicable	Burguillos, M.A. *et al. Nature*; published online March 9, 2011; doi:10.1038/nature09788 **Contact:** Bertrand Joseph, Karolinska Institute, Stockholm, Sweden e-mail: bertrand.joseph@ki.se
Neurology	Protein phosphatase 1 regulatory inhibitor subunit 15A (PPP1R15A; PEG-3)	An *in vitro* study suggests that the generic antihypertensive **guanabenz** could help treat neurodegenerative diseases. In HeLa cells, guanabenz decreased accumulation of pathogenic misfolded proteins compared with no treatment. Next steps include testing the effects of guanabenz in animal models of neurodegenerative diseases. ***SciBX* 4(12); doi:10.1038/scibx.2011.345** **Published online March 24, 2011**	Patent and licensing status undisclosed	Tsaytler, P. *et al. Science*; published online March 3, 2011; doi:10.1126/science.1201396 **Contact:** Anne Bertolotti, MRC Laboratory of Molecular Biology, Cambridge, U.K. e-mail: aberto@mrc-lmb.cam.ac.uk
Pain	μ-Opioid receptor (OPRM1; MOR); κ-opioid receptor (OPRK1; KOR)	Cell culture and mouse studies suggest that *N*-naphthoyl-β-naltrexamine (NNTA) agonizes OPRM1 and OPRK1 oligomers to help treat pain with lower risk of developing dependency than current treatments. In mice, injection of NNTA decreased physical pain at a lower concentration than the opioid agonist **morphine**. In a mouse model of drug dependency, NNTA did not increase dependency-associated behaviors compared with saline and morphine. Next steps include preclinical studies of NNTA in nonhuman primates. ***SciBX* 4(12); doi:10.1038/scibx.2011.346** **Published online March 24, 2011**	Patent application filed; available for licensing through the University of Minnesota Office of Technology Commercialization	Yekkirala, A.S. *et al. Proc. Natl. Acad. Sci. USA*; published online March 7, 2011; doi:10.1073/pnas.1016277108 **Contact:** Philip S. Portoghese, University of Minnesota, Minneapolis, Minn. e-mail: porto001@umn.edu
Parkinson's disease (PD)	Leucine-rich repeat kinase 2 (LRRK2)	Studies in mice and in cell culture identified a selective LRRK2 inhibitor that could help treat PD. *In vitro*, the small molecule LRRK2-IN-1 had IC_{50} values of 13 and 6 nM against wild-type LRRK2 and a mutant LRRK2 found in PD patients, respectively. Next steps could include evaluating LRRK2-IN-1 in animal models of PD. H. Lundbeck A/S has partnerships with two biotech companies—Zenobia Therapeutics Inc. and Vernalis Group plc—for LRRK2 inhibitors that are in preclinical development. TauTaTis Inc.'s TTT-3002, an LRRK2 inhibitor, is in preclinical development for PD. ***SciBX* 4(12); doi:10.1038/scibx.2011.347** **Published online March 24, 2011**	Patent and licensing status unavailable	Deng, X. *et al. Nat. Chem. Biol.*; published online March 6, 2011; doi:10.1038/nchembio.538 **Contact:** Nathanael S. Gray, Dana-Farber Cancer Institute, Boston, Mass. e-mail: nathanael_gray@dfci.harvard.edu **Contact:** Dario R. Alessi, University of Dundee, Dundee, U.K. e-mail: d.r.alessi@dundee.ac.uk

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Ophthalmic disease				
Glaucoma	Complement component 1 q subcomponent A chain (C1QA); endothelin 2 (EDN2)	Mouse studies suggest that antagonists of C1QA and endothelin receptors could help treat glaucoma. Compared with healthy mice, those with glaucoma had upregulated *C1qa* and *Edn2* at early stages of the disease. Also in the glaucoma mice, compared with wild-type or untreated mice, *C1qa* knockout and an endothelin receptor antagonist decreased disease severity. Future studies could include developing and testing C1QA antagonists in models of glaucoma. At least five companies market endothelin receptor antagonists to treat pulmonary arterial hypertension (PAH). ***SciBX* 4(12); doi:10.1038/scibx.2011.348** **Published online March 24, 2011**	Patent and licensing status unavailable	Howell, G.R. *et al. J. Clin. Invest.*; published online March 7, 2011; doi:10.1172/JCI44646 **Contact:** Simon W.M. John, The Jackson Laboratory, Bar Harbor, Maine e-mail: simon.john@jax.org
Various				
