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TRPping up overactive bladder

By Chris Cain, Staff Writer

A collaboration between researchers at **Hydra Biosciences Inc.** and **Catholic University Leuven** has found that antagonizing the ion channel TRPV4 could provide a new mechanism to treat overactive bladder.[1] The biotech expects that blocking the target will elicit fewer side effects than marketed anticholinergic therapies.

Overactive bladder develops when the nervous system is unable to properly control bladder muscle contraction. Its causes range from systemic neurological disorders like multiple sclerosis (MS) to localized inflammation of the bladder in the case of urinary tract infections. The majority of approved drugs for overactive bladder antagonize muscarinic acetylcholine receptors, which regulate the contraction of smooth muscle in the bladder.

However, because these receptors are found throughout the body, the antagonists can cause a host of side effects, including blurred vision, dry mouth and constipation.

The first clue that TRPV4 (transient receptor potential vanilloid 4; VRL2) could be a therapeutic target came in 2007, when researchers including Thomas Voets, professor of molecular cell biology at the Catholic University Leuven, showed lower bladder function in *Trpv4* mutant mice than in wild-type controls.[2]

Voets began the current study by showing that in a model of urinary bladder inflammation, *Trpv4* mutant mice had less intense symptoms of overactive bladder than wild-type controls. But to nail down the therapeutic potential of antagonizing TRPV4, he needed a small molecule inhibitor to probe the channel's role in urinary incontinence.

This led to the collaboration with Hydra, which develops small molecules that target ion channels. The company had recently synthesized HC-067047, a potent and selective TRPV4 antagonist, which Hydra thought could be useful for a variety of indications including pain, osteoporosis and overactive bladder.

Voets and Hydra now have shown that in mouse and rat models of urinary bladder inflammation, HC-067047 decreased urination frequency and increased urine volume compared with vehicle controls.

There were no systemic adverse effects on body temperature, heart rate, fluid intake, thermal selection behavior or motor coordination.

Results were published in the *Proceedings of the National Academy of Sciences*.

"Antimuscarinics target bladder contraction, as do most drugs in development for urinary disorders," noted Christopher Fanger, senior

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director of lead discovery at Hydra. "Blocking TRPV4, on the other hand, would target the problem at its origin: sensing the filling state of the bladder. By focusing on the unpleasant sensation itself rather than bladder voiding, we think TRPV4 blockers may be preferable to the patient."

"What this Belgian team has demonstrated is the possibility that TRPV4 inhibition can be accomplished therapeutically without lethal side effects—a relatively surprising finding," said Wolfgang Liedtke, assistant professor and attending physician at **Duke University**. He was the first author on the initial description of TRPV4 in *Cell* ten years ago.[3]

Side effects were a primary concern, noted Liedtke, because previous studies published by **GlaxoSmithKline plc** showed that activating Trpv4 led to severe cardiovascular side effects and death in rats, raising questions about the safety of modulating TRPV4.[4]

The current work represents the first time that researchers have tried to block the target *in vivo*.

In addition, Liedtke said, there are early indications that inhibiting TRPV4 could have other clinical uses, including the treatment of bronchitis or colitis. He cited studies showing that TRPV4 activation can lead to colitis and that TRPV4 regulates ciliary clearance function in mammalian airway epithelia.[5,6]

When asked about the potential for side effects, Hydra suggested that at the dose used there may be complete inhibition in the bladder but not necessarily in other tissues.

GSK filed a patent application covering its own TRPV4 antagonists. The pharma declined to comment on the status of the application or whether it has any TRPV4 modulators in development.

Hydra did say it needs to modify HC-067047 to generate a candidate that is suitable for clinical development. HC-067047 is not sufficiently orally bioavailable, and the company believes an injectable medication would be undesirable for an indication such as overactive bladder.

Hydra has filed for patents covering HC-067047 and hopes to partner its TRPV4 program, which includes HC-067047 and other TRPV4-modulating compounds.

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Duke University, Durham, N.C.
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Going APOA1 in cancer

By Steve Edelson, Executive Editor

Researchers at the **University of California, Los Angeles** and colleagues have shown that apolipoprotein A-1, the major component of high-density lipoprotein, could have a therapeutic effect in ovarian cancer.[1] **Resverlogix Corp.**, a biotech with an apolipoprotein A-1 program in cardiovascular disease, is considering out-licensing options for oncology based on the findings.

Apolipoprotein A-1 (APOA1) is a key component of the reverse cholesterol transport pathway. The lipoprotein removes cholesterol from cells in the periphery and helps shuttle it to the liver, where cholesterol is excreted. Given APOA1's role in cholesterol-related disorders such as atherosclerosis, companies pursuing APOA1 or its mimics in the cardiovascular space include two sets of biotech-pharma partners.

On top of its cholesterol transport function, APOA1 also has been shown to bind to proinflammatory phospholipids, which give it anti-inflammatory properties.[2] Those findings provided the hint that APOA1 could be therapeutic in cancer, as some phospholipids—the lysophospholipids—can prompt cancer cells to start growing.

Indeed, APOA1's potential involvement in ovarian cancer does not come as a complete surprise—the protein is one of the biomarkers measured by the Ova1 Test from **Vermillion Inc.** and **Quest Diagnostics Inc.** The *in vitro* diagnostic multivariate index (IVDMIA) test is used to help assess the likelihood that an ovarian mass is benign or malignant.

What was unknown was whether APOA1 is correlative or causative in the disease.

A UCLA-led team suspected the latter. "Because lipid transport, inflammation, and oxidative stress are associated with the development and progression of cancer, we hypothesized that the reduced levels of apoA-I in ovarian cancer patients may have been causal in disease progression," the group wrote in a paper published in the *Proceedings of the National Academy of Sciences.*

In addition to UCLA, the article included researchers from **The University of Alabama at Birmingham**.

To answer their question, the researchers first generated transgenic mice overexpressing human *APOA1*. Those animals survived significantly longer than wild-type littermates following an injection of ovarian cancer cells ($p<0.0001$). The increase in survival was accompanied by a significant decrease in the development of tumors compared with that in controls ($p<0.01$).

Next, the researchers used a pair of compounds from **Bruin Pharmaceuticals Inc.**, a biotech formed by UCLA and UAB to develop APOA1 peptide mimics. The oral and subcutaneous mimics decreased ovarian tumor burden in mice compared with a scrambled peptide.

Patents covering the peptide mimics described in *PNAS* are licensed to Bruin from UCLA and UAB. In 2005, Bruin licensed the mimetics to **Novartis AG**. The pharma did not return calls seeking comment on the program.

Mechanism still unknown

The precise mechanism by which APOA1 elicited its positive effects remains unclear. The researchers did show that apoptosis is not the culprit. Instead, they suspect that APOA1's removal of lysophosphatidic acid (LPA) leads to inhibition of cell growth.

