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By *Joanne Kotz, Senior Editor*

A team from the **Northwestern University Feinberg School of Medicine** and the **Broad Institute of MIT and Harvard** has shown that inhibiting Aurora kinase A induces cancer cell differentiation in acute megakaryoblastic leukemia, thus reducing tumor load and increasing survival in a mouse model of the disease.<sup>1</sup> The researchers hope to start clinical trials of Aurora kinase A inhibitors in patients with adult acute megakaryoblastic leukemia next summer.

Acute megakaryoblastic leukemia (AMKL) is a rare form of acute myelogenous leukemia (AML) that is characterized by immature, hyperproliferative megakaryoblasts. Standard of care is chemotherapy.

Megakaryocytes—bone marrow cells that produce platelets—typically develop from hematopoietic stem cells that differentiate to megakaryoblasts and then to mature megakaryocytes. During maturation these cells undergo an unusual process in which the cellular DNA is replicated but the cell does not divide. As a result, mature, platelet-producing megakaryocytes are polyploid—commonly containing as many as 16 sets of chromosomes.

AMKL can be caused by multiple underlying genetic alterations. As a result, targeting any particular alteration would only be expected to provide a therapeutic benefit in a subset of patients.

A team led by John Crispino and Andrew Stern hypothesized that molecules that induced the differentiation of AMKL cells into mature, polyploid megakaryocytes might help take the underlying genetic diversity out of the equation and broadly treat the cancer. Crispino is a professor in the division of hematology/oncology at Northwestern. Stern is associate director of novel therapeutics at the Broad Institute.

“If you look at the genetics that have been associated with AMKL what you see is quite a bit of diversity,” said Stern. “The leap here was to ask if there would be a common mechanism that would circumvent the block of differentiation. That’s why we took a phenotypic screening approach.”

To identify differentiation-inducing small molecules, the team screened a library for compounds that could increase polyploidy in a human AMKL cell line. The group then looked to see which of the hits induced expression of mature megakaryocyte markers and focused its attention on dimethylfasudil, a broad kinase inhibitor.

In all nine AMKL cell lines tested, which represented a variety of the genetic alterations that underlie the disease, dimethylfasudil induced polyploidy and differentiation.

In a mouse model of AMKL, the compound also induced tumor cells in the bone marrow to become polyploid and to differentiate. About 45% of AMKL mice treated with dimethylfasudil survived at least 70 days,

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whereas no vehicle-treated mice survived beyond 20 days.

The key question was which kinase was the relevant target for the differentiation-promoting effects of dimethylfasudil. A combination of biochemical, proteomic and genetic approaches all pointed to Aurora kinase A (AURKA; Aurora-A).

Thus, the team turned to alisertib, a selective Aurora-A inhibitor from **Takeda Pharmaceutical Co. Ltd.**'s **Millennium Pharmaceuticals Inc.** subsidiary. As predicted, alisertib induced tumor cell polyploidy and decreased disease load compared with vehicle in AMKL mice.

Alisertib (MLN8237) is in Phase III testing in peripheral T cell lymphoma and is in Phase II testing in other hematological malignancies and solid tumors.

Data were published in *Cell*.

"In my mind the screen for inducers of polyploidization is the most novel and exciting aspect of this work. It has been known for more than two decades that retinoic acid and arsenic induce differentiation in acute promyelocytic leukemia, but these agents were identified empirically, and the mechanism was determined after they were in the clinic," said Ross Levine, an associate member in the Human Oncology & Pathogenesis Program and a physician in the leukemia service at **Memorial Sloan-Kettering Cancer Center**.

"I think what was innovative here was to take the approach of looking for a specific process that is part of the normal differentiation of these cells. I've not seen that done in this way before," added Neil Thompson, SVP of biology at **Astex Pharmaceuticals Inc.**

Astex's AT9283, which inhibits multiple kinases including Aurora-A, Aurora-B (AURKB), Janus kinase-2 (JAK-2) and FMS-like tyrosine kinase 3 (FLT3; CD135), is in Phase II testing in multiple myeloma (MM) and in Phase I studies in pediatric leukemia and solid tumors.

**Putting differentiation on trial**

The logical next step is testing Aurora-A inhibitors specifically in patients with AMKL.

"The preclinical data in this paper are as good as it gets. I don't think I'd be looking for any additional preclinical studies. They've used the preclinical models that come closest to the clinical situation," said Thompson.

Millennium has completed a Phase II study of alisertib in AML. Liviu Niculescu, senior medical director of global medical affairs at Millennium, said the overall response rate was 13%.

Niculescu added that no patients with AMKL were treated in the study.

**"In my mind the screen for inducers of polyploidization is the most novel and exciting aspect of this work. It has been known for more than two decades that retinoic acid and arsenic induce differentiation in acute promyelocytic leukemia, but these agents were identified empirically, and the mechanism was determined after they were in the clinic."**

**—Ross Levine,  
Memorial Sloan-Kettering  
Cancer Center**

“The outcomes following Aurora-A inhibition in AMKL nonclinical models demonstrated in this paper, polyploidization followed by differentiation, provide a strong rationale for testing Aurora-A inhibitors

**“The outcomes following Aurora-A inhibition in AMKL nonclinical models demonstrated in this paper, polyploidization followed by differentiation, provide a strong rationale for testing Aurora-A inhibitors in AMKL patient.”**

—Liviu Niculescu,  
Millennium Pharmaceuticals Inc.

in AMKL patients,” he noted.

Crispino told *SciBX* that the team is in discussions with Millennium about opening up an adult AMKL-specific trial with alisertib and is in preliminary discussions with two pediatric oncology groups to test Aurora-A inhibitors in patients with pediatric

AMKL. Crispino said the team hopes to open the adult AMKL trial next summer.

Millennium would not comment on whether the company is in ongoing discussions, and Niculescu noted that “no plans for an AMKL-specific study have been confirmed at this time.”

In addition to Millennium and Astex, at least six other companies have Aurora-A inhibitors in preclinical or clinical development in cancer.

#### Exploring indications, inhibitors

The Northwestern-Broad team now is looking at the mechanism of action in additional disease contexts and whether Aurora-A inhibitors with improved activity can be developed.

Myeloproliferative disorders, particularly primary myelofibrosis and essential thrombocytosis, involve megakaryocyte hyperproliferation,

noted Crispino. The team therefore wants to test the effects of dimethylfasudil and alisertib in preclinical models of these diseases alone and in combination with Jakafi ruxolitinib.

Jakafi is a JAK-1 and JAK-2 inhibitor marketed by **Incyte Corp.** and **Novartis AG** to treat myeloproliferative disorders.

The team also is working to develop new inhibitors. “What we’ve done is identify Aurora-A as the major target but not necessarily the only target” of dimethylfasudil, said Stern. Thus, Crispino said the group is optimizing dimethylfasudil “with the goal of developing analogs that we could put into Phase I trials.”

Northwestern has filed a patent application covering the results reported in the paper. The IP is available for licensing.

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**Novartis AG** (NYSE:NVS; SIX:NOVN), Basel, Switzerland

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# CDK8 inhibitor: Senex's best thing

By Michael J. Haas, Senior Writer

Chemotherapy is used to treat virtually every tumor type, but the drugs can blunt their own efficacy by inducing paracrine activity. Now, an international team led by **Senex Biotechnology Inc.** has mouse data showing that a cyclin dependent kinase 8 inhibitor can block the negative effects of at least one chemotherapeutic—doxorubicin.<sup>1</sup>

The unanswered questions include whether the cyclin dependent kinase 8 (CDK8) inhibitor enhances the efficacy of additional chemotherapies and targets cancer stem cells.

Doxorubicin is one of several chemotherapies that exert their efficacy by directly damaging DNA. However, this damage can induce the secretion of factors by host and tumor cells—so-called paracrine activities—that promote cancer cell growth, metastasis and drug resistance.<sup>2-5</sup> In addition, studies have shown that paclitaxel, which acts by stabilizing microtubules instead of damaging DNA, can also promote tumor invasion and metastasis.<sup>6-8</sup>

Although the molecular mechanisms that drive paracrine activities have been poorly understood, one clue emerged about a decade ago when researchers led by Igor Roninson, who was then at the **University of Illinois at Chicago**, found that cyclin-dependent kinase inhibitor 1A (p21, Cip1; CDKN1A; CIP1) regulated cellular responses to DNA damage.

The Chicago group showed that in a human cancer cell line, doxorubicin induced p21, which in turn upregulated multiple tumor-promoting antiapoptotic, mitogenic and angiogenic proteins.<sup>9,10</sup> Although p21 is known to regulate many transcription factors and several cyclin dependent kinases (CDKs) involved in transcription and the cell cycle, the studies did not elucidate p21's precise mechanism of action in promoting paracrine activities.

