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By *Tim Fulmer, Senior Writer*

Researchers at **The Johns Hopkins University School of Medicine** have identified a way to dial down excessive activation of T cells in rheumatoid arthritis and potentially other autoimmune diseases.¹ **Amplimmune Inc.** has in-licensed the IP and has a therapeutic in preclinical development that blocks activation of T cells before they can release proinflammatory cytokines; thus the compound works upstream of RA drugs that inhibit tumor necrosis factor- α (TNF- α).

Co-inhibitory and co-stimulatory molecules expressed on the surface of antigen-presenting cells (APCs) are essential for maintaining a balanced immune response that fights infection without triggering autoimmunity.²

Either enhanced co-stimulatory activity or impaired co-inhibitory activity can lead to the excess inflammation that is a hallmark of autoimmune diseases. Therefore, two avenues for reducing inflammation are antagonizing co-stimulatory pathways or agonizing co-inhibitory pathways.

RA drug Orenia abatacept from **Bristol-Myers Squibb Co.** takes the first road. The cytotoxic T lymphocyte-associated protein 4 (CTLA4; CTLA-4; CD152)-Ig fusion protein binds CD80 (B7-1) and CD86 (B7-2) on the surface of APCs to prevent those ligands from binding their receptors and stimulating the activity of T cells.

The Johns Hopkins group and Amplimmune are taking the latter route, agonizing a co-inhibitory pathway mediated by a molecule called v-set domain containing T cell activation inhibitor 1 (VTCN1; B7-H4).

Work by the Hopkins group and others previously implicated B7-H4 as an important co-inhibitory molecule in autoimmunity and cancer (see **Figure 1, "Enhancing immunosuppression in RA"**).³⁻⁵ Moreover, a rodent study showed that B7-H4 could exist in a soluble form during the proinflammatory response to ovarian cancer.⁶

As a result, the Johns Hopkins team hypothesized that soluble B7-H4 might be responsible for triggering unwanted proinflammatory responses in autoimmune disease.

They first looked at soluble B7-H4 serum levels in RA patients and saw significantly higher levels in these patients than in individuals with no history of autoimmune disease (65% vs. 13%; $p=0.0013$). Within the RA group, soluble B7-H4 levels were significantly higher in patients with severe disease than in patients in remission ($p=0.0032$).

With a correlation in hand between high soluble B7-H4 levels and RA severity, the next step was determining whether soluble B7-H4



Science-Business eXchange

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SciBX is produced by BioCentury Publications, Inc. and Nature Publishing Group Joint Steering Committee: Karen Bernstein, Ph.D., Chairman & Editor-in-Chief, BioCentury; David Flores, President & CEO, BioCentury; Bennet Weintraub, Finance Director, BioCentury; Steven Inchcoombe, Managing Director, Nature Publishing Group; Peter Collins, Ph.D., Publishing Director, NPG; Richard Hartgill, Chief Financial Officer, NPG.

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actually caused the disease. In a mouse model of arthritis, animals with forced overexpression of murine soluble B7-H4 had greater incidence and earlier development of arthritis than control mice that received a mock expression vector.

Additional B7-H4 knockout experiments suggested that soluble B7-H4 triggered a proinflammatory response by preventing cell-surface B7-H4 from suppressing T cell activation by binding its receptor on immune cells.

Finally, the researchers hypothesized that agonizing the B7-H4 receptor on T cells could restore immunosuppression and treat RA. To test this, they created a fusion protein consisting of the extracellular domain of B7-H4 linked to the Fc portion of IgG.

In mouse models of arthritis, the fusion protein significantly reduced disease progression compared with no treatment ($p < 0.01$).

The researchers published the results in *PLoS Medicine*. Patents covering the findings are exclusively licensed to Amplimmune, which was cofounded by corresponding author Lieping Chen, professor of oncology, immunology and dermatology at the Johns Hopkins school of medicine.

Agonizing therapy

Amplimmune is now working out the therapeutic implications of the findings.

Sol Langermann, VP of R&D, told *SciBX* that the biotech has developed a fusion protein, AMP-110, which is an optimized version of the agonist described in the paper. The company plans to finalize AMP-110's dosing schedule in rodents next year and hopes to start Phase I testing in an undisclosed autoimmune indication in 1H11.

Langermann said that compared with therapeutics such as anti-TNF- α mAbs that target specific proinflammatory cytokines, AMP-110 has "broad-spectrum activity."

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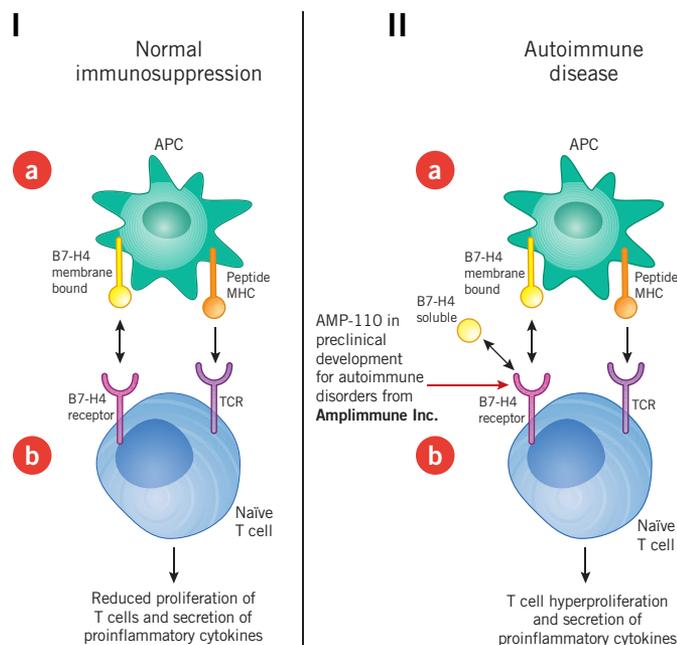


Figure 1. Enhancing immunosuppression in RA. In an article in *PLoS Medicine*, researchers described a way to restore immunosuppression in rheumatoid arthritis (RA) by targeting a pathway upstream of the proinflammatory cytokines inhibited by marketed biologics.

Under normal conditions, hyperproliferation of T cells and excess secretion of proinflammatory cytokines are held in check by an interaction between antigen-presenting cells (APCs) and naive T cells that requires two signals. The first signal involves the major histocompatibility complex (MHC)/antigen peptide complex engaging the T cell receptor (TCR). The second signal occurs when co-inhibitory ligands on APCs, like v-set domain containing T cell activation inhibitor 1 (VTCN1; B7-H4), interact with their receptors on T cells (I[a]). Once activated by their ligands, the cell-surface receptors trigger downstream signaling pathways that reduce immunoactivation (I[b]).

