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Turning back the malarial hordes

By **Tim Fulmer**, Senior Writer

Researchers from the **Wellcome Trust Sanger Institute** have identified a host receptor, basigin Ok blood group, that allows *Plasmodium falciparum* to invade erythrocytes and trigger a blood-stage malaria infection.¹ The researchers are now developing a vaccine to neutralize the *P. falciparum* antigen that binds the receptor. A vaccine targeting blood-stage infection could be more effective at preventing clinical symptoms of malaria than vaccines that target the asymptomatic liver stage of the parasite.

The life cycle of *P. falciparum* has three distinct stages. The liver and blood stages occur in the host, whereas the sexual stage occurs in the gut of the mosquito. The actual illness only occurs during blood-stage infection, which is triggered when the parasite is released from the liver, enters systemic circulation and invades erythrocytes.

Most malaria vaccines in development target liver-stage antigens because there is less antigenic variation at the liver stage than at the blood stage.² Nonetheless, blood-stage vaccines remain an active area of research, with the goal of preventing clinical symptoms caused by any parasites that manage to escape from the liver and enter the blood.

The invasion process is complex and involves multiple parasite antigens that interact with proteins on the exterior and interior of the red blood cell.³

Thus, to prevent parasite invasion “it will be necessary either to identify key essential invasion pathways or to simultaneously target multiple invasion pathways, which would increase the complexity of the vaccine,” said Joseph Smith, affiliate associate professor of global health at the **University of Washington**.

A team led by Julian Rayner and Gavin Wright hypothesized that *P. falciparum* reticulocyte-binding protein homolog 5 (PfRh5) might be the key antigen for invasion. Rayner is group leader in the Malaria Programme at Wellcome Trust. Wright is group leader of the cell surface signaling laboratory there.

The group was tipped off by a 2009 paper by Alan Cowman and colleagues that showed PfRh5 bound erythrocytes *in vitro* and, more importantly, was essential for growth in blood-stage cultures.^{4,5} Cowman is head of the division of infection and immunity at **The Walter and Eliza Hall Institute of Medical Research (WEHI)** and professor of medical biology at **The University of Melbourne**.

The Wellcome team reasoned that if PfRh5 was essential for invasion, the next step was identifying its binding partner on erythrocytes and then testing whether preventing PfRh5 from binding its receptor blocked invasion.



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Using published proteomics data,⁶ the researchers first generated a library of 40 abundant cell surface and secreted proteins expressed by human erythrocytes. They then screened purified PfRh5 against that library using a method developed in Wright's lab called AVEXIS (avidity-based extracellular interaction screen), which is designed to detect transient extracellular protein-protein interactions.⁷

A single erythrocyte protein interacted strongly with PfRh5: basigin Ok blood group (BSG; EMMPRIN; CD147), a ubiquitously expressed membrane glycoprotein involved in gestation, spermatogenesis, retinal development and leukocyte activation.

Indeed, anti-BSG antibodies blocked erythrocyte invasion by multiple strains of *P. falciparum* compared with isotype controls. Also, small hairpin RNA against BSG in two *P. falciparum* strains decreased invasion compared with scrambled control shRNA.

The data, which were published in *Nature*, suggest that interactions between the host receptor BSG and the malarial ligand PfRh5 are critical for erythrocyte invasion.

"The hope is that a vaccine based around PfRh5 would induce antibodies that prevent parasites from invading red blood cells and therefore protect against the worst symptoms and complications of malaria," corresponding author Rayner told *SciBX*.

"The major attractions of targeting the BSG-PfRh5 interaction are threefold," added Jacob Baum. "First, there's the apparently essential

"The hope is that a vaccine based around PfRh5 would induce antibodies that prevent parasites from invading red blood cells and therefore protect against the worst symptoms and complications of malaria."

—Julian Rayner,

Wellcome Trust Sanger Institute

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nature of the interaction across all *falciparum* strains tested. Second, PfRh5 is a relatively small member of the Rh family of proteins, which means there's a real possibility of using the whole protein as a vaccine antigen. Third, PfRh5 seems to have very limited polymorphism, which could facilitate its universality as a vaccine candidate."

Baum did much of the original work on PfRh5 when he was a researcher in Cowman's lab. He is now laboratory head in the division of infection and immunity at WEHI and a senior research fellow at the University of Melbourne.

Low polymorphism could be an important feature of a PfRh5-based vaccine because "one of the main challenges for blood-stage vaccines has been polymorphism in parasite invasion ligands," said Smith. "AMA1 [*P. falciparum* apical membrane antigen 1] is another parasite protein that plays a critical role in invasion. There has been significant work to make a vaccine against AMA1. The problem is that AMA1 is highly polymorphic, and anti-AMA1 antibodies are strain specific and do not confer broad protection."

Smith is also associate member and interim director of the malaria program at the **Seattle Biomedical Research Institute**.

Seattle Biomedical is developing live, attenuated malaria vaccines. In June, the institute published that a genetically modified malaria strain with attenuated growth at the liver stage was nonetheless able to induce a strong T cell response and protect mice from infection.⁸

Moving toward a vaccine

Rayner said his team has already begun to solve a key problem facing any vaccine program: antigen production. "If PfRh5 is to be used in a vaccine, we need to be able to produce it in large amounts. The system we used to produce PfRh5 in the paper is very efficient and may well be able to be scaled up to produce protein for testing in small clinical trials," he said.

Rayner declined to provide any additional details on next steps.

"It will be important to show whether recombinant PfRh5 proteins can elicit antibodies that inhibit parasite invasion and determine whether those antibodies inhibit different parasite strains," said Smith.

Although it is still early to compare a PfRh5-based blood-stage vaccine with the liver-stage vaccines in development, Rayner said,

"PfRh5 could well turn out to be complementary to those approaches. By targeting two different stages of the life cycle, we may be able to generate better protection than by targeting either stage alone."

The most advanced malaria vaccine, RTS,S (Mosquirix) from **GlaxoSmithKline plc**, targets a key antigen of the liver stage: the circumsporozoite protein. In October, GSK published in *The New England Journal of Medicine* Phase III data showing that the vaccine lowered the incidence of clinical malaria by 55.8% and severe malaria by 47.3% in children aged 5–17 months versus a nonmalaria comparator vaccine ($p < 0.001$ for both).⁹

Cowman told *SciBX* his lab is also working on a PfRh5-based malaria vaccine but declined to provide further details.

According to Rayner, the *Nature* findings are covered by a patent. He declined to disclose the licensing status of that IP.

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Stemming CSCs

By Kai-Jye Lou, Staff Writer

A Belgian team has identified VEGF and its co-receptor neuropilin 1 as promoters of cancer stem cell proliferation.¹ The results provide additional mechanistic validation for existing VEGF-based therapeutic approaches in cancer and for neuropilin 1–targeting strategies in development. The findings also suggest the potential to combine both approaches.

VEGF is well known for its ability to drive tumor growth by promoting the formation of tumor vasculature. There are at least five marketed drugs that target VEGF or VEGF receptors in cancer.

Neuropilin 1 (NRP1) originally was identified as a mediator of axon guidance in the developing nervous system. The link to cancer was established after multiple studies showed that this transmembrane glycoprotein is upregulated in various tumors and could act as a VEGF co-receptor.²

R7347, a recombinant human mAb that binds to NRP1, is the most advanced NRP1–targeting compound for cancer. The compound, being developed by Roche's Genentech Inc. unit, is in Phase I testing for solid tumors. Ark Therapeutics Group plc has small molecule NRP1 antagonists in preclinical development for cancer.