In the new study, a Roninson-led team from Senex set out to investigate the tumor-promoting pathways downstream of p21 to identify potential cancer targets.

First, the group used a p21-overexpressing cancer cell line developed by Roninson's previous team to screen compound libraries for small molecules that inhibited p21-induced expression of tumor-promoting factors. Several hits contained a 4-aminoquinazoline core, and optimization of this structure resulted in the lead compound, Senexin A.

Because Senexin A resembled known protein kinase inhibitors, the team screened the compound against 442 kinases and found it was a selective nanomolar inhibitor of CDK8 and a closely related isoform, CDK19 (CDC2L6). Additional *in vitro* experiments confirmed that the two kinases act downstream of p21 to induce the expression of multiple tumor-promoting proteins.

Next, the team injected mice with a human lung cancer cell line and mouse embryonic fibroblasts, which have paracrine activities similar to

those of tumor stromal cells in patients with cancer. In these xenograft models, Senexin A plus doxorubicin decreased tumor growth compared with doxorubicin alone.

Lastly, the group used a computational tool to search online microarray data for links between expression of the two kinases and survival in breast and ovarian cancer patients. They found that levels of each kinase correlated with poor relapse-free survival in both types of cancer, including ovarian cancers treated with DNA-damaging platinum chemotherapies. These findings suggest CDK8 and CDK19 are associated with the failure of such chemotherapies in the clinic and bolster the rationale for these kinases as cancer targets, the team wrote in its report in the *Proceedings of the National Academy of Sciences*.

The study also shows that Senexin A can block the oncogenic effects of CDK8 that do not require p21, such as the wingless-type MMTV integration site (WNT) and  $\beta$ -catenin (CTNNB1) pathway, Roninson told *SciBX*. “Thus, our compound inhibits CDK8 and its effects regardless of p21 expression in cells,” he said. CDK8 is upregulated in some colon and gastric cancers in which it activates WNT and CTNNB1 signaling.<sup>11,12</sup>

Roninson is founder, president and CSO of Senex and chair of translational cancer therapeutics and professor of pharmaceutical and biomedical sciences at the **University of South Carolina's** South Carolina College of Pharmacy. He formerly was professor of molecular genetics and head of the Division of Molecular Oncology at the University of Illinois at Chicago.

The team also included researchers at the **Ordway Research Institute, Rensselaer Polytechnic Institute, The Scripps Research Institute, the Hungarian Academy of Sciences** and the **University of Athens Medical School**.

“The potential for chemotherapeutic drugs to simultaneously inhibit tumor growth and stimulate or activate host mechanisms that may undercut the drugs' efficacy and hasten relapse is a topic of renewed—and growing—interest,” said John Ebos, assistant professor of oncology at **Roswell Park Cancer Institute**. “The potential for CDK8 blockade with Senexin A raises an interesting therapeutic possibility” for countering the cancer-promoting effects of chemotherapy.

William Nelson, director and professor of oncology at **The Johns Hopkins University** and director of JHU's Sidney Kimmel Comprehensive Cancer Center, agreed. He said the complexity of intercellular signaling in the tumor microenvironment has made it challenging to identify the key pathways that are involved in the tumor-promoting effects of chemotherapies. “The nomination of CDK8 and CDK19 as therapeutic targets for undermining survival signaling in cancers is intriguing,” he told *SciBX*.

Yuval Shaked, assistant professor and senior lecturer of molecular pharmacology at the **Technion-Israel Institute of Technology's** Ruth and Bruce Rappaport Faculty of Medicine, added that “an agent like Senexin A with such a specific target is potentially promising for clinical investigation since the probability of severe toxic side effects is low.”

**“The potential for chemotherapeutic drugs to simultaneously inhibit tumor growth and stimulate or activate host mechanisms that may undercut the drugs' efficacy and hasten relapse is a topic of renewed—and growing—interest.”**

**—John Ebos,  
Roswell Park Cancer Institute**

**Figure eights**

Other cancer researchers said the safety and specificity of Senexin A was not yet clear.

Nelson cautioned that inhibiting CDK8- or CDK19-regulated paracrine activities to augment the cancer-killing effects of doxorubicin might also increase the chemotherapy's toxicity in normal cells such as cardiomyocytes. Thus, he wanted to know whether Senexin A compromises paracrine activities that protect normal cells from doxorubicin toxicity.

Roninson said it is unknown whether paracrine activities protect normal cells from some degree of doxorubicin toxicity. He said it was theoretically possible that Senexin A could make the drug more toxic than usual to those cells, but he noted that "we don't see any indication in our studies that Senexin A increases doxorubicin's toxicity in normal tissues."

Irwin Gelman, chair of cancer genetics and professor of oncology at Roswell Park, said it would be important to confirm the specificity of Senexin A for CDK8 and CDK19. "Previous nonspecific CDK inhibitors haven't done well in clinical trials because of toxicity linked to their lack of specificity. Therefore, ongoing development of such compounds has had to take into account that lack, in terms of identifying appropriate indications, dosing regimens and combination therapies," he said.

As an example, he cited flavopiridol (alvocidib; HMR1275), a small molecule inhibitor of multiple CDKs that Aventis S.A. (now **Sanofi**) had in clinical development to treat undisclosed cancers until at least 2002. Sanofi now has the compound in Phase II testing to treat chronic lymphocytic leukemia (CLL).

Gelman added, "If Senexin A does not turn out to be specific for CDK8 and CDK19 *in vivo*, then its utility to treat cancer could be more limited" than the team suggests in the *PNAS* study.

Roninson said his team has not tested Senexin A against proteins other than kinases, "but their lack of cytotoxicity in cell culture and lack of systemic toxicity in our mouse studies suggests that significant off-target effects are unlikely."

He also noted that small hairpin RNA and other data in the *PNAS* paper demonstrate that CDK8 inhibition is responsible for the effects of Senexin A.

Nevertheless, Ebos said it would be important to test Senexin A as a monotherapy in animal models "to learn more about the feasibility and potential toxicity of targeting these CDKs—which, as Dr. Gelman has pointed out, it is challenging to do with true specificity."

**Larger circles**

In addition to the monotherapy studies, Ebos and Shaked want to see Senexin A tested in combination with doxorubicin in additional animal models of cancer, including metastatic cancers.

Shaked added that "it would be interesting to evaluate Senexin A in combination with other DNA-damaging drugs, such as cisplatin," or chemotherapies that do not directly damage DNA, such as paclitaxel.

He said studies in the past three years have shown that p21 is upregulated in cancer stem cells.<sup>13,14</sup> Those results suggest compounds

like Senexin A that target pathways downstream of p21 might have the added benefit of making cancer stem cells more susceptible to chemotherapy and thereby delaying or preventing tumor regrowth and relapse, he said.

Roninson agreed, citing a February study by a team from **Roche's Genentech Inc.** unit that suggested CDK8 plays a role in maintaining the cancer stem cell phenotype.<sup>15</sup> "We anticipate that our CDK8 inhibitors may be effective as single agents by blocking the tumor-initiating capacity of cancer stem cells," he said.

**"We anticipate that our CDK8 inhibitors may be effective as single agents by blocking the tumor-initiating capacity of cancer stem cells."**

**—Igor Roninson,  
Senex Biotechnology Inc.**

Roninson said Senex is testing Senexin B—an optimized version of Senexin A—in animal models of lung, breast, colon and prostate cancer in combination with doxorubicin and other undisclosed chemotherapies. The company also is testing Senexin B as a single agent to treat cancer, based in part on the ability of CDK8 inhibitors to block the WNT and CTNBN1 signaling pathway.

Additionally, Senex is conducting IND-enabling studies of Senexin B and seeking a corporate partner for clinical development of the compound, Roninson said.

Senex has patented the findings reported in *PNAS* and subsequent optimized inhibitors.

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**University of Athens Medical School**, Athens, Greece  
**University of Illinois at Chicago**, Chicago, Ill.  
**University of South Carolina**, Columbia, S.C.

# Broader is better

By Tracey Baas, Senior Editor

A team from the **Crucell Vaccine Institute** and **The Scripps Research Institute** has identified a trio of neutralizing human mAbs that protect mice from challenge with influenza viruses, including one mAb that protects against both A and B strains.<sup>1</sup> **Crucell N.V.**, one of the Janssen Pharmaceutical Companies of **Johnson & Johnson**, first plans to develop the antibodies to treat influenza-infected individuals and in the long run could use the antibody against A and B strains as a guide for developing a universal influenza vaccine.

