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SciBX: Science-Business eXchange *will not be published on Dec. 26, 2013 and Jan. 2, 2014. It will resume its schedule the week of Jan. 6, 2014.*

Oral nanoparticles

By Lauren Martz, Staff Writer

Researchers from **Brigham and Women's Hospital** and the **Massachusetts Institute of Technology** have developed targeted nanoparticles that could enable the oral delivery of biologics such as insulin.¹ The clinical translation of the approach will require identifying a suitable therapeutic payload and fine-tuning the pharmacology of the system.

Poor intestinal absorption prevents the oral delivery of many compounds and virtually all biologics. Factors that affect oral bioavailability include stability and size, as peptide therapeutics generally are degraded in the GI tract and large molecules cannot be passively absorbed through the intestinal epithelium.

Several companies have tried to develop oral delivery methods for biologics. In 2006, an oral insulin tablet from **Emisphere Technologies Inc.** failed in a Phase II trial in type 2 diabetes. In 2011, Emisphere and partners **Nordic Bioscience A/S** and **Novartis AG** discontinued development of the oral salmon calcitonin biologic SMC021 after it failed several Phase III trials in osteoarthritis and osteoporosis.

Emisphere is now using its Eligen oral drug delivery platform, which consists of binding small molecules to the therapeutic of interest to facilitate its passive transport into the cells, to develop oral formulations of **Novo Nordisk A/S'** glucagon-like peptide-1 (GLP-1) analogs for diabetes.

Altus Biologics Inc. discontinued development of the oral cross-linked pancreatic enzyme crystal biologic Trizytek liprotamase, which was in development to treat malabsorption caused by exocrine pancreatic insufficiency in patients with cystic fibrosis (CF). The company, which was creating oral biologics using the cross-linked enzyme crystal protein technology platform, filed for bankruptcy in 2009 and was acquired by **Althea Technologies Inc.** in 2010.

Omid Farokhzad and colleagues at Brigham and Women's Hospital decided to tackle oral biologics by marrying a drug-stabilizing approach with a method for improving the uptake of biologics. Farokhzad is an associate professor of anesthesia at Brigham and Women's Hospital.

For stability, the team opted for nanoparticles that encapsulate compounds or peptides. For uptake, the group chose to target neonatal Fc fragment of IgG receptor transporter- α (FCGRT; FCRN).^{2,3} FCRN normally functions to transport maternal IgG from breast milk to offspring; however, receptor expression persists in the adult intestines and is also present in tissues including the blood brain barrier, liver, lungs, vascular endothelium and kidneys.^{4,5}

A team from **The University of Nottingham** had previously shown that peptides bound to FCRN could be transported across the airway epithelium.⁶

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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; Christoph Hesselmann, Ph.D., Chief Financial Officer, NPG.

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Next, the Brigham and Women's Hospital team conjugated the Fc portion of IgG, which binds FCRN, to the surface of standard polylactic acid (PLA)-polyethylene glycol (PEG) nanoparticles using maleimide linkers. PEG-PLA nanoparticles have a hydrophilic PEG shell and a hydrophobic PLA core to carry drug payloads.

In vitro, the FCRN-targeting nanoparticles had twofold higher transport across a human epithelial colorectal adenocarcinoma cell monolayer, a common model used for drug permeability testing, than nontargeted nanoparticles.

Next, the group fed fluorescently labeled, FCRN-targeting nanoparticles to fasted mice. Transport of the targeted nanoparticles to the villi could be seen by microscopy, whereas no signal was seen for nontargeted nanoparticles.

Detailed biodistribution studies showed that the targeted nanoparticles accumulated in multiple organs in the mouse including the spleen, lungs, liver and heart. The targeted nanoparticles had an oral absorption efficiency of 13.7%; the efficiency for nontargeted nanoparticles was 1.2%.

The nanoparticles also were able to deliver a therapeutically relevant payload. In fasted mice, oral administration of targeted, insulin-loaded nanoparticles caused a hypoglycemic response that was greater than that caused by oral delivery of free insulin or insulin-loaded, nontargeted nanoparticles.

The hypoglycemic effect of the targeted nanoparticles lasted for 15 hours, whereas it lasted only 1.5 hours for injection of free insulin.

Results were published in *Science Translational Medicine*.

The paper also included researchers from MIT, **The David H. Koch Institute for Integrative Cancer Research at MIT** and the **MIT-Harvard Center of Cancer Nanotechnology Excellence**.

“Peptides need the protection of nanoparticles for stability through the GI tract, but until now the issue of poor uptake in the intestines has been unresolved. This system may allow us to overcome this major barrier.”

**—Edith Mathiowitz,
Brown University**

Going bigger

Farokhzad's team is planning to test the platform in larger animal models that more accurately replicate how the nanoparticles will behave in humans.

Edith Mathiowitz, a professor of medical science and engineering, director of the Biotechnology Graduate Program and a member of the Center for Biomedical Engineering at **Brown University**, said that manipulating the FCRN system to enable oral drug delivery is a major step forward.

“I am a believer that this is one of the technologies that can be used to deliver more therapeutic molecules orally, and specifically peptide therapeutics,” she said. “Peptides need the protection of nanoparticles for stability through the GI tract, but until now the issue of poor uptake in the intestines has been unresolved. This system may allow us to overcome this major barrier.”

Jeff Hrkach, SVP of technology and R&D at **Bind Therapeutics Inc.**, added that many small molecules with poor bioavailability could benefit from the approach. “This nanoparticle system has the potential to expand broadly for oral small molecule drugs by overcoming barriers like first-pass metabolism and liver toxicity. If you’re getting optimal systemic exposure via this pathway, it opens up the opportunity for more drugs with poor oral bioavailability,” he said.

The maleimide linker used to attach the IgG Fc fragment to the nanoparticles might need to be rethought, according to Jörg Kreuter, a professor of pharmaceutical chemistry at **Goethe University Frankfurt**. He was concerned that the linker will complicate preparation and increase the risk of GI toxicity.

“Such linkers could lead to interaction with the GI tract contents and could lead to an immunological reaction. For this reason, I would always try to avoid such linkers if you can,” he said.

Mathiowitz agreed that GI toxicity is a risk. “They also need to study the general toxicity of the method. The GI tract is designed to reject molecules like these from being absorbed into circulation, so we need to be sure that this does not cause any toxic effects.”

Farokhzad said that although maleimide linkers are used to induce immunogenicity for vaccines, he does not expect that immunogenicity should be a problem. “The relative ligand density on the nanoparticle surface is low, and there should not be any unconjugated linkers on the surface that could cause an immune response,” he said.

Thomas Rademacher, founder and CSO of **Midatech Ltd.**, added that broad tissue uptake by FCRN could also be a liability, particularly for insulin. “The clinical consequences of insulin release from organs such as the lungs, heart and spleen or other FCRN-rich tissues will take a long time to assess,” he said.

Midatech’s Midaform Insulin PharmFilm, an oral film formulation of insulin-coated gold nanoparticles for delivery through the cheek, has completed Phase I testing to treat diabetes.

Farokhzad said, “We should be able to design the nanoparticles to go where they need to go. In this proof of concept, the nanoparticles were not designed for localization but rather to enhance bioavailability, so we considered the fact that the particles were able to get to those organs to be a very good thing. In addition to IgG Fc, additional ligands could be added to the surface to fine-tune nanoparticle localization.”

Kreuter said that insulin may not have been the best choice for a proof-of-concept molecule because of its unique pharmacology issues.

“The biggest problem with the oral delivery of insulin bound to nanoparticles is the fact that it leads to a retarded and rather uncontrolled prolonged action, which may not be the optimal solution for a diabetic patient,” he said.

Farokhzad told *SciBX* that whether or not the oral insulin application will be pursued will be decided by the commercial entity that develops the technology.

“We do plan to test the insulin-loaded nanoparticles in larger animal models, which could serve to validate both the general

approach and the insulin platform, but there may be lower-hanging fruit. There is a high safety hurdle for diabetes, and there may be other indications with greater unmet need for our first platform-validation product,” he added.

Farokhzad noted that the approach has potential beyond insulin delivery. “We also plan to expand the platform within the oral application to test nanoparticles carrying other drugs,” he said.

Nano-tuning

Farokhzad is planning a number of steps to enhance the platform, including more specific tissue targeting that could open potential oral or pulmonary indications to nanoparticles.

“The lung and the placenta express FCRN, and it transports molecules in the correct direction needed for drug delivery. We may be able to tweak the current nanoparticle structure to target transport across those systems,” he said.

Farokhzad has cofounded three companies based on his earlier work with nanoparticles, including FCRN-targeting nanoparticles: **Selecta Biosciences Inc.**, **Blend Therapeutics Inc.** and **Bind Therapeutics Inc.** He said that the IP covering this extension of the technology that more broadly demonstrates proof of concept for the FCRN-binding technology is not yet licensed to any company.

Selecta licensed rights to the earlier targeted nanoparticle technology for vaccine and immunological applications, and Bind licensed the technology for all other indications. Bind is developing Accurins, which are targeted polymeric nanoparticles with prolonged circulation and controlled payload release, for oncology.

Farokhzad said that both companies may be interested in licensing the new IP.

Hrkach said that although Bind Therapeutics is focused on nanoparticles for cancer, which can be delivered intravenously, the company is interested in broadening its scope, and a technological advance such as this is very exciting.

“For Bind, this is a prototype for our technology platform and represents an interesting opportunity as we continue to expand our pipeline,” he said.

Farokhzad said that MIT and Brigham and Women’s Hospital have filed for a patent covering the extension of the FCRN technology. The IP is available for licensing.

Martz, L. *SciBX* 6(48); doi:10.1038/scibx.2013.1371
Published online Dec. 19, 2013

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COMPANIES AND INSTITUTIONS MENTIONED

Althea Technologies Inc., San Diego, Calif.
Bind Therapeutics Inc. (NASDAQ:BIND), Cambridge, Mass.
Blend Therapeutics Inc., Watertown, Mass.
Brigham and Women's Hospital, Boston, Mass.

Brown University, Providence, R.I.
The David H. Koch Institute for Integrative Cancer Research at MIT, Cambridge, Mass.
Emisphere Technologies Inc. (OTCBB:EMIS), Cedar Knolls, N.J.
Goethe University Frankfurt, Frankfurt, Germany
Massachusetts Institute of Technology, Cambridge, Mass.
Midatech Ltd., Abingdon, U.K.
MIT-Harvard Center of Cancer Nanotechnology Excellence, Cambridge, Mass.
Nordic Bioscience A/S, Herlev, Denmark
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Novo Nordisk A/S (CSE:NVO; NYSE:NVO), Bagsvaerd, Denmark
Selecta Biosciences Inc., Watertown, Mass.
The University of Nottingham, Nottingham, U.K.