"What I suspect is happening is we're taking away an important growth factor—LPA—from these immunocompetent mice," noted Alan Fogelman, executive chair of the Department of Medicine and director of the atherosclerosis research unit at UCLA's David Geffen School of Medicine. "I think the peptide mimics are tilting the battle between the immune system and the tumor in favor of the immune system by removing this potent promoter" of tumor formation.

"These are very interesting findings. The results come from the proteomics of APOA1 being a cancer risk factor, and the data fit with the mechanism of reverse cholesterol transport being anti-inflammatory," said Jan Johansson, SVP of medical affairs at Resverlogix. "It's possible that you could take a compound like ours and test its effects in ovarian cancer with other compounds" such as chemotherapeutics.

Resverlogix's RVX-208, an APOA1 transcription enhancer, is in Phase II testing to treat atherosclerosis in patients with acute coronary artery disease (CAD). Data are expected this month.

Because the company is focused on cardiovascular disease, President, CEO and cofounder Donald McCaffrey told *SciBX* that Resverlogix would be interested in licensing out rights to the compound in cancer. "We've kept up on the alternate uses of APOA1 in other diseases, but we're very focused on our cardio program," he said.

Roche's Michael Pech, section head for metabolic diseases, agreed that the findings in the *PNAS* article are intriguing but added that "whether we'd follow that initial finding and explore our APOA1 mimetic program in cancer, I can't say yet."

In February, Roche partnered with **Artery Therapeutics Inc.** to co-develop the biotech's APOA1 peptide mimetics. The lead compound, AT5261, is in preclinical testing and is being developed to treat atherosclerosis and prevent cardiovascular events in patients who have suffered a heart attack or stroke.

Pech told *SciBX*: "Looking at the *PNAS* paper, I don't know yet what a dose response would look like. In general, a challenge for APOA1 is that you might need quite large doses of the protein."

He also said that UCLA's planned mechanistic studies of APOA1 in ovarian cancer will be essential. "The finding seems to be affecting the proliferation rate of tumors but not apoptosis. Later in clinical development people will be very interested in the mechanism."

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Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
The University of Alabama at Birmingham, Birmingham, Ala.
University of California, Los Angeles, Calif.
Vermillion Inc. (NASDAQ:VRML), Austin, Texas

Change of heart on miR-21

By Joanne Kotz, Senior Editor

A team led by researchers at **The University of Texas Southwestern Medical Center at Dallas** and **miRagen Therapeutics Inc.** has reported that blocking microRNA-21 has no effect on stress-induced cardiac dysfunction. The findings prompted miRagen to drop its miR-21 program and pursue other miRNA targets for the indication. But **Regulus Therapeutics Inc.** is sticking by its miR-21 program in cardiac fibrosis based on its own positive preclinical data and maintaining that its program requires no course correction.

miRagen's interest in miR-21 dates to 2006, when Eric Olson and colleagues identified 21 miRNAs that were upregulated and 7 miRNAs that were downregulated in mouse models of cardiac stress compared with healthy controls. Of the upregulated miRNAs, miR-21 had the largest change in expression.[1]

Olson is chairman of molecular biology at UT Southwestern Medical Center and cofounder and chief scientific advisor of miRagen. Based on the findings, miRagen started preclinical programs evaluating a number of the miRNAs, including miR-21, as potential targets to treat heart failure.

A 2008 paper in *Nature* bolstered the case for the target. In it, a German research team and scientists at Regulus and **Alnylam Pharmaceuticals Inc.** reported that in a mouse model of stress-induced cardiac fibrosis, a chemically modified antisense oligonucleotide against miR-21 decreased cardiac expression of miR-21, cardiac fibrosis and cardiac hypertrophy compared with vehicle.[2]

Based on this evidence, Regulus established a preclinical program focused on miR-21 in 2009.

However, new findings stemming from miRagen's preclinical evaluation of the target run counter to those previous data. A team led by Olson and Eva van Rooij, cofounder and director of biology at miRagen, reported that modulating miR-21 produced no improvements in mice with cardiac fibrosis or hypertrophy.[3]

In the new work, the research team first looked at the effects of genetic ablation. In miR-21-deficient mice and wild-type controls, four different cardiac stresses each led to increases in cardiac hypertrophy or fibrosis.

In two mouse models of cardiac stress, a locked nucleic acid (LNA)-modified antisense oligonucleotide against miR-21 decreased expression of the target in the heart to levels prior to stress, but animals still had levels of cardiac hypertrophy similar to those in mice given nontargeting oligonucleotides.

The results were reported in *The Journal of Clinical Investigation*.

"The combination of the genetic deletion experiments and treatment with potent anti-miRNAs convinced us, and we're not going to move forward with miR-21," said miRagen cofounder, president and CEO William Marshall.

"The combination of the genetic deletion experiments and treatment with potent anti-miRNAs convinced us, and we're not going to move forward with miR-21."

—William Marshall, miRagen Therapeutics Inc.

miRNA validation

In contrast, Eric Marcusson, director of drug discovery at Regulus, said the *JCI* findings will have no impact on the company's preclinical development of anti-miR-21 therapeutics. The contrasting decisions result in part from different approaches for validating miRNA targets in animals.

At Regulus, Marcusson said genetic knockout experiments are a less important factor in decisions. "We know that knocking out a gene beginning in early development of an organism can have different effects from pharmacologically inhibiting a gene product in an adult animal," he said.

Instead, according to Marcusson, the company looks for targets in which inhibiting the miRNA across multiple disease models leads to a similar phenotype.

This has been the case for miR-21. Marcusson told *SciBX* that anti-miR-21 antisense oligonucleotides consistently produce a therapeutic benefit in preclinical models of both cardiac fibrosis and fibrosis in other organs.

miRagen places more emphasis on genetic validation of miRNA targets. "We believe that genetic ablation is an important point in the overall package," said Marshall. "We get concerned if the genetic and pharmacological phenotypes don't match."

For other miRNA targets the company is pursuing, such as miR-208 and miR-451, miRagen has seen congruence between genetic knockout and synthetic oligonucleotide inhibition experiments.

"Do I require genetic ablation to consider a target interesting? Not 100% of the time," said Marshall. Exceptions would include cases in which a family of miRNAs shares a common target-binding region. In such a situation, the knockout of one miRNA family member might be functionally compensated for by another during development, potentially obscuring a disease-modifying phenotype that would be seen with synthetic oligonucleotide inhibition in adult mice.

miR-21 has no obvious homologs, Marshall noted, and the closest potential homolog is not expressed in the heart and was not upregulated in the miR-21 knockout mouse.

Therapeutic impact

According to Marcusson, in addition to Regulus' doubts about the preclinical value of the genetic ablation data, it thinks the lack of therapeutic benefit seen in the *JCI* paper could be because "the shorter LNA oligonucleotides used in the studies are not very potent inhibitors compared with longer anti-miRNA inhibitors."