Despite the success of prophylactic vaccines, seasonal influenza epidemics—either by the A or B strain—still cause morbidity and mortality every year. Influenza A viruses cause seasonal flu as well as influenza pandemics and are associated with more severe clinical disease. Influenza B viruses are the cause of seasonal epidemics every two to four years.<sup>2</sup>

The seasonal trivalent inactivated influenza vaccine attempts to induce protection by including two influenza A subtypes and one influenza B lineage. However, seasonal influenza vaccine mismatches occurred in about 50% of the seasons from 1998–2010.<sup>3</sup>

In an effort to take guesswork out of the equation, the Crucell-Scripps team decided to focus on finding a broadly neutralizing antibody against both influenza A and B viruses. A mAb-based immunotherapy that delivers antibodies right to the immune system could be used as a treatment for people already severely infected with influenza, as a prophylactic in cases of pandemics or in people who do not respond well to vaccination.

The researchers used a soluble recombinant version of the influenza A virus hemagglutinin (HA) proteins from various subgroups (HA9, HA7, HA5, HA3 and HA1) and influenza B HA from two lineages (Yamagata and Victoria) to screen a combinatorial display library of human B cells from volunteers vaccinated with the seasonal influenza vaccine.

The HAs were selected to cover the two lineages and main phylogenetic branches of influenza B, as well as the major subtypes of influenza A. Hits were further screened for their ability to bind viruses of both influenza B lineages and influenza A subtypes.

Crucell identified mAbs CR8033, CR9114 and CR8071 that bound to the two influenza B lineages. CR9114 also bound influenza A virus HA1 and HA3 subtypes.

Because antibody effector functions—the antibody's ability to recruit immune cells to fight infection—have been suggested to contribute to the protective efficacy of broadly neutralizing antibodies, the researchers next evaluated the three antibodies in mice challenged with influenza.

In mice given a lethal dose of Yamagata or Victoria influenza B, pretreatment with CR8033, CR8071 or CR9114 produced dose-dependent decreases in weight loss and increased survival compared with vehicle pretreatment. CR9114 also protected mice from lethal doses of H1N1 or H3N2 influenza A, making CR9114 the first mAb to provide protection against both influenza A and B.

**“The fact that the Crucell-Scripps team found these three cross-neutralizing antibodies in B cells from influenza-vaccinated individuals provides an important proof of concept that humans can generate broadly protective responses.”**

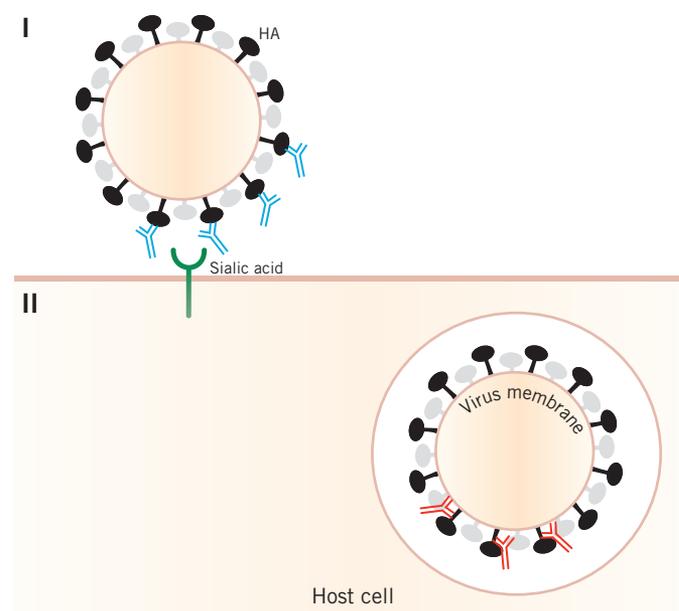
—Gary Nabel,  
National Institutes of Health

Notably, the three antibodies did not compete with each other for HA binding, suggesting they targeted different epitopes. Thus, the researchers turned to the crystal structures of the antibodies bound to virus to identify the actual epitopes and to understand how the antibodies achieved broad neutralization.

CR8033 bound an epitope in the HA head within the receptor-binding pocket of sialic acid and surrounding antigenic site. CR8071 bound to an epitope at the base of the HA head, distant from the receptor-binding site. CR9114 bound to an epitope in the HA stem, which explained its broadly protective nature.

mAbs directed to the globular head region of HA, which is highly variable and mediates attachment of influenza virus to the cellular receptors of the host cell (*see* Figure 1, “Antibodies can target the head or stalk of the hemagglutinin protein to provide different mechanisms of action,”

I.I), are typically strain specific and do not confer broad protective immunity. In contrast, mAbs directed to the conserved HA stem prevent membrane fusion and can broadly neutralize different influenza subtypes (*see* Figure 1.II).



**Figure 1. Antibodies can target the head or stalk of the hemagglutinin protein to provide different mechanisms of action.**

(I) Anti-influenza A virus hemagglutinin (HA) antibodies that bind to the HA globular head inhibit virus binding to host cells through the sialic acid receptor, thus preventing virus entry.

(II) Anti-HA antibodies that bind to the HA stalk region prevent the HA conformational changes needed to allow fusion of the viral envelop with the host membrane, impeding progression of the virus life cycle.

For example, **Celltrion Inc.**'s CT120 and **Humabs BioMed S.A.**'s FI6 both are antibodies that target the HA stem. The antibodies are in preclinical development for influenza A. FI6 is licensed to an undisclosed pharma.

The crystal structure also showed that CR9114's epitope was similar to the epitope of FI6. However, the structure of FI6 itself is dissimilar to that of CR9114. The researchers suggested that this explains why FI6 can neutralize influenza A, whereas CR9114 can neutralize both A and B.

To flesh out the antibodies' mechanisms of action, the researchers studied influenza-infected cell lines pretreated with the antibodies. The stem-binding CR9114—but not the head-binding CR8033 and CR8071—blocked the HA pH-induced conformational changes associated with membrane fusion (see **Figure 1.II**)

Curiously, CR8033 and CR8071 did not block viral entry and genome replication, which is how HA head-binding antibodies typically prevent virus propagation (see **Figure 1.I**). Instead, the antibodies interfered with the release of progeny virus from inside the cell into the supernatant, blocking the subsequent infection of neighboring cells. Surface electron microscopy images of the cell culture system showed dense aggregation of virus on the surface of the infected cells.

The images closely resembled what occurs in cells treated with the neuraminidase (NEU1; SIAL1) inhibitor Relenza zanamivir. **Biota Holdings Ltd.** and **GlaxoSmithKline plc** market Relenza to treat and prevent influenza.

Results were published in *Science*.

"The fact that the Crucell-Scripps team found these three cross-neutralizing antibodies in B cells from influenza-vaccinated individuals provides an important proof of concept that humans can generate broadly protective responses," said Gary Nabel, director of the Vaccine Research Center at the NIH.

### Entering the pipeline

Robert Friesen, lead principal investigator on the manuscript and VP of antibody discovery at Crucell, told *SciBX*, "We plan to transition our findings as therapeutic options to J&J's pipeline and to make this a smooth transition—these mAbs can be produced to sufficient quantity to take them into toxicology and safety studies."

"For these antibodies to be therapeutically actionable, the team is going to have to deal with manufacturing questions—how much antibody is needed to provide protection? Can they make enough of the antibody? Is the antibody stable enough?" said Peter Palese, chair of microbiology at the **Mount Sinai School of Medicine**.

Antonio Lanzavecchia, director of the **Institute for Research in Biomedicine** and cofounder of Humabs, also questioned the therapeutic potential of the antibodies. "Their study indicates that influenza A virus can escape from the broadest neutralizing antibody, CR9114, a fact that raises concern on the potential therapeutic use of this antibody," he said.

**"Simply knowing what epitope the antibody binds to does not guarantee that a universal vaccine based on this knowledge can happen."**

—Peter Palese,  
**Mount Sinai School of Medicine**

Both Lanzavecchia and Palese also wanted to see additional studies on the mechanism of protection for CR8033 and CR8071.

"We are very interested in further determining how CR8033 and CR8071 neutralize influenza B virus," agreed Friesen. "Because the structural work showed that they bound to or near the HA head, we

predicted they would prevent binding of the virus to the cell or conformational change of HA. Unexpectedly, our results suggest that they instead contribute to protection by preventing egress of the virus from an infected cell."

### The universe and everything

Although the Crucell-Scripps team identified the HA-stem epitope to which CR9114 binds, the key will be finding the specific antigen.

"Simply knowing what epitope the antibody binds to does not guarantee that a universal vaccine based on this knowledge can happen," said Palese.