More recently, a number of researchers have published data suggesting VEGF also drives tumor growth directly by acting on tumor cells.^{3,4} However, it has remained unclear whether VEGF's tumorigenic activity requires the presence of a particular cell type within the tumor.

In the current study, a Belgian group led by Cédric Blanpain has shown that a cancer cell subtype is required, specifically cancer stem cells (CSCs), which have self-renewal and differentiation properties that distinguish them from other tumor cells.

Blanpain is a researcher for the National Fund for Scientific Research and a Walloon Excellence in Life Sciences and Biotechnology (WELBIO) investigator at the Institute for Interdisciplinary Research in Biology at the Free University of Brussels.

In a mouse model of squamous skin tumors, the researchers first confirmed that a subpopulation of CD34⁺ CSCs existed in a vascular tumor microenvironment called the perivascular niche. Another European research group had previously identified CD34⁺ tumor epithelial cells as CSCs in the mouse skin tumor model,³ but their exact location was unclear.

Blanpain's group next asked whether VEGF was involved in the growth and function of those CSCs.

In the same mice, a series of studies using genetic deletion and overexpression as well as blocking antibodies showed that in addition to its proangiogenic effects on the tumor microenvironment, VEGF bound

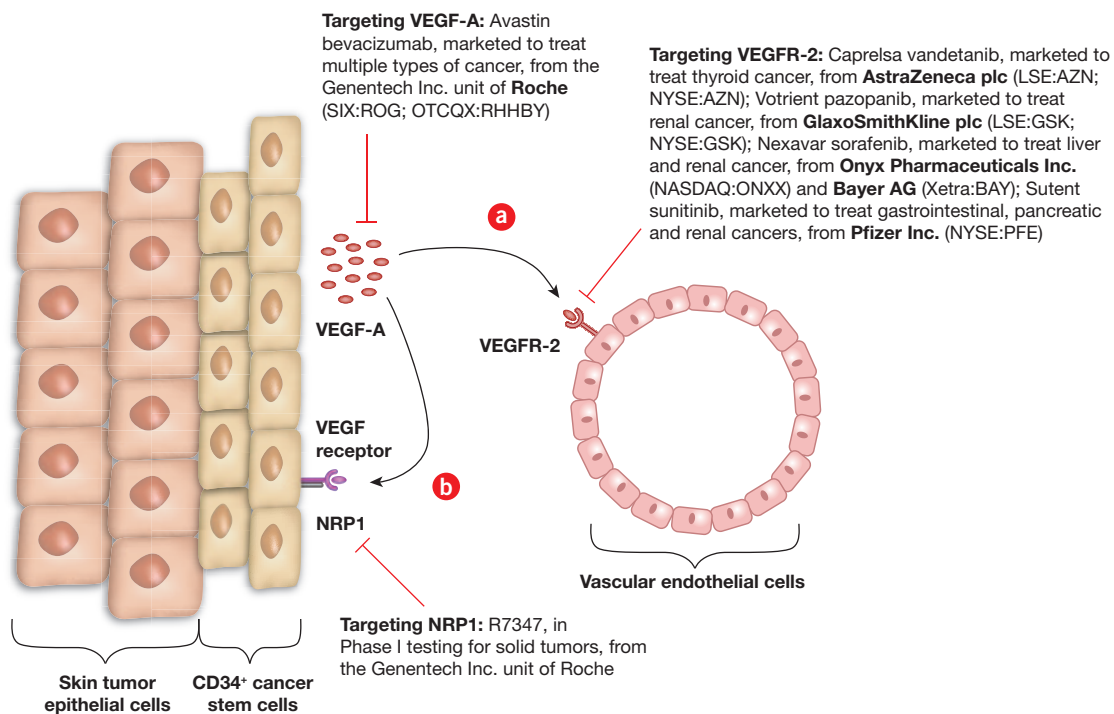


Figure 1. Model for VEGF-mediated skin tumor progression. VEGF is known to promote tumor progression by stimulating angiogenesis. As reported by Beck *et al.* in a mouse squamous skin tumor model, VEGF also may support tumor progression by promoting cancer stem cell (CSC) renewal and proliferation.

In the first role, tumor cell–derived VEGF-A signals through VEGF receptor 2 (KDR/Fik-1; VEGFR-2) on endothelial cells to promote angiogenesis and create a vascular microenvironment for CSCs [a].

In its second role, VEGF-A acts directly on cutaneous CD34⁺ CSCs themselves in a neuropilin 1 (NRP1)–dependent manner to promote their self-renewal and proliferation [b]. The researchers found that this autocrine loop contributes to CSC expansion and skin tumor initiation.

NRP1 is a VEGF co-receptor known to interact with VEGF-A.

to the co-receptor NRP1 on CSCs to promote their renewal, expansion and proliferation (see Figure 1, “Model for VEGF-mediated skin tumor progression”).

Results were published in *Nature*.

“Scientifically, the researchers have very clearly shown in this cancer model that this VEGF-neuropilin loop plays a role in regulating cancer stem cell function,” said

Chiang Li, CEO and CMO at **Boston Biomedical Inc.** “What I found to be surprising is that the cancer stem cells in this model are localized in a perivascular niche, because it is hypoxic regions that are generally thought to act as cancer stem cell repositories.”

Previously, only CSCs in gliomas were known to reside in the perivascular niche.⁵

Boston Biomedical’s lead compound is BBI608, an orally administered small molecule that targets both CSCs and nonstem cancer cells. It is in Phase Ib/II testing for advanced solid tumors. The company has not disclosed the molecular target.

Clinical relevance

Although researchers contacted by *SciBX* agreed that the reported results clearly link VEGF and NRP1 signaling to CSC function in the squamous skin tumor model, they noted that the clinical relevance of the findings still needs to be fleshed out.

Boston Biomedical’s Li pointed out that because skin squamous cell carcinomas are easy to remove and very rarely become a problem in practice, it is unlikely that an NRP1-targeted therapeutic approach will be developed for this particular indication.

However, Blanpain noted that *NRP1* is known to be overexpressed in other malignant human carcinomas, including lung squamous cell carcinomas and breast carcinomas.

“In such cancers, it is possible that targeting NRP1 might result in therapeutic benefits,” he told *SciBX*. “We are currently examining these questions in various human carcinomas.”

In addition, Meenhard Herlyn, a professor and leader of the Molecular & Cellular Oncogenesis Program and director of the Melanoma Research Center at **The Wistar Institute**, thinks the reported findings could lead one to consider adding an NRP1-targeted therapy to the regimen of cancer patients receiving anti-VEGF therapy.

Although the reported findings do suggest a possible new mode of action for existing VEGF-based therapies, Li cautioned that current

“Scientifically, the researchers have very clearly shown in this cancer model that this VEGF-neuropilin loop plays a role in regulating cancer stem cell function.”

—Chiang Li, Boston Biomedical Inc.

VEGF-targeting therapies have only had limited efficacy in the tumor types in which they are approved.

“If this pathway were critical for other tumor types, then why haven’t we seen a stronger effect for VEGF-targeted therapies in such tumors?” he asked.

Hence, Li thinks it will be important to characterize the relative importance of the

VEGF-NRP1 loop in various types of tumors in humans.

“If this loop is found to be active in human tumors, then one can explore the translational prospects of combining compounds that target this loop with those that target cancer stem cells directly to see if there will be an improved effect,” he said.