Regulus has looked at LNA inhibitors, which are only eight bases in length, in multiple models. The company has "always found them to be less potent" than longer antisense oligonucleotides, Marcusson noted.

Marshall countered that miRagen has seen therapeutic benefit from LNA-modified oligonucleotide inhibition of many miRNA targets in heart disease and other cardiovascular and musculoskeletal indications.

He added that multiple independent groups have also published reports demonstrating excellent activity with LNA-modified oligonucleotides in a wide range of targets and indications.

In addition to continuing to investigate miR-21 as a target in heart fibrosis, Regulus has preclinical programs targeting miR-21 for fibrosis in other organs as well as in oncology.

Regulus holds patents covering miR-21 in heart disease and other indications. In June of this year, the company formed a partnership with **sanofi-aventis Group** to develop therapeutics for four miRNA targets in fibrosis, including miR-21. The agreement included an upfront investment of $25 million with a potential of up to $750 million.

Meanwhile, miRagen has turned to other miRNA targets for heart failure in which Marshall is more comfortable with the biology and preclinical data. The company's most advanced inhibitor targets miR-208, which regulates expression of a pathway involved in cardiac contraction during cardiac hypertrophy and fibrosis.[4]

The compound has shown efficacy in multiple animal models of heart failure and has been dosed in nonhuman primates. The company hopes to begin Phase I trials in early 2012.

"Because of the data we generated on the target," Marshall told *SciBX*, "miRagen abandoned patent filings on miR-21."

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miRagen Therapeutics Inc., Boulder, Colo.
Regulus Therapeutics Inc., Carlsbad, Calif.
sanofi-aventis Group (Euronext:SAN; NYSE:SNY), Paris, France
The University of Texas Southwestern Medical Center at Dallas, Dallas, Texas

Fab libraries for antibody discovery

By Kai-Jye Lou, Staff Writer

Researchers at **Fabrus LLC** and **The Scripps Research Institute** have built a new type of antibody fragment library in which each Fab can be independently assayed via high throughput screening. The company expects the technology will help identify antibody candidates with targets and mechanisms seldom found using conventional antibody discovery technologies.[1]

Fabrus is now building larger Fab libraries and integrating them into its biologics discovery efforts.

Leads for all marketed antibody therapeutics to date were discovered *in vivo* by immunizing animals with an antigen of interest and then creating hybridomas or isolating B cells that produce antibodies against the antigen.

Current approaches for discovering and optimizing antibodies *in vitro* rely on libraries generated from display-based systems, in which potential candidates are presented on the surface of cells, phages or ribosomes.

Candidates isolated from both *in vitro* and *in vivo* approaches are selected from a pool based on their binding affinity for an antigen of interest.

Affinity-based selection does a good job at finding antagonists of a target but is generally unable to pick out candidates that could have other potentially desirable mechanisms of action like agonism, partial agonism, partial antagonism and allosteric modulation.

Display-based methods also have difficulty generating antibodies against certain classes of molecules like G protein–coupled receptors and ion channels. Moreover, conventional antibody libraries are not readily compatible with existing high throughput screening technologies such as those used to discover small molecules.

To address these issues, a group led by Fabrus founder and interim CEO Vaughn Smider developed an approach to building arrayed libraries of human Fabs, the antigen-binding fragments of an antibody (*see* **Figure 1, "Building Fab libraries for antibody discovery and optimization"**). Each member of the library is placed at a discrete location on a microarray, which allows the Fabs to be assayed independently from one another.

Because each member in the Fab library is evaluated in a separate reaction chamber, there is no direct competition with other members in the library. This is in contrast to affinity-based selection, in which weaker hits could be missed due to competition from stronger hits.

Smider's group screened a library of 10,024 Fabs against a set of 9 target antigens in parallel and identified 85 hits that were able to bind an antigen from the set. The group did not find hits against two of the nine antigens.

Importantly, one of the optimized Fabs against human delta-like ligand 4 (DLL4) had partial antagonist activity—a trait that is seldom found in candidates isolated via selection.

Results were published in *Nature Biotechnology*.

"Our method offers the potential to discover antibodies that wouldn't be easily discovered via conventional approaches," said Smider, who is also an assistant professor of molecular biology at Scripps and corresponding author on the paper. "These protein libraries could facilitate the discovery of antibodies with novel activities or antibodies against targets that are traditionally difficult to target with antibodies."

Smider added that the Fab libraries are screened in a manner similar to that used for small molecule libraries and could be plugged into existing high throughput screening platforms available at several companies.

"The researchers have done a good job showing that their method could be an alternative to selection-based techniques for antibody discovery," said Sachdev Sidhu, an associate professor of molecular genetics at the **University of Toronto**. "I was surprised that they were able to identify hits against the set of target antigens using such a small library. Display methods can require libraries with tens of millions of members."

"The classical phage display selection process, which has washing steps, favors the higher affinity binders, but higher affinity binders are not

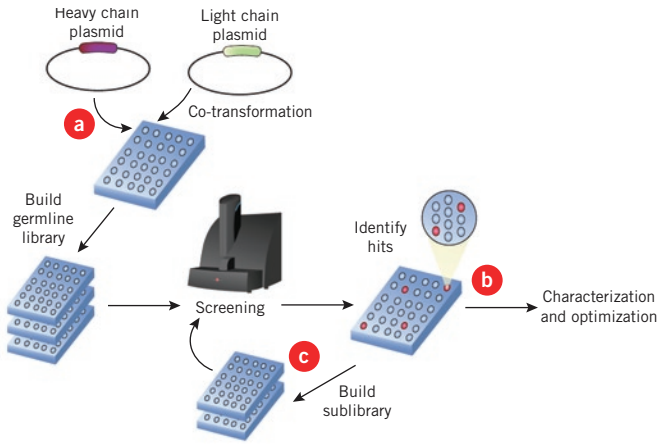

Figure 1. Building Fab libraries for antibody discovery and optimization. Conventional approaches for discovering antibodies rely on either animal immunization with a target antigen followed by the isolation of antibody-producing cells or display-based systems. In general, such approaches are not readily compatible with the existing high throughput screening methods used to discover small molecule lead candidates.

In *Nature Biotechnology*, researchers at **Fabrus LLC** and **The Scripps Research Institute** report that they have developed an approach to build antibody Fab libraries that can be screened with existing high throughput screening methodologies.

To build these libraries, researchers first co-transform *Escherichia coli* in wells with plasmids carrying recombined genetic sequences coding for antibody heavy and light chains. Plasmids carrying different heavy chain sequences are co-transformed with multiple light chain plasmids in parallel [**a**].

The Fabs are obtained after loading the transformed cells into an automated protein expression and purification system.