"How likely it is that you can generate these broadly neutralizing antibodies through vaccination remains to be seen," Nabel pointed out. "It is worth trying, but the antibodies themselves could still provide protection even if vaccination does not succeed," he added.

Friesen agreed. "In terms of going after a universal vaccine, the concept is so far removed from our current work that it is actually a spinoff project within Crucell led by an entirely different Crucell research team. Our first priority is to get the broadly neutralizing influenza antibodies into the clinic."

Crucell has filed for a patent covering the broadly neutralizing antibody work. The IP is not available for licensing.

Baas, T. *SciBX* 5(33); doi:10.1038/scibx.2012.859

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**Celltrion Inc.** (KOSDAQ:068270), Incheon, South Korea  
**Crucell N.V.** (Pink:CRXLY), Leiden, the Netherlands  
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# Keeping biofilms at bay

By Lev Osherovich, Senior Writer

Researchers at **The University of Nottingham** and the **Massachusetts Institute of Technology** have built a high throughput screening platform to identify polymers that are resistant to bacterial colonization.<sup>1</sup> The technique has yielded a new class of compounds that could prevent biofilm formation on the surface of medical devices.

Biofilms are slow-growing, hardy, drug-resistant bacterial conglomerates that can form on the surface of catheters and other surgical implants. The films can lead to local inflammation and serve as reservoirs of bacteria that cause local or systemic infection.

Venous catheters are especially prone to biofilms, and about 1% of patients implanted with i.v. catheters develop systemic infections with high risk of mortality.

“The current of standard care is to give preoperative i.v. antibiotics just prior to surgery and any implantation,” said David Grainger, professor of bioengineering and professor and chair of pharmaceuticals and pharmaceutical chemistry at **The University of Utah**.

If an infection arises, Grainger said patients “receive a six-week course of antibiotics and then typically require removal and replacement of the implant.” He added that these patients run high risks of reinfection upon reimplantation because of changes in the local tissue environment at the implant site that promote biofilm growth.

Patients with urinary catheters also have a high rate of infection, although such infections typically are not life threatening and can be treated with oral antibiotics.

Regardless, Morgan Alexander, professor of biomedical surfaces and head of the Division of Biophysics and Surface Analysis at the University of Nottingham and lead author of the manuscript, would like to forestall the need for antibiotics. The goal, he said, is “to prevent the attachment of bacteria, which is distinct from most strategies that attempt to kill bacteria with antibiotics.”

Alexander reasoned that if catheters were coated with a bacteria-resistant polymer, the bugs would be unable to form a hardy biofilm and would instead be destroyed by the host’s immune system.

“If you don’t form a biofilm in the first place, it may be easier to deal with bacteria near the surface of the implant without resorting to antibiotics,” he said.

## Biofilm club

The challenge was to find a suitable polymer. Prior efforts by industry and by Alexander’s collaborators at MIT focused on bactericidal metal coatings and protein-blocking zwitterionic materials, respectively. As an alternative, Alexander focused on hydrophobic materials that prevent microbial attachment by repelling water from coated surfaces.

The group created a library of 576 acrylate-based polymers and spotted them onto a chemically activated microscope slide to create a

microarray of covalently attached polymers.

The team then soaked these microarrays in cultures of three different bacterial pathogens—*Pseudomonas aeruginosa*, *Staphylococcus aureus* and pathogenic *Escherichia coli*—that were labeled with GFP.

When visualized under a fluorescent microscope, spots with lower than average fluorescence indicated the polymer coating on those spots made it difficult for bacteria to take root. The compounds coating the least luminous spots were isolated, modified with further polymerization and then rescreened for even greater prevention of bacterial growth.

With a set of lead polymers from this recursive microarray-based screen in hand, the team assessed the molecules in an *in vitro* assay of urinary catheter biofilm formation. Catheters coated with the most promising polymers had 30-fold fewer bacterial colonies growing on them than a silver-coated catheter, which is the standard of care.

The team saw similar results in a mouse model of urinary tract infection. Mice implanted with a polymer-coated catheter and challenged with a high dose of *S. aureus* had lower bacterial titers at the catheter implantation site, surrounding tissue and distal organs than animals implanted with an uncoated control.

Results were reported in *Nature Biotechnology*. The findings are patented and

are available for licensing.

## Ex catheter declaration

Christopher Loose, cofounder and CTO of **Semprus BioSciences Corp.**, said that Alexander’s materials add to a growing menu of potentially useful device coatings.

“This is a new class of materials that couldn’t have been predicted without this screening technique,” said Loose.

Semprus is developing zwitterionic surface modification materials for implantable devices. The company was cofounded by Robert Langer, professor of chemical and biomedical engineering at MIT, who is a coauthor of Alexander’s report.

In July, Semprus was acquired by medical device maker **Teleflex Inc.**

Loose said Semprus’ zwitterionic surface modifications work by a different principle than the hydrophobic materials described in the paper. Instead of excluding water from the surface, Semprus’ coatings attract water but block protein attachment to the device surface.

The company’s coated peripherally inserted central catheter (PICC) has received European CE Mark approval and is under review in the U.S.

Alexander said his lead compounds—a family of polymers with methacrylate or cyclic and aromatic acrylate groups—could be suitable for clinical development, but the polymers will need further testing in the context of real-world implantable devices.

For example, he noted that visualizing systemic bacterial infection in the mouse catheterization assay required “injecting a large dose of bacteria,” more than would be found in a real infection, so further dose-ranging studies will be needed.

Grainger wanted to know whether Alexander’s coating could prevent a modest number of bacteria from taking hold and proliferating over the course of several weeks because the coating reduced but did not completely eliminate bacterial growth.

**“If you don’t form a biofilm in the first place, it may be easier to deal with bacteria near the surface of the implant without resorting to antibiotics.”**

—Morgan Alexander,  
The University of Nottingham

“They use an immense amount of bacteria in their *in vivo* assay,” said Grainger. “While they reduced the bacterial burden after four days, there’s still an enormous burden remaining. They might get this initial knockdown, but it’s possible that by day 10 or day 20, the infection comes back.”

**“This is a new class of materials that couldn’t have been predicted without this screening technique.”**

—**Christopher Loose,**  
**Semprus BioSciences Corp.**

are prone to causing bacterial infections and to accumulation of thrombi. The ideal coating would be resistant to both bacteria and blood clots.

Alexander said his team is now testing whether the coatings are resistant to encrustation by urinary minerals, another common cause of catheter blockage and tissue inflammation.

Another concern is whether the most promising coatings can be applied consistently over the surface of the device.

“This study focuses on creating new types of coatings, but the next stage is to see how this behaves when you put it onto top-performing devices” such as market-leading venous and urinary catheters, said Loose. “In real devices, you have multiple types of materials and process steps that make it difficult to come up with surface modifications.”

Another question is whether the hydrophobic coatings would be suitable for use on something besides urinary catheters. Grainger said venous catheters

Alexander’s team is performing manufacturing and toxicology studies to determine how best to apply the new materials.

Grainger and Loose both said the screening platform could be further exploited to identify other biofilm-resistant compound classes and to probe the mechanism of bacterial attachment and pathogenesis at device surfaces.

“This study will pique further interest in studies about how these surfaces resist biofilm formation,” said Grainger. “Adhesion doesn’t necessarily lead to infection, and the mechanism of this virulent transition is a black box. This technique could allow us to correlate material biophysical properties of a material with its propensity for infection.”

Osherovich, L. *SciBX* 5(33); doi:10.1038/scibx.2012.860  
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#### COMPANIES AND INSTITUTIONS MENTIONED

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**Semprus BioSciences Corp.**, Cambridge, Mass.