Blanpain said the group is working to validate the effect of NRP1 inhibition on tumor cell self-renewal and subsequent tumor growth.

“We need to investigate the expression of NRP1 in other types of mouse epithelial cancers and determine genetically and pharmacologically whether targeting NRP1 in these other mouse cancer models will have benefit, as it does in the skin papilloma model,” said Blanpain. “We will also need to determine the expression of NRP1 using very sensitive techniques in a broad range of human cancers, develop new strategies to only inhibit NRP1 function in human tumor cells and determine the impact of NRP1 inhibition in xenograft tumor models.”

The findings have not been patented.

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Taken to heart

By Tracey Baas, Senior Editor

A study by **Stanford University School of Medicine** researchers suggests a mitochondrial enzyme activator called Alda-1 could help decrease the risk of cardiac injury in patients receiving nitroglycerin for cardiac conditions.¹ **ALDEA Pharmaceuticals Inc.** has already raised money to optimize Alda-1 for clinical use.

In the emergency room, nitroglycerin is typically delivered as a sublingual tablet or oral spray to individuals suffering chest pain, or as an i.v. drip or patch to heart attack patients. The tablet and spray doses are effective for a few minutes after administration, whereas the drip and patch are given for one to two days.

Nitroglycerin first is converted into nitric oxide (NO), which in turn activates soluble guanylate cyclase (sGC), an enzyme involved in vasodilation. The result is increased blood flow to the heart and decreased ischemia-induced pain.

But treatment longer than a few hours is associated with a gradual loss of effectiveness. The development of tolerance is due to inactivation of aldehyde dehydrogenase 2 family mitochondrial (ALDH2), an enzyme involved in converting nitroglycerin to NO.

To avoid this tolerance, physicians typically treat patients on a 16 hours on and 8 hours off cycle.

Because ALDH2 also has a cardioprotective role,² the Stanford team hypothesized that nitroglycerin tolerance and ALDH2 inactivation could put patients at risk for increased cardiac injury.

Indeed, they found that in rats with induced myocardial infarction (MI), animals that received 16 hours of nitroglycerin plus the ALDH2 activator benzodioxol dichlorobenzamide, dubbed Alda-1, had smaller infarct size and greater cardiac function than rats that underwent sustained nitroglycerin treatment without Alda-1.

Results were published in *Science Translational Medicine*. The team was led by Daria Mochly-Rosen, a professor of chemical and systems biology at Stanford University School of Medicine.

Other ALDH2 angles

The researchers now are optimizing Alda-1 by creating derivatives of the lead compound and are running preclinical safety studies. Next steps could include testing the ALDH2-activating compounds in patients typically given nitroglycerin.

The findings have been patented by Stanford and are licensed to ALDEA Pharmaceuticals, which was cofounded by Mochly-Rosen. The company, which has raised a \$1 million seed round from private offerings, will develop additional Aldas and test them for safety and efficacy before selecting a compound for development.

Mochly-Rosen thinks the findings could lead to a change in the use of nitroglycerin in clinical practice. In particular, the Stanford team hopes the findings will trigger a clinical study that will examine the benefit of using nitroglycerin as compared with other NO-producing drugs in patients at risk for MI.

Nitrates like nitroglycerin typically are used to alleviate angina in patients with ischemic heart disease and to treat congestive heart failure.

“We still give nitrates as a last-ditch effort in people with severe refractory angina, but these people are much less common than they used to be,” said David Harrison, professor of medicine and pharmacology, director of the Division of Clinical Pharmacology and director of the Center for Vascular Biology at **Vanderbilt University Medical Center**.

Indeed, the use of stents, bypass surgery and other drugs has decreased the number of patients who suffer from angina.

“Nitrates are still used for treatment of heart failure, often in combination with the commonly employed antihypertensive agent hydralazine,” Harrison said. “Prior studies in animals have shown that hydralazine can prevent nitrate tolerance, and this might explain why it is so effective when combined with long-acting nitrates.”

Mochly-Rosen thinks her team’s findings may be “particularly important for East Asian individuals who have an inactivating point mutation in *ALDH2*, which Alda-1 compensates for. The mutant enzyme has very low activity, and individuals with mutant *ALDH2* have a higher risk of cardiovascular diseases.” She noted that “there are almost 500 million people with this mutation in Southeast China, Taiwan, Japan and Korea.”

Harrison added that the findings could extend beyond the cardiovascular space. “*ALDH2* is a mitochondrial protein, and mitochondrial abnormalities have been found in numerous diseases, including neurological diseases such as autism and Alzheimer’s disease.

The precise role of *ALDH2* in these conditions is not known but would be of substantial interest. A drug such as Alda-1 that enhances the function of *ALDH2* might be useful in such disorders.”

Jonathan Stamler, professor of medicine, director of the Institute for Transformative Molecular Medicine and chair of cardiovascular innovation at **Case Western Reserve**

University, agreed. “Mochly-Rosen’s Alda-1 compound seems to be an efficient *ALDH2* activator. It would be interesting to see the compound developed for other indications associated with mitochondrial aldehyde dehydrogenase dysfunction, such as Alzheimer’s or Fanconi anemia, and subsequently tested for cardiac ischemia and heart failure.”

A recent publication from Ketan Patel at the **University of Cambridge** showed that *ALDH2* activation may be beneficial in Fanconi anemia.³ Mochly-Rosen has also published data suggesting that *ALDH2* activation may be beneficial in myocardial infarction⁴ and has published data with Roberto Levi at **Weill Cornell Medical College** suggesting that *ALDH2* activation may be beneficial in cardiac arrhythmia.⁵ In addition, Mochly-Rosen has published data with Quynh-Thu Le of the Stanford University School of Medicine describing an Alda activator of *ALDH3* and showed its use for enrichment of salivary gland stem cells *in vivo*.⁶

“There are a number of other indications where *ALDH2* activation may be beneficial,” Mochly-Rosen told *SciBX*. She declined to disclose details because the data are under review or being prepared for publication.

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“There are a number of other indications where *ALDH2* activation may be beneficial.”

—Daria Mochly-Rosen,
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COMPANIES AND INSTITUTIONS MENTIONED

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Stem cell jackpot for Parkinson's disease

By Lev Osherovich, Senior Writer

A **Memorial Sloan-Kettering Cancer Center** team has honed a protocol for producing large quantities of human dopaminergic neurons that could be used therapeutically by grafting them into patients with Parkinson's disease or as a platform for drug screening for the disease.¹ But scaling up the protocol remains a challenge, and therapeutic applications face major regulatory issues due to potential safety concerns.

Parkinson's disease (PD) is caused by degeneration of dopaminergic neurons throughout the brain, the effects of which are felt most acutely in the substantia nigra, a midbrain region involved in movement.

PD symptoms are treated with L-dopa, a dopamine precursor, but due to side effects, limited efficacy and the inconvenience of frequent dosing with this compound or other dopamine agonists, research has turned to finding a way to restore dopamine levels using neuronal implants.

Since the late 1980s, researchers have tried to replace dying neurons of the substantia nigra with dopaminergic cell grafts from aborted fetuses. But despite long-term engraftment and modest clinical efficacy, the limited availability of source material means that the approach cannot be scaled up.

Thus, "there has been an effort to increase the yield of dopaminergic cells in cell culture prior to transplantation," said Curt Freed, division head and professor of medicine at the **University of Colorado Denver School of Medicine**, who conducted the first fetal cell grafts in PD patients.