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Translational tidbits

By C. Simone Fishburn, Senior Editor, Lev Osherovich, Senior Writer, and Kai-Jye Lou, Senior Writer

Consorting with academia

GlaxoSmithKline plc has set up an immuno-oncology consortium that invites academics from six cancer centers to view its nonpublic early pipeline programs and share ideas for new therapeutic candidates.

The Oncology Clinical and Translational Consortium (OCTC) includes the **Gustave Roussy Institute**, **The University of Texas MD Anderson Cancer Center**, the **Memorial Sloan-Kettering Cancer Center**, the **Netherlands Cancer Institute**, the **Princess Margaret Cancer Centre** and the **Vall d'Hebron Institute of Oncology**.

Mining academia for ideas is not new for GSK, as it previously created partnerships through its Center for Excellence for External Drug Discovery, which ran from 2005 to 2012, and it continues scouting for new opportunities via its Discovery Partnerships with Academia group.

The pharma also is putting some molecules in the public domain by contributing compounds and related data from discontinued programs to the therapeutics discovery program run by the **NIH's National Center for Advancing Translational Sciences**.

Now, rather than giving out discontinued compounds or asking academics what they have in their labs, GSK is disclosing its own active, early stage programs and asking academics how they might leverage these with basic research findings to create improved therapeutics.

Axel Hoos, VP of the Immuno-Oncology and Combinations Discovery Performance Unit at GSK, is spearheading the consortium and told *SciBX* that there will be a significant—but not exclusive—focus on cancer immunotherapy combinations.

Hoos said that combination therapies in cancer frequently come about through ad hoc ideas based on what is already available. He expects the consortium will be a better way to have a science-driven approach to combining drugs to improve outcomes.

He said that the goal is for the academic scientists to provide mechanistic expertise on what compounds against specific targets might combine with the GSK pipeline compounds to produce new combinations. Ideas put forward by either GSK or the academics can then spawn new projects that might include either OTCT members or involve partnering with additional companies.

The consortium operates under an umbrella agreement with the participating centers. For each new project a contract will be negotiated with the relevant tech transfer office. Because there is no upfront investment, Hoos said that the OTCT is a low-cost way to increase the flow of ideas and to build the pipeline.

Despite that, Hoos acknowledges that there is some risk of leakage of proprietary GSK data to people outside of the alliance. Nevertheless, he believes the benefits of openness far outweigh those risks.

"You can't spark innovation if you don't share information," he told *SciBX*.

GSK has established several metrics to track the success of the consortium. These include the number of projects started in an undisclosed time frame, the speed at which new projects get started, the efficiency of enrolling patients in clinical trials and the speed of progress of preclinical projects.

The consortium is in a pilot phase. If successful, it could be expanded to include more centers.

GSK's West Coast beachhead

Half a year after GSK and **Avalon Ventures** partnered to launch up to 10 companies from the VC's biotech incubator, the pharma has decided it wants its own feet on the ground to help bring fledgling companies into the GSK fold. GSK now plans to open an R&D outpost in San Diego that will work with Avalon to help shape the nascent companies.

Under the April incubator deal, GSK and Avalon are providing seed funding of up to \$30 million from Avalon and up to \$465 million from the pharma. GSK will have options to acquire assets developed by Avalon's companies.¹

Avalon has a separate 10,000-square-foot facility that hosts five to six early stage companies. That facility and those companies are not part of the GSK deal.

GSK will deploy a team of 5–10 senior business development and discovery science staff to its new West Coast office by year end.

Damien McDevitt, VP of business development and site head of GSK's West Coast R&D satellite, said that the facility's primary mission is to inject pharma perspective into companies in Avalon's new incubator from the get-go.

GSK's team will provide technical knowledge and access to global R&D facilities for fledgling companies, the first of which is celiac disease play **Sitari Pharmaceuticals Corp.**

"As we select the companies and launch them, we will be working to make sure these companies are supported by GSK," said McDevitt. "The new companies will, for example, be starting up assays, so they'll need to work with our scientists to [eventually] transition the projects to GSK."

The GSK team also will manage regional research collaborations and scout new partnering opportunities with West Coast universities.

"GSK has about 20 major collaborations with companies in California. Having someone on the ground will really help us," said McDevitt.

The new office also will help the pharma "keep our finger on the pulse of breakthroughs in medical innovation coming out of the universities all along the West Coast," he added.

GSK is the latest pharma to set up shop in San Diego. Last year, **Johnson & Johnson** opened its Janssen Labs incubator in San Diego.² In J&J's incubator, up to 20 companies share a range of technical and administrative resources with one another and J&J's San Diego R&D facilities.

Unlike in the GSK-Avalon incubator, startups at Janssen Labs are not necessarily bound by equity or IP rights agreements with their pharma host, nor are they required to directly collaborate with J&J.

Public-private partnership roundup

A trio of new consortia secured grant funding from the EU's Framework Programme 7 in November to get their R&D projects going (*see Table 1*, "Selected public-private partnerships for November 2013").

The EPITARGET consortium received €11.9 million (\$16.1 million) to identify biomarkers and treatments for epilepsy; the BIOIMAGE-NMD consortium received €6 million (\$8.1 million) to work on imaging

Table 1. Selected public-private partnerships for November 2013. Public-private partnership activity was almost nonexistent in the U.S. in November, thanks in part to the Thanksgiving holiday, but ex-U.S. translational deals more than picked up the slack.

Source: BioCentury Archives

Companies	Institutions	Business area	Disclosed value	Purpose
Microvitae Technologies; to-BBB technologies B.V.	Academic Medical Center; Aix-Marseille University; Ben-Gurion University of the Negev; Imperial College London; Mario Negri Institute for Pharmacological Research; Hannover Medical School; Nencki Institute of Experimental Biology; University Hospital Bonn; University College London; University of Eastern Finland; University of Ferrara; Lund University; University of Veterinary Medicine, Vienna; European Commission	Neurology	€11.9 million (\$16.1 million)	Five-year EPITARGET consortium to identify biomarkers and develop therapeutics for preventing epileptogenesis and progression of epilepsy
Prosensa Holding N.V. (NASDAQ:RNA); Consultants for Research in Imaging and Spectroscopy; Scito S.A.	Institute of Myology; Catholic University Leuven; Leiden University Medical Center; Newcastle University; University College London; Catholic University of the Sacred Heart; European Commission	Musculoskeletal disease	€6 million (\$8.1 million)	BIOIMAGE-NMD consortium to develop imaging biomarkers for rare neuromuscular diseases, including Duchenne muscular dystrophy (DMD)
Summit Corp. plc (LSE:SUMM)	University of Oxford	Musculoskeletal disease	£3.3 million (\$5.4 million)	Partnership to develop treatments for DMD
ApoCell Inc.	Fraunhofer Institute for Cell Therapy and Immunology	Diagnostics	€4 million (\$5.3 million)	Partnership to develop ApoCell's ApoStream device for detection of circulating tumor cells
AmorChem L.P.	Center University Hospital of Quebec; Laval University	Cancer	Up to C\$2.5 million (\$2.4 million)	Partnership to develop compounds to treat endometriosis and estrogen-dependent cancers, with a focus on preclinical hydroxysteroid 17β dehydrogenase 1 (HSD17B1) inhibitors
BioSpring GmbH; Dr. Reddy's Laboratories Ltd. (NYSE:RDY); InteRNA Technologies B.V.; Quiet Therapeutics Ltd.; Laboratory of Pharmacology and Toxicology GmbH & Co. KG	VU University Medical Center; European Commission	Cancer	€1.2 million (\$1.6 million)	Two-year MiRacle consortium to develop tumor-selective, microRNA-based therapeutics to treat head and neck cancer
arGEN-X B.V.	Université Catholique de Louvain	Cancer	Undisclosed	Partnership to validate the biology of an undisclosed cancer immunomodulation target and develop therapeutic candidates
AstraZeneca plc (LSE:AZN; NYSE:AZN)	Agency for Science, Technology and Research (A*STAR)	Infectious disease	Undisclosed	Partnership to discover treatments for Gram-negative bacterial infections
BioNet-Asia Co. Ltd.; DBV Technologies (Euronext:DBV)	University of Geneva	Infectious disease; drug delivery	Undisclosed	Partnership to develop a booster vaccine against pertussis through Phase I proof of concept
Bionure Farma S.L.	Myelin Repair Foundation	Autoimmune disease	Undisclosed	Partnership to evaluate the neuroprotective capabilities of Bionure's BN201 in promoting myelin repair for multiple sclerosis (MS)
Evotec AG (Xetra:EVT)	Leukemia & Lymphoma Society	Cancer	Undisclosed	Partnership to support one of the society's screen-to-lead cancer programs
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK)	Cancer Research UK; The University of Manchester	Cancer	Undisclosed	Partnership to develop cancer drugs targeting an undisclosed protein involved in epigenetic regulation
HitGen Ltd.	Cancer Research UK; The University of Manchester	Cancer	Undisclosed	Partnership to discover candidates against undisclosed new cancer targets selected by the university

(Continues on p. 7)

Table 1. Selected public-private partnerships for November 2013. (continued)

Companies	Institutions	Business area	Disclosed value	Purpose
ImmunoGenes AG	Public Health England	Infectious disease; diagnostics	Unavailable	Partnership to discover and develop mAbs to detect and treat <i>Clostridium difficile</i> infection
Japan BCG Laboratory Ltd.; Dainippon Sumitomo Pharma Co. Ltd. (Tokyo:4506)	Aeras; National Institute of Biomedical Innovation	Infectious disease	Undisclosed	Partnership to jointly develop mucosal tuberculosis (TB) vaccines based on the institute's human parainfluenza type 2 vector technology
Johnson & Johnson (NYSE:JNJ)	MaRS Innovation	Pharmaceuticals; diagnostics	Undisclosed	Partnership to jointly identify and fund early stage life science technologies from MaRS' 16 member institutions
ModiQuest Research B.V.	Beckman Research Institute of the City of Hope	Antibodies	Undisclosed	Collaboration to use ModiSelect B cell selection technology to generate mAbs against an undisclosed target selected by the institute
Not applicable	MRC Technologies; University of Oxford	Neurology	Undisclosed	Partnership to screen selective and potent potassium channel K2p18.1 (KCNK18; TRESK) activators to develop compounds to treat migraines
Nuevolution A/S	Cancer Research UK	Cancer	Undisclosed	Partnership to use Nuevolution's Chemetics technology to discover small molecules against undisclosed targets to treat cancer
Redx Pharma Ltd.	Royal Liverpool and Broadgreen University Hospitals NHS Trust	Infectious disease	Undisclosed	Partnership to develop drugs to address antibiotic resistance

biomarkers for rare neuromuscular diseases; the MiRacle consortium received €1.2 million (\$1.6 million) to develop microRNA-based treatments for head and neck cancers.

