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Melanoma's hidden act

By Kai-Jye Lou, Staff Writer

Researchers at the **University of Bonn** and the **Johannes Gutenberg University Mainz** have shown that melanoma cells can acquire resistance to adoptive T cell transfer therapies by dedifferentiating themselves to hide antigens.¹ The group now is trying to circumvent this resistance mechanism and thinks doing so could improve treatment responses for current T cell therapy protocols.

Adoptive T cell transfer is one of three immunotherapy-based strategies used to treat metastatic melanomas and typically is used in patients for whom standard treatments have failed.

The two other immunotherapy approaches being developed for melanoma involve nonspecific immunostimulation and active immunization.

The two marketed immunotherapies for melanoma work via nonspecific immunostimulation: Proleukin aldesleukin IL-2 from **Novartis AG** and Yervoy ipilimumab, a human mAb against CTLA-4 (CD152) receptor from **Bristol-Myers Squibb Co.** Both drugs cause tumor regression in up to 15% of patients.^{2,3}

The two most advanced active immunizers for melanoma are talimogene laherparepvec from **Amgen Inc.** and GSK1572932A from **GlaxoSmithKline plc.** Talimogene laherparepvec is a modified herpes simplex virus type 1 (HSV-1) encoding granulocyte macrophage colony-stimulating factor (GM-CSF; CSF2). GSK1572932A is a vaccine against melanoma-associated antigen A3 (MAGEA3). Both compounds are in Phase III testing.

Adoptive cell transfer typically involves isolating, expanding and activating tumor-infiltrating lymphocytes or peripheral blood T cells and then infusing the cells back into the patient.

Although peripheral blood T cells are more plentiful and are easier to isolate than tumor-infiltrating lymphocytes, they lack tumor specificity and thus need to be engineered to express T cell receptors (TCRs) or chimeric antigen receptors that target tumor antigens before they are infused back into the patient.

Companies have avoided adoptive cell therapies because they need to be tailored to each patient. Clinical trials evaluating adoptive cell therapies are being run by research institutes, including the **National Cancer Institute (NCI)**.

NCI trials have shown objective tumor regression in up to 72% of patients.^{4,5} Response durations can range from just two months to over six years. The mechanisms underlying how melanomas develop resistance to these therapies over time are unclear.

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A research group led by Thomas Tüting, a professor of experimental dermatology and head of dermato-oncology at **University Hospital Bonn**, has been trying to better understand how melanomas acquire resistance to adoptive T cell therapies. Understanding such mechanisms could help improve the durability of the treatment response.

The group previously developed an immunocompetent genetically engineered mouse melanoma model and an adoptive transfer protocol that uses T cells engineered to recognize the melanocyte-specific antigen silver homolog (Silv; Pmel17; Gp100).⁶⁻⁸ Similar to patients who are treated with engineered T cells, tumors in this mouse model initially respond to therapy but often start growing again after two months.

Now, the researchers have used the mouse model to test an adoptive transfer protocol and elucidate the resistance mechanisms that lead to tumor relapse. They found that acquired resistance to T cell therapies stems from dedifferentiation and downregulated expression of multiple melanocytic antigens. The class of melanocytic antigens includes GP100, which is normally upregulated when cells differentiate into melanocytes (see Figure 1, “Resistance to adoptive T cell therapy via dedifferentiation”).

A series of transplantation and cell culture studies showed that the dedifferentiation and antigen loss were reversible and were associated with T cell-driven inflammation. The researchers identified tumor necrosis factor- α (TNF- α) as the key proinflammatory cytokine responsible for dedifferentiation and antigen loss.

Indeed, T cells engineered to recognize GP100 or another melanocytic antigen called melan-A (MLANA; MART1) showed less reactivity against human melanoma cells exposed to TNF- α than against unexposed melanoma cells. In contrast, two T cell lines engineered to recognize two different nonmelanocytic antigens showed unchanged and increased reactivity against TNF- α -exposed human melanoma cells, respectively.

Results were published in *Nature*.

“We found that tumor relapse after initially successful T cell immunotherapy involves a reversible adaptive process of dedifferentiation driven by proinflammatory mediators such as TNF- α secreted by tumor-infiltrating immune cells in the tumor microenvironment,” said corresponding author Tüting.

“These results are very interesting for adoptive cell therapies, as they could explain why we often see partial responses as opposed to complete responses in the patient’s lesions,” said Laszlo Radvanyi, a professor in the Department of Melanoma Medical Oncology at **The University of Texas MD Anderson Cancer Center**. “T cells produce proinflammatory cytokines during the antitumor immune response, and perhaps the TNF- α they produce causes loss of melanosomal antigens that these cells target.”

“The most interesting finding of the work was not the immune selection of antigen-specific variants but rather the fact that TNF- α ,

“The key challenge is to further improve treatment protocols by combining adoptive cell transfer with complementary strategies such as checkpoint blockade and inhibitors of oncogenic signaling pathways.”

**— Thomas Tüting,
University Hospital Bonn**

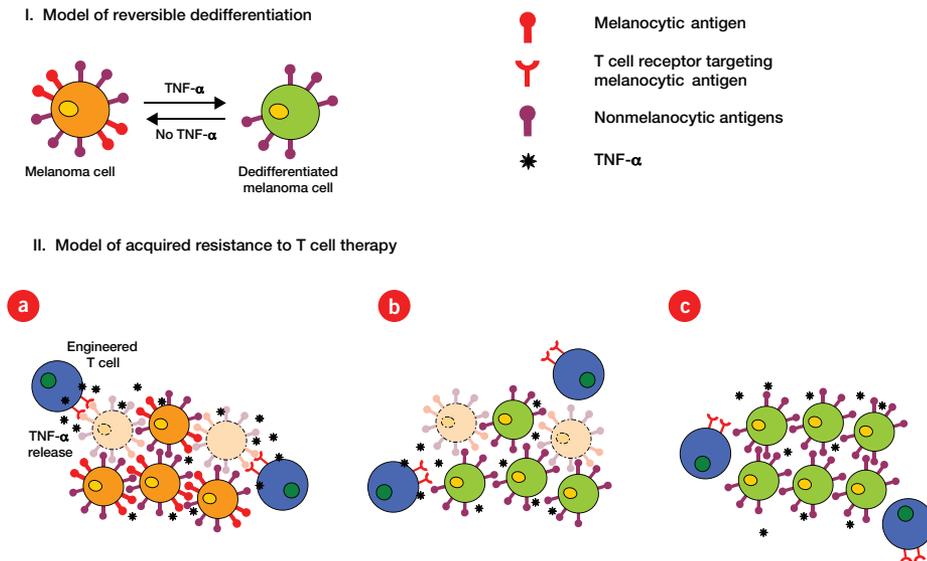


Figure 1. Resistance to adoptive T cell therapy via dedifferentiation. As reported by Landsberg *et al.*, melanoma cells can undergo inflammation-induced dedifferentiation. The process is a potential acquired resistance mechanism against adoptive cell transfer therapies.

(I) Melanoma cells exposed to the proinflammatory cytokine tumor necrosis factor- α (TNF- α) undergo reversible dedifferentiation. Cells with the dedifferentiated phenotype show downregulated expression of melanocytic antigens.

(II) Adoptive cell transfer therapies for melanoma can involve the infusion of T cells engineered to express antigen receptors that recognize melanocytic antigens. The dedifferentiation mechanism could contribute to resistance against such therapies.

