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Peripheral CNR1 antagonists to the fore

By Michael J. Haas, Senior Writer

In the three years following an FDA panel recommendation against approval of **sanofi-aventis Group**'s Acomplia rimonabant to treat obesity due to severe neurological side effects, centrally acting inhibitors of cannabinoid CB_1 receptor have all but disappeared from development. Now, researchers at the **NIH** and **Northeastern University** have taken the CNS out of the equation by showing that a peripheral inhibitor of the receptor treated obesity and related metabolic disorders without eliciting neurological side effects in mice even though it could not enter the CNS.[1]

The NIH group is now working with **Jenrin Discovery Inc.**, which has a number of peripheral cannabinoid CB_1 receptor (CNR1) inhibitors in preclinical development. The company hopes to select a lead compound to treat diabetes or liver disease.

CNR1 is expressed in the brain, where it regulates appetite, and in peripheral tissues such as the liver, pancreas, skeletal muscle and fat, where it regulates lipogenesis and other metabolic processes. A number of pharma companies developed brain-permeable CNR1 inhibitors for obesity, including rimonabant and **Merck & Co. Inc.**'s taranabant (MK-0364). The problem was that the efficacy of the compounds could not be separated from severe CNS side effects. As a result, all of the inhibitors had been discontinued by 2008.

But also that year, clues began to emerge that CNR1 inhibitors may not need to cross the blood brain barrier to elicit therapeutic effects. Researchers led by George Kunos showed that liver-specific knockout of *Cnr1* protected obese mice from diet-induced insulin resistance, hepatic steatosis (fatty liver) and other metabolic disorders.[2] Kunos is scientific director and chief of the laboratory of physiologic and pharmacologic studies at the NIH's **National Institute on Alcohol Abuse and Alcoholism** (NIAAA).

Kunos' group reasoned that selective inhibition of peripheral CNR1 could help treat metabolic disorders without inducing psychiatric side effects[2,3] but lacked molecules with which to test the hypothesis. Then his team heard about a peripherally restricted rimonabant analog (AM6545) from Alexandros Makriyannis, professor of biotechnology and bioorganic chemistry and director of the Center for Drug Discovery at Northeastern.

In its report in *The Journal of Clinical Investigation*, the NIH-Northeastern team has now shown that treatment with AM6545 resulted in at least 14-fold lower levels of the compound in the brains of normal mice than treatment with comparable doses of rimonabant. AM6545 did not elicit

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behavioral side effects associated with inhibition of CNR1 in the brain such as catalepsy, hypomotility and hypothermia.

At the same time, compared with rimonabant, AM6545 produced similar improvements in dyslipidemia, insulin resistance and hepatic steatosis in two mouse models of obesity: wild-type mice fed a high-fat diet and leptin-deficient mice fed a high-fat diet.

Peripheral advances

"There was the general perception that 100% of the weight loss induced by rimonabant resulted from the drug's inhibition of CNR1 in the brain and consequent suppression of appetite," said John McElroy, founder, president and CSO of Jenrin. "In fact, many people believed that all benefit in diabetes, lipid profile or liver disease was secondary to CNS-mediated weight loss. George Kunos has definitely blown this belief out of the water by showing that blockade of peripheral CNR1 is sufficient to have therapeutic benefit in diabetes, liver disease and dyslipidemia independent of its effects on weight."

Although the *JCI* findings showed that peripheral CNR1 inhibition induced only about half as much weight loss as rimonabant, McElroy thinks the effect was still sufficient to support treating obesity.

Moreover, he said, "by keeping CNR1 inhibitors out of the brain, you might be able to go to higher doses and see greater efficacy than was possible with rimonabant" due to its dose-limiting CNS toxicity.

McElroy added: "This greater efficacy is exactly what we have seen with our compounds in preclinical models of diabetes" and expect to see in models of weight loss as well.

Over a 28-day course of treatment, equivalent doses of AM6545 and rimonabant induced about 12% and 22% weight loss, respectively, in the

wild-type mouse models of obesity compared with vehicle control. In 4 Phase III trials of rimonabant, patients taking 20 mg daily with a hypocaloric diet lost about 14 pounds after 1 year compared with patients who lost about 3.5 pounds with a hypocaloric diet plus placebo.[4]

Like rimonabant, Jenrin's peripherally selective CNR1 inhibitors are inverse agonists, which block a receptor's ligand-binding site and reverse any constitutive activity it might have. Neutral antagonists—such as AM6545—only block the ligand-binding site.

"In-house preclinical results for our compounds are consistent with those reported by Kunos, and we have not observed any side effects from long-term dosing with peripherally selective CB_1 receptor antagonists," McElroy said.

"This paper should certainly generate more interest in the target and thus in our chemistry," said Robert Chorvat, VP of chemistry at Jenrin. "We have lead compounds in three structurally diverse cores and have IP on three additional series."

Christian Elling, VP of biology and development at **7TM Pharma A/S**, agreed that the *JCI* study should renew interest in CNR1 as a target.

"We are a small company, so we will need to partner eventually to develop our peripheral CNR1 inhibitor," he said. "The paper can help us forge meaningful partnerships because it adds to growing evidence that there is a way to target CB_1 receptors pharmacologically while avoiding the side effects" caused by rimonabant.

7TM's TM38837 has completed a Phase I trial to treat obesity and is in an ongoing Phase I trial designed to demonstrate the peripheral CNR1 inhibitor's lack of CNS exposure. The company expects to have results for the second trial by year end, Elling said.

In July the company announced results of PET imaging studies in macaques showing that TM38837 was restricted to the periphery. 7TM has also conducted preclinical studies in animal models of diabetes.

Elling said 7TM has not decided whether to pursue obesity or diabetes as a lead indication for future clinical trials of TM38837.

He added that the *JCI* study "nicely captured the effects of peripheral CNR1 inhibition on the liver and points to an opportunity to develop these inhibitors to treat liver disease. While this is not of interest to us, it is an important aspect of the findings."

On the horizon

Kunos said his NIH group is collaborating with Jenrin on preclinical studies of an undisclosed peripheral CNR1 inhibitor from the company. Preliminary results from those studies suggest the compound might be better than AM6545 at inducing weight loss and treating metabolic symptoms.

Unlike AM6545, Kunos added, "Jenrin's compound seems to cause a small but notable reduction in food intake. If the Jenrin compound turns out to be really effective, then I'm personally interested in taking it through IND-enabling toxicology studies and Phase I or Phase II clinical studies here at NIH."

For the company, McElroy said, "the first clinical indication will likely be diabetes or nonalcoholic hepatic steatosis" because those trials would be shorter and less expensive than obesity or dyslipidemia studies.

Apart from the Jenrin collaboration, Kunos said his team is investigating the molecular mechanisms by which activation of hepatic CNR1 causes insulin resistance in mouse models of diabetes.

Northeastern holds a patent on AM6545 and its uses.

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COMPANIES AND INSTITUTIONS MENTIONED

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Sorting out sortilin

By Tim Fulmer, Senior Writer

An international team of cardiovascular researchers has reported the largest ever genomewide association study meta-analysis, encompassing 46 data sets and leading to the identification of 59 new genetic variants associated with plasma lipid levels.[1] Potentially the most provocative finding is an association between coronary artery disease and a mutation in the gene for sortilin 1, an intracellular trafficking protein involved in hepatic lipid metabolism.[2]

The team is now studying the sortilin 1 (SORT1) pathway in animals and has partnered with RNAi company **Alnylam Pharmaceuticals Inc.**, which has exclusive rights to develop and commercialize any SORT1-targeting therapeutic that results from the research.