In Canada, **MaRS Innovation** paired up with J&J to jointly identify and fund early stage life science technologies from MaRS' 16 member institutions. In August 2010, MaRS partnered with the J&J Corporate Office of Science and Technology to cofund early stage, Toronto-based life sciences technologies.

Cancer Research Technology Ltd. (CRT), the commercialization arm of **Cancer Research UK**, had a busy November with three new partnerships.

CRT and **Nuevolution A/S** will use the biotech's Chemetics technology to discover small molecules against undisclosed targets to treat cancer.

CRT, GSK and **The University of Manchester** partnered to develop cancer drugs targeting an undisclosed protein involved in epigenetic regulation. CRT and the university also announced a deal with **HitGen Ltd.** to discover candidates against undisclosed new cancer targets selected by the university.

Fishburn, C.S. *et al. SciBX* 6(48); doi:10.1038/scibx.2013.1372
Published online Dec. 19, 2013

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COMPANIES AND INSTITUTIONS MENTIONED

Avalon Ventures, La Jolla, Calif.
Cancer Research Technology Ltd., London, U.K.
Cancer Research UK, London, U.K.
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Gustave Roussy Institute, Villejuif, France
HitGen Ltd., Chengdu, China
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
MaRS Innovation, Toronto, Ontario, Canada
Memorial Sloan-Kettering Cancer Center, New York, N.Y.
National Center for Advancing Translational Sciences, Bethesda, Md.
National Institutes of Health, Bethesda, Md.
Netherlands Cancer Institute, Amsterdam, the Netherlands
Nuevolution A/S, Copenhagen, Denmark
Princess Margaret Cancer Centre, Toronto, Ontario, Canada
Sitari Pharmaceuticals Corp., La Jolla, Calif.
The University of Manchester, Manchester, U.K.
The University of Texas MD Anderson Cancer Center, Houston, Texas
Vall d'Hebron Institute of Oncology, Barcelona, Spain

Lipid kinase enters the malaria stage

By Benjamin Boettner, Associate Editor

A Novartis AG–University of California, San Diego–led consortium has identified a new class of antimalarials that, unlike marketed drugs, eliminates *Plasmodium* at all stages of its infection cycle.¹ The pharma is developing derivatives of the lead inhibitor with improved drug-like properties.

Plasmodium's life cycle consists of several distinct stages. Mosquito-injected sporozoites rapidly populate liver cells, in which they either proliferate and produce merozoites that emerge in the bloodstream or enter a dormant phase as hypnozoites in the liver.

Emerging merozoites can undergo several cycles of asexual multiplication in the blood, resulting in thousands of infected red blood cells and causing malaria symptoms. Merozoites also can develop into sexual-stage gametocytes, which are taken up by mosquitoes and ultimately give rise to a new generation of sporozoites to be injected into the next host.²

Latent hypnozoites, on the other hand, can linger in the liver for long periods of time, causing disease relapse sometimes years after the initial infection when mobilized back into the bloodstream as merozoites.

Thus, eradicating malarial disease requires *Plasmodium* to be targeted at replicating stages in liver and blood, dormant stages in liver and sexual stages in blood.

Marketed drugs offer an either-or proposition. Chloroquine and artemisinin and its derivatives are only effective against the blood stages of the parasite. Marketed artemisinin derivatives include Novartis' Coartem artemether/lumefantrine, ASAQ artesunate/amodiaquine from Sanofi and Eurartesim dihydroartemisinin/piperaquine from Sigma-Tau Group.

Only one marketed drug eliminates liver-stage dormant hypnozoites: the generic 8-aminoquinoline primaquine. Primaquine also has very weak activity against the blood stages of *Plasmodium*, but it causes significant side effects.

Now, a Novartis-UCSD consortium has determined that inhibiting a single *Plasmodium* kinase—*Plasmodium* phosphatidylinositol 4-kinase III β (PI4KIII β)—can interfere with all stages of the *Plasmodium* life cycle.

Using a cell-based screen, the researchers identified a series of imidazopyrazines that were active against drug-sensitive and drug-resistant asexual blood-stage *Plasmodium*.

A lead imidazopyrazine derivative inhibited both the asexual and sexual blood stages of different *P. falciparum* and *P. vivax* strains *in vitro* and in mice. The compound also showed strong activity against liver-specific hypnozoites in models of dormant *Plasmodium* infection.

Based on these results, the team hypothesized that the compound's target was essential to all stages of the parasite's life cycle. Genetic studies revealed that the target was PI4KIII β .

Francisco Javier Gamo Benito told *SciBX* that the target's key role in lipid sorting and signaling “explains the diversity of stages of the

Plasmodium life cycle that are affected by PI4KIII β inhibitors.”

Gamo Benito is director of R&D for alternative discovery and development at GlaxoSmithKline plc's malaria discovery performance unit. GSK markets Malarone atovaquone to inhibit *Plasmodium* pyrimidine synthesis and has the malaria vaccines GSK257049 and PlaMaVax in Phase III and Phase II trials, respectively. The company also has the 8-aminoquinoline tafenoquine (SB 252263) in Phase II testing and the electron transport inhibitor GSK932121 in Phase I trials.

Although *Plasmodium* PI4KIII β shares 43% identity with the human kinase catalytic site, the team's lead compound had 1,000-fold selectivity for *P. falciparum* or *P. vivax* kinases over the human kinase. It also inhibited PI4KIII β with IC₅₀ values in the low nanomolar range.

Results were published in *Nature*. The team was led by the Genomics Institute of the Novartis Research Foundation, the Novartis Institute for Tropical Diseases and UCSD.

According to co-investigator Thierry Diagana, head of the Novartis Institute for Tropical Diseases in Singapore, “imidazopyrazine compounds have a unique spectrum of activities across the *Plasmodium* life cycle. There are no previously reported compounds that can interfere with all stages of the parasite in its host.”

“Our work shows that PI4KIII β would be worthwhile pursuing using target-based drug discovery,” added co-investigator Elizabeth Winzeler, a professor of pediatrics and

director of translational research at the UCSD Health Sciences Center for Immunity, Infection and Inflammation.

“Our work shows that PI4KIII β would be worthwhile pursuing using target-based drug discovery.”

—Elizabeth Winzeler,
University of California, San Diego

The resistance question

Diagana said that Novartis is selecting optimized derivatives of the imidazopyrazine and evaluating oral availability, stability, safety and other properties typically required for an antimalarial drug.

“The real jewel in the crown would be to see how data on hypnozoite relapse actually translate *in vivo*,” said Timothy Wells, CSO at the Medicines for Malaria Venture.

Although it is clear that the next step will be to show efficacy in a nonhuman primate model of malaria, an outstanding issue is the potential for emerging resistance.

“As is the case with other antimalarial drugs, the biggest problem is the rapidity with which that resistance occurs in asexual blood stages. Blood stages outnumber other life cycle stages by far and are where resistance and selection are proceeding the fastest,” said Louis Miller, chief of the malaria cell biology section at NIH's National Institute of Allergy and Infectious Diseases.

Both Diagana and Miller said that it would be important to incorporate any new clinical candidates into combination therapies to reduce the likelihood of resistance emergence.

Novartis has filed for patents covering the chemical matter of imidazopyrazine compounds. The compounds are not available for licensing.

Boettner, B. *SciBX* 6(48); doi:10.1038/scibx.2013.1373
Published online Dec. 19, 2013

(Continues on p. 9)

Balancing act in liver fibrosis

By Michael J. Haas, Senior Writer

CXCR7, one of the few chemokine receptors against which there are virtually no drug development efforts, may be a novel target for liver fibrosis, according to new findings from a U.S. team.¹ The results also pointed to the well-trodden family member CXCR4 in the indication, and the next steps are to figure out whether to deliver systemic or liver-specific modulators of the targets.

Liver fibrosis is the result of aberrant healing processes in response to acute or chronic liver injury. Although liver endothelial cells are capable of triggering liver regeneration following acute injury,²⁻⁴ chronic injury can overactivate endothelial cells, thereby promoting fibrosis instead of regeneration for reasons that are poorly understood.

Because endothelial cells also are involved in organ development during embryogenesis, a U.S. team led by Shahin Rafii hypothesized that liver development and regeneration might share endothelial cell signaling pathways that could be targeted to prevent or treat liver fibrosis.

Rafii is a professor of genetic and regenerative medicine at **Weill Cornell Medical College** and an investigator at the **Howard Hughes Medical Institute**.

The team found clues supporting this hypothesis in published studies. The papers showed that signaling between chemokine CXC motif ligand 12 (Cxcl12; Sdf-1) and its receptors—Cxcr7 (CXC chemokine receptor 7) and Cxcr4 (Npy3r)—on endothelial cells was required for normal embryonic development of the GI tract and heart in mice and might be involved in pathological remodeling of those tissues after injury.⁵⁻⁷

To determine whether the SDF-1 signaling pathway plays a role in liver regeneration and fibrosis, the team began by examining the effects of acute and chronic liver injury on levels of Cxcr7 and Cxcr4 in mouse models.

The team found that acute liver injury increased Cxcr7 levels on

liver endothelial cells compared with no injury but did not affect Cxcr4 levels. Chronic liver injury increased levels of Cxcr7, Cxcr4 and fibroblast growth factor receptor 1 (Fgfr1; Cd331) on liver endothelial cells compared with cells from uninjured controls.

Next, the team looked at mouse models of chronic liver injury that had endothelial cell-specific knockout of Cxcr7, Cxcr4 or Fgfr1. Cxcr7 deficiency decreased levels of inhibitor of DNA binding 1 (Id1)—a transcription factor essential for liver regeneration²—and increased hepatic levels of collagen and other profibrotic factors compared with wild-type expression. Conversely, deficiency in Cxcr4 or Fgfr1 decreased hepatic levels of collagen and other profibrotic factors.

In wild-type mouse models of chronic liver injury, a CXCR7 agonist increased Id1 expression and decreased hepatic levels of profibrotic factors compared with vehicle.