Infused T cells recognize antigens expressed by the melanoma cells and trigger an immune response (II[a]). However, TNF- α released by these T cells during the immune response also can trigger the dedifferentiation process (II[b]). The infused T cells are unable to recognize dedifferentiated melanoma cells. Over time, these dedifferentiated cells regrow and become the dominant cellular phenotype in the tumor (II[c]).

presumably generated from antigen-specific infiltrating effector T cells, was capable of generating passive resistance,” added Jeffrey Weber, a senior member and director of the Donald A. Adam Comprehensive Melanoma Research Center of Excellence at the **H. Lee Moffitt Cancer Center & Research Institute**.

According to Antoni Ribas, the findings might explain why adoptive transfer of tumor-infiltrating lymphocytes tends to elicit a more durable tumor response than adoptive transfer of engineered T cells. The reason is that tumor-infiltrating lymphocytes used in adoptive therapies target a broad range of tumor antigen epitopes and not just a single antigen epitope.

Ribas is a professor in the Department of Medicine at the **University of California, Los Angeles David Geffen School of Medicine** and director of the tumor immunology program at the university’s Jonsson Comprehensive Cancer Center.

From mechanism to therapies

The key question is whether the mechanism observed in the mouse model applies to melanoma patients who have received adoptive cell transfer.

“I think the data are intriguing, but I would want to hear about what confirmation could be obtained from ongoing adoptive cell

transfer trials in melanoma patients,” Weber told *SciBX*.

“If this mechanism applies in humans, and if TNF- α is a key cytokine responsible for reversibly downregulating expression of melanocytic antigens, it does open an opportunity to combine anti-TNF strategies with adoptive cell therapy,” added Radvanyi. “What the researchers should do now is show in their model that blocking TNF signaling with an anti-TNF antibody or TNF-targeted shRNA will reverse the dedifferentiation phenomenon.”

Ribas cautioned that the systemic immunosuppressive effects of anti-TNF therapies could end up working against the adoptive cell therapy. He thinks a more directed strategy could be to downregulate or prevent TNF- α expression in the transferred T cells themselves.

Ribas said the data in the paper might only apply to melanocytic antigens and not to other classes of melanoma-associated antigens. Thus, he thinks using mixed populations of engineered T cells that target different classes of antigens could help delay or prevent acquired resistance.

Tüting noted that combining adoptive cell therapies with other immunotherapies and other classes of targeted therapies for melanoma also could improve treatment responses.

“The key challenge is to further improve treatment protocols by combining adoptive cell transfer with complementary strategies such as checkpoint blockade and inhibitors of oncogenic signaling pathways,” Tüting told

SciBX. “The development of adequate timing and dosing schedules requires a better understanding of the different resistance mechanisms and the establishment of biomarkers and monitoring procedures.”

Tüting said the group is working to develop more clinically relevant models that will be useful for testing potential combinations with adoptive cell therapies.

The findings reported in *Nature* are unpatented.

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COMPANIES AND INSTITUTIONS MENTIONED

Amgen Inc. (NASDAQ:AMGN), Thousand Oaks, Calif.
Bristol-Myers Squibb Co. (NYSE:BMJ), New York, N.Y.
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
H. Lee Moffitt Cancer Center & Research Institute, Tampa, Fla.
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National Cancer Institute, Bethesda, Md.

Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
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China's new mAb institute

By Tim Fulmer, Senior Writer

The launch of the **Shanghai Institute for Advanced Immunochemical Studies** marks China's first attempt to establish a center of antibody research on par with research centers in the U.S. and Europe. Although details are still sparse, the institute will identify targets and develop antibodies to treat cancer as well as infectious, autoimmune and metabolic diseases.

This month, the **Chinese Academy of Sciences** held a ceremony in Shanghai marking the launch of the Shanghai Institute for Advanced Immunochemical Studies (SIIS) by the **University of Shanghai for Science and Technology** (USST) and the **Shanghai Advanced Research Institute**. American researcher Richard Lerner was appointed head of the governing advisory board of the new institute.

The board will function much like a scientific advisory board, said Lerner. The other board members have not been disclosed.

Lerner is former president and CEO of **The Scripps Research Institute**, where he now is professor of immunochemistry, a position he will retain.

"China is serious about getting into the mAb game now, and the purpose of the new institute is to get critical mass in modern immunochemistry by bringing together the right labs that work on antibodies and putting them under

the same roof," Lerner told *SciBX*. "That arrangement should make for solid collaborations and lead to innovative research."

SIIS will be located in its own building, which is being constructed on the USST campus. It will house the labs of researchers drawn from USST and potentially other institutes and universities in China.

SIIS will be run by a CEO and COO, who have been recruited but will be announced at a later time, according to Lerner. He could not disclose whether they are Chinese or have come from outside the country.

The overarching theme of the new institute is next-generation approaches to mAb therapeutics, said Lerner.

"Some initial areas of interest include orally delivered mAbs, cell-permeable mAbs, agonist mAbs and mAbs armed with organic small molecules. We will also look at indications not usually associated with mAb therapies such as metabolic disorders," he said. "There are also

plans to generate an antigenic map of human cells, which should allow for the identification of new mAb targets not identified by standard first-generation approaches that rely on combinatorial libraries."

Lerner said he and the CEO and COO are discussing what the institute's research focus areas should be and which labs might make the best fit.

USST and the Chinese Academy of Sciences did not respond to requests for an interview.

Lerner is not the first big-name U.S. scientist to take on a major role at a Chinese research institute. Over the past decade, life science researchers from multiple U.S. universities have been recruited to found and/or direct and advise institutes.¹

In 2002, Tian Xu, Min Han and Yuan Zhuang founded and became co-directors of the **Institute of Developmental Biology and Molecular Medicine** (IDM) at **Fudan University**. The IDM includes 10 primary faculty members and over 150 research personnel.

All three co-directors retain their U.S. academic positions. Xu is professor at the **Yale School of Medicine** and vice chair of the Department of Genetics. Han is professor of molecular, cellular and developmental biology at the **University of Colorado at Boulder**. Zhuang is professor of immunology and molecular genetics and microbiology at **Duke University**.

In 2003, Xiaodong Wang resigned his appointment as professor in biomedical science at **The University of Texas Southwestern Medical Center** to run Beijing's **National Institute of Biological Sciences** (NIBS), then a new research center in Beijing modeled after the **Howard Hughes Medical Institute**.

NIBS was formed as part of a government initiative to promote the development of science and technology in China.²

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COMPANIES AND INSTITUTIONS MENTIONED

Chinese Academy of Sciences, Beijing, China
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Fudan University, Shanghai, China
Howard Hughes Medical Institute, Chevy Chase, Md.
Institute of Developmental Biology and Molecular Medicine, Shanghai, China
National Institute of Biological Sciences, Beijing, China
The Scripps Research Institute, La Jolla, Calif.
Shanghai Advanced Research Institute, Shanghai, China
Shanghai Institute for Advanced Immunochemical Studies, Shanghai, China
University of Colorado at Boulder, Boulder, Colo.
University of Shanghai for Science and Technology, Shanghai, China
The University of Texas Southwestern Medical Center, Dallas, Texas
Yale School of Medicine, New Haven, Conn.

"China is serious about getting into the mAb game now, and the purpose of the new institute is to get critical mass in modern immunochemistry by bringing together the right labs that work on antibodies and putting them under the same roof."

—Richard Lerner,
The Scripps Research Institute

Myelination from neural stem cells

By Lauren Martz, Staff Writer

University of California, San Francisco, Oregon Health & Science University and StemCells Inc. have found that neural stem cell transplants could remyelinate axons and treat myelination disorders including Pelizaeus-Merzbacher disease.^{1,2} The biotech is planning a Phase II study of neural stem cell transplantation in the indication.