Previous GWA studies enrolling up to 20,000 individuals of European ancestry had identified SNP variants at 36 genetic loci that contributed to variation in plasma lipid levels. Those studies provided insights into the genetic variation underlying lipid metabolism and dyslipidemia but did not clarify how those loci might also contribute to cardiovascular conditions like coronary artery disease (CAD) and myocardial infarction (MI).

Thus, a group led by Sekar Kathiresan and Daniel Rader carried out a meta-analysis of 46 previously reported GWA studies to identify additional lipid-associated variants and determine whether any of those variants significantly contributed to cardiovascular disease.

Kathiresan is director of preventive cardiology at **Massachusetts General Hospital** and assistant professor of medicine at **Harvard Medical School**. Rader is director of the Preventive Cardiovascular Medicine and Lipid Clinic and professor of medicine at the **University of Pennsylvania School of Medicine**.

The meta-analysis of more than 100,000 individuals of European ancestry looked for associations between about 2.6 million SNPs and 4 heritable lipid traits: total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides.

With a threshold of statistical significance set at $p<5\times10^{-8}$, which is standard for GWA studies, the analysis identified SNPs in 95 loci—including 59 new ones—that were significantly associated with at least 1 of the 4 risk factors.

In additional cohorts of East Asians, South Asians and African Americans, a majority of the 95 loci showed the same level of association with the 4 risk factors that was seen in the European cohort. Thus, the researchers concluded in a paper in *Nature* that most of the loci "contribute to the genetic architecture of lipid traits widely across global populations."

The next question was how strongly the loci are associated with risk for CAD. To find out, the researchers genotyped 24,607 CAD patients of European descent and 66,197 non-CAD controls. Of the 95 lipid-related loci, 14 were significantly associated with CAD ($p<0.001$).

In an accompanying paper in *Nature*, the same researchers provided an example of how the GWA study findings might be used to guide the identification of new therapeutic targets.

Here, the team zeroed in on loci on chromosome 1p13. Of the new SNPs identified in the meta-analysis, those at the 1p13 loci were most strongly associated with LDL cholesterol, a marker of cardiovascular disease risk. Independent work by other researchers has shown an association between SNPs on 1p13 and MI in humans.[3,4]

Fine-mapping studies then led to the identification of a single SNP in a noncoding region of DNA that caused decreases in hepatic expression of SORT1, a Golgi protein that had not previously been associated with lipid or cardiovascular disorders.

The final question was whether low SORT1 expression caused the high plasma LDL levels that are associated with risk for MI and CAD.

To find the answer, the researchers used small interfering RNA knockdown to decrease Sort1 expression or adeno-associated viral (AAV) vectors to increase Sort1 activity in mice. The data showed a causal relation: high and low expression of Sort1 in the liver led to low and high plasma LDL, respectively.

The group concluded that the SORT1 pathway is "a promising new target for therapeutic intervention in the reduction of LDL-C and prevention of MI."[2]

The team on the paper describing the SORT1 research included researchers from Alnylam. According to Kevin Fitzgerald, the biotech's senior director of research, Alnylam holds rights to develop and commercialize any RNAi therapeutics that derive from the research collaboration between the company and the labs of Kathiresan and Rader.

> **"As we move forward, we'll initially focus on the 14 loci in the meta-analysis that are associated with both lipid levels and diseases such as CAD and MI."**
>
> *—Sekar Kathiresan, Harvard Medical School*

In a commentary accompanying the two papers, Alan Shuldiner and Toni Pollin wrote that the SORT1 study is an "example of how information from GWAS can be used to unravel new regulatory pathways that alter the risk of human disease, in this case myocardial infarction."[5]

Shuldiner is professor of medicine and Pollin is assistant professor of medicine at the **University of Maryland School of Medicine**'s Division of Endocrinology, Diabetes and Nutrition.

Sorting through SNPs

Although the findings imply that increasing SORT1 expression in the liver could reduce plasma LDL and thus lower the risk of cardiovascular disease, "more cell biology studies and mechanistic work is needed to determine whether the optimal way of doing that is targeting sortilin directly or targeting a regulator of sortilin activity," co-corresponding author Kathiresan told *SciBX*.

Going forward, the Kathiresan and Rader groups will continue to use a combination of GWA studies and animal work to sort through the 95 loci to home in on additional genes that drive variation in plasma lipid levels and contribute to cardiovascular disease.

"As we move forward, we'll initially focus on the 14 loci in the meta-analysis that are associated with both lipid levels and diseases such as CAD and MI," said Kathiresan. "That ongoing work includes studying the role of the sortilin pathway in lipid metabolism and cardiovascular disease and developing strategies for targeting that pathway."

Co-corresponding author Rader told *SciBX* the studies are looking at ways of modulating SORT1 expression in mice as well as in cultured human hepatocytes.

(Continues on p. 5)

Leukemia takes it up a NOTCH

By Lev Osherovich, Senior Writer

The Notch pathway has been linked to aggressive growth in a range of tumor types but had not previously been considered a prime target for myeloid leukemia therapies. Separate American teams now have identified two targets in the pathway that promote highly aggressive hematopoietic stem cell growth and possibly progression of late-stage chronic myeloid leukemia into acute myeloid leukemia. The work opens new therapeutic areas to the companies targeting the pathway for solid tumors.

Cancer stem cells are self-renewing, undifferentiated cells that are thought to fuel tumor growth. Ordinarily, stem cells divide to produce a copy of the original cell plus a daughter cell with some degree of differentiation, but cancer stem cells can divide without undergoing differentiation.

"A normal stem cell needs to decide whether to remain a stem cell or to differentiate," said Michael Kharas, instructor of hematological oncology at **Brigham and Women's Hospital**. "This decision point could be mutated in cancers."

Kharas is the lead author of a study published in *Nature Medicine* that identified the pathway's role in AML.[1] The other report showed the pathway's involvement in CML and was published in *Nature* by a team led by Tannishtha Reya, associate professor of pharmacology and cancer biology at **Duke University School of Medicine**.[2]

Kharas noted that in cancer, inappropriate activation of developmental pathways such as Notch signaling can cause stem cells to divide symmetrically to produce two more stem cells. Excess accumulation of these stem cells is a hallmark of many aggressive tumors. Moreover, the stem cells are hard to eradicate with conventional chemotherapy because they lack many of the targets and processes that drive the growth of the more differentiated cancer cells.

One new target, NUMB homolog, inhibits notch homolog 1 translocation-associated (NOTCH1) processing and activation. The other target, an RNA-binding protein called Musashi homolog 2 (MSI2), blocks the translation of NUMB homolog. The former could be therapeutically activated whereas the latter one could be inhibited.

Both targets offer an opportunity to intervene upstream of other Notch pathway targets, but hitting these intracellular proteins may be challenging.