To screen for hits, researchers load each Fab into another well plate in which each individual well has an array containing multiple antigens of interest [**b**]. These well plates allow for the screening of individual Fabs against multiple antigens in parallel.

Hits against each antigen can then be characterized and optimized or used to build a sublibrary that is then sent through successive rounds of screening [**c**].

necessarily the best candidates," noted Philippe Mondon, CTO and head of antibody engineering at **Millegen**. "This library could be a good solution for finding antibodies that do not need to have high affinity, such as those that agonize target function."

Smider agreed that the ability to identify lower affinity antibodies is a potential advantage. "Display technologies rely on biological selection, where the antibodies in a pool that bind best to a particular antigen are the ones that are selected for," said Smider. "We don't know the false negative rates in biological selection experiments, as the antibodies are competing with one another to bind to the target antigen. I would see our technology as a way to identify candidates that would be missed by the biological selection approach."

> **"I would see our technology as a way to identify candidates that would be missed by the biological selection approach."**
> *—Vaughn Smider, Fabrus LLC*

Indeed, the hits identified in the *Nature Biotechnology* paper had a wide range of binding affinities.

The new libraries also are able to offer functional screening. "For example," said Smider, "you could carry out an apoptosis functional screen to identify antibodies that induce apoptosis in cancer cells. It is difficult to move directly into a functional screen with display technologies in the absence of some preselection event."

Finally, Smider said his group's approach is amenable to multiplexed discovery, in which members of the Fab library are screened against multiple antigens in parallel. "We showed proof of concept using nine antigens, but we could conceivably scale this up to hundreds or thousands of antigens," he told *SciBX*.

Despite the potential advantages of the antibody discovery approach described in the *Nature Biotechnology* paper, Sidhu suggested the amount of time and resources needed to build these libraries could limit their broad application to antibody discovery.

"I think Fabrus would be able to get a lot of mileage out of these libraries for their own programs," he said. "However, it would take a lot of effort to build these protein libraries, and I don't think many labs would be able to use this method to discover antibodies unless they fully commit themselves to using these libraries."

Smider agreed that building large Fab libraries would require a significant investment but noted that academic labs should have the resources to build such libraries on a smaller scale.

"To build these libraries at the scale we're doing it at, with the amount of protein that we're producing, would be a resource-intensive process," he told *SciBX*. "However, it should be possible to build these libraries on a smaller scale and at a cost that would be reasonable to an academic lab."

Smider added that although their method would be more costly than phage display, it would still be considerably cheaper than building a combinatorial chemistry library. "It costs about $15 per well using our method, but for combinatorial chemistry libraries, it can cost $300 to $400 per well."

Millegen's Mondon thinks that integrating the Fab library into existing antibody discovery platforms will be difficult because the automation systems, such as that used in protein expression and purification, are very specific. He also noted that it will be necessary to integrate the approach with an efficient antibody maturation platform.

As a next step, Sidhu said it will be important for Fabrus to clearly show that its approach can discover candidates with properties not found using existing platforms.

"While it is theoretically possible to develop more complicated screens to identify candidates with more unique properties like agonism, they have yet to show this," he noted. "I think this approach could become an important technology if they are able to show that it can do what current antibody platforms are not able to do."

Millegen uses its directed molecular evolution platform and high throughput functional screening to discover and engineer human antibodies for therapeutic and diagnostic use.

Going bigger

Smider said his group is now building larger Fab libraries, which will be integrated into Fabrus' discovery efforts. He said the company will initially focus on oncology targets and could have a candidate ready for clinical testing in two to three years.

"While a library size of 10,000 is good enough to find hits against many targets, it could be too small to be optimal and we want to go up to libraries with hundreds of thousands of antibodies," Smider told *SciBX*. "We are also interested in running functional screens that could be used to identify antibodies that target cancer stem cells and antibodies that could be good candidates for building antibody-drug conjugates."

This week, Fabrus and protein optimization company **Ambrx Inc.** announced a joint research program to discover antibodies with properties that are optimized for use as antibody drug conjugates.

Fabrus has filed multiple patents covering the methods, protein libraries and hits from the screening studies. The technology and identified hits are available for licensing.

Smider said the company's antibody technology could circumvent royalty-stacking issues associated with conventional antibody discovery platforms.

"Most antibody engineering projects require some sort of display technology, like phage, ribosome or yeast display," he said. "There are a web of patents claiming various aspects of these display compositions and methods. The Fabrus spatially addressed libraries do not use display, nor hybridoma methods, so it is completely outside of this IP."

Fabrus' investors include **Pfizer Inc.**, **Opko Health Inc.** and multiple angel investors.

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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 disease	ζ-Chain (TCR) associated protein kinase 70kDa (ZAP70)	Cell culture studies suggest that inhibiting ZAP70 could help treat autoimmune disease. In mouse $Cd4^+$ T cells, a Zap70 inhibitor decreased activation and proliferation of proinflammatory T cells compared with vehicle control. In modified $Cd8^+$ T cells from the same mice, the inhibitor prevented cytokine production and memory responses compared with a vehicle control. Next steps include investigating the effects of Zap70 inhibition in mouse models of arthritis and multiple sclerosis (MS). ***SciBX* 3(44); doi:10.1038/scibx.2010.1315** **Published online Nov. 11, 2010**	Unpatented; mouse model available for licensing	Au-Yeung, B.B. *et al. Nat. Immunol.*; published online Oct. 31, 2010; doi:10.1038/ni.1955 **Contact:** Arthur Weiss, University of California, San Francisco, Calif. e-mail: aweiss@medicine.ucsf.edu
Multiple sclerosis (MS)	MicroRNA-155 (miR-155)	A study in mice suggests that inhibiting miR-155 in T cells may help treat MS. In an experimental autoimmune encephalomyelitis (EAE) mouse model of MS, miR-155 deficiency led to less severe disease than normal expression of miR-155. In EAE mice, adoptive transfer of miR-155-deficient $Cd4^+$ T cells decreased disease severity compared with transfer of wild-type $Cd4^+$ T cells. Next steps include developing a delivery system for inhibiting miR-155 specifically in T cells. ***SciBX* 3(44); doi:10.1038/scibx.2010.1316** **Published online Nov. 11, 2010**	Patent application filed; available for licensing	O'Connell, R.M. *et al. Immunity*; published online Oct. 29, 2010; doi:10.1016/j.immuni.2010.09.009 **Contact:** David Baltimore, California Institute of Technology, Pasadena, Calif. e-mail: baltimo@caltech.edu
Cancer				
Brain cancer	IL-13; IL-13 receptor α2 (IL-13RA2; IL-13R; CD213A2)	Studies in mice suggest that IL-13-based gene therapy could help treat brain cancer. The gene therapy consisted of an adenoviral vector expressing *Pseudomonas* exotoxin linked to a mutant variant of IL-13 that was specific for IL-13R, which is commonly expressed in glioblastoma multiforme. In a mouse model of glioblastoma, the gene therapy prolonged survival and decreased tumor growth with no side effects compared with a control vector. Next steps could include optimizing dosing in additional preclinical models of glioblastoma multiforme. NeoPharm Inc.'s Cintredekin besudotox, an injectable fusion protein consisting of *Pseudomonas* exotoxin linked to wild-type IL-13, missed the primary endpoint in a Phase III trial to treat glioblastoma multiforme in 2006. ***SciBX* 3(44); doi:10.1038/scibx.2010.1317** **Published online Nov. 11, 2010**	Patent and licensing status unavailable	Candolfi, M. *et al. Proc. Natl. Acad. Sci. USA*; published online Oct. 25, 2010; doi:10.1073/pnas.1008261107 **Contact:** Pedro R. Lowenstein, Cedars-Sinai Medical Center, Los Angeles, Calif. e-mail: lowensteinp@cshs.org **Contact:** Maria G. Castro, same affiliation as above e-mail: castromg@cshs.org