Pelizaeus-Merzbacher disease (PMD) is a rare X-linked leukodystrophy disorder caused by mutations in proteolipid protein 1 (PLP1). These mutations disrupt the ability of oligodendrocytes to myelinate axons, which leads to neurological deficits and eventually degeneration.

In 2010, a University of California, Irvine team reported that human neural stem cells differentiated into mature oligodendrocytes and neurons and helped restore locomotor function in rodents with spinal cord injury.³

Building on that work, researchers from OHSU and StemCells decided to test whether these cells could differentiate into myelin-producing oligodendrocytes to help treat myelination disorders.

The team also included researchers from UC Irvine, the Stanford University School of Medicine and the Oregon National Primate Research Center.

The group transplanted human fetal neural stem cells into an immunodeficient mouse model of hypomyelination. The neonatal mice given the transplant showed widespread engraftment of the human cells, which differentiated into myelin-producing oligodendrocytes in appropriate brain regions and produced myelin sheaths on axons.

The team repeated the procedure in juvenile mice with extensive demyelination and found similar increases in myelinated neurons, suggesting the strategy could indeed replace lost myelin.

In tissue samples from both the juvenile and neonatal mouse brains, action potentials had higher amplitude in mice treated with neural stem cells than those in vehicle-treated or human liver mesenchymal stem cell-treated controls.

Based on these mouse data, StemCells sponsored a Phase I, open-label trial of the technique in four patients with early severe PMD. The trial was run by David Rowitch, professor of pediatrics and neurological surgery at UCSF and a Howard Hughes Medical Institute investigator, and Nalin Gupta, associate professor of neurological surgery and pediatrics and chief of pediatric neurological surgery at UCSF Benioff Children's Hospital.

Patients received 3×10^8 human fetal neural stem cells injected through 4 bilateral brain holes followed by 9 months of immunosuppressive therapy.

At 12 months post-transplant, all patients were stable or had modest gains in motor function. Patients also had minor gains in cognitive function.

Diffusion MRI, which maps the diffusion of water molecules to determine the composition of tissues, suggested the presence of myelin in the patients. None of the patients had detectable myelin before surgery.

The human and mouse studies were published as separate papers in the same issue of *Science Translational Medicine*.

According to Gupta, "In general, patients with severe forms of PMD demonstrate a progressively worsening clinical course. The changes we observed in some of the transplanted children amounted to better motor function and improvement in developmental milestones."

Future trials

The patients from the Phase I trial are being studied by the UCSF team in a four-year follow-up.

"We will be looking primarily for any adverse effects of the cells in the follow-up study, but we will also be monitoring MRI and clinical outcomes," said Rowitch. "We are interested to see how the story continues to evolve and see if the signs that the cells have engrafted and are producing myelin continue to become more obvious with time."

"They do need to determine if the cells are safe in the long term. Tumorigenesis has been caused by neural stem cells in isolated examples," said Spyros Dfeterios, VP of drug discovery at Biovista Inc.

Biovista has BVA-101 and the BVA-20x class of compounds with undisclosed mechanisms in preclinical testing to treat multiple sclerosis (MS). The company did not disclose further details.

"Tumors are a risk that we are watching out for," acknowledged Rowitch. "Because this is such an early generation trial, we can't be exactly sure what the potential adverse effects of the cells will be. In the first year of the study, we have had a very favorable safety profile."

Mike Gresser, CSO of the Myelin Repair Foundation (MRF), and Robert Mays, head of neuroscience at Athersys Inc., both were concerned about the duration of immunosuppressant use.

Gresser told *SciBX*, "In order for the recipient to receive these donor cells, the patient will have to be treated with immune-suppressing drugs to keep their immune systems from rejecting the donated cells, just as organ transplant recipients have to be treated with immune-suppressing drugs. Immune suppression carries the risk of infections and adverse effects."

"Researchers need to understand for how long and at what level immunosuppression would be required for this type of treatment to have meaningful, long-term benefit," said Mays. Athersys is developing MultiStem, a multipotent adult progenitor cell-based approach to reduce neuroinflammation associated with CNS injuries and disease. MultiStem cells are in preclinical testing to treat MS and in clinical trials to treat ischemic stroke.

Rowitch told *SciBX* that his team has not seen any changes in immune reaction toward the transplanted cells after ceasing immunosuppressive therapy.

"We noted persistence of the MRI signals after discontinuing immunosuppression. In future studies, it will be important to carefully

"In general, patients with severe forms of PMD demonstrate a progressively worsening clinical course. The changes we observed in some of the transplanted children amounted to better motor function and improvement in developmental milestones."

—Nalin Gupta,
UCSF Benioff Children's Hospital

monitor and manage the potential for cell rejection by the patient,” he said.

Deftereos suggested that a solution to the issue of immunogenicity would be to use autologous stem cells. “The technology exists to dedifferentiate a patient’s cells into pluripotent cells, then redifferentiate them into neural stem cells,” he said.

Jason Hamilton, senior scientist at Athersys, said autologous cells could be a solution to myelination disorders that are not known to be caused by a genetic mutation, such as MS. However, he said, autologous stem cells isolated from patients with PMD or other genetic myelination disorders will have the same mutations as the dysfunctional, myelin-producing cells causing the disease, which may limit their effectiveness as a treatment option.

Other myelination disorders

In parallel with the Phase I extension study, StemCells is planning a Phase II trial.

In addition to the program in PMD, StemCells thinks the transplantation strategy could extend to other neurological disorders, “including certain cerebral palsies, transverse myelitis and even spinal cord injury in certain cases,” said Stephen Huhn, VP and head of the CNS program at StemCells.

He added, “MS is another potential indication. The issue is that it will require unique clinical considerations. MS is an autoimmune disease, and cell therapy could play a role in MS, but it would also be necessary to control the autoimmunity.”

Indeed, MRF’s Gresser was skeptical about the potential for the cell-based approach in MS.

“MS is not associated with a known genetic mutation that may impair their ability to myelinate axons. Due to this lack of genetic variation, we feel that this strategy will most likely not be applicable for MS patients but instead could be beneficial for patients with a genetic disorder such as PMD,” he said.

Hamilton added, “In the case of an autoimmune disease like MS, in which the demyelination is caused by a systemic autoimmune reaction, this type of cell-based approach would be limited if you don’t use an

adjunctive therapy to address the autoimmune component. There would be no way to stop the body from attacking the production of new myelin by the transplanted cells.”

“There could be synergy between the approaches described in these papers and strategies that modulate the negative effects of neuroinflammation. For example, treatment with MultiStem cells may slow or stop neuroinflammation and thereby give subsequently transplanted neural stem cells the chance to engraft and make myelin in a less hostile environment. We are excited about the idea of this synergistic potential,” added Mays.

Huhn told *SciBX* that StemCells holds patents related to both the human and mouse studies. The IP is available for licensing.