Having a blast

Reya's team created cancerous human hematopoietic stem cells and transplanted them into mice. Compared with early-stage CML cells, NUMB homolog was underexpressed in CML cells undergoing blast crisis, an aggressive late stage of the disease that resembles AML.

"We looked at leukemia progression from chronic to acute phase. The chronic phase is manageable but the acute phase grows very fast," she said.

NUMB homolog is a developmental factor in flies, but in leukemia it acts like a tumor suppressor. Indeed, mice transplanted with blast crisis cells that overexpressed NUMB homolog had better survival than mice with cells that lacked the protein.

(Continues on p. 6)

(Continued from **"Sorting out sortilin,"** p. 4)

Kathiresan and Rader are collaborating with Alnylam "to mechanistically evaluate the metabolic and molecular effects of novel genes implicated by human genetic studies in cardiovascular disease and to develop RNAi therapeutics against those gene candidates," said Alnylam's Fitzgerald.

RNAi helps link complex genetic loci to specific pathways and mechanisms and, ultimately, to individual target genes, he added.

In parallel with studies to identify new therapeutic targets, Kathiresan told *SciBX* he wants to explore using the 95 loci or a subset of them as a diagnostic to guide treatment of cardiovascular disorders.

"Given the potential link between those 95 loci and risk for lipid disorders and cardiovascular disease, one could hypothesize the use of a risk score based on those loci that would inform, for example, when to put patients on early statins to help lower their risk for developing coronary artery disease and MI," Kathiresan said. Though it remains to be seen, a panel of risk loci could offer a more sensitive diagnostic for when to begin statin therapy than a single marker like plasma cholesterol, he added.

According to Kathiresan, the 95 loci and SNPs identified in the two papers, including SORT1, are in the public domain.

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Alnylam Pharmaceuticals Inc. (NASDAQ:ALNY), Cambridge, Mass.
Harvard Medical School, Boston, Mass.
Massachusetts General Hospital, Boston, Mass.
University of Maryland School of Medicine, Baltimore, Md.
University of Pennsylvania School of Medicine, Philadelphia, Pa.

Because numb is regulated by musashi in flies, Reya's team examined levels of Musashi family members in human blast crisis CML cells and found that MSI2 was overexpressed compared with its expression in slow-growing CML controls.

The team went on to show that knocking down Msi2 slowed tumor growth and increased survival in a mouse model of blast crisis CML.

"We found that MSI2 was massively upregulated as disease went from chronic to acute phases," said Reya. "This is consistent with the idea that MSI2 suppresses NUMB homolog."

> **"We found that MSI2 was massively upregulated as disease went from chronic to acute phases. This is consistent with the idea that MSI2 suppresses NUMB homolog."**
>
> ***—Tannishtha Reya, Duke University School of Medicine***

Comfortably numb

Separately, a team led by Kharas and George Daley came across MSI2 while studying gene expression in normal hematopoietic stem cells (HSCs) in mice.

Daley is professor of hematology and director of the stem cell transplantation program at **Children's Hospital Boston** and professor of biological chemistry, molecular pharmacology and pediatrics at **Harvard Medical School**.

The Boston team found that HSCs with high MSI2 expression were less differentiated and more stem cell–like than bone marrow cells with low MSI2 expression.

Previous studies have linked a homolog of MSI2 called MSI1 to solid tumor progression.[3] Thus, Kharas and Daley tested whether MSI2 expression affected leukemia progression in mice. Their group found that MSI2 overexpression alone did not cause leukemia. However, combining excess MSI2 with a BCR-ABL oncogene, a common cause of CML, dramatically increased tumor proliferation compared with using only BCR-ABL.

The team also found that AML patients with high levels of MSI2 had faster-growing tumors and worse survival rates than patients with low MSI2 levels.

Mechanistically, the findings show that excess MSI2 leads to degradation of NUMB homolog mRNA, which in turn removes an impediment to the proteolytic processing of NOTCH1 by γ-secretase (*see* **Figure 1, "Musashi homolog 2 and NUMB homolog in cancer"**).

The studies also suggest that increased MSI2 can drive CML into an aggressive AML-like state and that many AML patients have high MSI2 levels. Thus, it is possible that AML patients with increased MSI2 may have started off with CML that shifted into overdrive due to MSI2 overexpression.

"Though we can't prove that all AML cases result from CML conversion via MSI2, a large majority of the patients have high MSI2 expression" in the most aggressive forms of both disorders, said Kharas.

Reya and Kharas also noted that other cancer pathways including tumor protein p53 (TP53; p53) and Hedgehog signaling may be regulated by MSI2. Both teams are working to identify other downstream targets of MSI2 besides NUMB homolog.

In addition, both Kharas and Reya think screening for increased MSI2 levels could be useful for catching the emergence of aggressive leukemias.

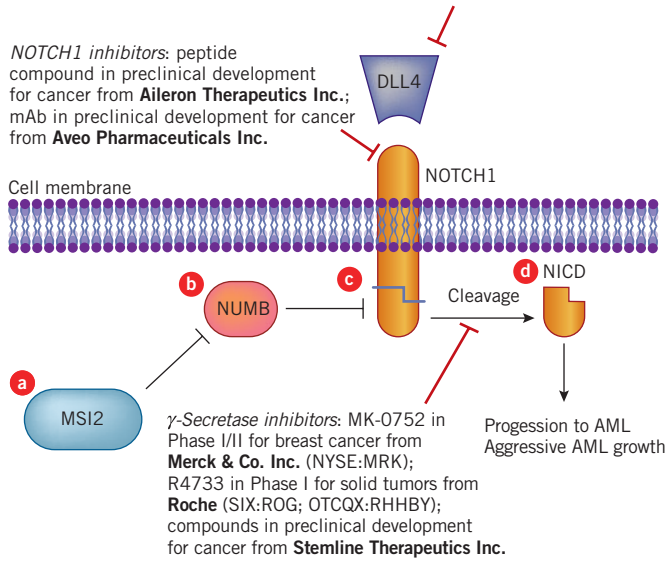

Figure 1. Musashi homolog 2 and NUMB homolog in cancer. Ito *et al.* and Kharas *et al.* have identified a pathway that activates Notch homolog 1 translocation-associated (NOTCH1) and promotes progression of chronic myeloid leukemia (CML) to acute myeloid leukemia (AML).

The RNA-binding protein Musashi homolog 2 (MSI2) [**a**] is overexpressed in blast crisis–stage CML cells and in AML cells. MSI2 blocks the translation of mRNA encoding Numb homolog (NUMB) [**b**]. Because NUMB normally inhibits the proteolytic cleavage and activation of NOTCH1 [**c**], low NUMB levels lead to higher levels of the NOTCH1 intracellular domain (NICD) [**d**], which activates genes involved in aggressive leukemia growth.

A number of cancer compounds are in development that target proteins in the pathway, including NOTCH1 and its ligand, delta-like ligand 4 (DLL4), and γ-secretase, an enzyme involved in the processing of NOTCH1 into NICD.

Not your average target

Although many of the players in the Notch pathway are familiar from previous developmental and cancer studies, the leukemia connection opens up new opportunities for companies developing antagonists of NOTCH1 signaling in hematological malignancies.