In some autoimmune diseases, excessive proinflammatory T cell activity occurs when the co-inhibitory ligand cannot bind and activate its receptor on T cells. Indeed, the results in the *PLoS Medicine* paper showed that high serum levels of a soluble form of B7-H4 prevented the membrane-bound B7-H4 from binding its receptor (II[a]), which led to a loss of immunosuppression, excessive proinflammatory T cell activity and RA (II[b]).

To counteract the effects of soluble B7-H4, the researchers developed a fusion protein that mimicked the membrane-bound form of the ligand, binding its receptor on T cells and dampening the immune response. An optimized version of the compound, called AMP-110, is being developed by **Amplimmune Inc.** and is in preclinical development for autoimmune disorders.

“We’ve shown that AMP-110 blocks multiple inflammatory cytokines and chemokines involved in disease,” he said, including TNF- α , IL-17, interferon- γ (IFNG; IFN- γ), IL-6 and monocyte chemoattractant protein-1 (MCP-1; CCL2). “That suggests the compound should work even in patients who are nonresponsive to TNF- α inhibitors,

one of the main classes of biologics to treat RA.”

Earlier this year, Amplimmune received funding from **Fast Forward LLC**, a subsidiary of the **National Multiple Sclerosis Society**, for preclinical development of AMP-110 to prevent abnormal immune responses associated with multiple sclerosis (MS).

Amplimmune has extended some of that funding to Stephen Miller, professor of immunology at **Northwestern University**. Miller, a consultant for the company, is testing a B7-H4 receptor agonist in rodent models of MS.

Miller told *SciBX* that the agonist has shown efficacy in experimental autoimmune encephalitis (EAE) rodent models of MS.

Biomarking the territory

Although Amplimmune is forging ahead with its B7-H4-based fusion protein, the Johns Hopkins group is now focused on soluble B7-H4’s utility as a disease biomarker.

“We are doing a larger-scale survey to detect soluble B7-H4 in patients with RA and other rheumatoid diseases. This will validate the value of detection of soluble B7-H4 as a method to predict progression of RA and other autoimmune diseases,” said Chen.

According to Weiping Zou, professor of surgery and director of translational research at the **University of Michigan Medical School**, “It’s important to extend the paper’s study to a larger population of RA patients who have varying stages of disease, as well as to patients who are already being treated with anti-inflammatory medications.” That should help show how broadly relevant the soluble B7-H4 marker is to different stages of disease, he said.

Zou told *SciBX* it also would be useful to look at soluble B7-H4 levels in patients with other autoimmune disorders.

Haidong Dong, assistant professor of immunology at the **Mayo Clinic**, thinks the first step should be showing that the structure of soluble B7-H4 remains identical across stages of a single disease and across multiple autoimmune diseases. Thus, it will be important to determine the amino acid sequence of the soluble B7-H4 identified in the paper’s RA patients and to confirm its identity as disease progresses and becomes severe, said Dong.

Fulmer, T. *SciBX* 2(44); doi:10.1038/scibx.2009.1618
Published online Nov. 12, 2009

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Silencing cytokines

By Michael J. Haas, Senior Writer

A group led by **Resolvix Pharmaceuticals Inc.** cofounder Charles Serhan has shown that the endogenous bioactive lipid resolvin D2 improves symptoms in sepsis.¹ The findings could expand the number of indications addressed by Resolvix, which is developing resolvins for inflammatory indications, although the company has not disclosed how it will utilize the findings.

Resolvins are lipid mediators produced through the oxygenation of the ω -3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). In multiple inflammatory conditions, resolvins manage the immune response.

Resolvix began operations in late 2005 after exclusively licensing a patent portfolio of endogenous resolvins and their analogs from **Brigham and Women's Hospital**, where Serhan is director of the Center of Experimental Therapeutics and Reperfusion Injury. He is also a professor of anesthesiology at **Harvard Medical School**.

The company's most advanced compounds are based on resolvin E1 (RvE1), which is derived from EPA. Studies by Serhan and colleagues in 2007 and 2008 demonstrated the potential of RvE1 to treat acute inflammation and airway inflammation, respectively.^{2,3} Since then Serhan has been investigating the therapeutic potential of resolvin D2 (RvD2), which is derived from DHA.

"It took us some time to establish the complete stereochemistry for RvD2 and begin to appreciate the broad basis of its actions in mammalian systems," Serhan told *SciBX*.

In mouse models of surgery-induced microbial sepsis, his latest team has now shown that RvD2 treatment reduced levels of proinflammatory cytokines associated with poor outcomes in sepsis and inhibited excessive leukocyte infiltration into the peritoneum compared with vehicle treatment. The compound achieved both effects without blocking the pathways that activate immune cells and thus stimulated endogenous pro-resolution mechanisms without exerting an immunosuppressive effect.

RvD2 also recruited phagocytes to increase the clearance of bacteria from the peritoneum and blood and increased mouse survival compared with that of controls.

"Our experiments show that RvD2 is a master regulator of the cytokine storm" associated with sepsis, said Serhan. "Our data suggest that RvD2 silences the outflow of all cytokines from macrophages as they're eating infected cells. The exciting part about this biology is that it goes against the grain of current therapeutic strategies of treating excessive inflammation with immunosuppression."

In contrast, he said, "RvD2 facilitates the resolution of inflammation."

Results were reported in *Nature*. The team included researchers from Barts and the London School of Medicine and Dentistry, which is part of **Queen Mary, University of London**, and the **University of Southern California**.

Indications of resolution

Serhan said RvD2 potentially could be combined with existing antibiotics

to treat sepsis. He said the combination might reduce the required dose of antibiotic and thus the potential for antibiotic resistance.

"Our RvD2 study is a demonstration of a new type of endogenous molecule that acts on the effector immune system to enhance the killing of bacteria but is not an antibiotic" and so is not properly described as an anti-infective, Serhan said. "It requires a new word that I haven't found yet."

He also thinks RvD2 might have a protective effect in situations in which bowel mucosal damage could lead to sepsis, such as GI surgery or radiation therapy used for treating cancer or during bone marrow transplant.

Serhan acknowledged that more work with the surgical models of sepsis would be needed to determine how many types of bacterial infections RvD2 could clear. "But this is beyond the capability of an academic lab to test," he said.

Resolvix CSO Philip Vickers said the findings by Serhan and colleagues underscore the potential of resolvins to treat diverse inflammatory indications without suppressing the immune system. "This

is especially important in an inflammatory indication with an underlying infection—like sepsis—where immunosuppression would be counterproductive," he said.

"The *Nature* paper shows that resolvin D2 promotes active clearance of the infection to decrease bacterial load," said Vickers. "It doesn't provide just passive protection from inflammation."

Thus, Vickers has added indications such as periodontitis, oral mucositis and acute respiratory distress syndrome (ARDS) to the list of possible indications where RvD2 might

be effective. But he declined to say whether the company planned to pursue them.