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COMPANIES AND INSTITUTIONS MENTIONED

Athersys Inc. (NASDAQ:ATHX), Cleveland, Ohio
Biovista Inc., Charlottesville, Va.
Howard Hughes Medical Institute, Chevy Chase, Md.
Myelin Repair Foundation, Saratoga, Calif.
Oregon Health & Science University, Portland, Ore.
Oregon National Primate Research Center, Beaverton, Ore.
Stanford University School of Medicine, Stanford, Calif.
StemCells Inc. (NASDAQ:STEM), Newark, Calif.
UCSF Benioff Children’s Hospital, San Francisco, Calif.
University of California, Irvine, Irvine, Calif.
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B_{reg}-ging rights

By Lev Osherovich, Senior Writer

Duke University School of Medicine researchers have developed a way to grow large quantities of regulatory B cells.¹ The team used an infusion of B_{reg} cells to suppress a murine form of multiple sclerosis and now wants to test the immunomodulatory cells in other autoimmune diseases. They are hoping to launch a company based on the technology.

B_{reg} cells produce the anti-inflammatory cytokine IL-10 and can counteract excessive immune activation in autoimmune and inflammatory diseases.²

In previous studies, a team led by Thomas Tedder, professor of research in immunology at Duke, engineered mice deficient in B_{reg} cells and showed that the animals were more susceptible to autoimmune and inflammatory diseases than wild-type animals.³ However, because B_{reg} cells constitute only a tiny fraction of circulating B cells, it was not possible to harvest enough cells to test whether infusing B_{reg}-deficient animals with B_{reg} cells would have a beneficial effect.

The new work by Tedder's team solves the B_{reg} cell supply problem. The researchers determined the conditions that promote the development of B_{reg} cells in the spleens of mice and reproduced those conditions *ex vivo* to grow large numbers of the cells.

"We can now identify subsets of B_{reg} cell precursors, purify that subset and adoptively transfer it" to mice unable to make their own B_{reg} cells, said Tedder. "If you want to treat autoimmune disease, being able to expand these cells is an advance."

Isolate and activate

The team began by purifying general B cell precursors from the spleens of mice and treating them *in vitro* with a range of cytokines suspected to influence B_{reg} cell development.

B cell precursors activated with IL-21 secreted IL-10, whereas controls treated with media or with other cytokines did not. When transferred into B_{reg}-deficient mice, the *in vitro*-activated cells decreased symptoms of experimental autoimmune encephalitis (EAE) compared with unactivated B cell precursors.

Because B cell activation typically is enhanced by T helper cells, the natural source of IL-21, the team suspected that other T cell molecules might further promote B_{reg} cell activation and growth. Indeed, IL-21 activation of B_{reg} cells was further increased by CD40, a B cell co-receptor that binds to CD40 ligand (CD40LG; CD40L; CD154), found on the surface of T cells.

Using this information, the researchers developed a streamlined procedure for growing B_{reg} cells *in vitro*. They transfected a fibroblast cell line with CD154 and BlyS (BAFF), a general B cell-activating protein, and then cocultured B cell precursors with these fibroblasts in the presence of IL-21.

The resulting number of activated B_{reg} cells was about four million times the initial number of inactive cells. Reinfusion of those cells prevented the initial onset of EAE and decreased disease severity in mice that already had developed the condition compared with no treatment.

Results were published in *Nature*.

"The novel finding here is the ability to expand murine regulatory B cells in cell culture," said Abdolmohamad Rostami, professor of neuro-

logy at **Thomas Jefferson University**. "The next step is to extend this observation into humans—they should take whole B cells and treat them with human IL-21."

B_{reg}-adon

Tedder thinks infusions of large numbers of patient-derived, *ex vivo*-activated B_{reg} cells could help to rapidly shut down autoimmune diseases.

He said B_{reg} cells specific for autoimmunity-associated antigens already are present in patients with autoimmune disease but that there are too few of them to affect disease. The hope is that boosting overall levels of B_{reg} cells would tip the balance of immune activity toward suppression of autoimmunity.

"Nature has already created a set of B_{reg} cells with immunomodulatory activity," said Tedder. "If you have an autoimmune disease, these cells are already responding. Our job is just to expand them."

Tedder noted that because B_{reg} cells act in an antigen-specific manner, there is little danger of the broad immunosuppression that is a concern with immunomodulatory therapies.

The team "did show that the mice were not immunosuppressed, which is a major problem with many medications for autoimmune disease," said Rostami. "With conventional immunosuppression, there is a risk that you would suppress the suppressor cells, too."

The challenge, Tedder said, is to grow enough of the human cells *in vitro* to achieve the kind of disease-suppressing effects seen in mice. Tedder said his laboratory is now working on reproducing and scaling up the B_{reg} cell expansion procedure with human cells, which grow more slowly than mouse cells.

Both Tedder and Rostami said the technique will allow researchers to compare B_{reg} cells head-to-head with T_{reg} cells, another type of immunomodulatory cell.

Last year, a trio of academic teams reported procedures for amplifying and reinfusing human T_{reg} cells in humanized mouse models of autoimmune disease.⁴⁻⁷

Tedder thinks T_{reg} cells might be best suited for chronic inflammatory conditions, whereas B_{reg} cells appear to be most effective in acute conditions.

His technique is patented and is available for licensing. Tedder said he is hoping to launch a company based on the technology and is in the process of finding investors and commercial development partners.

Osherovich, L. *SciBX* 5(42); doi:10.1038/scibx.2012.1103
Published online Oct. 25, 2012

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e-mail: thomas.tedder@duke.edu
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COMPANIES AND INSTITUTIONS MENTIONED

Duke University School of Medicine, Durham, N.C.
Thomas Jefferson University, Philadelphia, 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
Cancer				
Cancer	Mdm2 p53 binding protein homolog (MDM2; HDM2); p53	SAR studies identified a series of MDM2-p53 interaction inhibitors that could be useful for treating cancer. In the first study, <i>in vitro</i> assays identified piperidone compounds that bound the N-terminal tail of MDM2 and stabilized the protein's structure, and decreased p53 binding compared with vehicle. In the second study, cell culture and mouse studies identified orally available, high-affinity pyrrolidone inhibitors of the MDM2-p53 interaction that decreased tumor growth more effectively than a reference compound. Next steps include further lead optimization and selection of preclinical candidates from both series. SciBX 5(42); doi:10.1038/scibx.2012.1104 Published online Oct. 25, 2012	Findings in first study covered by pending patent; licensing status undisclosed Findings in second study covered by pending patent; available for licensing	Michelsen, K. <i>et al. J. Med. Chem.</i> ; published online Sept. 19, 2012; doi:10.1021/ja305839b Contact: Leszek Poppe, Amgen Inc., Thousand Oaks, Calif. e-mail: lpoppe@amgen.com Contact: Xin Huang, same affiliation as above e-mail: hxin@amgen.com Zhuang, C. <i>et al. J. Med. Chem.</i> ; published online Oct. 9, 2012; doi:10.1021/jm300969t Contact: Wannian Zhang, Second Military Medical University, Shanghai, China e-mail: zhangwnk@hotmail.com Contact: Chunquan Sheng, same affiliation as above e-mail: shengcq@hotmail.com
Cancer	Pyruvate kinase M2 isozyme (PKM2)	<i>In vitro</i> and cell culture studies suggest PKM2 activators could help treat cancers with low tumor serine levels. High throughput screening and hit optimization identified mid-nanomolar activators of the cancer-associated glycolytic enzyme PKM2. In a human lung cancer cell line, a PKM2 activator inhibited proliferation only when serine was absent from the culture media, supporting a link between cancer cell glycolysis and serine biosynthesis. Next steps could include identifying cancer cell lines that are highly sensitive to PKM2 activators due to alterations in the serine biosynthetic pathway. Agios Pharmaceuticals Inc. has a discovery-stage program targeting PKM2 in cancer. Dynamix Pharmaceuticals Ltd.'s PKM2 activator, DNX-3000, is in preclinical development in cancer. SciBX 5(42); doi:10.1038/scibx.2012.1105 Published online Oct. 25, 2012	Patent and licensing status undisclosed	Kung, C. <i>et al. Chem. Biol.</i> ; published online Sept. 21, 2012; doi:10.1016/j.chembiol.2012.07.021 Contact: Lenny Dang, Agios Pharmaceuticals Inc., Cambridge, Mass. e-mail: lenny.dang@agios.com