**Teleflex Inc.** (NYSE:TFX), Limerick, Pa

**The University of Nottingham**, Nottingham, U.K.

**The University of Utah**, Salt Lake City, Utah

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## This week in therapeutics

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

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

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
<b>Autoimmune disease</b>				
Rheumatoid arthritis (RA)	Adenosine A <sub>2A</sub> receptor (ADORA <sub>2A</sub> ); ecto-5'-nucleotidase (NT5E; NT; CD73)	<p>Mouse studies suggest activation of ADORA<sub>2A</sub> receptors by CD73-dependent prodrugs could help treat RA while avoiding the vasodilatory effects associated with marketed ADORA<sub>2A</sub> agonists. In mouse models of collagen-induced arthritis, a phosphorylated ADORA<sub>2A</sub> agonist that is activated by CD73 on immune cells decreased joint inflammation but did not lower blood pressure compared with no treatment. Next steps include evaluating the CD73-activated ADORA<sub>2A</sub> agonists in additional inflammatory indications, such as ischemia/reperfusion injury and sepsis.</p> <p>Lexiscan, a short-acting ADORA<sub>2A</sub> agonist from Gilead Sciences Inc. and Astellas Pharma Inc., is marketed as a cardiovascular imaging agent.</p> <p>CorVue binodenoson for injection, a selective ADORA<sub>2A</sub> agonist from Pfizer Inc., is under review as a cardiovascular imaging agent.</p> <p>At least seven other companies have ADORA<sub>2A</sub> agonists in Phase III testing or earlier to treat various indications.</p> <p><b>SciBX 5(33); doi:10.1038/scibx.2012.861</b> Published online Aug. 23, 2012</p>	Patent application filed; available for licensing	Flögel, U. <i>et al. Sci. Transl. Med.</i> ; published online Aug. 8, 2012; doi:10.1126/scitranslmed.3003717 <b>Contact:</b> Jürgen Schrader, Heinrich Heine University Duesseldorf, Duesseldorf, Germany e-mail: <a href="mailto:schrader@uni-duesseldorf.de">schrader@uni-duesseldorf.de</a>
<b>Cancer</b>				
Breast cancer	Rho-associated coiled-coil containing protein kinase 1 (ROCK1); ROCK2	<p><i>In vitro</i> and mouse studies identified an inhibitor of ROCK1 and ROCK2 that could help treat breast cancer. <i>In vitro</i>, a pyridylthiazole-based compound inhibited ROCK1 with an IC<sub>50</sub> value of 14.5 nM and ROCK2 with an IC<sub>50</sub> value of 6.2 nM. In human breast cancer cell lines, the inhibitor decreased migration, invasion and anchorage-independent growth compared with vehicle. In a mouse xenograft model of human breast cancer, the inhibitor decreased tumor growth compared with vehicle. Next steps include additional preclinical testing prior to an IND submission.</p> <p>Kadmon Corp. LLC's ROCK2 inhibitor, KD025, is in Phase I testing to treat inflammation and is in preclinical testing to treat cancer.</p> <p><b>SciBX 5(33); doi:10.1038/scibx.2012.862</b> Published online Aug. 23, 2012</p>	Patent application filed; available for licensing	Patel, R.A. <i>et al. Cancer Res.</i> ; published online July 30, 2012; doi:10.1158/0008-5472.CAN-12-0954 <b>Contact:</b> Said M. Sebti, H. Lee Moffitt Cancer Center & Research Institute, Tampa, Fla. e-mail: <a href="mailto:said.sebti@moffitt.org">said.sebti@moffitt.org</a>