Additional experiments in normal human liver endothelial cell lines showed that stimulation of FGFR1 signaling upregulated CXCR4 and downregulated CXCR7.

Lastly, the team showed that SDF-1 or a CXCR7 agonist upregulated proregenerative ID1 in wild-type human liver endothelial cell culture. SDF-1 did not upregulate ID1 in liver endothelial cells deficient in either CXCR4 or CXCR7—indicating that induction of ID1

requires cooperation between the two receptors, the team wrote in its report in *Nature*.

Seventh heaven

Collectively, the findings show that agonizing CXCR7, or antagonizing CXCR4 or FGFR1, might treat or prevent liver fibrosis, Rafii told *SciBX*. Of the three targets, he said that CXCR7 appears most promising.

In the mouse models “the CXCR7 agonist induced an endothelial cell response that not only prevented fibrosis but also preferentially stimulated regeneration,” said Rafii. “It’s conceivable that specific activation of CXCR7 would induce regeneration of functional liver tissue and cells while avoiding irreversible scar formation” after acute liver injury.

Bi-Sen Ding, first author on the study, said that CXCR4 and FGFR1 were less promising because both proteins are involved in normal wound healing and angiogenesis in many tissues.

(Continues on p. 10)

“The team’s results provide a therapeutic road map to achieve hepatic regeneration without provoking fibrosis following liver injury.”

—Jim Chen,
TCM Biotech International Corp.

(Continued from “Lipid kinase enters the malaria stage,” p. 8)

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COMPANIES AND INSTITUTIONS MENTIONED

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Medicines for Malaria Venture, Geneva, Switzerland
National Institute of Allergy and Infectious Diseases, Bethesda, Md.
National Institutes of Health, Bethesda, Md.
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Novartis Institute for Tropical Diseases, Singapore
Sanofi (Euronext:SAN; NYSE:SNY), Paris, France
Sigma-Tau Group, Pomezia, Italy
University of California, San Diego, La Jolla, Calif.

Moreover, CXCR4 is required to stimulate proregenerative ID1 in liver endothelial cells.

“Inhibiting CXCR4 or FGFR1 might interfere with normal healing and regeneration processes that are required for liver repair,” he said. Ding is an assistant professor of genetic medicine at Weill Cornell.

The team included researchers from **Hofstra University**, **Yale School of Medicine**, **Angiocrine Bioscience Inc.** and **ChemoCentryx Inc.** Angiocrine isolated and cultured the mouse liver endothelial cells, and ChemoCentryx helped design the *Cxcr7* knockout experiments and interpreted the CXCR7 agonist data.

There are no disclosed CXCR7 agonists in development. ChemoCentryx’s CCX650 is the only disclosed CXCR7 antagonist. The small molecule is in preclinical testing to treat brain cancer.

Multiple companies are developing inhibitors of CXCR4 or FGFR1, although none is being tested in liver fibrosis.

Sanofi markets Mozobil plerixafor, a synthetic CXCR4 antagonist, to treat non-Hodgkin’s lymphoma (NHL) and multiple myeloma (MM). The drug also is in Phase I testing to treat acute myelogenous leukemia (AML). At least six other companies have CXCR4 antagonists in preclinical to Phase II testing to treat cancer, cardiovascular diseases, ophthalmic disorders and/or hematological diseases.

At least seven companies have compounds that inhibit FGFR1 in Phase II to Phase III testing to treat hematological malignancies and solid tumors.

“The team’s results provide a therapeutic road map to achieve hepatic regeneration without provoking fibrosis following liver injury,” said Jim Chen, a project manager at **TCM Biotech International Corp.**

TCM’s TCM-808FB is in preclinical development to treat and prevent liver fibrosis. The company has not disclosed the compound’s target or therapeutic modality.

Chen said that the team also showed that activation of CXCR7 and CXCR4 on liver endothelial cells regulated the recruitment of macrophages and inflammatory molecules involved in liver regeneration and fibrosis. “This suggests that the balance between those two processes is not determined solely by the two chemokine receptors,” he said.

Thus, Chen wants to know more about how other immune system and inflammatory factors affect the CXCR7-ID1 and FGFR1-CXCR4 pathways following liver injury.

He also said that it is not yet clear whether systemic or liver-specific delivery of therapies targeting CXCR7 or CXCR4 would be safer and thus preferable.

Rafii and Ding agreed that further work needs to be done to explore

the question of delivery modes but said that their findings already hint at the answer.

“Systemic therapies should work to a certain extent,” Rafii said. “But liver-specific delivery—or even liver endothelial cell-specific delivery—would be the optimal strategy, especially when devising approaches to inhibit CXCR4 or FGFR1,” in order to avoid interfering with their roles in healing and angiogenesis in other organs and tissues.

Alternatively, priming endothelial cells with SDF-1 or a CXCR7 agonist and then transplanting the cells into the liver “would be an ideal cell-based therapeutic strategy to stimulate regeneration without causing fibrosis,” Ding said.

Nevertheless, identifying liver-specific or cell-based therapies for liver fibrosis is not the

team’s top priority. “We first plan to test specific agonists of CXCR7 in the mouse models of liver injury to thoroughly investigate the potential therapeutic value of our findings,” Rafii said.

“In our ongoing work, we also want to delineate the differential functions of CXCR4 in stimulating regeneration and provoking fibrosis,” Ding said. “We hope to identify a specific approach or mechanism that enables proregenerative cooperation between CXCR4 and CXCR7.”

According to Ding, Weill Cornell has filed a patent application covering the findings, and the IP is available for licensing.

Haas, M.J. *SciBX* 6(48); doi:10.1038/scibx.2013.1374
Published online Dec. 19, 2013

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ChemoCentryx Inc. (NASDAQ:CCXI), Mountain View, Calif.
Hofstra University, Hempstead, N.Y.
Howard Hughes Medical Institute, Chevy Chase, Md.
Sanofi (Euronext:SAN; NYSE:SNY), Paris, France
TCM Biotech International Corp. (GreTai-E:4169), Taipei, Taiwan
Weill Cornell Medical College, New York, N.Y.
Yale School of Medicine, New Haven, Conn.

“It’s conceivable that specific activation of CXCR7 would induce regeneration of functional liver tissue and cells while avoiding irreversible scar formation.”

**—Shahin Rafii,
Weill Cornell Medical College**

This week in therapeutics

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

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

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cancer				
Acute myelogenous leukemia (AML)	Toll-like receptor 9 (TLR9); signal transducer and activator of transcription 3 (STAT3)	<p>Mouse studies suggest simultaneously activating TLR9 and inhibiting STAT3 could help treat AML. In a mouse model of AML, a CpG-siRNA conjugate containing a Tlr9-stimulating CpG oligonucleotide and a <i>Stat3</i>-specific siRNA decreased tumor cell burden in blood, bone marrow, spleen and lymph nodes by 70%–80%, whereas a CpG-<i>luciferase</i> siRNA control reduced tumor cell burden by 30%. In the same model, the CpG-siRNA conjugate promoted antitumor immunity by increasing AML-induced CD8⁺ T cell infiltration and activation compared with CpG-<i>luciferase</i> siRNA. Next steps include testing more stable serum nuclease-resistant oligonucleotides in mouse models.</p> <p>SciBX 6(48); doi:10.1038/scibx.2013.1375 Published online Dec. 19, 2013</p>	Patent covering CpG-siRNA conjugates and their application to cancer and other immune-related diseases held by City of Hope; available for licensing	<p>Hossain, D.M.S. <i>et al. Blood</i>; published online Oct. 29, 2013; doi:10.1182/blood-2013-07-517987 Contact: Marcin Kortylewski, Beckman Research Institute at City of Hope, Duarte, Calif. e-mail: mkortylewski@coh.org Contact: Ya-Huei Kuo, same affiliation as above e-mail: ykuo@coh.org</p>
Brain cancer	MicroRNA-17-92 (miR-17-92)	<p>Cell culture and mouse studies suggest inhibiting miR-17-92 could help treat medulloblastoma. In a mouse model of medulloblastoma, miRNAs from the miR-17-92 cluster were overexpressed in medulloblastoma cells but not in normal cerebellum cells. In a mouse xenograft model of medulloblastoma, anti-miR-17 and anti-miR-19, which target miRNAs from the miR-17-92 cluster, decreased tumor proliferation and increased survival compared with saline. Next steps could include determining whether anti-miRNAs cross the blood brain barrier in patients with brain cancer or adopting new delivery strategies such as nanoparticles.</p> <p>SciBX 6(48); doi:10.1038/scibx.2013.1376 Published online Dec. 19, 2013</p>	Patent and licensing status unavailable	<p>Murphy, B.L. <i>et al. Cancer Res.</i>; published online Oct. 21, 2013; doi:10.1158/0008-5472.CAN-13-0927 Contact: Martine F. Roussel, St. Jude Children's Research Hospital, Memphis, Tenn. e-mail: martine.roussel@stjude.org</p>
Breast cancer	Phosphatidylinositol-5-phosphate 4-kinase type II α (PIP4K2A); PIP4K2B	<p>Mouse and cell culture studies suggest inhibiting PIP4K2A and PIP4K2B could help treat p53⁻ breast cancer. In human breast cancer samples, deletion of <i>TP53</i>, which encodes p53, increased <i>PIP4K2B</i> levels compared with no alteration. In cultured <i>TP53</i>-deficient breast cancer cells and mouse xenografts, knockdown of both <i>PIP4K2A</i> and <i>PIP4K2B</i> decreased cancer cell proliferation and tumor formation compared with no alteration. In <i>Tp53</i>-deficient mice, homozygous deletion of <i>Pip4k2a</i> and heterozygous deletion of <i>Pip4k2b</i> decreased tumor formation. Next steps could include studies to understand the relationship between PIP4K2A and PIP4K2B and glucose metabolism in tumors.</p> <p>SciBX 6(48); doi:10.1038/scibx.2013.1377 Published online Dec. 19, 2013</p>	Patent and licensing status unavailable	<p>Emerling, B.M. <i>et al. Cell</i>; published online Nov. 7, 2013; doi:10.1016/j.cell.2013.09.057 Contact: Lewis C. Cantley, Harvard Medical School, Boston, Mass. e-mail: lcantley@med.cornell.edu</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Cancer	c-Ros proto-oncogene 1 receptor tyrosine kinase (ROS1)	<p>Mouse and cell culture studies suggest foretinib could help treat cancers harboring oncogenic ROS1 fusions and point mutations. In multiple cancer cell lines and in a mouse cholangiocarcinoma model expressing an oncogenic Ros1 variant, foretinib suppressed tumor cell proliferation more efficiently than the anaplastic lymphoma kinase (ALK) inhibitor Xalkori crizotinib, which also is known to inhibit ROS1. Cancer cells expressing ROS1-mutant proteins resistant to Xalkori were sensitive to foretinib. Next steps include evaluating foretinib in a clinical trial in patients with lung cancer carrying ROS1 fusions, including patients with crizotinib-resistant tumors. The trial is being designed by GlaxoSmithKline plc in partnership with the Oregon Health & Science University.</p> <p>GSK's foretinib (GSK1363089) is in Phase I/II testing to treat breast, liver, non-small cell lung and renal cancer.</p> <p>Pfizer Inc. markets Xalkori to treat non-small cell lung cancers (NSCLCs) carrying ALK fusions.</p> <p>SciBX 6(48); doi:10.1038/scibx.2013.1378 Published online Dec. 19, 2013</p>	Patent filed by OHSU; licensing details available from OHSU	<p>Davare, M.A. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Nov. 11, 2013; doi:10.1073/pnas.1319583110</p> <p>Contact: Brian J. Druker, Oregon Health & Science University, Portland, Ore. e-mail: drukerb@ohsu.edu</p>
Cancer	K-Ras (KRAS) G12C	<p><i>In vitro</i> and cell culture studies identified a covalent inhibitor of mutant KRAS G12C that could help treat cancer. About 10%–20% of all Ras-driven cancers and about 50% of Ras-driven lung adenocarcinomas carry the KRAS G12C mutation. <i>In silico</i> analyses informed the design of a covalent and selective KRAS G12C inhibitor that stabilized the inactive state of the enzyme. In cultured cells, the compound decreased KRAS G12C activity, activation of downstream signaling pathways and KRAS G12C-driven cell proliferation compared with a control compound. Next steps include improving the cellular activity of the compound with prodrug and bioisosteric replacement strategies.</p> <p>SciBX 6(48); doi:10.1038/scibx.2013.1379 Published online Dec. 19, 2013</p>	Patent and licensing status undisclosed	<p>Lim, S.M. <i>et al. Angew. Chem. Int. Ed.</i>; published online Nov. 20, 2013; doi:10.1002/anie.201307387</p> <p>Contact: Nathanael S. Gray, Dana-Farber Cancer Institute, Boston, Mass. e-mail: nathanael_gray@dfci.harvard.edu</p>
Cancer	Not applicable	<p><i>In vitro</i> and mouse studies suggest combining copper chelators with glycolysis inhibitors could help treat cancer. In a mouse model of pancreatic islet cell carcinoma, 20 μM of copper in drinking water increased tumor volume and number. Treating the mice with a copper chelator decreased tumor volume compared with no chelator and delayed angiogenesis. In the mouse model, the copper chelator decreased ATP production by oxidative phosphorylation, and addition of two different glycolysis inhibitors enhanced the antiproliferative effect. Next steps include testing for synergistic effects with other glycolysis inhibitors.</p> <p>SciBX 6(48); doi:10.1038/scibx.2013.1380 Published online Dec. 19, 2013</p>	Unpatented; unavailable for licensing	<p>Ishida, S. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Nov. 11, 2013; doi:10.1073/pnas.1318431110</p> <p>Contact: Douglas Hanahan, Swiss Federal Institute of Technology Lausanne, Lausanne, Switzerland e-mail: dh@epfl.ch</p>