Resolvix has DHA-derived resolvins in preclinical development to treat asthma, arthritis and inflammatory bowel disease (IBD).

Resolvix's RX-10045, an isopropyl ester prodrug of a synthetic RvE1 analog formulated as a topical solution, completed a Phase I/II study to treat dry eye early this year.

Vickers said that RX-10001, an oral solution of synthetic RvE1, has just completed Phase I testing to treat asthma, arthritis and IBD. The company plans to take the compounds into Phase III and Phase II testing, respectively, in 2010.

Haas, M.J. *SciBX* 2(44); doi:10.1038/scibx.2009.1619
Published online Nov. 12, 2009

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COMPANIES AND INSTITUTIONS MENTIONED

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"The *Nature* paper shows that resolvin D2 promotes active clearance of the infection to decrease bacterial load. It doesn't provide just passive protection from inflammation."

**—Philip Vickers,
Resolvix Pharmaceuticals Inc.**

Threading the needles on immunity

By Michael J. Haas, Senior Writer

Intradermal vaccine developer **Apogee Technology Inc.** thinks it has found a polymer that kills two birds with one stone—acting as both a coating agent for the company's microneedle delivery device and serving as a vaccine adjuvant. The latter feature was a pleasant surprise, because although the polymer, poly[(dicarboxylatophenoxy)phosphazene], is a known adjuvant for intramuscular vaccines, such adjuvants have rarely been compatible with intradermal delivery.

Intradermal vaccines alone typically induce stronger immune responses than intramuscular vaccines alone because the skin is home to a larger population of dendritic cells than muscle tissue. Combining an intradermal vaccine with an adjuvant could further increase immune response, thereby reducing the dose required to provide protection and lowering the cost of vaccines.

Apogee's microneedle-based intradermal vaccine technology is a square centimeter patch of 50 microneedles that are 600 μm long.

Recognizing the dual properties of poly[(dicarboxylatophenoxy)phosphazene] (PCPP), Apogee and collaborators coated the intradermal system with a formulation of HBV antigen and the polymer. Because PCPP doubled as a coating agent during fabrication of the microneedle arrays, it obviated the need for other agents that could be toxic or adversely affect vaccine performance, according to Alexander Andrianov, VP of R&D.

Application of the arrays to the skin of healthy pigs elicited anti-HBV antibody levels that were 10-fold greater than those elicited by intramuscular injection of the same HBV antigen/PCPP formulation and up to 1,000 times greater than levels elicited by intramuscular injection of HBV antigen alone.

Results were published in the *Proceedings of the National Academy of Sciences*.¹ Andrianov was first author of the paper. The team was led by George Mutwiri, a professor of public health, a senior scientist and program manager of vaccine formulation and delivery at the Vaccine and Infectious Disease Organization at the **University of Saskatchewan**.

Another coauthor was Mark Prausnitz, a professor of chemical and biomolecular engineering at the **Georgia Institute of Technology**. His research group invented the microneedle array technology that Apogee is developing.^{2,3}

Skin in the game

The team's results demonstrated that intradermal vaccines can be more effective than injectable ones and that intradermally delivered adjuvants can increase vaccine efficacy, said Alexander von Gabain, CSO and cofounder of intradermal and intramuscular vaccine developer **Intercell AG**.

Nevertheless, von Gabain said any intradermal vaccine technology has to demonstrate clear advantages against the benchmark of intramuscular delivery.

"Intramuscular vaccines are reasonably effective in most people, so being more effective is not necessarily enough of an advantage for an intradermal vaccine," he said. "An intradermal vaccine has to prove itself acceptable in other ways too."

Intramuscular vaccines do have short-term local side effects, such as pain at the injection site or stiffness in the arm. "The multiple and increasing number of childhood vaccination schedules and the repetitive seasonal flu vaccine have made many people reluctant to accept intramuscular vaccinations," von Gabain told *SciBX*.

On the other hand, intradermal delivery has the potential for different side effects, such as skin irritation. "The art will be to sell to the customer that there are side effects from intradermal vaccines but that they are negligible or more easily tolerated compared with intramuscular vaccines," von Gabain said.

He wants to see more preclinical studies on the side effects of PCPP-adjuvanted microneedle vaccines. "If you are too hard on the skin, what is the advantage of the intradermal vaccine over the intramuscular vaccine?" he said.

Andrianov agreed that Apogee has more work to do before taking its PCPP-adjuvanted microneedle vaccines into the clinic.

At the same time, Andrianov noted that the pigs in his team's study experienced no significant adverse events. "As expected, mildly red skin marks, apparently corresponding to

microneedle insertion sites, were noticed immediately after application of the patch," but these quickly disappeared, he said.

Andrianov added that Apogee's microneedles can potentially be self-administered and are "practically painless."

With a good adjuvant in hand, Apogee is focused on optimizing the fabrication process of the microneedle technology, the dosing and the product stability. Andrianov declined to disclose indications the company might pursue.

Apogee has filed patent applications on the findings described in *PNAS* and is open to partnering discussions. "Establishing partnerships is probably the fastest way to develop the technology and even to go into clinical trials, especially in the vaccine industry," Andrianov said.

Haas, M.J. *SciBX* 2(44); doi:10.1038/scibx.2009.1620
Published online Nov. 12, 2009

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CIRM's expanding reach

By Tim Fulmer, Senior Writer

The **California Institute for Regenerative Medicine's** newest batch of grants differs from previous stem cell research awards in two key ways—they are later stage and reflect CIRM's collaboration with agencies outside of California.

CIRM has awarded about \$1 billion to support a total of 321 grants since it was founded in November 2004. But the most recent set of awards—a total of \$229.8 million to 14 teams—is the first expected to result in IND submissions when work under the four-year grants is completed.

Canada's **Cancer Stem Cell Consortium** (CSCC) and the U.K.'s **Medical Research Council** (MRC) will provide an additional \$35 million and \$8 million, respectively, to fund portions of research carried out in labs located in those countries.

Unlike the Early Translational Research grants that CIRM issued in April, the latest round is highly disease oriented, with each research proposal focused on a single area such as cancer, HIV, type 1 diabetes, macular degeneration and stroke (see **Table 1, "CIRM grants"**).

Only two biotech companies received grants: **Novocell Inc.** and **Calimmune Inc.** CIRM spokesperson Don Gibbons did not disclose if other biotechs applied for funding and were turned down or if this round of applicants was dominated by university researchers simply by chance. Nor did he disclose how the institute determined the amount of funding extended to the companies.

A \$20 million grant to a Novocell-led group will support the development of encapsulated insulin-producing cells derived from human embryonic stem cells (hESCs) to treat type 1 diabetes.

Novocell SVP and CSO Emmanuel Baetge told *SciBX* that encapsulating the insulin-producing cells in a semipermeable polyethylene glycol (PEG)-based coating ensures ample transport of nutrients and oxygen into the cells while protecting them from a potential host immune response and thus reducing the need for long-term immunosuppression. Moreover, the cells will be implanted subcutaneously to allow for monitoring and retrieval if necessary.