## This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cancer	Topoisomerase I (TOP1); TOP2	<p><i>In vitro</i> and mouse studies suggest a class of dual inhibitors of TOP1 and TOP2 could help treat cancer. Chemical synthesis, <i>in vitro</i> testing and computational modeling of evodiamine analogs identified multiple compounds as dual inhibitors of TOP1 and TOP2 that inhibited growth of multiple human cancer cell lines at low nanomolar concentrations. In mice with human lung or colon tumors, several of the compounds were safe and decreased tumor growth compared with vehicle. Ongoing work includes optimization of the most potent compounds.</p> <p>Pfizer Inc. and Yakult Honsha Co. Ltd. market Camptosar irinotecan, a semisynthetic derivative of a camptothecin small molecule TOP1 inhibitor, to treat colorectal cancer and non-small cell lung cancer (NSCLC).</p> <p>Dainippon Sumitomo Pharma Co. Ltd. and Celgene Corp. market Calsed amrubicin, a third-generation synthetic anthracycline TOP2 inhibitor, to treat NSCLC and small cell lung cancer.</p> <p>GlaxoSmithKline plc markets the TOP1 inhibitor Hycamtin topotecan hydrochloride to treat small cell lung and cervical cancers.</p> <p><b>SciBX 5(33); doi:10.1038/scibx.2012.863</b> Published online Aug. 23, 2012</p>	Patented by Second Military Medical University; available for licensing or partnering	<p>Sheng, C. <i>et al. J. Med. Chem.</i>; published online Aug. 6, 2012; doi:10.1021/jm300605m</p> <p><b>Contact:</b> Chunquan Sheng, Second Military Medical University, Shanghai, China e-mail: <a href="mailto:shengcq@hotmail.com">shengcq@hotmail.com</a></p>
Non-small cell lung cancer (NSCLC)	Annexin A2 (ANXA2)	<p>Patient sample, mouse and cell culture studies suggest inhibiting ANXA2 could help treat NSCLC. In human NSCLC samples, ANXA2 levels were greater than those in healthy lung tissue and correlated with poor overall survival. In mice injected with human NSCLC cells, small hairpin RNA against ANXA2 decreased tumor growth compared with control shRNA. In cultured NSCLC cells, small interfering RNA against ANXA2 increased tumor suppressor p53 levels and cell-cycle arrest compared with scrambled siRNA. Next steps include determining other physiological effects of inhibiting ANXA2.</p> <p><b>SciBX 5(33); doi:10.1038/scibx.2012.864</b> Published online Aug. 23, 2012</p>	Findings unpatented; licensing status not applicable	<p>Wang, C.-Y. <i>et al. J. Biol. Chem.</i>; published online Aug. 2, 2012; doi:10.1074/jbc.M112.351957</p> <p><b>Contact:</b> Chiou-Feng Lin, National Cheng Kung University, Tainan, Taiwan e-mail: <a href="mailto:cflin@mail.ncku.edu.tw">cflin@mail.ncku.edu.tw</a></p>
Skin cancer	Nuclear factor (erythroid-derived 2)-like 2 (NFE2L2; NRF2)	<p>Cell culture studies identified NRF2 activators that could help prevent skin cancer. In human keratinocytes, NRF2 activators decreased UVB-induced apoptosis compared with vehicle, and the two lead activators showed lower toxicity than reference NRF2 activators. Next steps include developing derivatives of the lead NRF2 activator that are more suitable for skin delivery and evaluating their long-term effects in the mouse model.</p> <p>Biogen Idec Inc.'s BG-12, an oral dimethyl fumarate that activates the NRF2 pathway, is under review to treat multiple sclerosis (MS).</p> <p>Reata Pharmaceuticals Inc., Abbott Laboratories and Kyowa Hakko Kirin Co. Ltd. have bardoxolone methyl, a small molecule activator of NRF2, in Phase III testing to treat renal disease and Phase I testing to treat diabetic nephropathy.</p> <p>XenoPort Inc.'s XP23829, an oral prodrug of methyl hydrogen fumarate (MHF) that induces and activates the NRF2 pathway, is in preclinical development for Alzheimer's disease (AD) and Parkinson's disease (PD).</p> <p><b>SciBX 5(33); doi:10.1038/scibx.2012.865</b> Published online Aug. 23, 2012</p>	Unpatented; licensing status not applicable	<p>Lieder, F. <i>et al. J. Biol. Chem.</i>; published online July 31, 2012; doi:10.1074/jbc.M112.383430</p> <p><b>Contact:</b> Sabine Werner, Swiss Federal Institute of Technology Zurich (ETHZ), Zurich, Switzerland e-mail: <a href="mailto:sabine.werner@cell.biol.ethz.ch">sabine.werner@cell.biol.ethz.ch</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Endocrine/metabolic disease</b>				
Obesity; diabetes	Peroxisomal reductase activating PPAR $\gamma$ (PexRAP); peroxisome proliferation-activated receptor- $\gamma$ (PPARG; PPAR $\gamma$ )	Cell culture and mouse studies suggest inhibiting PexRAP could help treat diabetes and obesity. In mouse adipocytes, small hairpin RNA against PexRAP decreased expression of PPAR $\gamma$ target genes compared with scrambled shRNA. In mice fed a high-fat diet, shRNA against PexRAP decreased adiposity and increased leanness compared with scrambled shRNA and improved glucose tolerance. Next steps include defining the biology of PexRAP in various tissues and determining the physiological effects of genetic inactivation in animal models.  <b>SciBX 5(33); doi:10.1038/scibx.2012.866</b> <b>Published online Aug. 23, 2012</b>	Unpatented; licensing status not applicable	Lodhi, I.J. <i>et al. Cell Metab.</i> ; published online Aug. 2, 2012; doi:10.1016/j.cmet.2012.06.013 <b>Contact:</b> Clay F. Semenkovich, Washington University in St. Louis School of Medicine, St. Louis, Mo. e-mail: <a href="mailto:csemenko@wustl.edu">csemenko@wustl.edu</a>
<b>Hematology</b>				
Myeloproliferative disorder	Janus kinase-1 (JAK-1); JAK-2; heat shock protein 90 (Hsp90)	Patient tissue and cell culture studies suggest combining a JAK inhibitor with an Hsp90 inhibitor could improve treatment of myeloproliferative neoplasms (MPNs). In <i>ex vivo</i> granulocytes from patients with MPN, Jakafi ruxolitinib decreased JAK-2 signaling in treatment-naïve patients but not in patients chronically treated with the drug. In MPN cells resistant to Jakafi, an Hsp90 inhibitor decreased JAK-2 protein levels and cell viability compared with vehicle. Next steps include testing JAK inhibitors in combination with Hsp90 inhibitors in preclinical MPN models. Jakafi, a JAK-1 and JAK-2 inhibitor from Incyte Corp. and Novartis AG, is approved to treat myeloproliferative disorder.  <b>SciBX 5(33); doi:10.1038/scibx.2012.867</b> <b>Published online Aug. 23, 2012</b>	Unpatented; available for licensing	Koppikar, P. <i>et al. Nature</i> ; published online July 22, 2012; doi:10.1038/nature11303 <b>Contact:</b> Ross L. Levine, Memorial Sloan-Kettering Cancer Center, New York, N.Y. e-mail: <a href="mailto:leviner@mskcc.org">leviner@mskcc.org</a>
<b>Infectious disease</b>				
Bacterial infections	CD300A	Mouse studies suggest antagonizing CD300A could help treat bacterial infections. In mice undergoing cecal ligation and puncture (CLP), <i>Cd300a</i> receptor knockout mice showed greater bacterial clearance and survival than wild-type mice. In wild-type mice that underwent CLP, a mouse anti-Cd300a antibody increased bacterial clearance and survival compared with saline control. Next steps include clinical testing of an antibody against human CD300A.  <b>SciBX 5(33); doi:10.1038/scibx.2012.868</b> <b>Published online Aug. 23, 2012</b>	Patent application filed; available for licensing	Nakahashi-Oda, C. <i>et al. J. Exp. Med.</i> ; published online July 23, 2012; doi:10.1084/jem.20120096 <b>Contact:</b> Akira Shibuya, University of Tsukuba, Tsukuba, Japan e-mail: <a href="mailto:ashibuya@md.tsukuba.ac.jp">ashibuya@md.tsukuba.ac.jp</a>
HIV/AIDS	CXC chemokine receptor 4 (CXCR4; NPY3R)	<i>In vitro</i> and cell culture studies identified cyclic modified peptides that could help treat HIV infection. A structure-based approach identified a modified cyclic pentapeptide that binds to CXCR4 with a subnanomolar IC <sub>50</sub> value. In an HIV replication assay, the lead cyclic peptidomimetic molecule inhibited HIV activity with an EC <sub>50</sub> value of 29 nM. Next steps include testing the compounds in animal models of HIV infection.  <b>SciBX 5(33); doi:10.1038/scibx.2012.869</b> <b>Published online Aug. 23, 2012</b>	Patent application filed; unlicensed	Demmer, O. <i>et al. Angew. Chem. Int. Ed.</i> ; published online July 3, 2012; doi:10.1002/anie.201202090 <b>Contact:</b> Horst Kessler, Technical University Munich, Munich, Germany e-mail: <a href="mailto:kessler@tum.de">kessler@tum.de</a>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Neurology</b>				
Addiction	$\mu$ -Opioid receptor (OPRM1; MOR); OPRK1 (KOR); OPR	Rat studies suggest buprenorphine and naltrexone could help treat cocaine addiction in nonopioid-dependent individuals. Use of the synthetic opioid buprenorphine is associated with a risk of opioid dependence. In rat models of cocaine addiction, daily treatment for five days with buprenorphine and low-dose naltrexone decreased cocaine self-administration compared with vehicle treatment. The co-treatment also decreased opioid dependence and withdrawal symptoms compared with buprenorphine alone. Future studies could include longer-term animal studies of the combination. Buprenorphine, a generic MOR agonist and KOR antagonist, is marketed to treat opioid dependence and pain. Naltrexone, a generic OPR antagonist, is marketed to treat alcohol dependence and opioid dependence.  <b>SciBX 5(33); doi:10.1038/scibx.2012.870</b> <b>Published online Aug. 23, 2012</b>	Patent and licensing status unavailable	Wee, S. <i>et al. Sci. Transl. Med.</i> ; published online Aug. 8, 2012; doi:10.1126/scitranslmed.3003948 <b>Contact:</b> George F. Koob, The Scripps Research Institute, La Jolla, Calif. e-mail: <a href="mailto:gkoob@scripps.edu">gkoob@scripps.edu</a>
Huntington's disease (HD)	Huntingtin (HTT)	Fly, mouse and neuron culture studies suggest methylene blue, a compound known to reduce aggregation of $\beta$ -amyloid (A $\beta$ ) and microtubule-associated protein- $\tau$ (MAPT; TAU; FTDP-17), could help treat HD. In cultured mouse primary cortical neurons expressing mutant Htt, methylene blue decreased Htt aggregate levels and increased neuron survival compared with no treatment. In a <i>Drosophila</i> model of HD, methylene blue decreased htt aggregation and neurodegeneration compared with vehicle control. In a mouse model of HD, methylene blue decreased Htt levels and HD-associated impairments compared with vehicle control. Next steps include testing the compound in clinical trials. TauRx Pharmaceuticals Ltd.'s Rember methylene blue is in Phase II testing to treat Alzheimer's disease (AD).  <b>SciBX 5(33); doi:10.1038/scibx.2012.871</b> <b>Published online Aug. 23, 2012</b>	Unpatented; licensing status not applicable	Sontag, E.M. <i>et al. J. Neurosci.</i> ; published online Aug. 8, 2012; doi:10.1523/JNEUROSCI.0895-12.2012 <b>Contact:</b> Leslie M. Thompson, University of California, Irvine, Calif. e-mail: <a href="mailto:lmthomps@uci.edu">lmthomps@uci.edu</a>
Stroke	Tumor necrosis factor- $\alpha$ -induced protein 8-like 2 (TNFAIP8L2; TIPE2)	Mouse studies suggest increasing TIPE2 signaling could help treat stroke. In mice, <i>Tipe2</i> knockout led to larger infarct volumes and more severe neurological impairment than normal <i>Tipe2</i> expression. In wild-type mice, protective <i>Tipe2</i> expression increased after inducing cerebral ischemia compared with baseline. Next steps could include developing and evaluating compounds that increase TIPE2 signaling in animal models of stroke.  <b>SciBX 5(33); doi:10.1038/scibx.2012.872</b> <b>Published online Aug. 23, 2012</b>	Patent and licensing status unavailable	Zhang, Y. <i>et al. J. Biol. Chem.</i> ; published online Aug. 2, 2012; doi:10.1074/jbc.M112.348755 <b>Contact:</b> Fan Yi, Shandong University School of Medicine, Shandong, China e-mail: <a href="mailto:fanyi@sdu.edu.cn">fanyi@sdu.edu.cn</a>
<b>Ophthalmic disease</b>				
Blindness	Bardet-Biedl syndrome 12 (BBS12)	Mouse studies suggest inhibiting the proapoptotic, unfolded protein response could help prevent retinal degeneration in Bardet-Biedl syndrome, which is associated with mutations in <i>BBS</i> genes. In mice, a <i>Bbs12</i> deficiency led to retinal abnormalities and increased photoreceptor apoptosis compared with normal <i>Bbs12</i> expression. In <i>Bbs12</i> -deficient mice, two compounds that inhibited the proapoptotic unfolded protein response via different mechanisms slowed photoreceptor loss compared with no treatment. Next steps could include screening for additional inhibitors of the unfolded protein response in the mouse model.  <b>SciBX 5(33); doi:10.1038/scibx.2012.873</b> <b>Published online Aug. 23, 2012</b>	Patent and licensing status unavailable	Mockel, A. <i>et al. J. Biol. Chem.</i> ; published online Aug. 6, 2012; doi:10.1074/jbc.M112.386821 <b>Contact:</b> Vincent Marion, Institut National de la Santé et de la Recherche Médicale (INSERM) and University of Strasbourg, Strasbourg, France e-mail: <a href="mailto:vincent.marion@unistra.fr">vincent.marion@unistra.fr</a>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Transplantation</b>				
Graft-versus-host disease (GvHD)	Major histocompatibility complex (MHC)	<p>A retrospective SNP analysis suggests screening for rs887464 and rs2281389 could lower risk of GvHD. The study included 4,205 transplants and analyzed a 4.9 Mb MHC region encompassing 1,120 SNPs. In a SNP analysis of patients and donors that had undergone human leukocyte antigen (HLA)-matched donor hematopoietic cell transplantation, donor-recipient mismatch of rs887464 was associated with decreased disease-free survival and mismatch of rs2281389 was associated with increased risk for acute GvHD compared with matching of the SNPs. Next steps could include testing the effects of matching rs887464 and rs2281389 between donors and recipients in a prospective study.</p> <p><b>SciBX 5(33); doi:10.1038/scibx.2012.874</b> Published online Aug. 23, 2012</p>	Patent and licensing status undisclosed	<p>Petersdorf, E.W. <i>et al. Sci. Transl. Med.</i>; published online July 25, 2012; doi:10.1126/scitranslmed.3003974 <b>Contact:</b> Effie W. Petersdorf, University of Washington, Seattle, Wash. e-mail: <a href="mailto:epetersd@fhcrc.org">epetersd@fhcrc.org</a></p>