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cancer	Not applicable	<p>Mouse studies suggest antibiotics could inhibit the potency of DNA-alkylating agents. In healthy or tumor-bearing mice, the generic DNA-alkylating agent cyclophosphamide disrupted gut mucosal integrity and induced commensal bacteria translocation to secondary lymphoid organs, which resulted in polarization of splenic naïve T cells toward an antitumor T helper type 17 (Th17) cell phenotype. In tumor-bearing mice, those receiving cyclophosphamide plus broad-spectrum antibiotics showed less antitumor Th17 cell differentiation and greater tumor volume than mice receiving cyclophosphamide alone. Next steps could include investigating probiotics to establish commensal gut bacteria beneficial for cancer treatments.</p> <p>SciBX 6(48); doi:10.1038/scibx.2013.1381 Published online Dec. 19, 2013</p>	Patent application filed; available for partnering	<p>Viaud, S. <i>et al. Science</i>; published online Nov. 22, 2013; doi:10.1126/science.1240537 Contact: Laurence Zitvogel, Gustave Roussy Institute, Villejuif, France e-mail: laurence.zitvogel@gustaveroussy.fr</p>
Cancer	Smoothened (SMO)	<p>Structural and cell culture studies suggest oxysterol-based inhibitors could help treat cancers driven by hedgehog signaling. SMO is associated with patched 1 (PTCH1) at the plasma membrane and activated by the PTCH1 ligand sonic hedgehog homolog (SHH) or oncogenic mutations in SMO itself. In cells expressing wild-type or an oncogenic mutant version of SMO, oxysterol-based compounds prevented SHH-dependent transcriptional activation. Structural studies showed that oxysterol ligands bound to the protein's extracellular, cysteine-rich domain, suggesting a mode of inhibition distinct from other known inhibitors. Next steps include investigating SARs of the oxysterol-binding site and developing the compounds into more potent inhibitors.</p> <p>Roche's Genentech Inc. unit markets the SMO inhibitor Erivedge vismodegib to treat basal cell carcinoma.</p> <p>At least four other companies have SMO inhibitors in Phase III or earlier testing to treat different cancers.</p> <p>SciBX 6(48); doi:10.1038/scibx.2013.1382 Published online Dec. 19, 2013</p>	Unpatented; licensing status not applicable	<p>Nachtergaele, S. <i>et al. eLife</i>; published online Oct. 29, 2013; doi:10.7554/eLife.01340 Contact: Christian Siebold, University of Oxford, Oxford, U.K. e-mail: christian@strubi.ox.ac.uk Contact: Rajat Rohatgi, Stanford University School of Medicine, Stanford, Calif. e-mail: rrohathgi@stanford.edu</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Chronic myelogenous leukemia (CML)	Parathyroid hormone (PTH)	<p><i>In vitro</i> and mouse studies suggest PTH could help treat CML. In a mouse model of CML-like myeloproliferative neoplasia, overexpression of PTH in the bone marrow microenvironment, which mediates bone turnover, increased survival and decreased leukemia stem cell proliferation, frequency and maintenance compared with normal PTH expression. In contrast, overexpression of PTH in a mouse model of acute myelogenous leukemia (AML) increased tumor growth. In wild-type mice with established CML-like disease, PTH plus Gleevec imatinib increased long-term survival compared with either treatment alone or saline. Next steps could include testing PTH in additional animal models of CML.</p> <p>Eli Lilly and Co. markets Forteo teriparatide, a PTH fragment, to treat osteoporosis.</p> <p>At least seven other companies have therapeutics targeting the PTH receptor in Phase III or earlier testing for various indications.</p> <p>Novartis AG markets the tyrosine kinase inhibitor Gleevec to treat AML, CML and other cancers.</p> <p>SciBX 6(48); doi:10.1038/scibx.2013.1383 Published online Dec. 19, 2013</p>	Patent and licensing status unavailable	<p>Krause, D.S. <i>et al. Nat. Med.</i>; published online Oct. 27, 2013; doi:10.1038/nm.3364</p> <p>Contact: David T. Scadden, Massachusetts General Hospital, Boston, Mass.</p> <p>e-mail: dscadden@mgh.harvard.edu</p>
Colon cancer	Retinoid X receptor- γ (RXRG; RXR γ)	<p><i>In vitro</i> and mouse studies suggest spironolactone or RXRγ agonists could help treat colon cancer. In colon cancer cells, the generic mineralocorticoid receptor antagonist spironolactone increased levels of killer cell lectin-like receptor subfamily K member 1 (KLRK1; CD314; NKG2D) ligands, which led to greater tumor cell lysis by NK cells than vehicle. In mouse xenograft models of colon cancer, spironolactone plus NK cells suppressed tumor growth and metastasis, whereas either treatment alone did not. In culture, genetic depletion of the mineralocorticoid receptor did not alter the effect of spironolactone on tumor cells, but siRNAs targeting RXRγ did block the effects of spironolactone. Next steps include identifying RXRγ agonists or RXRα (RXRA) antagonists.</p> <p>SciBX 6(48); doi:10.1038/scibx.2013.1384 Published online Dec. 19, 2013</p>	Provisional patent application filed; available for licensing	<p>Leung, W.-H. <i>et al. J. Exp. Med.</i>; published online Nov. 4, 2013; doi:10.1084/jem.20122292</p> <p>Contact: Wing Leung, St. Jude Children's Research Hospital, Memphis, Tenn.</p> <p>e-mail: wing_leung@stjude.org</p>
Melanoma	BRAF; MEK; microphthalmia-associated transcription factor (MITF); histone deacetylase (HDAC)	<p>Cell culture and mouse studies suggest combining MEK and HDAC inhibitors could help treat BRAF-mutant melanoma. An overexpression screen of 15,906 open reading frames in a BRAF-mutant melanoma cell line identified resistance mechanisms to small molecule BRAF, MEK or MAPK inhibitors. Hits from the screen, which included the melanocyte developmental regulator MITF, suggested MAPK and cAMP signaling could mediate resistance to these compounds. In a drug-resistant melanoma cell line, an HDAC inhibitor plus a BRAF or MEK inhibitor decreased MITF expression and cell viability compared with a BRAF or MEK inhibitor alone. Next steps could include animal studies of the combination strategy.</p> <p>SciBX 6(48); doi:10.1038/scibx.2013.1385 Published online Dec. 19, 2013</p>	Patent and licensing status unavailable	<p>Johannessen, C.M. <i>et al. Nature</i>; published online Nov. 3, 2013; doi:10.1038/nature12688</p> <p>Contact: Levi A. Garraway, Broad Institute of MIT and Harvard, Cambridge, Mass.</p> <p>e-mail: levi_garraway@dfci.harvard.edu</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Pancreatic cancer	Plectin (PLEC)	<i>In vitro</i> and mouse studies suggest inhibiting PLEC could help treat pancreatic cancer. Compared with human pancreatic epithelial cells, human pancreatic cancer cell lines expressed higher surface levels of PLEC and produced exosomes containing increased levels of PLEC. In the cancer cell lines, <i>PLEC</i> shRNA decreased exosome secretion, proliferation, migration and invasiveness compared with a scrambled control shRNA. In both immunocompromised and immunocompetent mice, injection of a human pancreatic cell line after <i>PLEC</i> shRNA knockdown decreased both pancreatic tumor burden and the number of metastases compared with injection of unmodified cells. Future studies could include identifying antibodies blocking surface PLEC and testing them in mouse models of pancreatic cancer. SciBX 6(48); doi:10.1038/scibx.2013.1386 Published online Dec. 19, 2013	Patent and licensing status unavailable	Shin, S.J. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Nov. 11, 2013; doi:10.1073/pnas.1309720110 Contact: Kimberly A. Kelly, University of Virginia School of Engineering and Applied Science, Charlottesville, Va. e-mail: kak3x@virginia.edu
Cardiovascular disease				
Heart failure	SMT3 suppressor of <i>mif two 3</i> homolog 1 (SUMO1); ATPase Ca ⁺⁺ transporting cardiac muscle slow twitch 2 (ATP2A2; SERCA2A)	Pig studies suggest <i>SUMO1</i> gene therapy could help treat heart failure. Previous work in mouse models of heart failure showed that an adeno-associated viral (AAV) vector expressing mouse <i>Sumo1</i> increased cardiac function compared with an AAV vector expressing GFP. In pig models of heart failure, an AAV serotype 1 (AAV1) vector expressing human <i>SUMO1</i> , human <i>SERCA2A</i> or both all led to similar increases in cardiac function compared with saline control. Ongoing work includes selecting which AAV vector and promoter to advance to IND-enabling toxicology studies. Celladon Corp.'s Mydicar, a recombinant AAV vector bearing <i>SERCA2A</i> , is in Phase II testing to treat heart failure and preclinical testing to treat hypertension. SciBX 6(48); doi:10.1038/scibx.2013.1387 Published online Dec. 19, 2013	Patented by the Icahn School of Medicine at Mount Sinai; unlicensed	Tilemann, L. <i>et al. Sci. Transl. Med.</i> ; published online Nov. 13, 2013; doi:10.1126/scitranslmed.3006487 Contact: Roger J. Hajjar, Icahn School of Medicine at Mount Sinai, New York, N.Y. e-mail: roger.hajjar@mssm.edu Contact: Kiyotake Ishikawa, same affiliation as above e-mail: kiyotake.ishikawa@mssm.edu Contact: Ahyoung Lee, same affiliation as above e-mail: ahyoung.lee@mssm.edu Contact: Lisa Tilemann, same affiliation as above e-mail: lisa.tilemann@googlemail.com
Venous thromboembolism (VTE); thrombosis	Factor Xa; thrombin (factor IIa; F2)	<i>In vitro</i> and rat studies identified a dual factor Xa and thrombin inhibitor that could help treat thrombosis. <i>In vitro</i> , the inhibitor, SAR107375, blocked both factor Xa and thrombin with low nanomolar potency. In a rat model of venous thrombosis, i.v. and oral dosing of SAR107375 had antithrombotic activity. In a rat model of arterial thrombosis, oral dosing of SAR107375 decreased bleeding compared with oral dosing of the factor Xa inhibitor Xarelto rivaroxaban or the thrombin inhibitor Pradaxa dabigatran and had comparable antithrombotic activity. Next steps include further assessing advantages of SAR107375 such as reduced bleeding risks relative to existing anticoagulants. Boehringer Ingelheim GmbH markets the thrombin inhibitor Pradaxa to treat VTE. Bayer AG and Johnson & Johnson market Xarelto to treat deep vein thrombosis (DVT), fibrillation, pulmonary embolism (PE), stroke and VTE. SciBX 6(48); doi:10.1038/scibx.2013.1388 Published online Dec. 19, 2013	Patent application filed covering inhibitor; licensed to an undisclosed Chinese company	Meneyrol, J. <i>et al. J. Med. Chem.</i> ; published online Oct. 31, 2013; doi:10.1021/jm4005835 Contact: Gilbert Lassalle, Sanofi R&D, Toulouse, France e-mail: gilbert.lassalle@sanofi.com