In nonhuman primates, Novocell has shown that encapsulated islet cells derived from same-species donors required immunosuppression for 30 days following implantation, after which the islets functioned for 20 months without the need for additional immunosuppression.

Meanwhile, Novocell has developed a method to generate functional islets from hESCs. Last year, company researchers reported that pancreatic endoderm derived from hESCs generated glucose-responsive, insulin-secreting cells in mice.¹

The next step is to encapsulate those hESC-derived islet cells.

Baetge told *SciBX* that the company's approach potentially solves a key difficulty facing all encapsulation technologies: balancing accessibility to serum nutrients with the need for disguise from the host immune system.

The coating's semipermeability ensures glucose and insulin can freely diffuse into and out of the islets, whereas the PEG molecules provide a biocompatible barrier that prevents the islets from contacting host immune cells and triggering an immune response, he said.

Calimmune and the **University of California, Los Angeles** (UCLA)

Table 1. CIRM grants. Below is a list of 14 research grants awarded by the California Institute for Regenerative Medicine (CIRM) to develop stem cell-based therapies.

Lead institution	Lead principal investigator	CIRM funding (\$M)	Proposal summary
Cedars-Sinai Medical Center	Eduardo Marbán	5.6	Repair heart tissue damaged by heart attack using autologous heart stem cells
City of Hope	Karen Aboody	18.0	Treat brain tumors using neural stem cells modified to carry a tumor-killing drug
City of Hope	John Zaia	14.6	Treat HIV using genetically modified autologous hematopoietic stem cells that give rise to HIV-resistant T cells
Novocell Inc.	Emmanuel Baetge	20.0	Treat type 1 diabetes by implanting islet cells generated from human embryonic stem cells (hESCs)
Salk Institute for Biological Studies	Samuel Pfaff	15.6	Treat amyotrophic lateral sclerosis (ALS) by implanting precursor astrocyte cells derived from hESCs
Stanford University	Alfred Lane	11.7	Treat epidermolysis bullosa using genetically modified induced pluripotent stem cells derived from the patient's skin cells
Stanford	Gary Steinberg	20.0	Treat stroke using implanted neural stem cells derived from hESCs
Stanford	Irving Weissman	20.0	Develop a mAb that targets leukemia stem cells
University of California, Los Angeles (UCLA)	Irvin Chen ^A	20.0	Treat HIV using RNAi-modified autologous hematopoietic stem cells that give rise to HIV-resistant T cells
UCLA	Donald Kohn	9.2	Treat sickle cell disease using genetically modified hematopoietic stem cells that become normal red blood cells
UCLA	Dennis Slamon	20.0	Develop compounds that target cancer stem cells in solid tumors
University of California, San Diego	Dennis Carson	20.0	Develop mAbs and small molecules that destroy leukemia stem cells
University of California, San Francisco	Mitchel Berger	19.2	Treat brain tumors using neural stem cells modified to carry a tumor-killing drug
University of Southern California	Mark Humayun	15.9	Treat macular degeneration using transplanted retinal cells derived from hESCs
Total		229.8	

^AGeoff Symonds at biotech company **Calimmune Inc.** is also a principal investigator.

received a \$20 million grant to develop RNAi-modified hematopoietic stem cells that differentiate into HIV-resistant T cells.

Irvin Chen, co-principal investigator on the grant, told *SciBX* that his lab and the biotech will split research responsibilities. Calimmune will shoulder late preclinical development, including “clinical assay development and validation, therapeutic gene vector production and management of regulatory issues,” he said. Chen is professor of microbiology and immunology at UCLA and director of the UCLA AIDS Institute.

In 2007, Chen and colleagues at UCLA, the **California Institute of Technology** and NIH’s **National Heart, Lung, and Blood Institute** reported that RNAi-based stem cell transplants developed into lymphocytes. The lymphocytes were less susceptible to infection in nonhuman primate models of HIV than lymphocytes not expressing the RNAi.²

Next year, CIRM expects to award two sets of grants supporting early preclinical research, Gibbons told *SciBX*.

“One of those sets will focus on basic stem cell biology and will include some funding from Japanese sources to support researchers

in that country,” he said. “A second set of grants, which will focus on immunology and stem cells, will involve Australian researchers and include funding from Australian sources.”

Fulmer, T. *SciBX* 2(44); doi:10.1038/scibx.2009.1621
Published online Nov. 12, 2009

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COMPANIES AND INSTITUTIONS MENTIONED

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Cancer Stem Cell Consortium, Toronto, Ontario, Canada
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Medical Research Council, London, U.K.
National Heart, Lung, and Blood Institute, Rockville, Md.
National Institutes of Health, Bethesda, Md.
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This week in therapeutics

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

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

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Autoimmune disease				
Autoimmune	Protein tyrosine phosphatase non-receptor type 22 (PTPN22; LYP)	<i>In vitro</i> studies identified gold-based LYP inhibitors that could help treat autoimmune disorders. A screen for protein tyrosine phosphatase inhibitors identified a gold complex that had an IC_{50} value of 1.5 ± 0.3 mM. The compound, (2-pyridine)(Ph ₂)P-Au-Cl, had 10-fold greater selectivity for LYP than for other protein tyrosine phosphatases. <i>In vitro</i> , the compound inhibited LYP in Jurkat T antigen human T cells and primary mouse thymocytes. Next steps could include testing the LYP inhibitor in animals. SciBX 2(44); doi:10.1038/scibx.2009.1622 Published online Nov. 12, 2009	Patent and licensing status unavailable	Karver, M. <i>et al. J. Med. Chem.</i> ; published online Oct. 19, 2009; doi:10.1021/jm901220m Contact: Amy M. Barrios, University of Utah, Salt Lake City, Utah e-mail: amy.barrios@utah.edu
Cancer				
Cancer	Cyclin D1 (CCND1; BCL1); hypoxia-inducible factor prolyl hydroxylase 1 (EGLN2; HIF-PH1; PHD1)	Studies in mice and in cell culture suggest that inhibiting EGLN2 could help treat cancer. In a mouse model of human breast cancer, small hairpin RNA-mediated knockdown of <i>EglN2</i> led to less tumor growth than that seen using scrambled shRNA. In multiple human breast cancer cell lines, shRNA-mediated knockdown of EGLN2 reduced CCND1-mediated cell proliferation. Next steps could include evaluating EGLN2 inhibitors in animal models of cancer. SciBX 2(44); doi:10.1038/scibx.2009.1623 Published online Nov. 12, 2009	Patent and licensing status unavailable	Zhang, Q. <i>et al. Cancer Cell</i> ; published online Nov. 2, 2009; doi:10.1016/j.ccr.2009.09.029 Contact: William G. Kaelin Jr., Harvard Medical School, Boston, Mass. e-mail: william_kaelin@dfci.harvard.edu
Cancer	DNA	A study in mice and in cell culture identified a nitrochloromethylbenzindoline-based prodrug that could help treat cancer. In a panel of 11 human cancer cell lines grown under hypoxic conditions such as often occur in solid cancers, the prodrug had 19- to 330-fold better cytotoxicity than in the same cell lines grown under nonhypoxic conditions. In mice with hypoxic, radiation-resistant human cervical cancer, the prodrug plus radiation significantly increased antitumor activity compared with radiation alone ($p < 0.01$). Next steps include improving the solubility of the compounds while preserving the hypoxia-selective activity. SciBX 2(44); doi:10.1038/scibx.2009.1624 Published online Nov. 12, 2009	Multiple patents pending covering use in cancer treatment; licensed to an undisclosed party	Tercel, M. <i>et al. J. Med. Chem.</i> ; published online Oct. 30, 2009; doi:10.1021/jm901202b Contact: Moana Tercel, The University of Auckland, Auckland, New Zealand e-mail: m.tercel@auckland.ac.nz