## 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
<b>Assays &amp; screens</b>			
Assay measuring impact of secreted proteins on kinase inhibitor sensitivity in human tumor-derived cell lines	An assay measuring the impact of secreted proteins on kinase inhibitor sensitivity in human tumor-derived cell lines could guide the development of combination therapies to prevent drug resistance. A cell-based assay screened the potential of 3,482 secreted proteins to activate alternative kinase pathways and cause resistance to kinase inhibitors in tumor cells. A number of secreted proteins induced resistance, with ligands of epidermal growth factor receptor 1 (EGFR1; HER1; ErbB1), fibroblast growth factor receptor (FGFR) and c-Met proto-oncogene (MET; HGFR) families showing a broad ability to compensate for inhibition of the original targeted kinase. Next steps could include analyzing the effects of secreted proteins in additional kinase-activated, human tumor-derived cell lines.	Patent and licensing status undisclosed	Harbinski, F. <i>et al. Cancer Discov.</i> ; published online Aug. 10, 2012; doi:10.1158/2159-8290.CD-12-0237 <b>Contact:</b> Ralph Tiedt, Novartis Institutes for BioMedical Research, Basel, Switzerland e-mail: <a href="mailto:ralph.tiedt@novartis.com">ralph.tiedt@novartis.com</a>
	<b>SciBX 5(33); doi:10.1038/scibx.2012.875</b> <b>Published online Aug. 23, 2012</b>		
<i>In situ</i> monitoring of dopamine metabolism to identify improved monoamine oxidase (MAO) inhibitors	A method of <i>in situ</i> monitoring of dopamine metabolism could be used to identify improved MAO inhibitors to treat neurological diseases. An isotope-labeled dopamine that could be used with NMR to detect MAO-mediated dopamine metabolism was synthesized. In a mouse liver tissue homogenate, the method identified analogs of an MAO inhibitor that were more potent inhibitors of dopamine metabolism <i>in situ</i> than the parent compound, despite being less potent inhibitors of the enzyme <i>in vitro</i> . Next steps include using the method to screen for additional MAO inhibitors with improved <i>in situ</i> potency. At least 10 companies have MAO inhibitors in development stages from preclinical to marketed for neurological conditions and other diseases.	Unpatented; licensing status not applicable	Ueki, R. <i>et al. J. Am. Chem. Soc.</i> ; published online July 19, 2012; doi:10.1021/ja305051u <b>Contact:</b> Shinsuke Sando, Kyushu University, Fukuoka, Japan e-mail: <a href="mailto:ssando@ifrc.kyushu-u.ac.jp">ssando@ifrc.kyushu-u.ac.jp</a>
	<b>SciBX 5(33); doi:10.1038/scibx.2012.876</b> <b>Published online Aug. 23, 2012</b>		
Metabochip custom genotyping arrays for detection of disease-associated SNP markers	The Metabochip genotyping array could be useful for detecting disease-associated SNP markers of endocrine, metabolic and cardiovascular diseases. The Metabochip is designed to genotype individuals for 196,725 SNPs associated with various diseases including coronary artery disease (CAD), myocardial infarction (MI) and type 2 diabetes, as well as SNPs linked to blood pressure and levels of lipid, insulin and glucose. In 67 samples genotyped from a study by the International Haplotype Map Project, the Metabochip array showed 99.9% overall concordance with the HapMap data for common SNP variants and 98.9% and 97.8% concordance for sets of less common SNPs. Next steps could include developing additional custom genotyping arrays to detect sets of SNP markers associated with other disease indications.	Patent and licensing status unavailable	Voight, B.F. <i>et al. PLoS Genet.</i> ; published online Aug. 2, 2012; doi:10.1371/journal.pgen.1002793 <b>Contact:</b> Michael Boehnke, University of Michigan, Ann Arbor, Mich. e-mail: <a href="mailto:boehnke@umich.edu">boehnke@umich.edu</a> <b>Contact:</b> Gonçalo R. Abecasis, same affiliation as above e-mail: <a href="mailto:goncalo@umich.edu">goncalo@umich.edu</a> <b>Contact:</b> Mark I. McCarthy, University of Oxford, Oxford, U.K. e-mail: <a href="mailto:mark.mccarthy@drl.ox.ac.uk">mark.mccarthy@drl.ox.ac.uk</a> <b>Contact:</b> David Altshuler, Broad Institute of MIT and Harvard, Cambridge, Mass. e-mail: <a href="mailto:altshuler@molbio.mgh.harvard.edu">altshuler@molbio.mgh.harvard.edu</a>
	<b>SciBX 5(33); doi:10.1038/scibx.2012.877</b> <b>Published online Aug. 23, 2012</b>		

## This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
<b>Chemistry</b>			
Biofilm-resistant polymers	<p>Mouse and <i>in vitro</i> studies suggest methacrylate polymer coatings could help prevent biofilm formation in implantable medical devices. A microarray-based screen identified a class of methacrylates that resisted colonization by <i>Pseudomonas aeruginosa</i>, <i>Staphylococcus aureus</i> and <i>Escherichia coli</i>. In a mouse model of biofilm formation, subcutaneously implanted catheters coated with the lead methacrylates showed less bacterial colonization than control catheters. Next steps include toxicology studies and preclinical testing of coated urinary and venous catheters.</p> <p>Semprus BioSciences Corp. has biofilm-resistant polymer coatings for a range of biomedical devices in preclinical development (see <a href="#">Keeping biofilms at bay</a>, page 8).</p> <p><b>SciBX 5(33); doi:10.1038/scibx.2012.878</b> Published online Aug. 23, 2012</p>	Patent pending; available for licensing	<p>Hook, A.L. <i>et al. Nat. Biotechnol.</i>; published online Aug. 12, 2012; doi:10.1038/nbt.2316</p> <p><b>Contact:</b> Morgan R. Alexander, The University of Nottingham, Nottingham, U.K. e-mail: <a href="mailto:morgan.alexander@nottingham.ac.uk">morgan.alexander@nottingham.ac.uk</a></p>
Rapid, inexpensive gram-scale synthesis of prostaglandins	<p>A method for synthesizing prostaglandins could help generate new compounds using fewer manufacturing steps. Synthesis of prostaglandin analogs is complicated, and drugs such as Xalatan latanoprost are still manufactured via a 20-step process. A two-step reaction sequence from inexpensive starting materials produced gram-scale quantities of a bicyclic enal intermediate. A five-step reaction sequence converted the enal intermediate to gram-scale quantities of prostaglandin F<sub>2α</sub> (PGF<sub>2α</sub>). Ongoing work includes testing the biological activity of compound libraries generated from the enal intermediate.</p> <p>Xalatan, a prostaglandin F receptor (PTGFR) agonist from Pfizer Inc., is marketed to decrease intraocular pressure in glaucoma. At least 11 companies market prostaglandins or prostaglandin analogs to treat cardiovascular, ophthalmic, genitourinary and gastrointestinal diseases.</p> <p><b>SciBX 5(33); doi:10.1038/scibx.2012.879</b> Published online Aug. 23, 2012</p>	Patented; available for licensing	<p>Coulthard, G. <i>et al. Nature</i>; published online Aug. 15, 2012; doi:10.1038/nature11411</p> <p><b>Contact:</b> Varinder K. Aggarwal, University of Bristol, Bristol, U.K. e-mail: <a href="mailto:v.aggarwal@bristol.ac.uk">v.aggarwal@bristol.ac.uk</a></p>
<b>Disease models</b>			
Genetic mouse model of multiple myeloma (MM)	<p>A genetic mouse model of MM could help identify new compounds to treat the disease. Mice were engineered to express the MM-associated oncogene <i>v-maf musculoaponeurotic fibrosarcoma oncogene homolog B (MafB)</i> in hematopoietic stem and progenitor cells. In these mice, hematopoietic cells terminally differentiated into B cells expressing the oncogene, and the animals developed features that recapitulated MM in humans, including lytic bone lesions and plasma cell tumors. Next steps include using the model to test therapeutic candidates for MM.</p> <p><b>SciBX 5(32); doi:10.1038/scibx.2012.880</b> Published online Aug. 23, 2012</p>	Patented; available for licensing	<p>Vicente-Dueñas, C. <i>et al. EMBO J.</i>; published online Aug. 17, 2012; doi:10.1038/emboj.2012.227</p> <p><b>Contact:</b> Isidro Sánchez-García, Spanish National Research Council and University of Salamanca, Salamanca, Spain e-mail: <a href="mailto:isg@usal.es">isg@usal.es</a></p> <p><b>Contact:</b> César Cobaleda, Spanish National Research Council and Autonomous University of Madrid, Madrid, Spain e-mail: <a href="mailto:ccobaleda@cbm.uam.esv">ccobaleda@cbm.uam.esv</a></p>
Induced pluripotent stem (iPS) cell-derived motor neurons from patients with familial amyotrophic lateral sclerosis (ALS) for <i>in vitro</i> therapeutic screening	<p><i>In vitro</i> studies suggest iPS cell-derived motor neurons from patients with familial ALS could be used to screen for new therapeutics. In cultured iPS cell-derived motor neurons from patients with familial ALS carrying TAR DNA binding protein 43 (TDP-43; TARDBP) mutations, levels of TDP-43 protein and cytosolic aggregates were greater than those in iPS cell-derived motor neurons from healthy controls. In the ALS patient-derived motor neurons, the histone acetyltransferase inhibitor anacardic acid reversed the disease phenotype. Next steps include testing the safety and efficacy of anacardic acid in additional cellular and animal models.</p> <p><b>SciBX 5(33); doi:10.1038/scibx.2012.881</b> Published online Aug. 23, 2012</p>	Patent application filed covering prophylactic and therapeutic applications of anacardic acid; provisional application filed covering screening applications; available for licensing	<p>Egawa, N. <i>et al. Sci. Transl. Med.</i>; published online Aug. 1, 2012; doi:10.1126/scitranslmed.3004052</p> <p><b>Contact:</b> Haruhisa Inoue, Japan Science and Technology Agency, Tokyo, Japan e-mail: <a href="mailto:haruhisa@cira.kyoto-u.ac.jp">haruhisa@cira.kyoto-u.ac.jp</a></p>