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Cancer	B cell lymphoma 2 (BCL-2; BCL2); BCL-X_L; myeloid leukemia cell differentiation protein (MCL-1); BCL2-related protein A1 (BCL2A1; BFL1)	*In vitro* and mouse studies identified a pan-BCL-2 inhibitor that could help treat cancer. *In vitro*, the lead analogs of gossypol, a pan-inhibitor of BCL-2, inhibited BCL-2, BCL-X_L, MCL-1 and BCL2A1 at low micromolar concentrations. In human prostate, lung, lymphoma and leukemia cell lines, the lead analog was cytotoxic with low to submicromolar EC_{50} values. In mice bearing xenograft prostate tumors, the lead analog decreased tumor growth compared with gossypol. Planned work includes testing the lead analog in animal models of leukemia, lymphoma, melanoma, breast and lung cancers. AT-101, a small molecule pan-inhibitor of the BCL-2 family of proteins from Ascenta Therapeutics Inc., is in Phase I/II and Phase II testing to treat multiple cancers, including prostate, lung and brain cancers and B cell malignancies. Obatoclax (GX15-070), an i.v. formulation of a small molecule pan-inhibitor of the BCL-2 family of proteins from Gemin X Pharmaceuticals Inc., is in Phase I and Phase II testing to treat multiple solid tumor cancers and hematological malignancies. ***SciBX* 3(44); doi:10.1038/scibx.2010.1318** **Published online Nov. 11, 2010**	Patented by the Sanford-Burnham Medical Research Institute; available for licensing	Wei, J. *et al. J. Med. Chem.*; published online Oct. 29, 2010; doi:10.1021/jm100746q **Contact:** Maurizio Pellecchia, Sanford-Burnham Medical Research Institute, La Jolla, Calif. e-mail: mpellecchia@sanfordburnham.org
Cancer	Cyclin dependent kinase (CDK)	Studies in rodents identified 2-anilino-4-(thiazol-5-yl) pyrimidine–based CDK inhibitors that could help treat cancer. In a mouse model of leukemia, one of the CDK inhibitors resulted in greater survival than vehicle ($p<0.0001$). In a mouse model of human colorectal cancer, the same CDK inhibitor delayed tumor growth compared with vehicle controls ($p<0.05$). Next steps include identifying the molecular subtypes of cancer that are sensitive to the CDK inhibitors. Seliciclib, an inhibitor of CDK2E, CDK2A, CDK7 and CDK9 from Cyclacel Pharmaceuticals Inc., is in Phase II testing to treat non–small cell lung cancer (NSCLC) and nasopharyngeal cancer. The lead CDK inhibitor identified in the study is in preclinical development. At least eight other companies have CDK inhibitors in clinical or preclinical development to treat various cancers. ***SciBX* 3(44); doi:10.1038/scibx.2010.1319** **Published online Nov. 11, 2010**	Multiple patents pending; available for partnering	Wang, S. *et al. Chem. Biol.*; published online Oct. 29, 2010; doi:10.1016/j.chembiol.2010.07.016 **Contact:** Peter M. Fischer, The University of Nottingham, Nottingham, U.K. e-mail: peter.fischer@nottingham.ac.uk **Contact:** David G. Blake, Cyclacel Pharmaceuticals Inc., Dundee, U.K. e-mail: dblake@cyclacel.com
Cancer	Not applicable	*In vitro* and mouse studies identified polyenylpyrrole analogs that could help treat cancer. Two analogs had IC_{50} values of 0.6 and 0.01 μM and were cytotoxic in non–small lung cancer (NSCLC) cell lines but not in normal lung cells. In mice with human lung cancer xenografts, the most potent analog inhibited tumor growth better than vehicle control. Next steps could include further optimization of the compounds. ***SciBX* 3(44); doi:10.1038/scibx.2010.1320** **Published online Nov. 11, 2010**	Patent and licensing status unavailable	Fang, Z. *et al. J. Med. Chem.*; published online Oct. 22, 2010; doi:10.1021/jm100619x **Contact:** Yulin Lam, National University of Singapore, Singapore e-mail: chmlamyl@nus.edu.sg
Cancer	Not applicable	*In vitro* and mouse studies suggest that osmium arene complexes could help treat cancer. *In vitro*, three lead osmium arene phenylazopyridine complexes were cytotoxic at low or subnanomolar concentrations in human bladder, breast, colon, lung, prostate, ovarian and cisplatin-resistant ovarian cancer cell lines. In mice with xenograft colon tumors, two of the lead compounds had maximum tolerated doses at least sixfold higher than those of the generic chemotherapeutic cisplatin. Ongoing work includes testing the efficacy of the lead compounds in animal models of cancer and elucidating their mechanism of action. ***SciBX* 3(44); doi:10.1038/scibx.2010.1321** **Published online Nov. 11, 2010**	Patented by The University of Warwick; available for licensing	Fu, Y. *et al. J. Med. Chem.*; published online Oct. 26, 2010; doi:10.1021/jm100560f **Contact:** Peter J. Sadler, The University of Warwick, Coventry, U.K. e-mail: P.J.Sadler@warwick.ac.uk