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Chronic myelogenous leukemia (CML)	BCR-ABL tyrosine kinase	<p>Cell culture studies suggest Bosulif bosutinib plus danusertib could help treat CML resistant to Gleevec imatinib. In primary cancer cells isolated from a patient with Gleevec-resistant CML, bosutinib and danusertib synergistically decreased cell proliferation compared with vehicle. The combination did not show a synergistic antiproliferative effect in cells from a patient with Gleevec-sensitive CML. Next steps could include testing the combination in a mouse model of Gleevec-resistant CML.</p> <p>Novartis AG markets the BCR-ABL inhibitor Gleevec to treat CML and gastrointestinal stromal tumors (GISTs).</p> <p>Pfizer Inc.'s Bosulif, a dual inhibitor of BCR-ABL and Src, is approved to treat CML.</p> <p>Nerviano Medical Sciences s.r.l.'s aurora kinase inhibitor, danusertib (PHA-739358), is in Phase I and Phase II testing to treat various cancers.</p> <p>SciBX 5(42); doi:10.1038/scibx.2012.1106 Published online Oct. 25, 2012</p>	Patent and licensing status unavailable	<p>Winter, G.E. <i>et al. Nat. Chem. Biol.</i>; published online Sept. 30, 2012; doi:10.1038/nchembio.1085</p> <p>Contact: Giulio Superti-Furga, Research Center for Molecular Medicine of the Austrian Academy of Sciences, Vienna, Austria e-mail: gsuperti@cemm.oeaw.ac.at</p>
Colorectal cancer	MAP kinase kinase 8 (MAP3K8; COT; TPL2); c-Met proto-oncogene (MET; HGFR); hepatocyte growth factor/scatter factor (HGF/SF)	<p>Mouse studies suggest increasing TPL2 signaling could help prevent colitis-associated cancer. <i>Tpl2</i>-deficient mice showed greater susceptibility to colitis-induced tumor formation and developed higher-grade tumors than nondeficient controls. In mice, inhibiting Hgf/sf-mediated activation of Met prevented the increased susceptibility to tumor formation caused by <i>Tpl2</i> deficiency. Next steps include studying the mechanism by which TPL2 regulates HGF/SF production in intestinal fibroblasts.</p> <p>SciBX 5(42); doi:10.1038/scibx.2012.1107 Published online Oct. 25, 2012</p>	Unpatented; mouse model licensed to an undisclosed pharma and available for licensing	<p>Koliaraki, V. <i>et al. J. Clin. Invest.</i>; published online Oct. 15, 2012; doi:10.1172/JCI63917</p> <p>Contact: George Kollias, Alexander Fleming Biomedical Sciences Research Center, Vari, Greece e-mail: kollias@fleming.gr</p>
Lymphoma	Anaplastic lymphoma kinase (ALK); nucleophosmin (NPM1; B23); platelet derived growth factor receptor A (PDGFRA; PDGFR2; CD140A); PDGFRB (PDGFR1; CD140B)	<p>Studies in mice and in a single patient suggest inhibiting PDGFR2 could help treat anaplastic large cell lymphomas driven by the NPM1-ALK oncoprotein. In a mouse model of NPM1-ALK-driven anaplastic large cell lymphoma, inhibition of Pdgfr1 with Gleevec imatinib decreased tumor mass and increased survival compared with no treatment. In the mouse model, imatinib plus the ALK inhibitor Xalkori crizotinib caused greater tumor growth inhibition than either compound alone.</p> <p>In a single relapsed, chemotherapy-refractory patient, imatinib led to PDGFR1 levels that were lower than those before treatment and led to complete clinical remission. Next steps include designing a clinical trial to test imatinib in additional patients with NPM1-ALK-driven lymphomas and studying the role of PDGFR2 on the tumor microenvironment.</p> <p>Novartis AG markets the BCR-ABL tyrosine kinase inhibitor Gleevec to treat chronic myelogenous leukemia (CML) and gastrointestinal stromal tumors. Pfizer Inc. markets Xalkori to treat non-small cell lung cancer (NSCLC). The drug also is in Phase I testing to treat solid tumors.</p> <p>SciBX 5(42); doi:10.1038/scibx.2012.1108 Published online Oct. 25, 2012</p>	Patented; licensed to Akron Molecules GmbH	<p>Laimer, D. <i>et al. Nat. Med.</i>; published online Oct. 14, 2012; doi:10.1038/nm.2966</p> <p>Contact: Lukas Kenner, Medical University of Vienna, Vienna, Austria e-mail: lukas.kenner@meduniwien.ac.at</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Dermatology				
Dermatitis	Leukotriene B4 (LTB4); leukotriene A4 hydrolase (LTA4H);	Mouse studies suggest inhibiting LTB4 could help treat atopic dermatitis. In a mouse model of atopic dermatitis, knockout of <i>Lta4h</i> or intraperitoneal injection of an inhibitor of the LTB4-synthesizing enzyme LTB4H decreased neutrophil accumulation at dermatitis sites compared with normal <i>Lta4h</i> expression or vehicle injection. In another mouse model of atopic dermatitis, intraperitoneal injection of the LTB4H inhibitor before antigen challenge prevented development of allergic skin inflammation. Next steps include testing topical inhibitors of both LTB4 synthesis and the LTB4 type 1 receptor (BLT1) in an animal model. SciBX 5(42); doi:10.1038/scibx.2012.1109 Published online Oct. 25, 2012	Patent application filed; available for licensing	Oyoshi, M.K. <i>et al. Immunity</i> ; published online Oct. 11, 2012; doi:10.1016/j.immuni.2012.06.018 Contact: Raif S. Geha, Boston Children's Hospital, Boston, Mass. e-mail: raif.geha@childrens.harvard.edu Contact: Michiko K. Oyoshi, same affiliation as above e-mail: michiko.oyoshi@childrens.harvard.edu
Itch	MAS-related GPR member D (MRGPRD)	Human and mouse studies suggest blocking activation of MRGPRD could help treat histamine-independent itch. β -Alanine is known to activate MRGPRD receptors in humans and rodents. In 11 healthy subjects, intradermal injection of the muscle-building supplement β -alanine induced itching. <i>Mrgprd</i> -deficient mice were insensitive to itch induced by β -alanine injection but still showed an itch response to histamine injection. Next steps include developing MRGPRD antagonists and determining whether β -alanine is an endogenous mediator of chronic itch. SciBX 5(42); doi:10.1038/scibx.2012.1110 Published online Oct. 25, 2012	Work unpatented; licensing status not applicable	Liu, Q. <i>et al. J. Neurosci.</i> ; published online Oct. 17, 2012; doi:10.1523/JNEUROSCI.3509-12.2012 Contact: Xinzhong Dong, The Johns Hopkins University School of Medicine, Baltimore, Md. e-mail: xdong2@jhmi.edu Contact: Robert H. LaMotte, Yale School of Medicine, New Haven, Conn. e-mail: robert.lamotte@yale.edu
Endocrine/metabolic disease				
Dyslipidemia	X-box binding protein 1 (XBP1); endoplasmic reticulum to nucleus signaling 1 (ERN1; IRE1)	Studies in mice suggest antagonizing XBP1 or IRE1 could help treat dyslipidemia. In mice fed a high-fat diet, hepatocyte-specific deletion of IRE1, a bifunctional kinase and nuclease that promotes XBP1 activity, or small interfering RNA against <i>Xbp1</i> decreased triglyceride and cholesterol levels compared with control vector. Next steps include testing IRE1 inhibitors in mice with dyslipidemia. SciBX 5(42); doi:10.1038/scibx.2012.1111 Published online Oct. 25, 2012	Patent pending for findings in first study; available for licensing Patent and licensing status undisclosed for findings in second study	So, J.-S. <i>et al. Cell Metab.</i> ; published online Oct. 3, 2012; doi:10.1016/j.cmet.2012.09.004 Contact: Ann-Hwee Lee, Harvard School of Public Health, Boston, Mass. e-mail: anl2042@med.cornell.edu Wang, S. <i>et al. Cell Metab.</i> ; published online Oct. 3, 2012; doi:10.1016/j.cmet.2012.09.003 Contact: Randal J. Kaufman, Sanford-Burnham Medical Research Institute, La Jolla, Calif. e-mail: rkaufman@sbmri.org
Glycosphingolipid storage disorders	Unknown	Cell culture studies suggest compounds that improve lysosomal exocytosis could help treat lysosomal storage disorders such as Niemann-Pick type C disease and Wolman disease. In fibroblasts isolated from patients with Niemann-Pick type C disease or Wolman disease, δ -tocopherol increased lysosomal exocytosis and decreased disease markers compared with no treatment. Next steps could include screening for more potent enhancers of lysosomal exocytosis and evaluating them in models of lysosomal storage disorders. δ -Tocopherol is a generic form of vitamin E. SciBX 5(42); doi:10.1038/scibx.2012.1112 Published online Oct. 25, 2012	Patent and licensing status unavailable	Xu, M. <i>et al. J. Biol. Chem.</i> ; published online Oct. 3, 2012; doi:10.1074/jbc.M112.357707 Contact: Wei Zheng, National Institutes of Health, Bethesda, Md. e-mail: wzheng@mail.nih.gov