## This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Mouse model of systemic lupus erythematosus (SLE) induced by nucleic acid-containing amyloid fibrils	A mouse model of SLE induced by nucleic acid-containing amyloid fibrils could help screen and evaluate potential lupus therapies. In healthy mice, immunization with DNA-containing amyloid fibrils induced a rapid interferon response, infiltration of plasmacytoid dendritic cells (pDCs) at the inoculation site, autoantibody production and proteinuria. In those mice, mAb-mediated depletion of pDCs decreased the interferon response and amyloid fibril-induced generation of several autoantibodies compared with IgG control. Next steps include developing additional SLE models using delivery of different types of amyloids to generate different types of autoantibodies.  <b>SciBX 5(33); doi:10.1038/scibx.2012.882</b> <b>Published online Aug. 23, 2012</b>	Unpatented; model available for licensing	Di Domizio, J. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Aug. 17, 2012; doi:10.1073/pnas.1206923109 <b>Contact:</b> Wei Cao, The University of Texas MD Anderson Cancer Center, Houston, Texas e-mail: <a href="mailto:wcao@mdanderson.org">wcao@mdanderson.org</a>
<b>Drug platforms</b>			
Expression of herpes simplex virus (HSV) thymidine kinase in human embryonic stem cells (hESCs) as a strategy to prevent teratoma formation	<i>In vitro</i> and mouse studies identified a strategy to prevent teratoma formation in hESC-derived cellular therapies. hESCs were engineered to express HSV thymidine kinase, which is not expressed by differentiated cells or healthy human cells. In culture, the thymidine kinase inhibitor Zirgan ganciclovir induced death of engineered hESCs but not differentiated cells derived from the engineered hESCs. In mice transplanted with the engineered hESCs or partially differentiated engineered hESCs, ganciclovir prevented teratoma formation whereas saline did not. Next steps include testing the strategy in disease models. Laboratoires Thea S.A. markets Zirgan to treat HSV infection.  <b>SciBX 5(33); doi:10.1038/scibx.2012.883</b> <b>Published online Aug. 23, 2012</b>	Findings unpatented; available for licensing	Rong, Z. <i>et al. J. Biol. Chem.</i> ; published online Aug. 4, 2012; doi:10.1074/jbc.M112.383810 <b>Contact:</b> Yang Xu, University of California, San Diego, La Jolla, Calif. e-mail: <a href="mailto:yangxu@ucsd.edu">yangxu@ucsd.edu</a>
Fluorescent cellular assays that monitor protein tyrosine phosphatase activity	Fluorescent cellular assays that monitor tyrosine phosphatase activity could be useful for drug screening. The assay uses a human T cell line incubated with cell-permeable, phosphorylated peptides that emit a fluorescent signal when dephosphorylated by tyrosine phosphatases. The assay was used to screen chemical libraries for small molecule inhibitors of tyrosine phosphatase CD45 and identified four hits. In a validation study using human T cell and macrophage cell lines, the four hits inhibited CD45. Next steps include developing probes selective for other phosphatases.  <b>SciBX 5(33); doi:10.1038/scibx.2012.884</b> <b>Published online Aug. 23, 2012</b>	Patent application filed covering system to monitor intracellular phosphatase activity; available for licensing from the University of Southern California <b>Contact:</b> Chris Moulding, University of Southern California, Los Angeles, Calif. e-mail: <a href="mailto:moulding@stevens.usc.edu">moulding@stevens.usc.edu</a>	Stanford, S.M. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Aug. 13, 2012; doi:10.1073/pnas.1205028109 <b>Contact:</b> Nunzio Bottini, La Jolla Institute for Allergy & Immunology, La Jolla, Calif. e-mail: <a href="mailto:nunzio@liai.org">nunzio@liai.org</a>
Nanofibrous composite scaffolds with tunable pore size	Nanofibrous composite scaffolds with variable pore sizes could be useful for promoting musculoskeletal repair and regeneration. The composite scaffolds contain poly( $\epsilon$ -caprolactone) fibers and water-soluble poly(ethylene oxide) fibers that can be selectively removed to increase pore size and improve scaffold colonization by cells. In rats, implantation of the composite scaffolds and subsequent removal of the water-soluble fibers yielded cellularized constructs with mechanical properties comparable to those of normal tissue. Ongoing studies include testing the composite scaffold in sheep models of meniscus repair.  <b>SciBX 5(33); doi:10.1038/scibx.2012.885</b> <b>Published online Aug. 23, 2012</b>	Multiple pending patents; available for licensing from the University of Pennsylvania Center for Technology Transfer <b>Contact:</b> Shilpa Bansali, University of Pennsylvania, Philadelphia, Pa. e-mail: <a href="mailto:sbhansali@ctt.upenn.edu">sbhansali@ctt.upenn.edu</a>	Baker, B.M. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Aug. 7, 2012; doi:10.1073/pnas.1206962109 <b>Contact:</b> Robert L. Mauck, University of Pennsylvania, Philadelphia, Pa. e-mail: <a href="mailto:lemauck@mail.med.upenn.edu">lemauck@mail.med.upenn.edu</a>
VEGF-containing, self-assembling peptide nanofiber scaffolds for promoting arteriogenesis	VEGF-containing, self-assembling peptide nanofiber scaffolds could help promote tissue repair following myocardial infarction (MI). In rat and porcine models of MI, intramyocardial injection of the VEGF-containing nanofiber scaffold increased cardiac function, angiogenesis and arteriogenesis compared with injection of scaffold or VEGF alone. In the rat model, intramyocardial injection of the VEGF-containing nanofiber scaffold decreased systemic adverse effects compared with injection of VEGF itself. Next steps include studies to evaluate the scaffold's long-term effects and determine its therapeutic window in the post-MI setting.  <b>SciBX 5(33); doi:10.1038/scibx.2012.886</b> <b>Published online Aug. 23, 2012</b>	Patent application filed; available for licensing	Lin, Y.-D. <i>et al. Sci. Transl. Med.</i> ; published online Aug. 8, 2012; doi:10.1126/scitranslmed.3003841 <b>Contact:</b> Patrick C.H. Hsieh, National Cheng Kung University Hospital, Tainan, Taiwan e-mail: <a href="mailto:phsieh@mail.ncku.edu.tw">phsieh@mail.ncku.edu.tw</a>

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