Human embryonic stem cells (ESCs), which can be cultured indefinitely, are potentially a scalable alternative to primary fetal tissue. However, obtaining high yields of stable

dopaminergic cells without also producing unwanted nondopaminergic cells has been a challenge.

Now, a team led by Lorenz Studer, professor of developmental biology and director of the Center for Stem Cell Biology at Sloan-Kettering, has optimized an ESC culture procedure that yields large quantities of precisely the kind of dopaminergic cells needed to treat PD.

"The idea of stem cells for PD is not new, but we've never had a good source of enriched dopaminergic cells for transplantation," said Studer.

Cells well

Studer got a hint of how to obtain the dopaminergic cells from his team's earlier efforts to coax ESCs into forming various neuronal precursors. In one of those prior studies, the team identified markers for midbrain dopaminergic neuron precursors and developed a procedure to grow a specialized subset of those cells, called floor plate precursors, *in vitro*.²

In the new study, Studer's team converted the floor plate cells into functioning midbrain neurons by simultaneously manipulating several signaling pathways that influence neuronal development.

"The way to go from stem cells to highly specialized nerve cells is to give a series of instructions for differentiation," said Studer. The key signal to make the right kind of neurons turned out to be activation of the wingless-type MMTV integration site (WNT) signaling pathway.

Studer's technique involves treating floor plate precursors with a trio of compounds—a small molecule inhibitor of glycogen synthase kinase 3 β (GSK3B) that activates the WNT signaling pathway, a sonic hedgehog homolog (SHH) agonist and recombinant fibroblast growth factor 8 (FGF8). ESCs treated with all three agents showed high levels of midbrain dopaminergic neuron markers compared with cells treated only with the SHH agonist and FGF8.

In cell culture, the ESC-derived neurons behaved like natural dopaminergic neurons, secreting more dopamine and lower amounts of other neurotransmitters like serotonin and γ -aminobutyric acid (GABA) than neurons generated by previous *in vitro* methods. Immunohistochemical analysis showed that Studer's method also produced more dopaminergic neurons than other types of neurons.

Next, Studer's team transplanted the *in vitro*-generated dopaminergic neurons into mouse, rat and monkey models of PD and found that the neurons successfully engrafted, survived indefinitely and restored dopaminergic activity in the midbrain. PD animals receiving Studer's dopaminergic neuron grafts had higher midbrain dopaminergic neuron density and better performance in gait assays than animals given dopaminergic neurons made by prior methods.

Studer's dopaminergic neuron grafts appear to be stable over the long term. Mice receiving these cells stably expressed dopaminergic cell markers, showed no signs of contaminating cell overgrowth and showed improved performance in an assay of amphetamine-induced motion disorder as late as 16 weeks after transplantation compared with controls receiving neuronal preparations made by prior methods.

Raising yield

Academic experts polled by *SciBX* said that from a technical standpoint, Studer's new method is an incremental advance over previous methods, but the resulting increase in efficiency is potentially a game changer for manufacturing dopaminergic cells.

"The novelty of the report is the accomplishment of a differentiation protocol that more reliably generates the correct cell type," said Ole Isacson, professor of neuroscience and neurology at **Harvard Medical School**. "This is definitely an improvement on prior protocols reported by the same group a few years ago."

Isacson noted that his own team recently reported that transplantation of mouse ESC-derived midbrain dopaminergic neurons isolated by fluorescence-activated cell sorting (FACS) can ameliorate a rat model of PD.³ Studer's method provides a potential source of large numbers of such neurons without the need for time-consuming and inefficient FACS protocols.

Although about 80% of the cells in Studer's *in vitro* preparation are dopaminergic neurons, it is not clear what fraction of the starting ESCs are converted into neurons by Studer's complex procedure.

"The next challenge is to achieve sufficient yield," said Isacson. "It's not clear whether they've generated more neurons overall or a higher percentage of the right neurons."

Studer's method could solve several challenges to ESC therapies for PD, including concerns about graft purity and the potential for tumor formation.

"The idea of stem cells for PD is not new, but we've never had a good source of enriched dopaminergic cells for transplantation."

—Lorenz Studer,
Memorial Sloan-Kettering
Cancer Center

Freed and Isacson said that previous ESC culture methods ran the risk of generating unwanted cells, in particular serotonergic neurons, which can interfere with the activity of dopaminergic cells. In contrast, Studer's team showed that neurons cultured according to the new protocol did not secrete serotonin. Indeed, at 4.5 months after transplantation, mice receiving grafts grown by Studer's new method had very few transplanted cells with markers of nondopaminergic cell identity compared with mice receiving conventional neural grafts.

Freed said that for regulators to accept the cells as therapeutic candidates, long-term preclinical safety studies would be needed to exclude the possibility of tumor formation. Freed said that in contrast to his original fetal cell graft studies, which at the time did not fall under FDA regulation, today the regulatory environment for cell therapies is much more stringent.

"A renegade stem cell is a potential disaster," said Freed. "FDA might say that because Studer didn't report much data about tumors, they would like to see 100 mice for a year who have no tumors with this preparation."

"We now have right cells," said Studer. "The question is now how to make these cells in a format that's safe to use" in the clinic. Doing so would require making the cells under GMP conditions, which would likely require collaboration with a cell manufacturing company, he added.

Cell side

Cell therapies for PD have not made much headway since the cessation of fetal transplant studies in the 1990s. **NeuroGeneration Inc.**'s Phase II trial of its neural stem cell–derived dopaminergic cell therapy has been on hold since 2008 due to cell manufacturing concerns. Last month, **Geron Corp.** discontinued its ESC therapy program, which included a Phase I trial of oligodendrocyte progenitor cells in acute spinal cord injury (SCI).

Two companies—**BrainStorm Cell Therapeutics Inc.** and **International Stem Cell Corp.**—have preclinical programs to generate stem cell–derived therapies for PD. Those approaches use mesenchymal and parthenogenetically derived stem cells, respectively, but these cell types are not thought to be as readily programmable into specific neurons as ESCs.

Isacson, Freed and Studer all noted that the complexity of the regulatory path and pessimism about stem cell therapies mean that, in

the short term, the likeliest commercial use for the new dopaminergic cells would be in *in vitro* drug screening assays.

"Because these cells are much closer to the real dopaminergic cells [than previous cells], they are suitable for drug screening," said Studer.

Cellular reagent company **Cellular Dynamics International Inc.** is negotiating a license to Studer's technology. Chris Parker, VP and chief commercial officer of CDI, noted that Studer's cells would fit well with the company's portfolio of specialized neuronal cells for drug screening.

Parker said that to be commercially useful, Studer's protocol would need to be scaled up at least 1,000-fold, but such scaling often requires major changes to the cell culture protocols.

"In this paper, they make millions of cells per animal, but we would have to make billions and billions of cells for this to be useful as a screening platform," said Parker.

Scaling up the procedure will require considerable refinement.

"If you're going to make a product, you have to know how many of these cells will survive freezing and thawing, how many will stick to a matrix, how many of them form the appropriate cell type," said Parker. "For every cell line, the protocol must be optimized and modified."

Studer said his next step is to scale up production of his dopaminergic neurons.

He has filed a patent on his methods, which is available for licensing.