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cancer	Procaspase-3; procaspase-6; caspase-3 (CASP3; CPP32); caspase-6 (CASP6; MCH2)	<p>Studies in cell culture suggest that small molecule activators of procaspases could help treat cancer. High throughput screening identified a small molecule that activated procaspase-3 and procaspase-6, the precursors to apoptosis-inducing CASP3 and CASP6. The compound induced apoptosis in human breast and cervical cancer cell lines more efficiently than a nonspecific kinase inhibitor or a topoisomerase inhibitor. Next steps include synthesizing and testing analogs of the lead compound <i>in vitro</i> and <i>in vivo</i>. Antipodean Pharmaceuticals Inc.'s MitoQ caspase inhibitor has completed Phase II testing to treat raised liver enzyme levels associated with HCV. Gilead Sciences Inc.'s caspase inhibitor, GS-9450, is in Phase II testing to treat HCV infection and fibrosis.</p> <p>SciBX 2(44); doi:10.1038/scibx.2009.1625 Published online Nov. 12, 2009</p>	Patented by the University of California, San Francisco; available for licensing	<p>Wolan, D. <i>et al. Science</i>; published online Nov. 5, 2009; doi:10.1126/science.1177585</p> <p>Contact: James A. Wells, University of California, San Francisco, Calif. e-mail: jim.wells@ucsf.edu</p>
Cancer	Spliceosome	<p>Studies in mice and in cell culture have shown that synthetic analogs of FR901464 could help treat cancer. FR901464, a natural product isolated from <i>Pseudomonas</i>, is a spliceosome modulator that induces cell-cycle arrest. In a panel of 23 human cancer cell lines, one of the analogs inhibited proliferation with IC₅₀ values in the nanomolar to single-digit micromolar ranges. In a mouse model of human mantle cell lymphoma, the compound produced dose-dependent reductions in tumor proliferation compared with vehicle ($p < 0.0001$). Next steps include additional animal studies using better formulations of the compounds.</p> <p>SciBX 2(44); doi:10.1038/scibx.2009.1626 Published online Nov. 12, 2009</p>	Patent application filed covering compounds and their use in multiple types of cancer; available for licensing from the St. Jude Children's Research Hospital Office of Technology Licensing	<p>Lagiseti, C. <i>et al. J. Med. Chem.</i>; published online Oct. 30, 2009; doi:10.1021/jm901215m</p> <p>Contact: Thomas R. Webb, St. Jude Children's Research Hospital, Memphis, Tenn. e-mail: thomas.webb@stjude.org</p>
Cardiovascular disease				
Blood clots; thrombosis	Matrix metalloproteinase 2 (MMP2)	<p>A study in mice suggests that inhibiting MMP2 in platelets could help prevent thrombosis. In multiple models of thrombosis, animals with <i>MMP2</i> deficiency had longer bleeding times and smaller thrombi than mice with functional <i>MMP2</i>. In a mouse model of vascular injury, platelets from <i>MMP2</i>-deficient mice were less able to shorten bleeding time than platelets from wild-type mice. Next steps could include developing compounds that selectively inhibit <i>MMP2</i> in platelets.</p> <p>SciBX 2(44); doi:10.1038/scibx.2009.1627 Published online Nov. 12, 2009</p>	Patent and licensing status undisclosed	<p>Momi, S. <i>et al. J. Exp. Med.</i>; published online Oct. 6, 2009; doi:10.1084/jem.20090687</p> <p>Contact: Paolo Gresle, University of Perugia, Perugia, Italy e-mail: grespa@unipg.it</p>
Blood clots; thrombosis	Serpin peptidase inhibitor clade E (SERPINE2; PN1)	<p>A study in mice suggests that increasing platelet PN1 levels could help prevent thrombosis. In a mouse model of vascular injury, small veins and small arteries in <i>PN1</i>-deficient mice clotted more rapidly than those in wild-type controls. Venules from <i>PN1</i>-deficient mice were completely occluded at 20 minutes, whereas venules from wild-type controls only developed small thrombi and maintained blood flow. Next steps could include evaluating how altered PN1 activity affects risk for vascular thrombosis.</p> <p>SciBX 2(44); doi:10.1038/scibx.2009.1628 Published online Nov. 12, 2009</p>	Patent and licensing status unavailable	<p>Boulaftali, Y. <i>et al. Blood</i>; published online Oct. 23, 2009; doi:10.1182/blood-2009-04-217240</p> <p>Contact: Marie-Christine Bouton, Institut National de la Santé et de la Recherche Médicale (INSERM), Marseille, France e-mail: marie-christine.bouton@inserm.fr</p>