> **"If MSI2 is upregulated in CML, this implies that NUMB homolog is downregulated and Notch signaling is upregulated."**
> ***—Timothy Hoey, OncoMed Pharmaceuticals Inc.***

At least nine companies have compounds against various targets involved in transcriptional activation by the Notch pathway in preclinical and clinical development for solid tumors.

"MSI2 has not previously been known for its relevance to hematopoiesis," said Kristin Hope, associate professor of biochemistry and biomedical sciences at **McMaster Stem Cell and Cancer Research Institute**.

Hope and colleagues reported in *Cell Stem Cell* last month that MSI2 is one of several factors involved in stem cell division.[4]

"If MSI2 is upregulated in CML, this implies that NUMB homolog is downregulated and Notch signaling is upregulated," said Timothy Hoey, SVP of cancer biology at **OncoMed Pharmaceuticals Inc.** "This highlights CML as a potential opportunity for our NOTCH pathway antagonists."

He added that turning down NOTCH1 signaling "increases sensitivity to chemotherapeutic agents and reduces tumor recurrence and metastasis."

OncoMed's OMP-21M18, a mAb that targets the NOTCH1 activator delta-like ligand 4 (DLL4), has completed Phase I testing in solid tumors. The company plans to submit an IND for a mAb targeting NOTCH1 itself this year.

"The issue of self-renewal is central to cancer and is closely related to the asymmetric division" that is governed by MSI2, said Tom Cirrito, director of operations at **Stemline Therapeutics Inc.** He thinks blocking the action of MSI2 or its downstream components in the Notch pathway therefore could correct the imbalanced symmetric division that leads to cancer stem cell production.

"Symmetric cell division maintains the pool of cancer stem cells," he said. "We would want compounds that promote differentiation and get rid of cancer stem cells. These papers point to symmetric cell division as a process that can be targeted" to treat cancer.

Stemline has two γ-secretase inhibitors in preclinical development for solid tumors: SL301 and SL302. Stemline's lead program is SL401, a peptide that targets IL-3 receptor (CD123). The compound is in Phase I testing to treat AML.

Although blocking MSI2's activity or increasing levels of NUMB homolog should produce therapeutic effects, targeting these intracellular proteins will not be easy.

"MSI2 is an RNA-binding protein, not a kinase, so it's very hard to get at," said Reya. One tactic for antagonizing MSI2 might be to study the "post-translation modifications that regulate its function or its downstream targets," she added.

Besides trying to knock down MSI2 with small interfering RNA, Cirrito suggested making an RNA mimetic that binds and blocks MSI2's RNA-binding site. The effect of such an oligonucleotide-based agent would be to prevent the degradation of NUMB homolog mRNA and other MSI2 targets, he noted.

Both Kharas and Reya have filed for patents on diagnostic and therapeutic applications of their discoveries. The IP is available for licensing.

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COMPANIES AND INSTITUTIONS MENTIONED

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Cell-free joint regeneration

By Lauren Martz, Staff Writer

Columbia University Medical Center researchers have identified a cell-free tissue-regeneration strategy that not only helps replace lost bone but also regenerates cartilage, a feat that has stymied previous joint replacement efforts.[1]

Treatments for the structural breakdown of bone and cartilage that occurs in osteoarthritis include total joint replacement with a metallic or synthetic prosthetic. The devices do a good job of mimicking joint function, but wear between the patient's bone and the device can lead to loosening of the prosthetic, infection and failure after 10–15 years.[2]

Tissue regeneration using stem or progenitor cells represents an alternative to the devices but has its own risks, such as pathogen transmission, immune rejection and tumorigenesis. Other cell delivery challenges include preserving, maintaining and transporting the live cells, all of which drive up cost.[3]

Now, Columbia's Jeremy Mao and colleagues report a way to separate the benefits of tissue regeneration from the risks by using implantable bioscaffolds that contain growth factors. The goal is to encourage the patient's own cells to do the work, as the growth factors prompt endogenous chondrocyte- and osteoblast-like cells to migrate to damaged joints and regenerate both the cartilage and bone.

Mao is a professor at Columbia and director of the Tissue Engineering and Regenerative Medicine Laboratory at the medical center.

The researchers used laser scanning and computer-aided reconstruction to develop synthetic bioscaffolds made from poly-ε-caprolactone and hydroxyapatite that structurally matched rabbit proximal humeral joints.

In skeletally mature rabbits, the team replaced surgically excised joint surfaces with either bioscaffolds infused with transforming growth factor-β3 (TGFB3)-adsorbed collagen hydrogel, TGFB3-free bioscaffolds or no scaffolds.

Rabbits receiving the TGFB3-infused scaffolds recovered all weight-bearing and locomotor functions within three to four weeks. In contrast, animals treated with TGFB3-free scaffolds had inconsistent recovery, and untreated animals limped throughout the study.

After the study, the team removed the bioscaffolds and found that the TGFB3-infused scaffolds had recruited 130% more chondrocytes than the TGFB3-free bioscaffolds. The TGFB3-infused scaffolds also were covered in hyaline cartilage and integrated with the animals' own bone, and they regenerated subchondral bone and developed blood vessels.

In contrast, the TGFB3-free scaffolds had sporadic cartilage formation, and no cartilage formed in the joints of untreated animals.

The team, which also included researchers from the **University of Missouri–Columbia** and **Clemson University**, published its results in *The Lancet*.

> **"The advantage of this approach is the regeneration of articular cartilage covering the entire surface of the synovial joint without having to transplant cells, including stem or progenitor cells."**
>
> ***—Jeremy Mao, Columbia University Medical Center***

"The advantage of this approach is the regeneration of articular cartilage covering the entire surface of the synovial joint without having to transplant cells, including stem or progenitor cells," Mao told *SciBX*. "Cartilage is one of the most recalcitrant tissues for regeneration."

"Academics and researchers from industry have been trying for years to develop better approaches to regenerate cartilage and synovial joint defects—it's a huge unmet need," said Jeffrey Karp, assistant professor of medicine at **Harvard Medical School** and co-director of regenerative therapeutics in the Department of Medicine at the **Brigham and Women's Hospital**.

Leo Snel, SVP of R&D and protein chemistry at **BioMimetic Therapeutics Inc.**, likes that the approach "leverages the effects of biological signals to mobilize endogenous cells into a repair site and therefore bypasses the need to harvest, expand, process and implant reparative stem or progenitor cells. The strategy significantly simplified the logistics involved in developing a clinically relevant approach, as the harvest of stem cells from the patient and the time and work required for their expansion, conditioning and preparation for implantation are not necessary."

BioMimetic is developing Augment bone graft, which combines recombinant human platelet derived growth factor BB (PDGFBB) with a resorbable synthetic bone matrix to stimulate bone regeneration by attracting endogenous cells. The product is approved as an alternative to autografts in ankle, hindfoot and midfoot fusion surgeries in Canada. A premarket approval (PMA) is under FDA review.

According to Bridget Deasy, assistant professor in the Department of Orthopedic Surgery at the **University of Pittsburgh** and assistant professor at the **McGowan Institute for Regenerative Medicine**, "*ex vivo* manipulation of the stem cells makes other strategies risky because the chemicals introduced into the culture could change the identity of the cells, making them lose some of their stem cell properties and rendering them less effective, and could also induce DNA damage that could cause cancer."

Next steps

Columbia is seeking partners to pursue large animal studies and clinical trials of its bioactive scaffold.