Osherovich, L. *SciBX* 4(46); doi:10.1038/scibx.2011.1285

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Contact: Lorenz Studer, Memorial Sloan-Kettering Cancer Center, New York, N.Y.
e-mail: studerl@mskcc.org
2. Chambers, S.M. *et al. Nat. Biotechnol.* **27**, 275–280 (2009)
3. Hedlund, E. *et al. Stem Cells* **26**, 1526–1536 (2008)

COMPANIES AND INSTITUTIONS MENTIONED

BrainStorm Cell Therapeutics Inc. (OTCQB:BCLI), New York, N.Y.
Cellular Dynamics International Inc., Madison, Wis.
Geron Corp. (NASDAQ:GERN), Menlo Park, Calif.
Harvard Medical School, Boston, Mass.
International Stem Cell Corp. (OTCBB:ISCO), Carlsbad, Calif.
Memorial Sloan-Kettering Cancer Center, New York, N.Y.
NeuroGeneration Inc., Los Angeles, Calif.
University of Colorado Denver School of Medicine, Aurora, Colo.

This week in therapeutics

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

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

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cancer				
Acute myeloid leukemia (AML)	Mitochondrial translation	<p><i>In vitro</i> and mouse studies suggest Tygacil tigecycline could be repurposed to help treat AML. In xenograft mouse models of AML, Tygacil decreased mitochondrial translation, tumor size and leukemic engraftment compared with vehicle. Ongoing work includes a Phase I trial of Tygacil to treat AML.</p> <p>Tygacil tigecycline, a glycylcycline antibiotic from Pfizer Inc. that inhibits the bacterial ribosome, is approved to treat abdominal infection, skin and skin structure infection (SSSI) and pneumonia.</p> <p>Generic daunorubicin is marketed to treat AML and acute lymphocytic leukemia (ALL).</p> <p>Generic cytarabine is marketed to treat AML and non-Hodgkin's lymphoma (NHL).</p> <p>SciBX 4(46); doi:10.1038/scibx.2011.1286 Published online Dec. 1, 2011</p>	Patented by the University Health Network; available for licensing or partnering	<p>Škrtić, M. <i>et al. Cancer Cell</i>; published online Nov. 15, 2011; doi:10.1016/j.ccr.2011.10.015</p> <p>Contact: Aaron D. Schimmer, Ontario Cancer Institute, Toronto, Ontario, Canada e-mail: aaron.schimmer@utoronto.ca</p>
Brain cancer	Pyruvate kinase M2 isozyme (PKM2); β -catenin (CTNNB1)	<p>A study in mice and in cell culture suggests antagonizing interactions between PKM2 and CTNNB1 could help treat glioblastoma.</p> <p>In mice bearing a glioblastoma cell line with an activating <i>epidermal growth factor receptor (EGFR)</i> mutation, PKM2 or CTNNB1 depletion decreased tumor growth compared with normal PKM2 or CTNNB1 expression. Next steps include developing a therapeutic approach for disrupting the interaction.</p> <p>Agios Pharmaceuticals Inc. has a discovery-stage program targeting PKM2 in cancer.</p> <p>Dynamix Pharmaceuticals Ltd. has DNX-3000, a fructose bisphosphate mimic that activates PKM2, in preclinical development for cancer.</p> <p>SciBX 4(46); doi:10.1038/scibx.2011.1287 Published online Dec. 1, 2011</p>	Patent application filed; available for licensing	<p>Yang, W. <i>et al. Nature</i>; published online Nov. 6, 2011; doi:10.1038/nature10598</p> <p>Contact: Zhimin Lu, The University of Texas MD Anderson Cancer Center, Houston, Texas e-mail: zhiminlu@mdanderson.org</p>
Breast cancer	Cysteine-rich angiogenic inducer 61 (CYR61); sonic hedgehog homolog (SHH)	<p>Mouse studies suggest inhibiting CYR61 could help treat SHH-driven breast cancer. In a mouse xenograft model of SHH-driven human breast cancer, small hairpin RNA against <i>CYR61</i> lowered tumor growth and metastasis compared with scrambled shRNA ($p=0.01$ for both). Next steps could include identifying and evaluating inhibitors of CYR61 signaling in models of SHH-driven cancers.</p> <p>SciBX 4(46); doi:10.1038/scibx.2011.1288 Published online Dec. 1, 2011</p>	Patent and licensing status unavailable	<p>Harris, L.G. <i>et al. Oncogene</i>; published online Nov. 7, 2011; doi:10.1038/onc.2011.496</p> <p>Contact: L.A. Shevde, University of South Alabama Mitchell Cancer Institute, Mobile, Ala. e-mail: lsamant@usouthal.edu</p>

This week in therapeutics

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Breast cancer	Parathyroid hormone-like hormone (PTH LH; PTHRP)	<p>Mouse studies suggest inhibiting PTHRP could help prevent breast tumor progression and metastasis. In a mouse model of breast cancer, Pthrp deficiency delayed primary tumor initiation, progression and metastasis compared with those in nondeficient controls. In a mouse model of human breast cancer, two PTHRP-neutralizing mAbs reduced tumor progression and metastasis compared with IgG controls. Next steps include developing and evaluating a humanized mAb against PTHRP in <i>in vitro</i> and <i>in vivo</i> models.</p> <p>SciBX 4(46); doi:10.1038/scibx.2011.1289 Published online Dec. 1, 2011</p>	Covered by issued and pending patents; unlicensed	<p>Li, J. <i>et al. J. Clin. Invest.</i>; published online Nov. 7, 2011; doi:10.1172/JCI46134 Contact: Richard Kremer, McGill University Health Centre, Montreal, Quebec, Canada e-mail: richard.kremer@mcgill.ca</p>
Cancer	Ubiquitin specific peptidase 7 (USP7; HAUSP)	<p>Cell culture and mouse studies identified USP7-inhibiting peptides that could help treat cancer. In cultured lymphoma cells, cell-permeable, USP7-inhibiting peptides resulted in apoptosis compared with a non-cell permeable control peptide. In a xenograft mouse model of lymphoma, the USP7-inhibiting peptides induced tumor regression compared with control peptide. Next steps include increasing peptide stability, identifying small molecule mimics of the peptides and testing candidates in mouse models of cancer.</p> <p>Hybrigenics S.A. has HBX 19,818 and HBX 41,108, inhibitors of USP7, in preclinical development for chronic lymphocytic leukemia (CLL) and cancer, respectively.</p> <p>SciBX 4(46); doi:10.1038/scibx.2011.1290 Published online Dec. 1, 2011</p>	Patent application filed; available for licensing from the University of Southern California	<p>Lee, H.-R. <i>et al. Nat. Struct. Mol. Biol.</i>; published online Nov. 6, 2011; doi:10.1038/nsmb.2142 Contact: Jae U. Jung, University of Southern California, Los Angeles, Calif. e-mail: jaeujung@usc.edu Contact: Myung Hee Kim, Korea Research Institute of Bioscience & Biotechnology, Daejeon, South Korea e-mail: mhk8n@kribb.re.kr Contact: Tae-Kwang Oh, same affiliation as above e-mail: otk@kribb.re.kr</p>
Colon cancer	Chitinase 3-like 1 cartilage glycoprotein-39 (CHI3L1; YKL40)	<p>Cell culture and mouse studies suggest inhibiting CHI3L1 could help treat colorectal cancer. In xenograft mice, colon cancer cells overexpressing CHI3L1 had greater tumor growth than colon cancer cells with normal CHI3L1 expression. In human colorectal cancer cells, CHI3L1-specific microRNA suppressed cell proliferation compared with scrambled miRNA control. Next steps could include identifying an inhibitor of CHI3L1.</p> <p>SciBX 4(46); doi:10.1038/scibx.2011.1291 Published online Dec. 1, 2011</p>	Patent and licensing status unavailable	<p>Kawada, M. <i>et al. Oncogene</i>; published online Nov. 7, 2011; doi:10.1038/onc.2011.498 Contact: H. Seno, Kyoto University, Kyoto, Japan e-mail: seno@kuhp.kyoto-u.ac.jp Contact: M. Kawada, same affiliation as above e-mail: kawadam@kuhp.kyoto-u.ac.jp</p>
Non-small cell lung cancer (NSCLC)	Diablo homolog (DIABLO; SMAC)	<p><i>In vitro</i> and mouse studies suggest the SMAC mimetic JP1201 could sensitize nonresponsive NSCLCs to chemotherapy. In NSCLC xenograft mice, JP1201 plus chemotherapy decreased tumor burden compared with either agent alone. Next steps include testing JP1201 in combination with chemotherapies in another NSCLC mouse model.</p> <p>Joyant Pharmaceuticals Inc. is a spinoff from The University of Texas Southwestern Medical Center founded in 2005 that is planning a clinical trial of JP1201 with vinorelbine or both of these drugs in combination with cisplatin for NSCLC.</p> <p>SciBX 4(46); doi:10.1038/scibx.2011.1292 Published online Dec. 1, 2011</p>	JP1201 is patented and licensed by Joyant Pharmaceuticals	<p>Greer, R.M. <i>et al. Cancer Res.</i>; published online Nov. 2, 2011; doi:10.1158/0008-5472.CAN-10-3947 Contact: John D. Minna, The University of Texas Southwestern Medical Center, Dallas, Texas e-mail: john.minna@utsouthwestern.edu</p>