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Hypertension	Peroxisome proliferation-activated receptor-g (PPARG; PPARg)	<p>Studies in mice suggest that increasing PPARg levels could help treat hypertension. In mice, a twofold increase in PPARg levels resulted in mean blood pressure that was about 2.8 mm Hg lower than that in controls ($p < 0.05$). Reducing PPARg levels by 50% led to a mean blood pressure that was about 2.8 mm Hg higher than that of control mice ($p < 0.01$). Next steps could include evaluating the effect of increasing PPARg expression in animal models of hypertension.</p> <p>Multiple PPARg agonists are on the market to treat type 2 diabetes.</p> <p>SciBX 2(44); doi:10.1038/scibx.2009.1629 Published online Nov. 12, 2009</p>	Patent and licensing status unavailable	<p>Tsai, Y.-S. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Nov. 2, 2009; doi:10.1073/pnas.0909657106 Contact: Nobuyo Maeda, The University of North Carolina at Chapel Hill, Chapel Hill, N.C. e-mail: nobuyo@med.unc.edu Contact: Jenny Langenbach, same affiliation as above e-mail: jenny_langenbach@med.unc.edu</p>
Ischemia; reperfusion injury	Cyclooxygenase (COX); lactate dehydrogenase (LDH); protein kinase C (PKC)	<p>Studies in rats suggest that the generic COX inhibitor sulindac could help precondition and protect the heart from ischemia- and reperfusion-induced oxidative damage. In a rat model of ischemia and reperfusion injury, sulindac led to smaller infarcts and reduced levels of LDH, a tissue necrosis marker. Next steps include determining whether sulindac can protect skin cells from UV-induced oxidative damage.</p> <p>SciBX 2(44); doi:10.1038/scibx.2009.1630 Published online Nov. 12, 2009</p>	Patented by Florida Atlantic University; in-licensed by CHS Resources LLC	<p>Moench, I. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Nov. 2, 2009; doi:10.1073/pnas.0911046106 Contact: Herbert Weissbach, Florida Atlantic University, Boca Raton, Fla. e-mail: hweissba@fau.edu</p>
Pulmonary arterial hypertension (PAH)	Notch homolog 3 (NOTCH3)	<p><i>In vitro</i> and mouse studies suggest that inhibiting NOTCH3 could help treat PAH. In biopsies from 20 PAH patients, <i>NOTCH3</i> expression was higher than that in biopsies from non-PAH controls. In cultured human small pulmonary artery smooth muscle cells (sPASCs) from PAH patients, NOTCH3 levels were higher than those in sPASCs from healthy controls. In mice, <i>Notch3</i> knockout protected against the development of PAH. Next steps include using NOTCH3 inhibitors to prevent PAH in pigs.</p> <p>SciBX 2(44); doi:10.1038/scibx.2009.1631 Published online Nov. 12, 2009</p>	Invention disclosure filed; licensing status not applicable	<p>Li, X. <i>et al. Nat. Med.</i>; published online Oct. 25, 2009; doi:10.1038/nm.2021 Contact: Patricia Thistlethwaite, University of California, San Diego, La Jolla, Calif. e-mail: pthistlethwaite@ucsd.edu</p>
Endocrine disease				
Obesity	Toll-like receptor 4 (TLR4)	<p>Studies in mice suggest that antagonizing TLR4 could help treat obesity-induced insulin resistance. In a murine model of high-fat diet-induced obesity, mice with macrophage-specific <i>Tlr4</i> knockout had improved hyperinsulinemia, insulin resistance and glucose tolerance compared with wild-type controls. The liver and adipose tissue of mice with <i>Tlr4</i>-deficient macrophages had decreased levels of proinflammatory cytokines that interfere with insulin signaling. Ongoing studies are seeking to identify TLR4's specific mechanism of action in insulin resistance and to test TLR4 antagonists in animal models of insulin resistance and other metabolic diseases.</p> <p>Eritoran (E5564), a TLR4 antagonist from Eisai Co. Ltd., is in Phase III testing to treat severe sepsis. NovImmune S.A.'s NI-0101, a humanized mAb against TLR4, is in preclinical testing to treat autoimmune and inflammatory indications.</p> <p>SciBX 2(44); doi:10.1038/scibx.2009.1632 Published online Nov. 12, 2009</p>	Patent and licensing status undisclosed	<p>Saberi, M. <i>et al. Cell Metab.</i>; published online Nov. 3, 2009; doi:10.1016/j.cmet.2009.09.006 Contact: Jerrold M. Olefsky, University of California, San Diego, La Jolla, Calif. e-mail: jolefsky@ucsd.edu</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Infectious disease				
Bacterial infection	Not applicable	<i>In vitro</i> studies identified silver(III) nanoparticles that could be used as antibacterial agents. <i>In vitro</i> , the nanoparticles showed activity against four Gram-positive bacteria, four Gram-negative bacteria and methicillin-resistant <i>Staphylococcus aureus</i> (MRSA). Next steps include using the compounds to treat bacterial infections in animals. SciBX 2(44); doi:10.1038/scibx.2009.1633 Published online Nov. 12, 2009	Patent and licensing status unavailable	Pal, S. <i>et al. J. Am. Chem. Soc.</i> ; published online Oct. 21, 2009; doi:10.1021/ja9051125 Contact: Joon Myong Song, Seoul National University, Seoul, South Korea e-mail: jmsong@snu.ac.kr
Herpes simplex virus (HSV); Varicella zoster virus (VZV)	Lysine-specific histone demethylase 1 (LSD1)	<i>In vitro</i> and <i>ex vivo</i> studies suggest that LSD1 inhibitors could help treat HSV and VZV infections. In VZV-infected human cells, blocking <i>LSD1</i> expression led to decreased amounts of viral mRNA and viral protein. In HSV-infected cells, a monoamine oxidase inhibitor (MAOI), which blocks the activity of LSD1, lowered viral yields compared with those in controls. In murine ganglion explants, an MAOI significantly reduced reactivation of HSV compared with that in controls ($p < 0.005$). Next steps include studying topical and systemic MAOIs in a mouse model of HSV infection. Three companies market MAOIs to treat Parkinson's disease (PD). At least 15 MAOIs are marketed as antidepressants. SciBX 2(44); doi:10.1038/scibx.2009.1634 Published online Nov. 12, 2009	Patent applications filed; patents are property of the NIH; available for licensing from the National Institute of Allergy and Infectious Diseases Office of Technology Development	Liang, Yu. <i>et al. Nat. Med.</i> ; published online Oct. 25, 2009; doi:10.1038/nm.2051 Contact: Thomas M. Kristie, National Institutes of Health, Bethesda, Md. e-mail: thomas_kristie@nih.gov
Inflammation				
Inflammation	Superoxide ions	<i>In vitro</i> and mouse studies identified manganese complexes that scavenge superoxide anions and could help treat inflammation. <i>In vitro</i> , several polyamine-polycarboxylic-manganese complexes scavenged superoxide ions. In a mouse model of acute peritoneal inflammation, the lead compound decreased pain and was not toxic. Next steps include testing the compounds in additional animal models. SciBX 2(44); doi:10.1038/scibx.2009.1635 Published online Nov. 12, 2009	Patent application filed for the manganese and cobalt complexes and their use; available for licensing through the University of Florence	Failli, P. <i>et al. J. Med. Chem.</i> ; published online Oct. 27, 2009; doi:10.1021/jm901298x Contact: Andrea Bencini, University of Florence, Florence, Italy e-mail: andrea.bencini@unifi.it
Neurology				
Addiction	Methamphetamine	<i>In vitro</i> studies identified hapten molecules that could be used to generate antibodies to help treat methamphetamine overdose or addiction. <i>In vitro</i> , two haptens were synthesized, conjugated to a carrier protein and used to generate mAbs against methamphetamines. Next steps include humanizing the antibodies. SciBX 2(44); doi:10.1038/scibx.2009.1636 Published online Nov. 12, 2009	Multiple patent applications filed and two patents issued; all patents and applications licensed by Intervexion Therapeutics LLC	Carroll, F. <i>et al. J. Med. Chem.</i> ; published online Oct. 29, 2009; doi:10.1021/jm901134w Contact: F. Ivy Carroll, Research Triangle Institute, Research Triangle Park, N.C. e-mail: fic@rti.org