Harvard's Karp suggested that the next set of preclinical studies should examine exactly how the bioscaffold functions. "More work is required to elucidate the mechanism for cell recruitment and to determine if the cells are homing from the bloodstream or migrating locally from the peri-wound compartment," he said.

"If we know where the cells are migrating from, we may be able to enhance the therapeutic efficacy for this application and others," said Karp. "If they are coming from the bone marrow, for example, we may be able to develop relevant model systems to screen for agents that target the right cell type to mobilize and home to diseased or damaged tissues more efficiently."

Snel noted that the five- to six-month-old rabbits used in the study were skeletally mature but still relatively young. As a result, he said, the animals' intrinsic repair capacities may not be the best proxy for the adults that would receive the therapy in a clinical trial.

"As we age, our intrinsic capacity for tissue repair diminishes. This is, in part, due to the decreased number of reparative cells and/or their reparative capacity," he said.

Snel added that any strategy that mobilizes endogenous reparative cells to an injury site will only work if patients have a sufficiently large pool of such cells.

Deasy noted that "one of the downsides of using the host cells is that they could be compromised in the patients to begin with. The patients are often older or have cells that are damaged simply due to the fact that they have the disease."

This could be a problem, she said, because the rabbit model does not give a good indication of the length of time for recovery in humans. "This will depend on the type of tissue that is damaged and the size of the tissue. Without a good supply of healthy endogenous cells, recovery could be very slow," Deasy said.

Although the Columbia bioscaffolds circumvent the potential side effects associated with cell therapies, the approach's use of growth factors carries its own risks.

"To achieve the desired tissue regeneration, the addition of a potent growth factor is required. This is potentially costly and may involve other untoward side effects," noted Molly Stevens, CSO of **RepRegen Ltd.**

RepRegen's StronBone bone graft substitute received European Conformity (CE) mark approval in the EU for hard tissue repair and regeneration. StronBone is a bioactive glass material that incorporates metal ions including strontium.

According to Snel, a growth factor–based strategy needs to show it can "elicit appropriate responses and not result in undesired effects such as exuberant or uncontrolled tissue growth, toxicities or malignancies."

Columbia has filed for a patent covering the technology.

Martz, L. *SciBX* 3(32); doi:10.1038/scibx.2010.975
Published online Aug. 19, 2010

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3. Muschler, G.F. *et al. Tissue Eng. Part B Rev.* **16**, 123–145 (2010)

COMPANIES AND INSTITUTIONS MENTIONED

BioMimetic Therapeutics Inc. (NASDAQ:BMTI), Franklin, Tenn.
Brigham and Women's Hospital, Boston, Mass.
Clemson University, Clemson, S.C.
Columbia University Medical Center, New York. N.Y.
Harvard Medical School, Boston, Mass.
McGowan Institute for Regenerative Medicine, Pittsburgh, Pa.
RepRegen Ltd., London, U.K.
University of Missouri–Columbia, Columbia, Mo.
University of Pittsburgh, Pittsburgh, Pa.

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 disease	Rho-associated coiled-coil containing protein kinase 2 (ROCK2); IL-17; IL-21	*In vitro* and mouse studies suggest that inhibiting *ROCK2* could help treat autoimmune diseases. In cultured human T cells, greater *ROCK2* expression led to higher levels of proinflammatory IL-21 and IL-17, whereas the ROCK2 inhibitor Eril fasudil prevented the increased levels. In mouse models of autoimmune arthritis and lupus, Eril decreased production of Il-17 and Il-21 and reduced arthritis compared with no treatment. Next steps include developing selective ROCK2 inhibitors. Asahi Kasei Pharma Corp. markets Eril fasudil to treat aneurysm. ***SciBX* 3(32); doi:10.1038/scibx.2010.976** **Published online Aug. 19, 2010**	Patent pending covering work; available for licensing	Biswas, P.S. *et al. J. Clin. Invest.*; published online Aug. 9, 2010; doi:10.1172/JCI42856 **Contact:** Alessandra B. Pernis, Hospital for Special Surgery, New York, N.Y. e-mail: pernisa@hss.edu
Cancer				
Acute lymphoblastic leukemia (ALL)	IL-23; microRNA-15a (miR-15a)	*In vitro* and mouse studies suggest that IL-23 and miR-15a could help treat pediatric ALL. In ALL patient samples and human ALL cell lines, IL-23 upregulated miR-15a, which led to greater apoptosis than no treatment. In mouse models of pediatric ALL, human IL-23 or forced overexpression of miR-15a decreased tumor growth compared with vehicle control or expression of an irrelevant miRNA precursor. Future studies could include testing miR-15a in animal models of ALL. ***SciBX* 3(32); doi:10.1038/scibx.2010.977** **Published online Aug. 19, 2010**	Patent and licensing status unavailable	Cocco, C. *et al. Blood*; published online July 29, 2010; doi:10.1182/blood-2009-10-248245 **Contact:** Irma Airoldi, G. Gaslini Institute, Genoa, Italy e-mail: irmaairoldi@ospedale-gaslini.ge.it
Acute myeloid leukemia (AML); chronic myeloid leukemia (CML)	Musashi homolog 2 (MSI2)	A study in mice and in humans suggests that antagonizing MSI2 could help treat AML and late-stage CML. In murine hematopoietic stem cells, overexpression of MSI2 led to abnormal cell proliferation and leukemia-like properties compared with those in vector-transfected controls. In AML and late-stage (blast crisis) CML patients, high *MSI2* expression was associated with a worse prognosis than low MSI2 levels. Next steps include identifying potential targets of MSI2, an mRNA-binding protein, and further characterizing how MSI2 affects cancer signaling pathways (*see* **Leukemia takes it up a NOTCH, page 5**). ***SciBX* 3(32); doi:10.1038/scibx.2010.978** **Published online Aug. 19, 2010**	Patent pending; available for licensing	Kharas, M.G. *et al. Nat. Med.*; published online July 8, 2010; doi:10.1038/nm.2187 **Contact:** George Q. Daley, Brigham and Women's Hospital, Boston, Mass. e-mail: george.daley@childrens.harvard.edu **Contact:** Michael G. Kharas, same affiliation as above e-mail: mkharas@partners.org