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Hematology				
Hemophilia	Factor IX	<p>Mouse studies suggest lentivirus-mediated delivery of a hyperfunctional mutant factor IX could help treat hemophilia. In a mouse model of hemophilia B, low doses of lentiviral vectors encoding an optimized hyperfunctional R338L factor IX mutant led to a 15-fold gain in factor IX activity, and greater factor IX protein levels and less blood loss in a tail-clipping assay than vectors encoding a wild-type or nonoptimized factor IX. None of the tested vectors induced immunogenicity or antibodies against factor IX. Next steps include testing the strategy in larger animal models, including in canines.</p> <p>At least six companies have recombinant factor IX or delivery methods for the coagulation factor in development stages ranging from preclinical to marketed to treat hemophilia.</p> <p>SciBX 5(42); doi:10.1038/scibx.2012.1113 Published online Oct. 25, 2012</p>	Patent status unavailable; available for licensing	<p>Cantore, A. <i>et al. Blood</i>; published online Oct. 4, 2012; doi:10.1182/blood-2012-05-432591 Contact: Thierry VandenDriessche, Free University of Brussels, Brussels, Belgium e-mail: thierry.vandendriessche@vub.ac.be</p>
Infectious disease				
Herpes simplex virus (HSV)	Chemokine CXC motif ligand 9 (CXCL9; MIG); CXCL10 (IP-10)	<p>Mouse studies suggest a prime-pull vaccination strategy could help prevent HSV-2 infection. In mice transplanted with HSV-2 antigen-specific human CD8⁺ T cells, a subcutaneous HSV-2 vaccine (prime) and vaginal application of chemokines CXCL9 and CXCL10 (pull) increased vaginal levels of the CD8⁺ T cells for at least 12 weeks compared with vaccine and vehicle. In normal mice immunized with the prime-pull combination, lethal vaginal HSV-2 challenge resulted in fewer symptoms of infection, lower viral titers in peripheral dorsal root ganglia and longer survival than vaccine immunization alone. Ongoing work includes testing the prime-pull strategy as prophylaxis in nonhuman primate models of HIV infection.</p> <p>SciBX 5(42); doi:10.1038/scibx.2012.1114 Published online Oct. 25, 2012</p>	Patented by Yale University; available for licensing	<p>Shin, H. & Iwasaki, A. <i>Nature</i>; published online Oct. 17, 2012; doi:10.1038/nature11522 Contact: Akiko Iwasaki, Yale School of Medicine, New Haven, Conn. e-mail: akiko.iwasaki@yale.edu</p>
Influenza virus	Neuraminidase (NEU1; SIAL1)	<p><i>In vitro</i> and mouse studies identified oseltamivir phosphonate derivatives that could help treat drug-resistant influenza. <i>In vitro</i>, the oseltamivir phosphonate tamiphosphor and three of its derivatives inhibited neuraminidases from influenza strains including an oseltamivir-resistant strain. In influenza-infected mice, oral treatment with the compounds increased survival and decreased weight loss compared with treatment using water. Next steps include designing a formula with improved bioavailability.</p> <p>Gilead Sciences Inc. and Roche market Tamiflu oseltamivir to treat and prevent influenza. GlaxoSmithKline plc markets Relenza zanamivir to treat and prevent influenza.</p> <p>SciBX 5(42); doi:10.1038/scibx.2012.1115 Published online Oct. 25, 2012</p>	Findings patented; licensed to an undisclosed biotech company	<p>Fang, T.-J.R. <i>et al. J. Med. Chem.</i>; published online Sept. 25, 2012; doi:10.1021/jm3008486 Contact: Chi-Huey Wong, Academia Sinica, Taipei, Taiwan e-mail: chwong@gate.sinica.edu.tw Contact: Jim-Min Fang, same affiliation as above e-mail: jmfang@ntu.edu.tw Contact: Oliver Yoa-Pu Hu, National Defense Medical Center, Taipei, Taiwan e-mail: hyp@ndmctsgh.edu.tw</p>