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Ataxia	Frataxin (FXN); histone deacetylase 3 (HDAC3)	Studies in cell culture suggest that inhibiting HDAC3 could help treat Friedreich's ataxia, a hereditary neurodegenerative disease caused by reduced expression of the <i>FXN</i> gene. In a human Friedreich's ataxia lymphoblast cell line, HDAC3-specific inhibitors increased <i>FXN</i> expression compared with inhibitors that targeted other HDACs. Additional preclinical studies of the inhibitors are underway. Repligen Corp. has HDAC inhibitors in preclinical development for Friedreich's ataxia. SciBX 2(44); doi:10.1038/scibx.2009.1637 Published online Nov. 12, 2009	Patent application filed; licensed to Repligen	Xu, C. <i>et al. Chem. Biol.</i> ; published online Sept. 25, 2009; doi:10.1016/j.chembiol.2009.07.010 Contact: Joel M. Gottesfeld, The Scripps Research Institute, La Jolla, Calif. e-mail: joelg@scripps.edu
Nerve damage; spinal cord injury (SCI)	Histone deacetylase 6 (HDAC6)	A study in cell culture suggests that inhibiting HDAC6 could help treat nerve damage. Cultured rat primary cortical neurons treated with HDAC6 inhibitors were protected against oxidative stress-induced death as compared to untreated neurons ($p < 0.001$). In rat primary cortical and dorsal root ganglion neurons exposed to oxidative stress, the HDAC6 inhibitors also increased neurite outgrowth compared with vehicle. Next steps include <i>in vivo</i> studies in SCI models. SciBX 2(44); doi:10.1038/scibx.2009.1638 Published online Nov. 12, 2009	HDAC6-selective inhibitors covered by an issued patent and multiple pending patents; available for licensing from the Georgetown University Office of Technology Commercialization Contact: David Humphrey, Georgetown University, Washington, D.C. phone: 202-687-2702 e-mail: dh265@georgetown.edu	Rivieccio, S.F. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Oct. 26, 2009; doi:10.1073/pnas.0907935106 Contact: Brett Langley, Weill Medical College of Cornell University, New York, N.Y. e-mail: bcl2002@med.cornell.edu
Pain	Adrenergic receptor α_2c (ADRA2C); ADRA2A	<i>In vitro</i> and mouse studies suggest imidazoline analogs that target ADRA2C and ADRA2A could be used to reduce side effects associated with the pain drug morphine. In mouse models of pain, the analogs in combination with morphine induced longer-lasting analgesia with less sedation than morphine plus a placebo. Ongoing work includes analyzing the isomeric forms of the analogs. Adrenex Pharmaceuticals Inc.'s Clonicef clonidine, a modified release formulation of the ADRA2 agonist clonidine, is in registration to treat attention deficit hyperactivity disorder (ADHD). SciBX 2(44); doi:10.1038/scibx.2009.1639 Published online Nov. 12, 2009	Unpatented; unlicensed	Cardinaletti, C. <i>et al. J. Med. Chem.</i> ; published online Nov. 3, 2009; doi:10.1021/jm901262f Contact: Maria Pignini, University of Camerino, Camerino, Italy e-mail: maria.pignini@unicam.it
Pain	Monoacylglycerol lipase (MAGL); MGL	<i>In vitro</i> studies identified terpenoid compounds that inhibited MAGL and could be useful for treating pain. In enzyme inhibition assays, two terpenoids potently and reversibly inhibited MAGL activity. Molecular modeling and mutational analyses identified a common binding site for the two terpenoids. Next steps could include identifying additional therapeutics that reversibly interact with the binding site and inhibit the enzyme as well as studying those compounds in preclinical models of pain. SciBX 2(44); doi:10.1038/scibx.2009.1640 Published online Nov. 12, 2009	Work unpatented; licensing status not applicable	King, A.R. <i>et al. Chem. Biol.</i> ; published online Oct. 30, 2009; doi:10.1016/j.chembiol.2009.09.012 Contact: Daniele Piomelli, University of California, Irvine, Calif. e-mail: piomelli@uci.edu

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Ophthalmic disease				
Blindness	Transient receptor potential cation channel subfamily M member 1 (TRPM1)	<p>Three genomics studies in humans identified <i>TRPM1</i> mutations as potential targets to treat complete congenital stationary night blindness (cCSNB). At least 20 different mutations in <i>TRPM1</i> were identified in patients with the condition. Electroretinographic evidence from two of the studies supported the hypothesis that <i>TRPM1</i> mutations caused dysfunction in bipolar cells, which transmit signals from rod cells to retinal neurons under low-light conditions. Ongoing work includes studying signaling pathways in bipolar cells and looking for additional genes that might cause cCSNB.</p> <p>SciBX 2(44); doi:10.1038/scibx.2009.1641 Published online Nov. 12, 2009</p>	<p>For the first paper: patent and licensing status unavailable</p> <p>For the second and third papers: unpatented; unlicensed</p>	<p>Li, Z. <i>et al. Am. J. Hum. Genet.</i>; published online Oct. 29, 2009; doi:10.1016/j.ajhg.2009.10.003 Contact: Andrew R. Webster, University College London Institute of Ophthalmology, London, U.K. e-mail: andrew.webster@ucl.ac.uk</p> <p>van Genderen, M. <i>et al. Am. J. Hum. Genet.</i>; published online Nov. 5, 2009; doi:10.1016/j.ajhg.2009.10.012 Contact: Maarten Kamermans, Netherlands Institute for Neuroscience, Amsterdam, the Netherlands e-mail: m.kamermans@nin.knaw.nl</p> <p>Audo, I. <i>et al. Am. J. Hum. Genet.</i>; published online Nov. 5, 2009; doi:10.1016/j.ajhg.2009.10.013 Contact: Christina Zeitz, Institut National de la Santé et de la Recherche Médicale (INSERM), Paris, France e-mail: christina.zeitz@inserm.fr</p>
Pulmonary disease				
Pulmonary fibrosis	Lactadherin (MFGE8; HMFG)	<p>Studies in mice suggest that increasing MFGE8 could help treat pulmonary fibrosis. In a mouse model of pulmonary fibrosis, <i>Mfge8</i>-deficient animals showed greater deposition of collagen and pulmonary fibrosis than nondeficient controls. In the <i>Mfge8</i>-deficient mice, collagen degradation was lower than that in controls. Next steps include showing that administration of MFGE8 reduces or reverses fibrosis in a disease model.</p> <p>SciBX 2(44); doi:10.1038/scibx.2009.1642 Published online Nov. 12, 2009</p>	<p>Work unpatented; available for licensing from the University of California, San Francisco Office of Technology Management</p>	<p>Atabai, K. <i>et al. J. Clin. Invest.</i>; published online Nov. 2, 2009; doi:10.1172/JCI40053 Contact: Dean Sheppard, University of California, San Francisco, Calif. e-mail: Dean.Sheppard@ucsf.edu</p>