Cancer; Alzheimer's disease (AD)	Protein phosphatase methylesterase 1 (PPME1); protein phosphatase 2 (PPP2CA; PP2A)	*In vitro* and mouse studies identified aza-β-lactam molecules as PPME1 inhibitors that could help treat cancer and AD. In an *in vitro* screen of over 300,000 small molecules, aza-β-lactams were low nM inhibitors of PPME1. In human breast cancer cells, the most potent compound blocked oncogenic PPME1-mediated demethylation of PP2A compared with vehicle control. In brain slices from mice, the lead compound selectively inhibited PPME1 and decreased PP2A demethylation compared with vehicle controls. Next steps include preclinical testing of PPME1 inhibitors in models of cancer and AD. ***SciBX* 4(12); doi:10.1038/scibx.2011.349** **Published online March 24, 2011**	Unpatented; licensing status undisclosed	Bachovchin, D.A. *et al. Proc. Natl. Acad. Sci. USA*; published online March 11, 2011; doi:10.1073/pnas.1015248108 **Contact:** Gregory C. Fu, Massachusetts Institute of Technology, Cambridge, Mass. e-mail: gcf@mit.edu **Contact:** Benjamin F. Cravatt, The Scripps Research Institute, La Jolla, Calif. e-mail: cravatt@scripps.edu
Huntington's disease (HD); hearing loss	Not applicable	Mouse studies suggest that creatine could help treat or prevent hearing impairment in HD patients. In mouse models of HD, a creatine-supplemented diet prevented hearing impairments and motor coordination problems compared with control diet. Next steps include testing the effects of creatine on hearing impairment in HD patients. ***SciBX* 4(12); doi:10.1038/scibx.2011.350** **Published online March 24, 2011**	Findings unpatented; unavailable for licensing	Lin, Y.-S. *et al. J. Clin. Invest.*; published online March 14, 2011; doi:10.1172/JCI43220 **Contact:** Yijuang Chern, Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan e-mail: bmychern@ibms.sinica.edu.tw

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
Assays & screens			
Colorimetric immunoassay readouts	Copper(I) oxide nanoparticles could be useful for creating colorimetric immunoassays. Modified copper(I) oxide nanoparticles were used to label a secondary antibody used in immunoassays. In an ELISA system, the assay detected ovalbumin and HIV-1 gp41 antigen in samples, and the results could be interpreted with the unaided eye. Next steps include developing similar colorimetric assays for detecting other types of proteins. ***SciBX* 4(12); doi:10.1038/scibx.2011.351** **Published online March 24, 2011**	Patent applications filed; available for licensing	Qu, W. *et al. Angew. Chem. Int. Ed.*; published online March 8, 2011; doi:10.1002/anie.201006025 **Contact:** Xingyu Jiang, National Center for Nanoscience and Technology, Beijing, China e-mail: xingyujiang@nanoctr.cn **Contact:** Zhuo Wang, same affiliation as above e-mail: wangz@nanoctr.cn
Disease models			
In vitro model of Parkinson's disease (PD)	Dopaminergic neurons generated from patient-derived induced pluripotent stem (iPS) cells may provide a model of PD. Fibroblasts from a PD patient were reprogrammed to generate iPS cells, which then were differentiated into dopaminergic neurons. The neurons had PD-related phenotypes including increased α-synuclein (SNCA) accumulation compared with neurons derived from healthy control fibroblasts. Next steps include using the cells to screen for neuroprotective compounds. ***SciBX* 4(12); doi:10.1038/scibx.2011.352** **Published online March 24, 2011**	Patent applications filed; available for licensing	Nguyen, H.N. *et al. Cell Stem Cell*; published online March 4, 2011; doi:10.1016/j.stem.2011.01.013 **Contact:** Renee Reijo Pera, Stanford University, Stanford, Calif. e-mail: reneer@stanford.edu **Contact:** Theo D. Palmer, same affiliation as above e-mail: tpalmer@stanford.edu