This week in therapeutics

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Pancreatic cancer	NEDD8 activating enzyme (NAE)	<i>In vitro</i> and mouse studies suggest NAE inhibitors could help sensitize pancreatic cancers to radiation therapy. In mice with human prostate cancer xenografts, MLN4924 plus radiation inhibited tumor growth better than MLN4924 or radiation alone. Next steps could include testing whether MLN4924 sensitizes other cancers to radiation therapy. Takeda Pharmaceutical Co. Ltd.'s Millennium Pharmaceuticals Inc. subsidiary has MLN4924 in Phase I testing to treat various cancers. SciBX 4(46); doi:10.1038/scibx.2011.1293 Published online Dec. 1, 2011	Unpatented; unavailable for licensing	Wei, D. <i>et al. Cancer Res.</i> ; published online Nov. 9, 2011; doi:10.1158/0008-5472.CAN-11-2866 Contact: Yi Sun, University of Michigan, Ann Arbor, Mich. e-mail: sunyi@umich.edu
Cardiovascular disease				
Cardiovascular disease	Collagen type VI $\alpha 2$ (COL6A2); Down syndrome cell adhesion molecule (DSCAM)	<i>Drosophila</i> , mouse and human cell line studies suggest mutations causing DSCAM and COL6A2 overexpression could help predict risk of congenital heart disease (CHD). In <i>Drosophila</i> overexpressing candidate CHD genes, DSCAM and COL6A2 disrupted heart function. In mice, overexpression of both genes led to increased heart defects, including hypertrophy, compared with overexpression of either gene alone. Next steps include identifying compounds that lower levels of DSCAM and COL6A2. SciBX 4(46); doi:10.1038/scibx.2011.1294 Published online Dec. 1, 2011	Findings unpatented; available for licensing from the University of California, San Diego	Grossman, T.R. <i>et al. PLoS Genet.</i> ; published online Nov. 3, 2011; doi:10.1371/journal.pgen.1002344 Contact: Ethan Bier, University of California, San Diego, La Jolla, Calif. e-mail: ebier@ucsd.edu
Cardiovascular disease	<i>Fc γ-receptor IIa</i> (CD32A; FCGR2A)	A genomewide association study identified a SNP in FCGR2A that could help predict susceptibility to Kawasaki disease, which is characterized by systemic vasculitis. In 2,173 patients and 9,383 controls, rs1801274 in FCGR2A was associated with increased disease risk ($p=7.35 \times 10^{-11}$). Next steps could include determining the functional relationship between FCGR2A variants and susceptibility to Kawasaki disease. SciBX 4(46); doi:10.1038/scibx.2011.1295 Published online Dec. 1, 2011	Patent and licensing status unavailable	Khor, C.C. <i>et al. Nat. Genet.</i> ; published online Nov. 13, 2011; doi:10.1038/ng.981 Contact: Martin L. Hibberd, Genome Institute of Singapore, Singapore e-mail: hibberdml@gis.a-star.edu.sg
Ischemia; reperfusion injury	Chemokine CX3C motif ligand 1 (CX3CL1; fractalkine)	Rodent studies suggest CX3CL1 could help decrease ischemia-induced tissue damage. In a mouse model of middle cerebral artery occlusion, intracerebroventricular injection of human CX3CL1 lowered ischemia-induced infarct volume compared with vehicle injection. In a rat model of cerebral ischemia, human CX3CL1 reduced infarct volume and improved functional outcomes compared with vehicle control. Next steps could include studying the effects of CX3CL1 administration after the ischemic insult. SciBX 4(46); doi:10.1038/scibx.2011.1296 Published online Dec. 1, 2011	Patent and licensing status unavailable	Cipriani, R. <i>et al. J. Neurosci.</i> ; published online Nov. 9, 2011; doi:10.1523/JNEUROSCI.3611-11.2011 Contact: Cristina Limatola, Sapienza University of Rome, Rome, Italy e-mail: cristina.limatola@uniroma1.it