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
B cell lymphoma (BCL)	MicroRNA-21 (miR-21)	A study in mice suggests that inhibiting miR-21 could help treat BCL. Mice that overexpressed miR-21 in hematopoietic tissue developed pre-BCL, whereas mice with wild-type miR-21 expression did not (p<0.0001). In miR-21-overexpressing mice with established lymphomas, decreasing miR-21 levels increased survival compared with continued overexpression of miR-21 (p<0.0001). Next steps include studies of miR-21 in additional mouse models of cancer. Regulus Therapeutics Inc. has an antisense oligonucleotide targeting miR-21 in preclinical development to treat heart failure. ***SciBX* 3(32); doi:10.1038/scibx.2010.979** **Published online Aug. 19, 2010**	Unpatented; licensing status not applicable	Medina, P.P. *et al. Nature*; published online Aug. 8, 2010; doi:10.1038/nature09284 **Contact:** Frank J. Slack, Yale University, New Haven, Conn. e-mail: frank.slack@yale.edu
Gallbladder cancer	Liver X receptor-β (NR1H2; LXR-β)	Studies in mice suggest that agonizing LXR-β could help treat gallbladder cancer in women. *Lxr-β* knockout led to gallbladder carcinoma in 30% of female mice, whereas no carcinoma developed in wild-type female controls. Next steps include measuring levels of LXR-β and its ligands in human gallbladder cancer samples. ***SciBX* 3(32); doi:10.1038/scibx.2010.980** **Published online Aug. 19, 2010**	Unpatented; licensing status undisclosed	Gabbi, C. *et al. Proc. Natl. Acad. Sci. USA*; published online Aug. 2, 2010; doi:10.1073/pnas.1009483107 **Contact:** Jan-Åke Gustafsson, Karolinska Institute, Novum, Sweden e-mail: jan-ake.gustafsson@mednut.ki.se
Kaposi's sarcoma (KS)	Angiopoietin-like 4 (ANGPTL4)	*In vitro* and mouse studies suggest that inhibiting ANGPTL4 could help treat KS. In experimental and patient KS lesions, ANGPTL4 levels were greater within the lesions than outside them. In a KS tumor allograft mouse model, anti-*Angptl4* small hairpin RNA decreased tumor vascularization, vascular permeability and growth compared with scrambled shRNA. Next steps include better characterizing ANGPTL4's signaling pathway. LG842, a mAb against ANGPTL4 from Genentech Inc. and Lexicon Pharmaceuticals Inc., is in preclinical testing to treat dyslipidemia. ***SciBX* 3(32); doi:10.1038/scibx.2010.981** **Published online Aug. 19, 2010**	Patent and licensing status unavailable	Ma, T. *et al. Proc. Natl. Acad. Sci. USA*; published online July 26, 2010; doi:10.1073/pnas.1001065107 **Contact:** Silvia Montaner, University of Maryland, Baltimore, Md. e-mail: smontaner@umaryland.edu
Liver cancer	IL-12; granulocyte macrophage colony-stimulating factor (CSF2; GM-CSF); pigment epithelium derived factor (SERPINF1; PEDF); endostatin (ED)	A study in woodchucks suggests that a combination of antiangiogenic factors and cytokines could help treat advanced liver cancer. In woodchucks with hepatocellular carcinomas, two antiangiogenic factors (PEDF and ED) in combination with two cytokines (GM-CSF and IL-12) decreased tumor size compared with antiangiogenic factors alone (p<0.05). In the subset of woodchucks with large tumors, the four factors reduced tumor size compared with cytokines alone (p=0.004). Next steps include toxicology studies of the combination of antiangiogenic factors plus cytokines. EGEN-001, an IL-12-expressing plasmid formulated with a lipopolymeric gene delivery system from Egen Inc., is in Phase I testing for ovarian cancer. Endostar, a recombinant human ED, is marketed in China by Simcere Pharmaceutical Group to treat non–small cell lung cancer (NSCLC). ***SciBX* 3(32); doi:10.1038/scibx.2010.982** **Published online Aug. 19, 2010**	Patent application filed; licensing status undisclosed	Huang, K.-W. *et al. Proc. Natl. Acad. Sci. USA*; published online Aug. 2, 2010; doi:10.1073/pnas.1009534107 **Contact:** Ding-Shinn Chen, National Taiwan University Hospital, Taipei, Taiwan e-mail: chends@ntu.edu.tw **Contact:** Lih-Hwa Hwang, National Yang-Ming University, Taipei, Taiwan e-mail: lhhwang@ym.edu.tw

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Non–small cell lung cancer (NSCLC)	BRF2, subunit of RNA polymerase III transcription initiation factor, BRF1-like (BRF2)	A study in cell culture and in patient samples suggests that inhibiting BRF2 could help treat lung cancer. In an NSCLC squamous cell carcinoma cell line, small interfering RNA–mediated knockdown of BRF2 decreased cell proliferation compared with that seen using nontargeting siRNA. In human lung tissue samples, BRF2 expression was activated in the early stages of squamous cell carcinomas but not in normal lung tissue. Next steps could include comparing the effects of BRF2 in mice with squamous cell carcinomas and other types of NSCLC. ***SciBX* 3(32); doi:10.1038/scibx.2010.983** **Published online Aug. 19, 2010**	Patent and licensing status unavailable	Lockwood, W.W. *et al. PLoS Med.*; published online July 27, 2010; doi:10.1371/journal.pmed.1000315 **Contact:** William W. Lockwood, BC Cancer Agency Research Centre, Vancouver, British Columbia, Canada e-mail: wlockwood@bccrc.cas
Ovarian cancer	Salt-inducible kinase 2 (SIK2)	*In vitro* and mouse studies suggest that inhibiting SIK2 could help increase the sensitivity of ovarian tumors to taxane-based chemotherapy. In cultured ovarian cancer cells, as compared with control-transfected cells, anti-*SIK2* small interfering RNA decreased the dose of paclitaxel needed to inhibit cell growth. In ovarian cancer mouse xenografts, siRNA knockdown of *SIK2* increased tumor cell sensitivity to paclitaxel and decreased tumor volume compared with those seen using a nontargeting siRNA plus paclitaxel. In 59 ovarian cancer samples, SIK2 expression correlated with poor clinical outcome and paclitaxel resistance. Next steps include identifying a SIK2 inhibitor. Paclitaxel is a generic taxane. ***SciBX* 3(32); doi:10.1038/scibx.2010.984** **Published online Aug. 19, 2010**	Unpatented; available for licensing	Ahmed, A.A. *et al. Cancer Cell*; published online Aug. 16, 2010; doi:10.1016/j.ccr.2010.06.018 **Contact:** Robert C. Bast Jr., The University of Texas M.D. Anderson Cancer Center, Houston, Texas e-mail: rbast@mdanderson.org **Contact:** Ahmed Ashour Ahmed, same affiliation as above e-mail: ahmed.ahmed@obs-gyn.ox.ac.uk
Cardiovascular disease				
Coronary artery disease (CAD)	*UDP-N-acetyl-α-D-galactosamine:polypeptide N-acetylgalacto-saminyltransferase 2* (*GALNT2*); *protein phosphatase 1 regulatory subunit 3B* (*PPP1R3B*); *tetratricopeptide repeat domain 39B* (*TTC39B*)	A meta-analysis of human genomewide association studies identified 95 gene variants that could help treat hyperlipidemia and CAD or predict risk of the conditions. Genetic analysis of over 100,000 individuals of European descent showed significant associations between serum lipid levels and 95 SNP-associated genes ($p<5\times10^{-8}$). Fourteen of the identified SNPs correlated with CAD risk ($p<0.001$). In mice, small hairpin RNA–mediated knockdown of *Galnt2* or *Ttc39b*, two candidate genes associated with high-density lipoprotein (HDL), led to greater HDL cholesterol levels than normal expression of the genes. In mice, overexpression of a third gene, *Ppp1r3b*, led to lower HDL cholesterol levels than those in controls. Next steps include mechanistic studies of the candidate genes in animal models of metabolic and cardiovascular disease (*see* **Sorting out sortilin, page 4**). ***SciBX* 3(32); doi:10.1038/scibx.2010.985** **Published online Aug. 19, 2010**	Findings unpatented; all 95 SNPs available in public domain	Teslovich, T.M. *et al. Nature*; published online Aug. 5, 2010; doi:10.1038/nature09270 **Contact:** Sekar Kathiresan, Massachusetts General Hospital, Boston, Mass. e-mail: skathiresan@partners.org