Mouse model for tuberous sclerosis complex (TSC)	Mice lacking a single copy of *tuberous sclerosis complex tumor suppressor 1* (*Tsc1*) in neuron subpopulations could aid the development of therapies for TSC, a genetic disorder characterized by hyperactivity of mammalian target of rapamycin (mTOR; FRAP; RAFT1) signaling and intractable seizures. The *Tsc1*-deficient mice had discrete tuber-like lesions in the brain and lower thresholds to chemically induced seizures compared with wild-type control animals. Next steps could include using the mice to study the mechanisms underlying seizure in TSC. ***SciBX* 4(12); doi:10.1038/scibx.2011.353** **Published online March 24, 2011**	Model unpatented; licensing status not applicable	Feliciano, D.M. *et al. J. Clin. Invest.*; published online March 14, 2011; doi:10.1172/JCI44909 **Contact:** Angélique Bordey, Yale School of Medicine, New Haven, Conn. e-mail: angelique.bordey@yale.edu
Drug delivery			
Carbon nanoparticle delivery of chemotherapeutic agents	Delivery of chemotherapy using carbon nanoparticles could help treat cancer. In human cancer cell lines, complexes of the carbon nanoparticles and doxorubicin resulted in greater apoptosis compared with doxorubicin alone. In two mouse models of cancer, the nanoparticle-doxorubicin complex decreased tumor growth and increased survival compared with doxorubicin alone. Ongoing studies include testing the safety and efficacy of the nanoparticles in mice and in larger animal models of cancer. At least six companies have liposomal formulations of doxorubicin that are approved to treat cancer. Doxorubicin transdrug (BA-003), a nanoparticle formulation of doxorubicin from BioAlliance Pharma S.A., is in Phase II/III testing to treat liver cancer. ***SciBX* 4(12); doi:10.1038/scibx.2011.354** **Published online March 24, 2011**	Patented by Northwestern University; available for licensing or partnering	Chow, E.K. *et al. Sci. Transl. Med.*; published online March 9, 2011; doi:10.1126/scitranslmed.3001713 **Contact:** Dean Ho, Northwestern University, Chicago, Ill. e-mail: d-ho@northwestern.edu

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Drug platforms			
Short-term immunosuppression for embryonic or induced pluripotent stem cell transplant	A study in mice suggests that short-term immunosuppression with a trio of molecules could help improve engraftment following stem cell transplantation. In mice transplanted with embryonic stem cells (ESCs), temporary treatment with three antibodies against CTLA-4 (CD152), CD40 ligand (CD40LG; CD40L; CD154) and integrin β_2 (LFA-1; MAC-1; CD18) prolonged stem cell survival compared with treatment using control small molecule immunosuppressants. In mice receiving human induced pluripotent stem (iPS) cells, the three antibodies increased engraftment and stem cell survival compared with no treatment. Next steps could include evaluating the combination in additional models of ESC and iPS cell transplantation. *SciBX* 4(12); doi:10.1038/scibx.2011.355 Published online March 24, 2011	Patent and licensing status unavailable	Pearl, J.I. *et al. Cell Stem Cell*; published online March 3, 2011; doi:10.1016/j.stem.2011.01.012 **Contact:** Joseph C. Wu, Stanford University School of Medicine, Stanford, Calif. e-mail: joewu@stanford.edu **Contact:** Mark M. Davis, same affiliation as above e-mail: mmdavis@stanford.edu
Markers			
Noninvasive diagnostic for Down syndrome	A study in humans suggests that screening fetal DNA in the blood of pregnant women could help diagnose Down syndrome. In a quantitative PCR assay, fetal DNA isolated from the blood of 80 women carrying fetuses with Down syndrome had higher levels of methylation compared with DNA from healthy control fetuses. Next steps include testing the predictive power of the technique in a larger population sample and developing related methods to detect other fetal chromosomal abnormalities. *SciBX* 4(12); doi:10.1038/scibx.2011.356 Published online March 24, 2011	Patent pending; licensed to NIPD Genetics Ltd.	Papageorgiou, E.A. *et al. Nat. Med.*; published online March 6, 2011; doi:10.1038/nm.2312 **Contact:** Philippos C. Patsalis, The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus e-mail: patsalis@cing.ac.cy

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