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Endocrine/metabolic disease				
Diabetes	Glucagon receptor (GCGR)	<i>In vitro</i> and mouse studies identified an allosteric GCGR antibody that could help treat type 2 diabetes. <i>In vitro</i> , an allosteric anti-GCGR antibody bound to and inhibited activation of GCGR. In a mouse model of diabetes, the allosteric antibody decreased blood glucose levels compared with no treatment and improved glucose tolerance. Next steps could include testing the antibody in additional diabetes models. Ligand Pharmaceuticals Inc., Isis Pharmaceuticals Inc. and Eli Lilly and Co. have anti-GCGR programs in Phase I or II trials to treat diabetes.	Patent and licensing status unavailable	Mukund, S. <i>et al. J. Biol. Chem.</i> ; published online Nov. 4, 2013; doi:10.1074/jbc.M113.496984 Contact: Bernard B. Allan, Genentech Inc., South San Francisco, Calif. e-mail: allanb2@gene.com Contact: Christopher M. Koth, same affiliation as above e-mail: kothc@gene.com
SciBX 6(48); doi:10.1038/scibx.2013.1389 Published online Dec. 19, 2013				
Obesity; diabetes	Glucagon-like peptide-1 receptor (GLP-1R; GLP1R); glucagon receptor (GCGR); glucose-dependent insulinotropic polypeptide receptor (GIP receptor)	Mouse studies suggest peptides that agonize GLP1R, GCGR and GIP receptor could be used to treat obesity and diabetes. In a mouse model of obesity with diabetes or in mice fed a high-fat diet, a peptide that activated all three receptors decreased plasma glucose levels and increased insulin levels after glucose challenge compared with peptide hormones for individual receptors. In the high-fat diet-fed model, the peptide induced weight loss and decreased overall glucose exposure compared with saline. Next steps could include optimizing the pharmacology of the peptide. At least six companies market agonists for GLP1R and GCGR to treat cardiovascular or endocrine/metabolic disease.	Patent and licensing status unavailable	Gault, V.A. <i>et al. J. Biol. Chem.</i> ; published online Oct. 28, 2013; doi:10.1074/jbc.M113.512046 Contact: Nigel Irwin, University of Ulster, Londonderry, U.K. e-mail: n.irwin@ulster.ac.uk
SciBX 6(48); doi:10.1038/scibx.2013.1390 Published online Dec. 19, 2013				
Hepatic disease				
Liver fibrosis	CXC chemokine receptor 4 (CXCR4; NPY3R); CXCR7	Mouse studies suggest agonizing CXCR7 or inhibiting CXCR4 could help prevent or treat liver fibrosis. In mouse models of chronic liver injury, Cxcr7 deficiency in liver endothelial cells increased hepatic levels of collagen and other profibrotic factors compared with wild-type Cxcr7 expression. In the models, Cxcr4 deficiency or a Cxcr7 agonist decreased hepatic levels of profibrotic factors compared with wild-type Cxcr4 expression or vehicle. Planned work includes further testing of CXCR7 agonists in mouse models of liver injury. Sanofi markets Mozobil plerixafor (AMD3100), a synthetic CXCR4 antagonist, to treat multiple myeloma (MM) and non-Hodgkin's lymphoma (NHL) and has the compound in Phase I testing to treat acute myelogenous leukemia (AML). TaiGen Biotechnology Co. Ltd. has the CXCR4 inhibitor burixafor (TG-0054) in Phase II testing for stem cell transplant in patients with cancer. Biokine Therapeutics Ltd. and BioLineRx Ltd. have the CXCR4 antagonist BL-8040 in Phase II testing to treat AML and Phase I/II trials to treat cancer (<i>see Balancing act in liver fibrosis, page 9</i>).	Patented by Weill Cornell Medical College; unlicensed	Ding, B.-S. <i>et al. Nature</i> ; published online Nov. 20, 2013; doi:10.1038/nature12681 Contact: Shahin Rafii, Weill Cornell Medical College, New York, N.Y. e-mail: rafii@med.cornell.edu
SciBX 6(48); doi:10.1038/scibx.2013.1391 Published online Dec. 19, 2013				

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Infectious disease				
HIV/AIDS	Cleavage and polyadenylation specific factor 6 (CPSF6); cyclophilin A (CYPA; PPIA)	Cell culture studies suggest blocking interaction between HIV capsid protein and host factors CPSF6 or CYPA could help prevent viral replication. In primary human monocyte-derived macrophages, depletion of CPSF6 or mutation to prevent interaction between the capsid and CPSF6 or CYPA blocked HIV-1 replication and triggered innate immune sensors. In the cells, blocking capsid-host factor interaction using cyclosporine or its derivatives suppressed HIV infection. Next steps include understanding the molecular details of the mechanism of action of cyclosporine and its derivatives as well as the mechanism of the antiviral response. SciBX 6(48); doi:10.1038/scibx.2013.1392 Published online Dec. 19, 2013	Patent application filed covering composition of matter of a series of compounds; available for licensing through UCL Business plc Contact: Abigail Watts, UCL Business plc, London, U.K. e-mail: a.watts@uclb.com	Rasaiyaah, J. <i>et al. Nature</i> ; published online Nov. 6, 2013; doi:10.1038/nature12769 Contact: Greg J. Towers, University College London, London, U.K. e-mail: g.towers@ucl.ac.uk Contact: Mahdad Noursadeghi, same affiliation as above e-mail: m.noursadeghi@ucl.ac.uk
Malaria	<i>Plasmodium</i> phosphatidylinositol 4-kinase III β (<i>Plasmodium</i> PI4KIII β)	<i>In vitro</i> and <i>in vivo</i> studies suggest targeting <i>Plasmodium</i> PI4KIII β could help treat malaria. In cell-, mouse- or rhesus macaque-based assays monitoring different stages of the <i>Plasmodium</i> life cycle, optimized imidazopyrazine compounds killed liver stage, asexual blood stage and sexual stage <i>Plasmodium</i> species. Genetic and biochemical analysis showed that the compounds inhibited <i>Plasmodium</i> PI4KIII β but not related human proteins. Next steps include further improving the potency of <i>Plasmodium</i> PI4KIII β inhibitors and testing them in rhesus macaques (<i>see Lipid kinase enters the malaria stage, page 8</i>). SciBX 6(48); doi:10.1038/scibx.2013.1393 Published online Dec. 19, 2013	Patent application filed by Novartis AG covering the compounds; unavailable for licensing	McNamara, C.W. <i>et al. Nature</i> ; published online Nov. 27, 2013; doi:10.1038/nature12782 Contact: Elizabeth A. Winzeler, University of California, San Diego, La Jolla, Calif. e-mail: ewinzeler@ucsd.edu Contact: Thierry T. Diagana, Novartis Institute for Tropical Diseases, Singapore e-mail: thierry.diagana@novartis.com
Neurology				
Amyotrophic lateral sclerosis (ALS)	Fusion (involved in t(12;16) in malignant liposarcoma) (FUS; TLS)	Cell culture studies suggest oligonucleotides that induce <i>FUS</i> exon seven skipping could help prevent the accumulation of mutant <i>FUS</i> protein in ALS motor neurons. <i>FUS</i> is a DNA- and RNA-binding protein that is frequently mutated in patients with ALS and accumulates in the cytoplasm to become neurotoxic. <i>In vitro</i> and in cultured cells, wild-type <i>FUS</i> autoregulated its own expression by binding to exon seven of its own pre-mRNA transcript and promoting exon skipping and pre-mRNA degradation. In cells expressing mutant <i>FUS</i> variants with defective autoregulation, antisense oligonucleotides targeting a flanking splice site in the <i>FUS</i> pre-mRNA restored exon seven skipping. Next steps include optimizing the oligonucleotides. SciBX 6(48); doi:10.1038/scibx.2013.1394 Published online Dec. 19, 2013	Patent and licensing status unavailable	Zhou, Y. <i>et al. PLoS Genet.</i> ; published online Oct. 31, 2013; doi:10.1371/journal.pgen.1003895 Contact: Geoffrey G. Hicks, University of Manitoba, Winnipeg, Manitoba, Canada e-mail: hicksgg@cc.umanitoba.ca