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Myocardial infarction (MI)	Sortilin 1 (SORT1)	Human and mouse studies suggest that increasing SORT1 expression in the liver may help lower plasma lipid levels and prevent MI. Genomewide association studies identified a SNP that was associated with decreased low-density lipoprotein (LDL) cholesterol levels and higher Sort1 expression. In mice, adenoviral-mediated Sort1 overexpression in the liver significantly reduced plasma cholesterol compared with that seen using a nonexpressing control vector (p=4×10^{-5}). Next steps include additional mechanistic studies in mice and cultured hepatocytes (*see* **Sorting out sortilin, page 4**). ***SciBX* 3(32); doi:10.1038/scibx.2010.986** **Published online Aug. 19, 2010**	Findings unpatented; licensing status undisclosed	Musunuru, K. *et al. Nature*; published online Aug. 4, 2010; doi:10.1038/nature09266 **Contact:** Daniel J. Rader, University of Pennsylvania, Philadelphia, Pa. e-mail: rader@mail.med.upenn.edu
Endocrine disease				
Diabetes	IL-2	A study in mice suggests that low doses of IL-2 could help treat type 1 diabetes. In nonobese diabetic mice, IL-2 reversed established disease compared with nonactive, denatured IL-2. Next steps include designing a Phase I/II trial with the Pitié-Salpêtrière Hospital in Paris and determining both the optimal dose of IL-2 for diabetes and the biomarkers for monitoring IL-2's effects in humans. Novartis AG markets Macrolin aldesleukin IL-2 for melanoma and renal cancer. ***SciBX* 3(32); doi:10.1038/scibx.2010.987** **Published online Aug. 19, 2010**	Unpatented; unavailable for licensing	Grinberg-Bleyer, Y. *et al. J. Exp. Med.*; published online Aug. 2, 2010; doi:10.1084/jem.20100209 **Contact:** Eliane Piaggio, University of Pierre and Marie Curie, Paris, France e-mail: elianepiaggio@yahoo.com
Diabetes	Ribosomal protein S6 kinase (RSK)	*In vitro* studies identified an RSK inhibitor that could help treat type 1 diabetes. In mouse α cells, low micromolar concentrations of the RSK inhibitor increased β cell–like morphology, expression of β cell markers and insulin production compared with solvent control. In primary human pancreatic islets, the inhibitor increased glucose-stimulated insulin secretion and expression of endocrine-related genes compared with solvent. Next steps could include determining the mechanism of the inhibitor's effects on human islets. ***SciBX* 3(32); doi:10.1038/scibx.2010.988** **Published online Aug. 19, 2010**	Patent and licensing status unavailable	Fomina-Yadlin, D. *et al. Proc. Natl. Acad. Sci. USA*; published online Aug. 9, 2010; doi:10.1073/pnas.1010018107 **Contact:** Stuart L. Schreiber, Harvard University, Cambridge, Mass. e-mail: stuart_schreiber@harvard.edu
Infectious disease				
Bacterial infection	Bacterial topoisomerase IIA	A cell culture and X-ray crystal structure study identified a topoisomerase IIA inhibitor that could help treat antibiotic-resistant bacterial infections. In a panel of Gram-positive and Gram-negative bacteria, GSK299423 showed broad-spectrum antibacterial activity, even toward bacteria with mutations that cause resistance to marketed fluoroquinolone antibiotics. A crystal structure of GSK299423 complexed with *Staphylococcus aureus* topoisomerase IIA and DNA showed that the compound binds between two active sites on the enzyme, a position that is distinct from the two binding sites of fluoroquinolone antibiotics. GSK299423 is a research reagent from GlaxoSmithKline plc, and next steps include developing a topoisomerase IIA inhibitor as a therapeutic candidate. ***SciBX* 3(32); doi:10.1038/scibx.2010.989** **Published online Aug. 19, 2010**	Patent status undisclosed; unavailable for licensing	Bax, B.D. *et al. Nature*; published online Aug. 4, 2010; doi:10.1038/nature09197 **Contact:** Michael N. Gwynn, GlaxoSmithKline plc, Collegeville, Pa. e-mail: mick.gwynn@gsk.com

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
HIV/AIDS	Lymphocyte antigen 75 (LY75; DEC205); HIV p24	A study in mice identified DEC205-targeting mAbs that could help deliver a protein-based vaccine to treat HIV. In mice expressing human DEC205, an anti-DEC205 mAb conjugated to HIV p24 produced a stronger immune response than a nontargeting mAb conjugated to HIV p24. Next steps could include humanizing the mAbs used in the study. ***SciBX* 3(32); doi:10.1038/scibx.2010.990** **Published online Aug. 19, 2010**	Patent and licensing status unavailable	Cheong, C. *et al. Blood*; published online July 28, 2010; doi:10.1182/blood-2010-06-288068 **Contact:** Ralph M. Steinman, The Rockefeller University, New York, N.Y. e-mail: steinma@mail.rockefeller.edu
Viral infection	PD-1 receptor (PDCD1; PD-1; CD279); programmed cell death 1 ligand 1 (CD274 molecule; PD-L1; B7-H1); hepatitis A virus cellular receptor 2 (HAVCR2; TIM3)	A study in mice suggests that combined inhibition of TIM3 and PD-1 could help treat chronic viral infection. In mice chronically infected with lymphocytic choriomeningitis virus (LCMV), an antibody against PD-L1 plus a TIM3-targeting fusion protein increased proliferation of antigen-specific $CD8^+$ T cells and decreased viral loads compared with either compound alone. Next steps include studying the effects of inhibiting the two pathways in conjunction with other antivirals. MDX-1106 (ONO-4538), a humanized anti-PD-1 antibody from Ono Pharmaceutical Co. Ltd. and Bristol-Myers Squibb Co., is in Phase I testing to treat cancer and HCV. AMP-224, a fusion protein that blocks the interaction between PD-1 and PD-L1, from Amplimmune Inc. and GlaxoSmithKline plc, is in preclinical development to treat cancer and infectious disease. ***SciBX* 3(32); doi:10.1038/scibx.2010.991** **Published online Aug. 19, 2010**	Patented; available for licensing	Jin, H.-T. *et al. Proc. Natl. Acad. Sci. USA*; published online Aug. 2, 2010; doi:10.1073/pnas.1009731107 **Contact:** Rafi Ahmed, Emory University School of Medicine, Atlanta, Ga. e-mail: rahmed@emory.edu
Musculoskeletal disease				
Tissue damage	Connective tissue growth factor (CTGF)	Cell culture studies suggest that CTGF could help treat connective tissue damage. In cultured bone marrow–derived mesenchymal stem cells, recombinant CTGF induced differentiation of cells into fibroblasts and increased collagen synthesis compared with no treatment. Next steps include improvements in microencapsulating CTGF for delivery. ***SciBX* 3(32); doi:10.1038/scibx.2010.992** **Published online Aug. 19, 2010**	Patent filed; available for licensing	Lee, C.H. *et al. J. Clin. Invest.*; published online Aug. 2, 2010; doi:10.1172/JCI43230 **Contact:** Jeremy J. Mao, Columbia University Medical Center, New York, N.Y. e-mail: jmao@columbia.edu
Neurology				
Alzheimer's disease (AD)	β-Amyloid (Aβ)	A study in mice identified a mAb that could help treat AD. The mAb against a synthetic Aβ oligomer restored cognitive performance in mice with AD to levels comparable to those in healthy controls. In a separate mouse model of AD, the mAb significantly increased synaptic spine density in hippocampal pyramidal neurons compared with saline control ($p<0.05$). Next steps could include testing the mAb in additional rodent AD models. At least 17 companies have Aβ-targeting compounds in Phase III or earlier to treat AD. ***SciBX* 3(32); doi:10.1038/scibx.2010.993** **Published online Aug. 19, 2010**	Patent and licensing status unavailable	Hillen, H. *et al. J. Neurosci.*; published online Aug. 4, 2010; doi:10.1523/JNEUROSCI.5721-09.2010 **Contact:** Ulrich Ebert, Abbott Laboratories, Ludwigshafen, Germany e-mail: ulrich.ebert@abbott.com **Contact:** Heinz Hillen, same affiliation as above e-mail: heinz.hillen@abbott.com