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This week in techniques

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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			
Identification of protein-binding agents using a small molecule-based microarray	A small molecule-based microarray can identify combinations of compounds as protein-binding agents for high throughput assays and screening applications. The microarray plate consisted of >5,000 spots containing different combinations of small molecules. Incubation of the array with a protein gave a quantitative readout of the protein's binding affinity for each spot. Each of four tested proteins had a distinct pattern of binding affinities on the array, thus enabling the identification of small molecule combinations that had a desired binding affinity for the protein. Ongoing work is extending the technology to affinity-based IgG purification and proteomics-based biomarker identification. SciBX 2(44); doi:10.1038/scibx.2009.1643 Published online Nov. 12, 2009	Patented by Receptors LLC; available for partnering	Roska, R. <i>et al. J. Am. Chem. Soc.</i> ; published online Oct. 29, 2009; doi:10.1021/ja9046944 Contact: Robert E. Carlson, Receptors LLC, Chaska, Minn. e-mail: bc@receptorsllc.com
Disease models			
Myocardin (Myocd)-deficient mice as a model for heart failure	Mice with a cardiomyocyte-specific deficiency in myocardin could aid in the development of apoptosis-blocking therapies for heart failure. Myocd-deficient hearts from adult mice were enlarged and had impaired cardiac pumping output compared with control hearts expressing functional <i>Myocd</i> . The Myocd-deficient hearts showed widespread cardiomyocyte apoptosis. Next steps include determining the contribution of apoptosis to various types of heart failure. SciBX 2(44); doi:10.1038/scibx.2009.1644 Published online Nov. 12, 2009	Work unpatented; licensing status not applicable	Huang, J. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Oct. 19, 2009; doi:10.1073/pnas.0910749106 Contact: Michael S. Parmacek, Penn Cardiovascular Institute, Philadelphia, Pa. e-mail: michael.parmacek@uphs.upenn.edu
Drug delivery			
<i>Ex vivo</i> IL-10 gene therapy for functional repair of human donor lungs	<i>Ex vivo</i> IL-10 gene therapy to repair damaged donor human lungs could expand the supply of organs available for transplant. More than 80% of donor lungs become injured during brain death or from complications in the intensive care unit and are unusable for transplant due to inflammation and disruption of the blood alveolar barrier. In pigs, lung transplants pretreated with adenovirus-mediated human IL-10 gene therapy had less inflammation and better lung function than lungs pretreated with vehicle. In an <i>ex vivo</i> perfusion system using injured human lungs, IL-10 gene therapy lowered the production of inflammatory cytokines and improved lung function compared with vehicle. Next steps include evaluating survival and rejection rates of treated lungs in large animal models. SciBX 2(44); doi:10.1038/scibx.2009.1645 Published online Nov. 12, 2009	Multiple patents filed covering gene therapy approach and diagnostic biomarkers for predicting lung transplant viability; available for licensing from the University Health Network	Cypel, M. <i>et al. Sci. Transl. Med.</i> ; published online Oct. 28, 2009; doi:10.1126/scitranslmed.3000266 Contact: Shaf Keshavjee, University Health Network, Toronto, Ontario, Canada e-mail: shaf.keshavjee@uhn.on.ca
Nanocarriers for targeted therapeutic delivery to cancer cells	<i>In vitro</i> and mouse studies suggest that peptide-phospholipid nanocarriers could help deliver cancer compounds to tumor cells. The nanocarriers were designed to target the surface receptor scavenger receptor class B member 1 (SCARB1), which is expressed on cancer cells at higher levels than on healthy cells. In mice carrying Scarb1 ⁺ and Scarb1 ⁻ tumors, the nanocarriers delivered payloads to the cytosol of tumor cells expressing the receptor. Next steps include modifying the technology to deliver small interfering RNA and small molecules. SciBX 2(44); doi:10.1038/scibx.2009.1646 Published online Nov. 12, 2009	Patent application filed; available for licensing	Zhang, Z. <i>et al. Angew. Chem. Int. Ed.</i> ; published online Oct. 28, 2009; doi:10.1002/anie.200903112 Contact: Gang Zheng, University of Toronto, Toronto, Ontario, Canada e-mail: gang.zheng@uhnres.utoronto.ca

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Nanospheres to deliver drugs to the brain	<i>In vitro</i> and mouse studies suggest that nanospheres conjugated to transferrin receptor (TFRC) antibodies could help deliver therapeutics to the brain. Polyethylene glycol-coated nanospheres were conjugated to a mouse mAb that bound TFRC on cerebral vasculature to help the nanospheres penetrate the blood brain barrier. In mice with middle cerebral artery occlusion, i.v. injection of the conjugated nanospheres loaded with a caspase-3 (CASP3; CPP32) inhibitor decreased infarct volume and neurological defects compared with injection of nonloaded or nonconjugated nanospheres. Next steps include testing the nanocarrier technique in larger animal models. SciBX 2(44); doi:10.1038/scibx.2009.1647 Published online Nov. 12, 2009	Findings unpatented; unavailable for licensing	Karatas, H. <i>et al. J. Neurosci.</i> ; published online Nov. 4, 2009; doi:10.1523/JNEUROSCI.4246-09.2009 Contact: Turgay Dalkara, Hacettepe University, Ankara, Turkey e-mail: tdalkara@hacettepe.edu.tr
Self-assembling polypeptide nanoparticles for delivery of chemotherapeutics	Self-assembling, pH-sensitive polypeptide nanoparticles could be useful for delivering cancer therapies. In a mouse model of colorectal cancer, the doxorubicin-conjugated nanoparticles increased median survival compared with free doxorubicin ($p=0.002$). Mice given the doxorubicin-conjugated nanoparticles had, on average, significantly smaller tumors ($p=0.03$) and greater doxorubicin concentration at the tumor site than controls given free doxorubicin. Next steps include evaluating the feasibility of using these nanoparticles to deliver other chemotherapeutic agents. SciBX 2(44); doi:10.1038/scibx.2009.1648 Published online Nov. 12, 2009	Patented for use in drug delivery across all indications; licensed to PhaseBio Pharmaceuticals Inc.	MacKay, J.A. <i>et al. Nat. Mater.</i> ; published online Nov. 8, 2009; doi:10.1038/nmat2569 Contact: Ashutosh Chilkoti, Duke University, Durham, N.C. e-mail: chilkoti@duke.edu

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