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cognitive dysfunction	NMDAR	<i>In vitro</i> and mouse studies suggest 24(S) hydroxycholesterol (24(S)-HC) could help treat cognitive dysfunction. In screening studies using patch-clamp recordings on mouse hippocampal neurons, 24(S)-HC was selected from a panel of sterol-based compounds as a potent submicromolar potentiator of NMDAR-mediated currents. In mouse hippocampal slices, 24(S)-HC produced long-term potentiation (LTP) from a subthreshold tetanus stimulus and reversed NMDAR antagonist-induced LTP suppression. In behavioral memory tests in mice, a 24(S)-HC analog reversed NMDAR agonist suppression of memory-dependent activity. Next steps are being performed by Sage Therapeutics Inc. and include optimizing 24(S)-HC analogs in models of schizophrenia. SciBX 6(48); doi:10.1038/scibx.2013.1395 Published online Dec. 19, 2013	Patent application filed by Sage Therapeutics; licensing information available from Sage Therapeutics Contact: Jeff Jonas, Sage Therapeutics Inc., Cambridge, Mass. e-mail: jeff@sagerx.com	Paul, S.M. <i>et al. J. Neurosci.</i> ; published online Oct. 30, 2013; doi:10.1523/JNEUROSCI.2619-13.2013 Contact: Steven M. Paul, Weill Cornell Medical College, New York, N.Y. e-mail: smpaulmd@med.cornell.edu
Neurology	Protein phosphatase 2 (PPP2CA; PP2A)	<i>In vitro</i> and mouse studies suggest inhibiting PPP2CA in the brain could help treat Opitz syndrome, an inherited neurological disorder. <i>Midline 1 (MID1)</i> is mutated in the X-linked form of Opitz syndrome and regulates the degradation of PPP2CA. In cultured primary mouse neurons, RNAi targeting <i>Mid1</i> increased abnormal axon growth and levels of Ppp2ca compared with those seen in wild-type neurons, and knockout of <i>Ppp2ca</i> restored normal axon growth. In mice, genetic depletion of <i>Mid1</i> disrupted normal axon growth, and a microRNA targeting <i>Ppp2ca</i> restored growth. Next steps include screening for inhibitors of PPP2CA. SciBX 6(48); doi:10.1038/scibx.2013.1396 Published online Dec. 19, 2013	Findings unpatented; unavailable for licensing	Lu, T. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Nov. 5, 2013; doi:10.1073/pnas.1303687110 Contact: Zhi Xiong, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai, China e-mail: xiongzhqi@ion.ac.cn Contact: Renchao Chen, same affiliation as above e-mail: rcchen@ion.ac.cn
Stroke	Histone deacetylase 6 (HDAC6)	Studies in mice suggest HDAC6 inhibitors could be useful for treating ischemic stroke. In a mouse model of ischemic stroke, a selective HDAC6 inhibitor increased expression of regulatory T cell markers and decreased infarct size compared with vehicle. Next steps could include testing HDAC6 inhibitors in other preclinical stroke models. Celgene Corp. and Acetylon Pharmaceuticals Inc. have the HDAC6 inhibitor ACY-1215 in Phase I/II testing to treat multiple myeloma (MM). Karus Therapeutics Ltd. has HDAC6 inhibitors in preclinical development to treat cancer and inflammation. SciBX 6(48); doi:10.1038/scibx.2013.1397 Published online Dec. 19, 2013	Patent and licensing status undisclosed	Liesz, A. <i>et al. J. Neurosci.</i> ; published online Oct. 30, 2013; doi:10.1523/JNEUROSCI.4901-12.2013 Contact: Roland Veltkamp, Heidelberg University, Heidelberg, Germany e-mail: roland.veltkamp@med.uni-heidelberg.de
Stroke	Transient receptor potential cation channel subfamily M member 2 (TRPM2); NMDA receptor NR2A subtype (GRIN2A; NR2A); GRIN2B (NR2B)	Mouse studies suggest inhibiting TRPM2 could help prevent ischemic damage to neurons. In a mouse model of stroke, <i>Trpm2</i> knockout mice showed decreases in the degree of cerebral ischemia compared with unaltered mice. In mouse hippocampal slices and extracts, <i>Trpm2</i> knockout increased the ratio of GRIN2A to GRIN2B subunits of synaptic NMDARs and increased levels of GRIN2A-mediated prosurvival signaling proteins compared with no alteration. Next steps could include testing TRPM2 inhibitors in preclinical models of stroke. SciBX 6(48); doi:10.1038/scibx.2013.1398 Published online Dec. 19, 2013	Patent and licensing status unavailable	Alim, I. <i>et al. J. Neurosci.</i> ; published online Oct. 30, 2013; doi:10.1523/JNEUROSCI.1729-13.2013 Contact: Michael Tymianski, Toronto Western Hospital, Toronto, Ontario, Canada e-mail: mike.tymianski@uhn.ca

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Renal disease				
Renal damage	Transient receptor potential cation channel subfamily C member 5 (TRPC5)	<i>In vitro</i> and mouse studies suggest inhibiting the calcium channel TRPC5 could help treat proteinuria. In mice, knockout or inhibition of <i>Trpc5</i> protected against both lipopolysaccharide (LPS)-induced albuminuria and protamine sulfate-induced kidney filter barrier disruption. In cultured podocytes, a TRPC5 inhibitor prevented protamine sulfate-induced increases in intracellular calcium and cytoskeletal dysregulation associated with breakdown of the filter barrier. Next steps include optimizing a TRPC5 inhibitor for clinical use. SciBX 6(48); doi:10.1038/scibx.2013.1399 Published online Dec. 19, 2013	Patent status undisclosed; available for licensing	Schaldecker, T. <i>et al. J. Clin. Invest.</i> ; published online Nov. 15, 2013; doi:10.1172/JCI71165 Contact: Anna Greka, Massachusetts General Hospital, Charlestown, Mass. e-mail: greka.anna@mgh.harvard.edu
Various				
Cancer; thrombosis	c-Mer proto-oncogene tyrosine kinase (MERTK)	<i>In vitro</i> studies suggest a new class of MERTK inhibitors could help treat cancer or thrombosis. Chemical synthesis, SAR and <i>in vitro</i> testing of pyridinepyrimidine analogs identified several compounds as selective, low nanomolar inhibitors of MERTK. In different blood and solid cancer cell lines, one lead compound inhibited MERTK phosphorylation and cellular proliferation at low nanomolar IC ₅₀ values. In <i>ex vivo</i> , platelet-rich human plasma, another lead compound decreased platelet aggregation compared with vehicle. Ongoing work includes optimizing the compounds and testing them in animal models of cancer and thrombosis. SciBX 6(48); doi:10.1038/scibx.2013.1400 Published online Dec. 19, 2013	Patented by The University of North Carolina; licensed to Meryx Inc.	Zhang, W. <i>et al. J. Med. Chem.</i> ; published online Nov. 6, 2013; doi:10.1021/jm401387j Zhang, W. <i>et al. J. Med. Chem.</i> ; published online Nov. 12, 2013; doi:10.1021/jm4013888 Contact: Xiaodong Wang, The University of North Carolina at Chapel Hill, Chapel Hill, N.C. e-mail: xiaodonw@unc.edu
Hypertension; renal disease	Uromodulin (UMOD; THP); solute carrier family 12 potassium-chloride transporter member 1 (SLC12A1; NKCC2)	<i>In vitro</i> and mouse studies suggest inhibiting UMOD could help treat hypertension and chronic kidney disease. In nephrectomy samples from patients homozygous for a <i>UMOD</i> promoter region risk allele that is associated with hypertension and chronic kidney disease risk, <i>UMOD</i> expression was twofold higher than that in samples from patients homozygous for a protective allele. In mice, transgenic overexpression of <i>Umod</i> caused salt-sensitive hypertension and renal damage and increased activity of the <i>Nkcc2</i> sodium transporter compared with wild-type <i>Umod</i> expression. In the mice, an NKCC2 inhibitor decreased blood pressure compared with no treatment. Next steps could include developing UMOD inhibitors. SciBX 6(48); doi:10.1038/scibx.2013.1401 Published online Dec. 19, 2013	Patent and licensing status unavailable	Trudu, M. <i>et al. Nat. Med.</i> ; published online Nov. 3, 2013; doi:10.1038/nm.3384 Contact: Luca Rampoldi, San Raffaele Scientific Institute, Milan, Italy e-mail: rampoldi.luca@hsr.it Contact: Olivier Devuyst, University of Zurich, Zurich, Switzerland e-mail: olivier.devuyst@uzh.ch
Obesity; neurology	Diacylglycerol lipase- α (DAGLA)	<i>In vitro</i> studies identified a selective inhibitor of DAGLA that could help treat obesity or neurodegenerative diseases. <i>In silico</i> modeling aided design of a tetrahydrolipstatin-based inhibitor of DAGLA that inhibited the enzyme with nanomolar potency and was selective over other serine hydrolases <i>in vitro</i> . In cultured human neuroblastoma cells, the inhibitor decreased DAGLA activity compared with vehicle. Ongoing studies include improving potency and selectivity of the inhibitor and showing safety and activity in animals. SciBX 6(48); doi:10.1038/scibx.2013.1402 Published online Dec. 19, 2013	Findings unpatented; not yet available for licensing	Baggelaar, M.P. <i>et al. Angew. Chem. Int. Ed.</i> ; published online Oct. 31, 2013; doi:10.1002/anie.201306295 Contact: Mario van der Stelt, Leiden University, Leiden, the Netherlands e-mail: m.van.der.stelt@chem.leidenuniv.nl