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Musculoskeletal disease				
Spinal muscular atrophy (SMA)	Survival of motor neuron 1 telomeric (SMN1); survival of motor neuron 2 centromeric (SMN2); stasimon (STAS; CG8408)	<p>Fruit fly and zebrafish studies suggest restoring SMN levels in specific neuronal subpopulations and promoting expression of the downstream protein STAS could help treat SMA. In fruit fly models of SMA, restoring <i>Smn</i> expression in proprioceptive neurons and interneurons rescued SMA-associated defects in motor neurons and muscle cells, whereas restoring <i>Smn</i> expression in motor neurons and muscle cells did not. Also in SMA fruit flies, injection of mRNA encoding human STAS decreased the SMA-associated muscular and neuronal defects compared with control mRNA injection. Next steps include studying whether other genes downstream of <i>SMN</i> also are involved in SMA and identifying specific neural circuits that are dysfunctional in the condition. The investigators have 4-aminopyridine (4-AP), a potassium channel blocker, in a Phase II/III trial to treat SMA.</p> <p>Ampyra dalfampridine, a sustained-release formulation of 4-AP, is marketed by Acorda Therapeutics Inc., Biogen Idec Inc. and Elan Corp. plc to improve walking ability in patients with multiple sclerosis (MS).</p> <p>SciBX 5(42); doi:10.1038/scibx.2012.1116 Published online Oct. 25, 2012</p>	Patent application filed for findings in both studies; available for licensing from Columbia Technology Ventures	<p>Imlach, W.L. <i>et al. Cell</i>; published online Oct. 12, 2012; doi:10.1016/j.cell.2012.09.011 Contact: Brian D. McCabe, Columbia University Medical Center, New York, N.Y. e-mail: brian@mccabelab.org</p> <p>Lotti, F. <i>et al. Cell</i>; published online Oct. 12, 2012; doi:10.1016/j.cell.2012.09.012 Contact: Brian D. McCabe, Columbia University Medical Center, New York, N.Y. e-mail: brian@mccabelab.org Contact: Livio Pellizzoni, same affiliation as above e-mail: lp2284@columbia.edu</p>
Neurology				
Alzheimer's disease (AD)	γ -Secretase; β -amyloid 42	<p><i>In vitro</i> and mouse studies identified metabolically stable γ-secretase modulators that could help treat familial AD. <i>In vitro</i>, triterpene-based γ-secretase modulators with carbamate or ester replacements at the C24 position inhibited pathogenic β-amyloid 42 and showed selectivity over β-amyloid 40. In mice, two of the compounds showed favorable pharmacokinetic and pharmacodynamic profiles and had blood brain barrier penetration, and decreased β-amyloid 42 levels in the brain compared with vehicle control. Next steps include safety studies on similar compounds.</p> <p>Satori Pharmaceuticals Inc. has γ-secretase inhibitors in preclinical testing to treat AD. At least six other companies have γ-secretase inhibitors in clinical and preclinical development to treat AD.</p> <p>SciBX 5(42); doi:10.1038/scibx.2012.1117 Published online Oct. 25, 2012</p>	Patent applications filed; available for licensing	<p>Hubbs, J.L. <i>et al. J. Exp. Med.</i>; published online Oct. 3, 2012; doi:10.1021/jm300976b Contact: Jed L. Hubbs, Satori Pharmaceuticals Inc., Cambridge, Mass. e-mail: jed.hubbs@satoripharma.com</p>
Fragile X syndrome	Ribosomal protein S6 kinase 70 kDa polypeptide 1 (RPS6KB1; S6K1); fragile X mental retardation 1 (FMR1)	<p>Mouse studies suggest inhibiting S6K1 could help treat fragile X syndrome. Phosphorylation of the FMR1 kinase S6K1 is greater in lymphocytes and brain tissue from patients with fragile X syndrome than in samples from healthy controls. In an <i>Fmr1</i> knockout mouse model for fragile X syndrome, <i>S6k1</i> deficiency decreased abnormal neuron morphology and social interaction deficits and increased motor skills and new object recognition compared with normal <i>S6k1</i> expression. The deficiency also reduced weight gain and macroorchidism. Ongoing work includes testing an S6K1 inhibitor in the <i>Fmr1</i> knockout model for fragile X syndrome.</p> <p>SciBX 5(42); doi:10.1038/scibx.2012.1118 Published online Oct. 25, 2012</p>	Unpatented; available for licensing or partnering	<p>Bhattacharya, A. <i>et al. Neuron</i>; published online Oct. 18, 2012; doi:10.1016/j.neuron.2012.07.022 Contact: Eric Klann, New York University, New York, N.Y. e-mail: eklann@cns.nyu.edu</p>

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Huntington's disease (HD)	<i>Huntingtin (HTT)</i>	Cell culture and mouse studies suggest zinc finger proteins (ZFPs) could help treat HD. In a patient-derived mesothelial cell line, a ZFP designed to bind the extended CAG repeats of <i>HTT</i> in patients with HD repressed <i>HTT</i> expression. In a mouse model of HD, brain injection of an adenoviral vector expressing the ZFP restored motor coordination to levels comparable to those in healthy controls. Next steps include testing alternative gene therapy vectors to optimize expression and running longer-term efficacy studies in additional HD models. SciBX 5(42); doi:10.1038/scibx.2012.1119 Published online Oct. 25, 2012	Patent application filed; available for licensing	Garriga-Canut, M. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Oct. 10, 2012; doi:10.1073/pnas.1206506109 Contact: Mark Isalan, Centre for Genomic Regulation, Barcelona, Spain e-mail: isalan@crg.es
Leukodystrophy	Proteolipid protein 1 (PLP1)	Mouse and patient studies suggest human neural stem cells could help treat hypomyelination diseases. In a mouse model of hypomyelination, human neural stem cells transplanted into three different sites of neonatal or juvenile mouse brains differentiated into oligodendrocytes and myelinated axons. Brain slices from mice receiving transplants showed longer duration for action potentials than mice receiving vehicle, indicating functional myelination. In four juvenile patients with Pelizaeus-Merzbacher disease, a leukodystrophy caused by mutations in <i>PLP1</i> , transplantation of human neural stem cells into the frontal lobe white matter plus nine months of immunosuppression led to modest gains in neurological function and motor performance. Magnetic resonance spectroscopy indicated increased axon myelination at one year postsurgery. Next steps could include Phase II clinical testing (<i>see Myelination from neural stem cells, page 6</i>). SciBX 5(42); doi:10.1038/scibx.2012.1120 Published online Oct. 25, 2012	Findings in both papers patented by StemCells Inc.; available for licensing	Uchida, N. <i>et al. Sci. Transl. Med.</i> ; published online Oct. 10, 2012; doi:10.1126/scitranslmed.3004371 Contact: Stephen A. Back, Oregon Health & Science University, Portland, Ore. e-mail: backs@ohsu.edu Contact: Nobuko Uchida, StemCells Inc., Newark, Calif. e-mail: nobuko.uchida@stemcellsinc.com Gupta, N. <i>et al. Sci. Transl. Med.</i> ; published online Oct. 10, 2012; doi:10.1126/scitranslmed.3004373 Contact: David H. Rowitch, University of California, San Francisco, Calif. e-mail: rowitchd@peds.ucsf.edu