This week in therapeutics

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Endocrine/metabolic disease				
Diabetes	Gap junction protein $\delta 2$, 36 kDa (GJD2; CX36; connexin-36)	<p>Mouse studies suggest increasing CX36 levels could help treat or prevent type 1 diabetes. CX36 is a transmembrane protein present in the junction between β cells and islet cells. In a mouse model of type 1 diabetes, higher expression of Cx36 prevented β cell apoptosis, decreased blood glucose levels and increased insulin levels compared with lower Cx36 expression. Next steps could include identifying a therapeutic approach for increasing CX36 levels.</p> <p>SciBX 4(46); doi:10.1038/scibx.2011.1297 Published online Dec. 1, 2011</p>	Patent and licensing status unavailable	<p>Klee, P. <i>et al. J. Clin. Invest.</i>; published online Nov. 7, 2011; doi:10.1172/JCI40509</p> <p>Contact: Paolo Meda, University of Geneva Medical School, Geneva, Switzerland e-mail: paolo.meda@unige.ch</p>
Diabetes	Nuclear receptor corepressor 1 (NCOR1); peroxisome proliferation-activated receptor- γ (PPARG; PPAR γ)	<p>Studies in mice suggest inhibiting interactions between NCOR1 and PPARγ could help treat diabetes. NCOR1 is a transcriptional regulator that interacts with PPARγ and regulates genes controlling insulin sensitivity. In mice, adipocyte-specific deletion of Ncor1 increased insulin sensitivity and lowered fasting blood glucose levels compared with those in wild-type mice. The knockout mice had greater weight gain but no increase in edema and heart weight, which was previously associated with PPARγ agonists. Next steps include exploring how the mechanism is connected to cyclin dependent kinase 5 (CDK5) phosphorylation of PPARγ, which has been shown to regulate insulin sensitivity. Actos pioglitazone, a PPARγ agonist from Takeda Pharmaceutical Co. Ltd., is marketed to treat type 2 diabetes. Avandia rosiglitazone, a PPARγ agonist from GlaxoSmithKline plc, is marketed in the U.S. to treat type 2 diabetes. Adipothermics Inc. has nonagonist compounds that reduce CDK5 phosphorylation of PPARγ in preclinical development.</p> <p>SciBX 4(46); doi:10.1038/scibx.2011.1298 Published online Dec. 1, 2011</p>	Unpatented; available for licensing	<p>Li, P. <i>et al. Cell</i>; published online Nov. 11, 2011; doi:10.1016/j.cell.2011.09.050</p> <p>Contact: Jerrold M. Olefsky, University of California, San Diego, La Jolla, Calif. e-mail: jolefsky@ucsd.edu</p>
Infectious disease				
Infectious disease	<i>Burkholderia pseudomallei</i> lethal factor 1 (BPSL1549); eukaryotic translation initiation factor 4A1 (EIF4A1)	<p><i>In vitro</i> and mouse studies identified a toxin from <i>B. pseudomallei</i> that could be blocked to treat the bacterial infection melioidosis. <i>In vitro</i>, purified BPSL1549, a toxin produced by <i>B. pseudomallei</i>, inhibited EIF4A1, a factor involved in protein translation. In mice, a <i>B. pseudomallei</i> strain lacking the toxin was less virulent than a wild-type strain expressing the toxin ($p < 0.001$). Next steps include determining whether the toxin can preferentially kill proliferating tumor cells by inhibiting protein translation.</p> <p>SciBX 4(46); doi:10.1038/scibx.2011.1299 Published online Dec. 1, 2011</p>	Patent application filed covering therapeutic use of BPSL1549; available for licensing	<p>Cruz-Migoni, A. <i>et al. Science</i>; published online Nov. 11, 2011; doi:10.1126/science.1211915</p> <p>Contact: Stuart A. Wilson, The University of Sheffield, Sheffield, U.K. e-mail: stuart.wilson@sheffield.ac.uk</p> <p>Contact: David W. Rice, same affiliation as above e-mail: d.rice@sheffield.ac.uk</p>

This week in therapeutics

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Malaria	<i>Plasmodium falciparum</i> reticulocyte-binding protein homolog 5 (PfRh5); basigin Ok blood group (BSG; EMMPRIN; CD147)	<i>In vitro</i> studies suggest a vaccine targeting the malarial antigen PfRh5 could be useful for preventing blood-stage malaria infection. In an <i>in vitro</i> screen, PfRh5 bound the receptor BSG on erythrocytes, suggesting that the PfRh5-BSG interaction is necessary for the parasite to invade red blood cells and trigger clinical symptoms. In cell culture, anti-BSG mAbs or small hairpin RNA against BSG decreased invasion compared with isotype mAbs and scrambled shRNA controls. Next steps include designing a PfRh5-based vaccine to neutralize the PfRh5-BSG interaction in patients with malaria (<i>see Turning back the malarial hordes</i> , page 1).	Patented; licensing status undisclosed	Crosnier, C. <i>et al. Nature</i> ; published online Nov. 9, 2011; doi:10.1038/nature10606 Contact: Julian Rayner, Wellcome Trust Sanger Institute, Cambridge, U.K. e-mail: jr9@sanger.ac.uk Contact: Gavin J. Wright, same affiliation as above e-mail: gw2@sanger.ac.uk
Neurology				
Parkinson's disease (PD)	Metabotropic glutamate receptor subtype 4 (mGluR4; GRM4)	<i>In vitro</i> and rat studies suggest mGluR4 positive allosteric modulators (PAMs) could be combined with existing PD therapies to treat PD. In a PD rat model of forelimb asymmetry, a selective mGluR4 PAM plus L-dopa increased forelimb function compared with either compound alone. In a PD rat model of catalepsy, an mGluR4 PAM plus preladenant improved behavior compared with either compound alone. Ongoing work includes investigating whether mGluR4 PAMs can decrease L-dopa-induced dyskinesias in animal models and optimizing a new series of mGluR4 PAMs to treat PD. Preladenant (MK-3814; SCH 420814), an adenosine A _{2A} receptor (ADORA _{2A}) antagonist from Merck & Co. Inc., is in Phase III testing to treat PD. Istradefylline (KW-6002), an ADORA _{2A} antagonist from Kyowa Hakko Kirin Co. Ltd., is in Phase III testing to treat PD. SYN115, a selective ADORA _{2A} antagonist from Biotie Therapies Corp. and UCB Group, is in Phase II testing to treat PD.	Unpatented; available for licensing from Vanderbilt University Contact: P. Jeffrey Conn, Vanderbilt Center for Neuroscience Drug Discovery, Nashville, Tenn. e-mail: jeffrey.conn@vanderbilt.edu Contact: Mary Kosinski, Vanderbilt Center for Technology Transfer and Commercialization, Nashville, Tenn. e-mail: mary.kosinski@vanderbilt.edu	Jones, C.K. <i>et al. J. Pharmacol. Exp. Ther.</i> ; published online Nov. 16, 2011; doi:10.1124/jpet.111.187443 Contact: Colleen M. Niswender, Vanderbilt University, Nashville, Tenn. e-mail: colleen.niswender@vanderbilt.edu
Renal disease				
Polycystic kidney disease (PKD)	Signal transducer and activator of transcription 6 (STAT6)	A study in mice suggests inhibiting STAT6 may help treat PKD. In PKD mice, Stat6 deficiency or Stat6 inhibition decreased cyst diameter and increased renal function compared with normal Stat6 expression. Undisclosed next steps are being pursued in collaboration with an undisclosed industry partner.	Patent status undisclosed; licensing status not applicable	Olsan, E.E. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Oct. 24, 2011; doi:10.1073/pnas.1111966108 Contact: Thomas Weimbs, University of California, Santa Barbara, Calif. e-mail: weimbs@lifesci.ucsb.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			
A targeted sequencing method to identify genetic alterations in fixed tumor samples	Targeted sequencing of clinical tumor samples could help guide treatment decisions for cancer patients. A DNA sequencing protocol was optimized to sequence 137 cancer-associated genes and 79 polymorphisms predicting sensitivity or resistance to chemotherapy. In tumor tissue from 3 breast cancer and 7 colon cancer patients, at least 1 genetic alteration that predicted response was identified in 90% of the samples. Next steps include establishing clinical protocols to begin using this method in patients in 2012, as well as expanding the panel to include known genomic rearrangements. SciBX 4(46); doi:10.1038/scibx.2011.1303 Published online Dec. 1, 2011	Unpatented; licensing status not applicable	Wagle, N. <i>et al. Cancer Disc.</i> ; published online Nov. 7, 2011; doi:10.1158/2159-8290.CD-11-0184 Contact: Levi A. Garraway, Dana-Farber Cancer Institute, Boston, Mass. e-mail: levi_garraway@dfci.harvard.edu
A yeast functional screen for identifying amyotrophic lateral sclerosis (ALS) genes	A yeast functional screen could aid the discovery of candidate genes that cause ALS. The screen was designed to detect RNA-binding proteins that form cytoplasmic aggregates toxic to yeast and identified 38 candidate proteins, including RNA polymerase II TATA box binding protein associated factor (TAF-15). In humans, <i>TAF-15</i> missense mutations were associated with ALS. Next steps include determining the relative contribution of TAF-15 variants to ALS risk compared with other known genetic risk factors for ALS. SciBX 4(46); doi:10.1038/scibx.2011.1304 Published online Dec. 1, 2011	Covered by issued and pending patents; licensed to FoldRx Pharmaceuticals Inc. (now part of Pfizer Inc.)	Couthouis, J. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Nov. 7, 2011; doi:10.1073/pnas.1109434108 Contact: Aaron D. Gitler, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pa. e-mail: gitler@mail.med.upenn.edu
Single-cell PCR analysis of tumor samples to identify prognostic gene expression signatures	A method to measure gene expression in individual tumor cells could help identify new cancer biomarkers and targets. Xenograft mouse tumors generated from a single colon cancer cell were surgically extracted, separated and sorted. Expression of selected genes was then measured by microfluidic single-cell PCR. Identification of genes expressed in specific subsets of tumor cells led to the discovery of a two-gene prognostic signature that could predict disease-free survival for patients with colorectal cancer. Next steps could include application of this methodology to clinical tumor samples. Stephen Quake and Michael Clarke, co-senior authors of the publication, are founders of Quanticele Pharmaceuticals Inc., which uses single-cell genomic analysis of patient tumor samples to identify predictive biomarkers. The company declined to comment on the licensing status of this work. SciBX 4(46); doi:10.1038/scibx.2011.1305 Published online Dec. 1, 2011	Patent application filed; licensing status unavailable	Dalerba, P. <i>et al. Nat. Biotechnol.</i> ; published online Nov. 13, 2011; doi:10.1038/nbt.2038 Contact: Stephen R. Quake, Stanford University, Stanford, Calif. e-mail: quake@stanford.edu Contact: Michael F. Clarke, same affiliation as above e-mail: mfclarke@stanford.edu