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Cancer	Phosphatidylinositol 3,4,5-triphosphate (PIP3); phosphoinositide 3-kinase (PI3K); 3-phosphoinositide dependent protein kinase-1 (PDPK1; PDK1); protein kinase B (PKB; Akt)	*In vitro* and mouse studies identified PIP3 inhibitors that could help treat cancer. In cancer cell lines, the inhibitors decreased PIP3 activation of the PI3K/PDK1/Akt signaling pathway and increased apoptosis compared with inactive control compounds. In a mouse model of metastatic breast cancer, micelle-encapsulated and nonencapsulated formulations of the lead compound decreased tumor growth by 95% and 58%, respectively, compared with vehicle control. Ongoing work includes optimizing and testing the lead compound in animal models of other cancers. ***SciBX* 3(44); doi:10.1038/scibx.2010.1322** **Published online Nov. 11, 2010**	Patented; available for licensing	Miao, B. *et al. Proc. Natl. Acad. Sci. USA*; published online Nov. 1, 2010; doi:10.1073/pnas.1004522107 **Contact:** Alexei Degterev, Tufts University School of Medicine, Boston, Mass. e-mail: alexei.degterev@tufts.edu
Colon cancer	Glucuronidase-β (GUSB)	*In vitro* and mouse studies identified inhibitors of GUSB that could help decrease gastrointestinal toxicity associated with the chemotherapeutic Camptosar irinotecan. In an enzymatic assay, four bacterial GUSB inhibitors did not impair the activity of human GUSB. In mice, irinotecan plus the most potent inhibitor decreased diarrhea and gastrointestinal tissue damage compared with irinotecan alone. Next steps include undisclosed preclinical studies. Pfizer Inc. markets Camptosar to treat non–small cell lung cancer (NSCLC) and colon cancer. ***SciBX* 3(44); doi:10.1038/scibx.2010.1323** **Published online Nov. 11, 2010**	Provisional patent application filed; unlicensed	Wallace, B.D. *et al. Science*; published online Nov. 4, 2010; doi:10.1126/science.1191175 **Contact:** Matthew R. Redinbo, The University of North Carolina at Chapel Hill, Chapel Hill, N.C. e-mail: redinbo@unc.edu
Ovarian cancer	Apolipoprotein A-1 (APOA1)	Cell culture and mouse studies suggest that APOA1 peptide mimetics could help treat ovarian cancer. Low APOA1 serum levels are prognostic for early stage ovarian cancer. In a mouse model of ovarian cancer, injection or oral dosing of an APOA1 mimetic peptide decreased tumor burden and size compared with injection of vehicle control. In cisplatin-resistant human ovarian cancer cell lines, APOA1 mimetics decreased cell proliferation and viability compared with vehicle control. Next steps could include animal studies of oral APOA1 mimetics to treat ovarian cancer. Arisaph Pharmaceuticals Inc.'s ARI-1778 is an APOA1 peptide mimetic in preclinical testing to treat atherosclerosis. At least three other companies have APOA1-enhancing compounds in development from preclinical to Phase II trials to treat cardiovascular diseases (*see* **Going APOA1 in cancer, page 3**). ***SciBX* 3(44); doi:10.1038/scibx.2010.1324** **Published online Nov. 11, 2010**	Patented by the University of California, Los Angeles and The University of Alabama at Birmingham; licensed to Bruin Pharmaceuticals Inc.	Su, F. *et al. Proc. Natl. Acad. Sci. USA*; published online Nov. 1, 2010; doi:10.1073/pnas.1009010107 **Contact:** Robin Farias-Eisner, University of California, Los Angeles, Calif. e-mail: rfeisner@mednet.ucla.edu **Contact:** Srinivasa T. Reddy, same affiliation as above e-mail: sreddy@mednet.ucla.edu
Cardiovascular disease				
Heart failure	MicroRNA-21 (miR-21)	A study in mice suggests that inhibiting miR-21 might not be effective for treating cardiac hypertrophy and fibrosis. In miR-21-deficient mice and wild-type mice, four different cardiac stresses each led to increased cardiac hypertrophy or fibrosis. In two mouse models of cardiac stress, locked nucleic acid (LNA)-modified antisense oligonucleotide inhibition of miR-21 led to lower levels of miR-21 in the heart but similar levels of cardiac hypertrophy compared with scrambled oligonucleotide controls. Based on these results, miRagen Therapeutics Inc. has discontinued their preclinical program evaluating miR-21 as a target in cardiovascular disease. Regulus Therapeutics Inc. has antagomir-21, an antisense oligonucleotide targeting miR-21, in preclinical development for cardiac fibrosis (*see* **Change of heart on miR-21, page 4**). ***SciBX* 3(44); doi:10.1038/scibx.2010.1325** **Published online Nov. 11, 2010**	Patent and licensing status not applicable	Patrick, D.M. *et al. J. Clin. Invest.*; published online Oct. 18, 2010; doi:10.1172/JCI43604 **Contact:** Eric N. Olson, The University of Texas Southwestern Medical Center at Dallas, Dallas, Texas e-mail: eric.olson@utsouthwestern.edu **Contact:** Eva van Rooij, miRagen Therapeutics Inc., Boulder, Colo. e-mail: evanrooij@miragenrx.com