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Pain	B-type natriuretic peptide (BNP; NPPB)	Rat studies suggest that BNP could help treat inflammatory pain. In two rat models of chemically induced inflammatory pain, intrathecal BNP decreased flinching behavior and thermal hyperalgesia compared with no treatment or pretreatment with BNP signaling inhibitors. Ongoing work includes testing BNP and an oral BNP analog in animal models of rheumatoid arthritis (RA). ***SciBX* 3(32); doi:10.1038/scibx.2010.994** **Published online Aug. 19, 2010**	Patent held by the Chinese Academy of Sciences; available for licensing	Zhang, F.-X. *et al. J. Neurosci.*; published online Aug. 11, 2010; doi:10.1523/JNEUROSCI.0657-10.2010 **Contact:** Xu Zhang, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai, China e-mail: xu.zhang@ion.ac.cn
Spinal cord injury (SCI)	Phosphatase and tensin homolog deleted on chromosome ten (PTEN; MMAC1; TEP1)	A study in mice suggests that inhibiting PTEN-mediated signaling in injured regions of the CNS could help treat SCI. In two mouse models of SCI, deletion of *Pten* resulted in greater sprouting of corticospinal tract neurons at the injury site than normal *Pten* expression. Next steps include studying the effects of PTEN deletion on CNS functional recovery in animals. ***SciBX* 3(32); doi:10.1038/scibx.2010.995** **Published online Aug. 19, 2010**	Findings patented; licensing status undisclosed	Liu, K. *et al. Nat. Neurosci.*; published online Aug. 8, 2010; doi:10.1038/nn.2603 **Contact:** Zhigang He, Harvard Medical School, Boston, Mass. e-mail: zhigang.he@childrens.harvard.edu

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			
Sampling method for tissue-based molecular diagnostics	A sampling method that improves tissue solubilization and preservation of biomolecules in living tissues may be useful for diagnosing skin diseases. In a mouse model of allergic dermatitis, the procedure detected higher levels of the allergy biomarker IgE in eczematic skin than in healthy skin. Next steps include further safety testing of the method. ***SciBX* 3(32); doi:10.1038/scibx.2010.996** **Published online Aug. 19, 2010**	Patent application filed; licensing status undisclosed	Paliwal, S. *et al. Proc. Natl. Acad. Sci. USA*; published online Aug. 8, 2010; doi:10.1073/pnas.1004302107 **Contact:** Samir Mitragotri, University of California, Santa Barbara, Calif. e-mail: samir@engineering.ucsb.edu
Disease models			
Canine model of X-linked myotubular myopathy	A Labrador retriever model could guide the development of new therapies for X-linked myotubular myopathy, a genetic disease caused by a defect in myotubularin 1 (MTM1). Muscle biopsies from seven Labrador retrievers with generalized weakness and muscle atrophy showed histological signs of X-linked myotubular myopathy. Genetic sequencing of *MTM1* in the dogs identified a missense mutation in exon 7 that was not found in healthy dogs. Next steps could include using the model to evaluate treatments for X-linked myotubular myopathy. ***SciBX* 3(32); doi:10.1038/scibx.2010.997** **Published online Aug. 19, 2010**	Patent and licensing status unavailable	Beggs, A.H. *et al. Proc. Natl. Acad. Sci. USA*; published online Aug. 2, 2010; doi:10.1073/pnas.1003677107 **Contact:** Alan H. Beggs, The Manton Center for Orphan Disease Research at Children's Hospital Boston, Boston, Mass. e-mail: beggs@enders.tch.harvard.edu
Mouse model of nickel-associated allergic contact dermatitis	A mouse model of nickel-associated allergic dermatitis could help guide the development of dermatitis therapies. In a human embryonic kidney cell line, mutations in two histidine residues of *toll-like receptor 4* (*TLR4*) lowered nickel-induced proinflammatory gene expression compared with nonmutated *TLR4*, confirming that TLR4 is a key mediator of nickel-associated dermatitis. Transgenic mice expressing human *TLR4* developed nickel-induced contact dermatitis, whereas those expressing only mouse *Tlr4*, which lacks a nickel-responsive region, did not. Next steps include using the transgenic mice to identify specific inhibitors of the nickel-responsive region of human TLR4. ***SciBX* 3(32); doi:10.1038/scibx.2010.998** **Published online Aug. 19, 2010**	Patent application filed covering contact allergies in humans; licensing inquiries should be directed to the University of Giessen	Schmidt, M. *et al. Nat. Immunol.*; published online Aug. 15, 2010; doi:10.1038/ni.1919 **Contact:** Matthias Goebeler, University of Giessen, Giessen, Germany e-mail: matthias.goebeler@derma.med.uni-giessen.de
Drug platforms			
Reprogramming cardiac fibroblasts to produce cardiomyocytes for cardiac regeneration	*In vitro* and mouse studies suggest that the transcription factors GATA binding protein 4 (GATA4), myocyte enhancing factor 2C (MEF2C) and T-box 5 (TBX5) could reprogram cardiac fibroblasts to generate cardiomyocytes for cardiac tissue regeneration. In cultured cardiac fibroblasts, expression of GATA4, MEF2C and TBX5 induced the display of cardiomyocyte-like genes and cell contractility compared with expression of other transcription factors. Reprogrammed cardiac fibroblasts injected into the hearts of mice differentiated into cardiomyocyte-like cells compared with fibroblasts that were not reprogrammed. Next steps could include testing the strategy in disease models. ***SciBX* 3(32); doi:10.1038/scibx.2010.999** **Published online Aug. 19, 2010**	Patent and licensing status unavailable	Ieda, M. *et al. Cell*; published online Aug. 5, 2010; doi:10.1016/j.cell.2010.07.002 **Contact:** Deepak Srivastava, University of California, San Francisco, Calif. e-mail: dsrivastava@gladstone.ucsf.edu **Contact:** Masaki Ieda, same affiliation as above e-mail: ieda@cpnet.med.keio.ac.jp

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