This week in techniques

Approach	Summary	Licensing status	Publication and contact information
Computational models			
Automated quantification of breast cancer morphology features in microscopic images for prognosis	<p>Microscopic quantitative analysis of breast cancer tissue morphology could help determine histological tumor grade. Using a set of breast cancer tissue histology images of a sample from whole tumors, the Computational Pathologist (C-Path) program measured 6,642 different tumor epithelial and stromal features to produce a prognostic model. In microscopic images from two independent cohorts of breast cancer patients, C-Path determined prognostic scores that were more accurate than those derived from classical epithelial characterization and were associated with overall survival ($p \leq 0.001$). Next steps include using the method on whole-tissue slide samples and conducting a prospective, multicenter trial.</p> <p>Digital Pathology Solution is an approved diagnostic for cancer from Aperio Technologies Inc.</p> <p>SciBX 4(46); doi:10.1038/scibx.2011.1306 Published online Dec. 1, 2011</p>	Unpatented; available for licensing	<p>Beck, A.H. <i>et al. Sci. Transl. Med.</i>; published online Nov. 9, 2011; doi:10.1126/scitranslmed.3002564 Contact: Daphne Koller, Stanford University School of Medicine, Stanford, Calif. e-mail: koller@cs.stanford.edu</p>
Drug delivery			
Poly(n-butyl cyanoacrylate) dextran polymers coated with polysorbate 80 (PBCA nanoparticles) for brain delivery of imaging agents	<p>Mouse studies suggest PBCA nanoparticles could be used to deliver imaging agents across the blood brain barrier (BBB) to help detect and diagnose neurological conditions, including Alzheimer's disease (AD). In wild-type mice, i.v. fluorophore-loaded PBCA nanoparticles crossed the BBB, whereas dye alone did not. In an AD mouse model, PBCA nanoparticles loaded with β-amyloid ($A\beta$) plaque-imaging agents stained $A\beta$ plaques in the brain. Next steps could include testing delivery in additional animal models.</p> <p>SciBX 4(46); doi:10.1038/scibx.2011.1307 Published online Dec. 1, 2011</p>	Patent and licensing status unavailable	<p>Koffie, R.M. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Nov. 7, 2011; doi:10.1073/pnas.1111405108 Contact: Tara L. Spires-Jones, Massachusetts General Hospital and Harvard Medical School, Charlestown, Mass. e-mail: tspires@partners.org</p>
Drug platforms			
An improved protocol to derive dopaminergic neurons from embryonic stem cells (ESCs) to treat Parkinson's disease (PD)	<p>Studies in cell culture, rodents and monkeys suggest an improved procedure for deriving dopaminergic neurons from ESCs could help treat PD. In cell culture, human ESCs treated with a sonic hedgehog homolog (SHH) agonist, fibroblast growth factor 8 (FGF8) and a glycogen synthase kinase 3β (GSK3B) inhibitor yielded more midbrain dopaminergic neurons than ESCs treated with an SHH agonist and FGF8. In mouse and rat models of PD, dopaminergic neurons produced by that method had higher levels of engraftment and dopaminergic function than transplanted neurons made using a prior protocol. In a monkey model of PD, transplanted dopaminergic neurons showed good survival and connectivity after two months. Next steps include scaling up the procedure to produce sufficient volumes of dopaminergic neurons for clinical trials as well as conducting <i>in vitro</i> drug screening assays (<i>see Stem cell jackpot for Parkinson's disease, page 8</i>).</p> <p>SciBX 4(46); doi:10.1038/scibx.2011.1308 Published online Dec. 1, 2011</p>	Patent pending; available for licensing	<p>Kriks, S. <i>et al. Nature</i>; published online Nov. 6, 2011; doi:10.1038/nature10648 Contact: Lorenz Studer, Memorial Sloan-Kettering Cancer Center, New York, N.Y. e-mail: studerl@mskcc.org</p>

This week in techniques

Approach	Summary	Licensing status	Publication and contact information
Embryonic stem cell (ESC)-derived anterior pituitary tissues for treating endocrine diseases	<i>In vitro</i> and mouse studies identified a method to generate anterior pituitary tissues from ESCs that could help treat endocrine diseases. Cultured mouse ESCs were first stimulated to aggregate into non-neural ectoderm and hypothalamic ectoderm layers. Subsequent treatment of the ectoderm with a hedgehog pathway agonist led to the formation of 3D anterior pituitary structures that produced endocrine cells. In mice, grafting of the cell structure increased hormone levels compared with those in sham-grafted controls. Next steps could include applying the strategy to human ESCs.	Patent and licensing status unavailable	Suga, H. <i>et al. Nature</i> ; published online Nov. 9, 2011; doi:10.1038/nature10637 Contact: Yoshiki Sasai, RIKEN Center for Developmental Biology, Kobe, Japan e-mail: yoshikisasai@cdb.riken.jp
Engineered pancreatic islets	Engineered pancreatic islets could help lower rejection risk in patients with type 1 diabetes. Isolated mouse islets were engineered to display the fas ligand (TNF superfamily, member 6; FASL). In a mouse model of type 1 diabetes, the engineered islet grafts restored normal blood glucose levels. In mice receiving transplants, the engineered islet grafts survived beyond 500 days, whereas control grafts lacking FasL were rejected within 30 days. Next steps could include evaluating the engineered islets in additional diabetes models.	Patent and licensing status unavailable	Yolcu, E.S. <i>et al. J. Immunol.</i> ; published online Nov. 7, 2011; doi:10.4049/jimmunol.1003266 Contact: Haval Shirwan, University of Louisville, Louisville, Ky. e-mail: haval.shirwan@louisville.edu Contact: Esma S. Yolcu, same affiliation as above e-mail: esma.yolcu@louisville.edu



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