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Endocrine disease				
Diabetes	ATPase Ca^{++} transporting cardiac muscle slow twitch 2b (ATP2A2b; SERCA2b)	Studies in mice suggest that increasing SERCA2b levels could help treat diabetes. In a mouse model of obesity, adenoviral expression of *Serca2b* in the liver decreased liver endoplasmic reticulum stress, triglyceride levels and blood glucose and increased serum insulin compared with control vector. Next steps could include screening for small molecule enhancers of SERCA2b activity. ***SciBX* 3(44); doi:10.1038/scibx.2010.1326** **Published online Nov. 11, 2010**	Patent and licensing status unavailable	Park, S.W. *et al. Proc. Natl. Acad. Sci. USA*; published online Oct. 25, 2010; doi:10.1073/pnas.1012044107 **Contact:** Umut Ozcan, Children's Hospital Boston, Harvard Medical School, Boston, Mass. e-mail: umut.ozcan@childrens.harvard.edu
Infectious disease				
Bacterial infection	*Cryptosporidium parvum* inosine monophosphate dehydrogenase (CpIMPDH)	An *in vitro* study identified CpIMPDH inhibitors that may help treat bacterial infections. *In vitro*, the lead compound inhibited purified IMPDH from *C. parvum*, *Helicobacter pylori* and *Streptococcus pyogenes* with nanomolar IC_{50} values. In cell culture, the compound inhibited the growth of *H. pylori* better than vehicle control. Next steps include optimizing the inhibitors to increase bacterial cell permeability and testing the effects of the inhibitors in *in vivo* models of bacterial infection. ***SciBX* 3(44); doi:10.1038/scibx.2010.1327** **Published online Nov. 11, 2010**	Patents pending; available for licensing **Contact:** Irene Abrams, Brandeis University, Waltham, Mass. e-mail: iabrams@brandeis.edu	Gollapalli, D.R. *et al. Chem. Biol.*; published online Oct. 29, 2010; doi:10.1016/j.chembiol.2010.07.014 **Contact:** Lizbeth Hedstrom, Brandeis University, Waltham, Mass. e-mail: hedstrom@brandeis.edu
Herpes simplex virus (HSV)	Myosin heavy chain 9 (MYH9); myosin light chain kinase (MYLK; MLCK)	Cell culture and mouse studies suggest that inhibiting MYH9 or MYLK could help treat HSV infection. In HSV-1–infected cells, anti-MYH9 antibody–containing serum or MYH9-targeting small hairpin RNA decreased levels of infection compared with control serum or a control shRNA. In cell culture and a mouse model of HSV-1 stromal keratitis, an inhibitor of MYLK, which regulates MYH9, decreased infection compared with no treatment. Next steps include developing a mAb against MYH9. ***SciBX* 3(44); doi:10.1038/scibx.2010.1328** **Published online Nov. 11, 2010**	Patent pending; licensing status undisclosed	Arii, J. *et al. Nature*; published online Oct. 14, 2010; doi:10.1038/nature09420 **Contact:** Yasushi Kawaguchi, The University of Tokyo, Tokyo, Japan e-mail: ykawagu@ims.u-tokyo.ac.jp
Inflammation				
Asthma	Chemokine CX3C motif receptor 1 (CX3CR1)	Studies in mice suggest that inhibiting CX3CR1 could help treat asthma. *Cx3cr1*-deficient mice had less intense asthma symptoms in response to allergen exposure than controls with functional *Cx3cr1*. In wild-type mice, antibodies and small molecules against Cx3cr1 led to less intense allergen-induced asthma symptoms than no treatment. Next steps include studying CX3CR1 expression in T cells from asthmatic patients and generating compounds to block the receptor. ***SciBX* 3(44); doi:10.1038/scibx.2010.1329** **Published online Nov. 11, 2010**	Work unpatented; available for licensing from the Institut National de la Santé et de la Recherche Médicale (INSERM) Technology Transfer Office	Mionnet, C. *et al. Nat. Med.*; published online Oct. 31, 2010; doi:10.1038/nm.2253 **Contact:** Valerie Julia, University of Nice Sophia Antipolis, Valbonne, France e-mail: vjulia@unice.fr
Metabolic disease				
Amyloidosis	Serum amyloid P component (SAP; APCS)	Studies in mice suggest that inhibiting SAP could help treat amyloidosis disorders. In a mouse model of amyloidosis, an anti-SAP antibody plus the small molecule CPHPC significantly decreased spleen and liver amyloid levels compared with no treatment or CPHPC alone ($p<0.001$). CPHPC targeted SAP in the serum, whereas the antibody targeted SAP in the serum and in amyloid deposits. GlaxoSmithKline plc has humanized the anti-SAP antibody and is further characterizing the antibody in preclinical models of amyloidosis. ***SciBX* 3(44); doi:10.1038/scibx.2010.1330** **Published online Nov. 11, 2010**	Patent application filed covering combination of anti-SAP antibody and CPHPC to treat amyloid disorders; exclusively licensed to GlaxoSmithKline	Bodin, K. *et al. Nature*; published online Oct. 20, 2010; doi:10.1038/nature09494 **Contact:** Mark B. Pepys, University College London, London, U.K. e-mail: m.pepys@ucl.ac.uk

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Neurology				
Alzheimer's disease (AD)	E1A binding protein p300 (EP300; p300)	*In vitro* and mouse studies suggest that inhibiting τ acetylation could help treat AD and other τ-associated disorders. In AD patients, levels of phosphorylated and acetylated τ were higher than those in healthy controls. In primary neurons, a small molecule inhibitor of the histone acetyltransferase p300 decreased acetylated τ, leading to less pathogenic phosphorylated τ than an inactive analog of the inhibitor. Next steps could include testing τ acetylation inhibitors in animal models of AD and other τ-associated disorders. ***SciBX* 3(44); doi:10.1038/scibx.2010.1331** **Published online Nov. 11, 2010**	Patent and licensing status unavailable	Min, S.-W. *et al. Neuron*; published online Sept. 23, 2010; doi:10.1016/j.neuron.2010.08.044 **Contact:** Li Gan, Gladstone Institute of Neurological Disease, San Francisco, Calif. e-mail: lgan@gladstone.ucsf.edu
Depression	S100 calcium binding protein A10 (S100A10; P11)	Mouse studies suggest that restoring P11 expression in the brain could help treat depression. Compared with using a control small hairpin RNA, adeno-associated virus (AAV) vector–mediated shRNA reduction of p11 in the nucleus accumbens of mice caused depression-like behaviors comparable to those seen with total p11 knockout. In p11 knockout mice, AAV vector–mediated restoration of p11 expression in the nucleus accumbens reversed depression-like behaviors compared with an AAV vector control. In human postmortem brain tissues, depressed patients had lower P11 levels than healthy controls. Next steps include studying *p11* gene therapy in nonhuman primates. ***SciBX* 3(44); doi:10.1038/scibx.2010.1332** **Published online Nov. 11, 2010**	Findings patented; exclusively licensed to Neurologix Inc.	Alexander, B. *et al. Sci. Transl. Med.*; published online Oct. 20, 2010; doi:10.1126/scitranslmed.3001079 **Contact:** Michael G. Kaplitt, Weill Cornell Medical College, New York, N.Y. e-mail: mik2002@med.cornell.edu
Stroke	$GABA_A$ receptor	Studies in mice suggest that $GABA_A$ receptor antagonists could help treat stroke. $GABA_A$ receptor–deficient mice showed greater motor recovery after stroke than wild-type controls. A $GABA_A$ receptor antagonist given three days post-stroke increased motor function in the mice compared with vehicle. Ongoing work includes testing $GABA_A$ receptor antagonists in additional mouse models of stroke and determining a therapeutic window. ***SciBX* 3(44); doi:10.1038/scibx.2010.1333** **Published online Nov. 11, 2010**	Patented by the University of California, Los Angeles; available for licensing	Clarkson, A.N. *et al. Nature*; published online Nov. 4, 2010; doi:10.1038/nature09511 **Contact:** S. Thomas Carmichael, University of California, Los Angeles, Calif. e-mail: scarmichael@mednet.ucla.edu
Ophthalmic disease				
Retinitis	Serine palmitoyltransferase long chain base subunit 1 (SPTLC1; LBC1)	Studies in mice suggest that inhibiting ceramide biosynthesis could help treat retinitis pigmentosa (RP). In a mouse model of RP, retinal ceramide levels were higher than those in wild-type controls. In the same model, topical application of nanoparticles loaded with an inhibitor of SPTLC1, a key enzyme in ceramide biosynthesis, decreased retinal ceramide levels and increased the number of functioning photoreceptor rods compared with application of unloaded nanoparticle controls. Ongoing work includes investigating both the duration of the treatment effects in photoreceptor rods and whether the therapeutic effect extends to photoreceptor cones. ***SciBX* 3(44); doi:10.1038/scibx.2010.1334** **Published online Nov. 11, 2010**	Patented by the University of Milan, the University of Pisa, the National Research Council and Nanovector s.r.l.; available for licensing	Strettoi, E. *et al. Proc. Natl. Acad. Sci. USA*; published online Oct. 11, 2010; doi:10.1073/pnas.1007644107 **Contact:** Enrica Strettoi, National Research Council, Pisa, Italy e-mail: enrica.strettoi@in.cnr.it

This week in techniques

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

This week in techniques includes findings about research tools, disease models and manufacturing processes that have the potential to enable or improve all stages of drug discovery and development.