This week in techniques

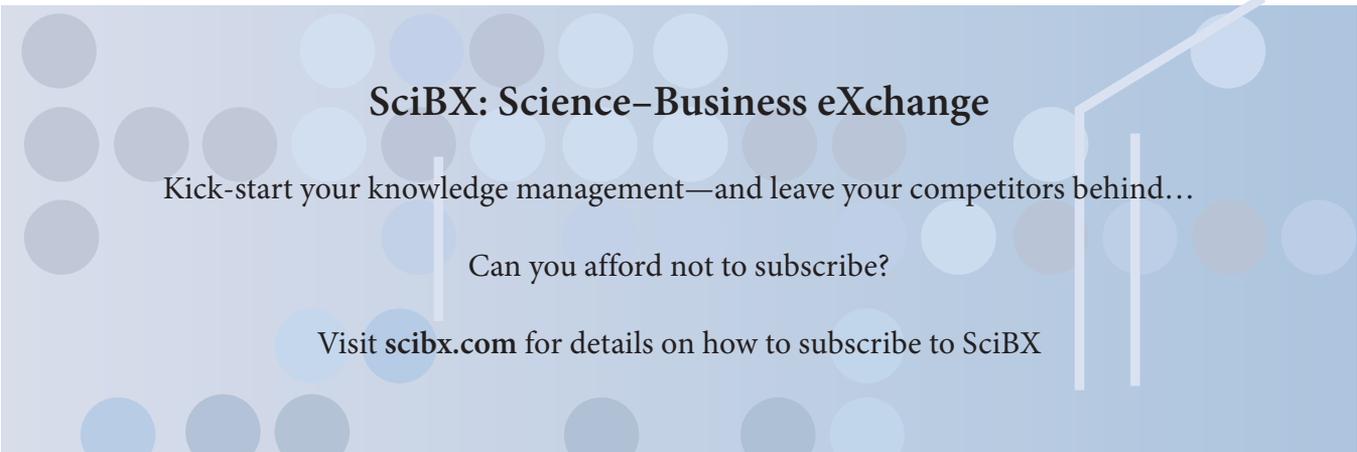
THE DISTILLERY brings you this week's most essential scientific findings in techniques, distilled by *SciBX* editors from a weekly review of more than 400 papers in 41 of the highest-impact journals in the fields of biotechnology, the life sciences and chemistry. The Distillery goes beyond the abstracts 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			
Multiplex screening for interacting compounds (MuSIC) to help identify drug combinations to treat HIV/AIDS	MuSIC could be used to help identify drug combinations to treat HIV infection. A primary screen using pooled compounds to increase throughput was used to evaluate about 500,000 drug pairs of 1,000 FDA-approved or clinically tested compounds in HIV-infected cells. The screen identified the glucocorticoid prednisolone and the antiprotozoal nitazoxanide as the top synergistic pair hit. The pair was confirmed by a separate screen and by two distinct methods to quantify drug synergy. Additional cell-based studies showed that prednisolone and nitazoxanide synergized with the HIV integrase inhibitor Isentress raltegravir. Ongoing work includes testing other combinations identified in the study and using MuSIC to identify combinations that could be used to treat other infectious diseases, cancer or asthma. SciBX 5(42); doi:10.1038/scibx.2012.1121 Published online Oct. 25, 2012	Unpatented; licensing status not applicable	Tan, X. <i>et al. Nat. Biotechnol.</i> ; published online Oct. 14, 2012; doi:10.1038/nbt.2391 Contact: Stephen J. Elledge, Harvard Medical School and Brigham and Women's Hospital, Boston, Mass. e-mail: selledge@genetics.med.harvard.edu
Disease models			
Model for T cell therapy resistance in melanoma	A mouse model for T cell resistance suggests T cell-based melanoma therapies should target both melanocytic and nonmelanocytic antigens to help prevent disease relapse. Mice were engineered to develop melanomas driven by overexpression of hepatocyte growth factor/scatter factor (Hgf/sf) and an oncogenic mutation in <i>cyclin dependent kinase 4 (Cdk4)</i> . In the mice, acquired resistance to T cell therapies was linked to inflammation-induced dedifferentiation and loss of melanocytic antigens in melanoma cells. Next steps include developing more clinically relevant models to test potential combinations of adoptive cell transfer therapies with marketed melanoma drugs (<i>see Melanoma's hidden act, page 1</i>). SciBX 5(42); doi:10.1038/scibx.2012.1122 Published online Oct. 25, 2012	Unpatented; licensing status not applicable	Landsberg, J. <i>et al. Nature</i> ; published online Oct. 10, 2012; doi:10.1038/nature11538 Contact: Thomas Tüting, University of Bonn, Bonn, Germany e-mail: thomas.tueing@ukb.uni-bonn.de
Drug platforms			
Autologous regulatory B (B _{reg}) cell therapy for autoimmune diseases	Cell culture and mouse studies suggest B _{reg} cells cultured <i>ex vivo</i> could be useful for treating autoimmune diseases. In cell culture, spleen-derived B cells stimulated with IL-21 and cocultured with T cells expressing CD40 ligand (CD40LG; CD40L; CD154) showed extensive proliferation and produced high levels of the anti-inflammatory cytokine IL-10, a marker of B _{reg} cells. In a mouse model of multiple sclerosis (MS), reinfusion of <i>ex vivo</i> -expanded B _{reg} cells decreased disease severity compared with vehicle infusion. Next steps include isolating and expanding human B _{reg} cells (<i>see B_{reg}-ging rights, page 8</i>). SciBX 5(42); doi:10.1038/scibx.2012.1123 Published online Oct. 25, 2012	Patent pending; available for licensing	Yoshizaki, A. <i>et al. Nature</i> ; published online Oct. 14, 2012; doi:10.1038/nature11501 Contact: Thomas Tedder, Duke University School of Medicine, Durham, N.C. e-mail: thomas.tedder@duke.edu
Expansion of embryonic stem cell (ESC)-derived progenitors in organ-matched mesenchymal cultures	Expansion of ESC-derived progenitors in organ-matched mesenchymal cell culture could be used to generate adequate cell numbers for cell-based therapies. Coculture of human ESC-derived pancreas endodermal cells and human primary pancreas mesenchymal cells led to a 65 million-fold expansion of the endodermal cells. The expanded endodermal cells could be differentiated into pancreatic progenitors that developed into glucose-sensing, insulin-producing cells after being injected under the kidney capsule in mice. In glucose tolerance tests, mice engrafted with pancreatic progenitors had blood glucose levels similar to those in mice engrafted with human islets. Next steps could include expansion of other types of organ-specific cells. SciBX 5(42); doi:10.1038/scibx.2012.1124 Published online Oct. 25, 2012	Patent and licensing status unavailable	Sneddon, J.B. <i>et al. Nature</i> ; published online Oct. 7, 2012; doi:10.1038/nature11463 Contact: Douglas A. Melton, Harvard University, Cambridge, Mass. e-mail: dmelton@harvard.edu

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Markers			
DNA methylation signatures in chronic lymphocytic leukemia (CLL)	DNA methylation signatures could help identify CLL subtypes and improve disease prognosis. In samples from 139 patients, epigenomic analysis revealed differences in CpG methylation patterns between naïve B cell-like and memory B cell-like CLLs and also identified a third subtype that is an intermediate between the molecular subtypes. In the patients, 20% of those with memory B cell-like disease, 43% of those with the intermediate disease phenotype and 100% of those with naïve B cell-like disease required treatment at 10 years. Next steps include validating the methylation signatures in additional patient cohorts. SciBX 5(42); doi:10.1038/scibx.2012.1125 Published online Oct. 25, 2012	Patent application filed covering use in CLL; available for licensing from the Innovation Department at the Fundacio Clinic for Biomedical Research	Kulis, M. <i>et al. Nat. Genet.</i> ; published online Oct. 14, 2012; doi:10.1038/ng.2443 Contact: José I. Martin-Subero, University of Barcelona, Barcelona, Spain e-mail: imartins@clinic.ub.es
Soluble APP770 as an early marker of acute coronary syndrome (ACS)	Cell culture, human sample and rodent studies suggest serum APP770 levels could help diagnose ACS. In cultured bone marrow endothelial cells, inflammatory cytokines or platelet activation increased secretion of the endothelial form of amyloid precursor protein (APP), APP770, compared with no treatment. Plasma samples from patients with acute myocardial infarction (MI) had higher soluble APP770 levels than samples from healthy controls. In a rat model of MI, elevation of soluble APP770 levels was detected before elevation of a diagnostic marker currently used to detect acute MI. Next steps could include additional biomarker validation in patient samples. SciBX 5(42); doi:10.1038/scibx.2012.1126 Published online Oct. 25, 2012	Patent and licensing status unavailable	Kitazume, S. <i>et al. J. Biol. Chem.</i> ; published online Oct. 2, 2012; doi:10.1074/jbc.M112.398578 Contact: Shinobu Kitazume, RIKEN Advanced Science Institute, Saitama, Japan e-mail: shinobuk@riken.jp



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