Approach	Summary	Licensing status	Publication and contact information
Assays & screens			
DNA-tagged small molecule and protein libraries for drug discovery	A method for identifying ligand-protein binding pairs from a mixture could help identify new drug leads. Small molecules and proteins were linked to DNA tags that were amplified by PCR when the small molecule ligand and protein target interacted. In a solution of five small molecule–protein target pairs, the method identified all known pairs. Next steps include generating DNA-linked small molecule and protein libraries suitable for large-scale discovery. ***SciBX* 3(44); doi:10.1038/scibx.2010.1335** **Published online Nov. 11, 2010**	Patent application filed; available for licensing	McGregor, L.M. *et al. J. Am. Chem. Soc.*; published online Oct. 15, 2010; doi:10.1021/ja107677q **Contact:** David R. Liu, Harvard University, Cambridge, Mass. e-mail: drliu@fas.harvard.edu
Drug delivery			
I.v. delivery of transgenes to the CNS	A method for improving delivery of transgenes to the brain could help treat neurological disorders. In mice, intraperitoneal injection of mannitol prior to i.v. injection of an SV-40–derived viral vector led to about a 10-fold increase in transgene expression in the motor and somatosensory cortex compared with that in mice not given mannitol ($p<0.001$). Next steps could include optimizing the drug delivery method for use in nonhuman primates. ***SciBX* 3(44); doi:10.1038/scibx.2010.1336** **Published online Nov. 11, 2010**	Unpatented; licensing status undisclosed	Louboutin, J.-P. *et al. Nat. Methods*; published online Oct. 17, 2010; doi:10.1038/nmeth.1518 **Contact:** David S. Strayer, Thomas Jefferson University, Philadelphia, Pa. e-mail: David.Strayer@jefferson.edu
Nanoparticles for lung-mediated drug delivery	A study in rats identified nanoparticles that could be useful for delivering therapeutics across the lung into systemic circulation. In rats, nanoparticles with a hydrodynamic diameter of less than 34 nm and a negative or neutral charge translocated from the lung into the lymph nodes and bloodstream. Also in rats, nanoparticles with both a positive and a negative charge and a hydrodynamic diameter of less than 6 nm moved from the lung into the bloodstream and were cleared by renal filtration. Next steps include studying nanoparticle biodistribution over longer times and characterizing drug-conjugated nanoparticles in animals. ***SciBX* 3(44); doi:10.1038/scibx.2010.1337** **Published online Nov. 11, 2010**	Unpatented; licensing status not applicable	Choi, H.S. *et al. Nat. Biotechnol.*; published online Nov. 7, 2010; doi:10.1038/nbt.1696 **Contact:** Akira Tsuda, Harvard School of Public Health, Boston, Mass. e-mail: atsuda@hsph.harvard.edu **Contact:** John V. Frangioni, Beth Israel Deaconess Medical Center, Boston, Mass. e-mail: jfrangio@bidmc.harvard.edu
Drug platforms			
Direct conversion of fibroblasts into hematopoietic progenitors	A method for directly converting human fibroblasts into hematopoietic progenitor cells could be useful for developing autologous cell-replacement therapies. Previous protocols for converting human fibroblasts into hematopoietic cells required an intermediate step of reverting cells into induced pluripotent stem (iPS) cells. In human fibroblasts, forced expression of the transcription factor *OCT4* generated cells that expressed the pan-leukocyte marker CD45 without requiring an iPS cell state. In the fibroblast-derived cells, a cytokine cocktail supporting hematopoietic progenitor cell development and expansion generated all myeloid cell lineages. Next steps include scaling up the direct conversion process. ***SciBX* 3(44); doi:10.1038/scibx.2010.1338** **Published online Nov. 11, 2010**	Multiple patents filed covering technologies to directly convert fibroblasts into blood progenitor cells; available for licensing	Szabo, E. *et al. Nature*; published online Nov. 7, 2010; doi:10.1038/nature09591 **Contact:** Mickie Bhatia, McMaster University, Hamilton, Ontario, Canada e-mail: mbhatia@mcmaster.ca

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
IL-27 antagonistic variants	Computational and biological analysis of binding sites on IL-27 could help generate IL-27 antagonists to treat inflammatory and autoimmune diseases. Researchers used site-directed mutagenesis on the IL-27 p28 subunit to identify amino acid residues important for binding site activity. In a mouse model of T helper type 1 (Th1) cell–mediated liver injury, a W197A mutant of Il-27 resulted in lower expression of two proinflammatory chemokines compared with vehicle. Next steps could include generating additional IL-27 variants with different levels of anti-inflammatory activity. ***SciBX* 3(44); doi:10.1038/scibx.2010.1339** **Published online Nov. 11, 2010**	Patent and licensing status unavailable	Rousseau, F. *et al. Proc. Natl. Acad. Sci. USA*; published online Oct. 25, 2010; doi:10.1073/pnas.1005793107 **Contact:** Hugues Gascan, University Hospital of Angers, Angers, France e-mail: hugues.gascan@univ-angers.fr
Rodent models of pericyte-mediated blood brain barrier (BBB) permeability	A pair of mouse studies generated a set of transgenic mouse models of the BBB that could aid the development of new CNS-targeting therapies. The transgenic mice had varying levels of platelet derived growth factor receptor-β (Pdgfrb; Pdgfr1; Cd140b), a protein that mediates BBB permeability. Low levels of Pdgfrb expression correlated with less pericyte coverage in CNS blood vessels and greater BBB permeability. Next steps could include using the mice to study the mechanisms by which pericytes regulate BBB permeability. ***SciBX* 3(44); doi:10.1038/scibx.2010.1340** **Published online Nov. 11, 2010**	Patent and licensing status unavailable	Daneman, R. *et al. Nature*; published online Oct. 13, 2010; doi:10.1038/nature09513 **Contact:** Richard Daneman, University of California, San Francisco, Calif. e-mail: richard.daneman@ucsf.edu Armulik, A. *et al. Nature*; published online Oct. 13, 2010; doi:10.1038/nature09522 **Contact:** Christer Betsholtz, Karolinska Institute, Stockholm, Sweden e-mail: christer.betsholtz@ki.se

Company and insitution index

Target and compound index