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			
Monitoring cell-free DNA in plasma to predict organ transplant rejection	<p>Cell-free DNA in plasma could be used to quantify viral load and predict risk of transplant rejection. In plasma obtained from patients that received heart or lung transplants, cell-free DNA was sequenced to identify changes in virus populations and quantify viral load. The data were analyzed to find correlations between antiviral and immunosuppressant regimes, viral load and risk of organ rejection. Decreased burden of anellovirus post-transplantation correlated with increased organ rejection, which was thought to reflect an increased level of patient immunocompetence. Next steps include using the method in larger patient cohorts and patients undergoing organ transplants other than heart and lung.</p> <p>ViraCor-IBT Laboratories Inc. markets ImmuKnow, an immune cell function assay that detects cell-mediated immune response in patients undergoing immunosuppressive therapy for organ transplant.</p> <p>SciBX 6(48); doi:10.1038/scibx.2013.1403 Published online Dec. 19, 2013</p>	Patent and licensing status undisclosed	<p>De Vlaminc, I. <i>et al. Cell</i>; published online Nov. 21, 2013; doi:10.1016/j.cell.2013.10.034</p> <p>Contact: Stephen R. Quake, Stanford University, Stanford, Calif. e-mail: quake@stanford.edu</p>
Chemistry			
Modifications to the siRNA guide strand 5' end that improve therapeutic potency	<p>Structure-guided computational screening identified modifications to the guide strand that could improve the therapeutic properties of siRNA therapeutics. Computational analysis of the structure of the siRNA guide strand in complex with argonaute RISC catalytic component 2 (AGO2) showed that incorporation of triazole derivatives into the siRNA guide strand enhanced binding to AGO2. In a human cell line, siRNA that incorporated triazole-based nucleotides into the guide strand 5' end had greater potency than unmodified siRNA with similar stability. Next steps include testing the modifications in therapeutically relevant siRNAs.</p> <p>SciBX 6(48); doi:10.1038/scibx.2013.1404 Published online Dec. 19, 2013</p>	Unpatented; licensing status not applicable	<p>Onizuka, K. <i>et al. J. Am. Chem. Soc.</i>; published online Oct. 23, 2013; doi:10.1021/ja4079754</p> <p>Contact: Peter A. Beal, University of California, Davis, Calif. e-mail: pabeal@ucdavis.edu</p> <p>Contact: Dean J. Tantillo, same affiliation as above e-mail: djtantillo@ucdavis.edu</p>
Disease models			
<i>Pten</i> (<i>Mmac1; Tep1</i>)-mutant mouse model of autism	<p>Mice with a heterozygous, autism-linked <i>Pten</i> deletion could be used to screen therapeutics for autism spectrum disorder. Brain slices from heterozygous <i>Pten</i> knockouts had higher levels of potassium channel KCa2.2 (Kcnn2) and had lower excitatory response after electrical and pharmacological stimulation than brain slices from wild-type controls. Next steps could include testing the effect of KCNN2 antagonists on neuronal excitability.</p> <p>Acesion Pharma ApS has inhibitors of KCNN2 and other small conductance calcium-activated potassium channels in discovery stage development to treat atrial fibrillation (AF).</p> <p>SciBX 6(48); doi:10.1038/scibx.2013.1405 Published online Dec. 19, 2013</p>	Patent and licensing status undisclosed	<p>Garcia-Junco-Clemente, P. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Oct. 21, 2013; doi:10.1073/pnas.1309207110</p> <p>Contact: Peyman Golshani, University of California, Los Angeles David Geffen School of Medicine, Los Angeles, Calif. e-mail: pgolshani@mednet.ucla.edu</p>

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Drug delivery			
Fc fragment of IgG receptor transporter- α (FCGRT; FCRN)-targeted nanoparticles for oral nanoparticle delivery	<i>In vitro</i> and mouse studies suggest FCRN-targeted nanoparticles could be used for oral drug delivery. Polylactic acid (PLA)-polyethylene glycol (PEG) nanoparticles with an IgG Fc fragment conjugated to the PEG shell had increased transport across a human epithelial colorectal adenocarcinoma monolayer and across the intestinal epithelium in mice compared with untargeted controls. In fasted mice, oral FcRn-targeted nanoparticles encapsulating insulin caused a hypoglycemic response that lasted longer than injection of free insulin, whereas oral delivery of untargeted nanoparticles had no effect. Next steps include testing whether the nanoparticle platform can be used for delivery across other biological barriers (see Oral nanoparticles, page 1). SciBX 6(48); doi:10.1038/scibx.2013.1406 Published online Dec. 19, 2013	Patent application filed; available for licensing	Pridgen, E.M. <i>et al. Sci. Transl. Med.</i> ; published online Nov. 27, 2013; doi:10.1126/scitranslmed.3007049 Contact: Omid C. Farokhzad, Brigham and Women's Hospital, Boston, Mass. e-mail: ofarokhzad@zeus.bwh.harvard.edu Contact: Frank Alexis, Harvard Medical School, Boston, Mass. e-mail: falexis@clemson.edu Contact: Rohit Karnik, Massachusetts Institute of Technology, Cambridge, Mass. e-mail: karnik@mit.edu
Drug platforms			
Lin-28 homolog A (LIN28A)-dependent metabolic reprogramming for tissue repair	Mouse studies suggest elevating LIN28A activity could help promote tissue regeneration after injury or in advanced age. In tissue injury assays in mice, Lin28a overexpression promoted regrowth of shaved hair and regeneration of amputated digits and complex tissues. The regenerative effects of Lin28a depended on repression of microRNA <i>let-7</i> (<i>Mirlet7</i> ; <i>Let-7</i>) and enhanced translation of Lin28a-bound mRNAs encoding key enzymes for glycolysis and oxidative phosphorylation. In shaved, Lin28a-overexpressing mice, pharmacological inhibition of glycolysis and oxidative phosphorylation suppressed hair regrowth. Next steps could include identifying stimulators of Lin28 activity in regenerating tissues. SciBX 6(48); doi:10.1038/scibx.2013.1407 Published online Dec. 19, 2013	Patent and licensing status unavailable	Shyh-Chang, N. <i>et al. Cell</i> ; published online Nov. 7, 2013; doi:10.1016/j.cell.2013.09.059 Contact: George Q. Daley, Boston Children's Hospital and Dana-Farber Cancer Institute, Boston, Mass. e-mail: george.daley@childrens.harvard.edu
Olfactory ensheathing cells (OECs) to increase myelination	Cell culture studies suggest OECs might make better transplant cells for spinal injury repair than Schwann cells. In cocultures of an astrocyte monolayer and a mixed embryonic spinal cord cell suspension, OECs increased levels of myelination compared with Schwann cells, which decreased levels of myelination. In the cocultures, media conditioned by Schwann cells also decreased levels of myelination compared with no treatment, which could be reversed with an antibody targeting connective tissue growth factor (CTGF). Next steps include identifying mechanisms that could confer OEC properties on Schwann cells. SciBX 6(48); doi:10.1038/scibx.2013.1408 Published online Dec. 19, 2013	Unpatented; licensing status not applicable	Lamond, R. & Barnett, S.C. <i>J. Neurosci.</i> ; published online Nov. 20, 2013; doi:10.1523/JNEUROSCI.3233-13.2013 Contact: Susan C. Barnett, University of Glasgow, Glasgow, U.K. e-mail: susan.barnett@glasgow.ac.uk
Spherical nucleic acid (SNA) nanoparticle conjugates to knock down oncogene expression	Systemic delivery of SNAs conjugated to siRNAs could be used to treat glioma. SNAs consist of gold nanoparticles covalently modified with densely packed, oriented siRNA duplexes. In cultured human glioma cell lines and patient- and mouse-derived neurospheres, SNAs conjugated to siRNAs targeting <i>BCL2-like 12</i> (<i>BCL2L12</i>) decreased expression of BCL2L12 compared with SNAs conjugated to scrambled siRNAs. In mouse models of human glioma, i.v. injection of the SNAs led to their accumulation in tumor but not normal tissue, and SNAs conjugated to siRNAs targeting <i>BCL2L12</i> decreased expression of BCL2L12 protein and RNA, decreased tumor burden and increased survival compared with control SNAs. Next steps could include elucidating the mechanism of SNA uptake into glioma cells and tumors or using SNA-based systemic delivery of siRNAs to study glioma. SciBX 6(48); doi:10.1038/scibx.2013.1409 Published online Dec. 19, 2013	Patent and licensing status unavailable	Jensen, S.A. <i>et al. Sci. Transl. Med.</i> ; published online Oct. 30, 2013; doi:10.1126/scitranslmed.3006839 Contact: Alexander H. Stegh, Northwestern University, Chicago, Ill. e-mail: a-stegh@northwestern.edu Contact: Chad A. Mirkin, same affiliation as above e-mail: chadnano@northwestern.edu

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Staurosporine analogs (staralogs) with improved selectivity toward analog-sensitive kinases	Staralogs could expand approaches to study kinase function using analog-sensitive kinase variants. Kinase variants with genetically engineered sensitivity to ATP analogs have been used in functional studies, but in some cases the ATP analogs also inhibit wild-type and unrelated kinases. In cultured cells, staralogs inhibited analog-sensitive variants of EPH receptor A4 (EPHA4), pyruvate dehydrogenase kinase 1 (PDK1) and ret proto-oncogene (RET) kinases but not their wild-type counterparts. Next steps include developing staurosporine analogs and analog-sensitive kinases for use in animal studies. SciBX 6(48); doi:10.1038/scibx.2013.1410 Published online Dec. 19, 2013	Patented; licensing status unavailable	Lopez, M.S. <i>et al. J. Am. Chem. Soc.</i> ; published online Oct. 30, 2013; doi:10.1021/ja408704u Contact: Kevan M. Shokat, University of California, San Francisco, Calif. e-mail: kevan.shokat@ucsf.edu
Markers			
Using innate immune markers to detect early stage tumor recurrence	Mouse studies suggest markers of the innate immune response could help detect early tumor recurrence. In a mouse melanoma model in which T cell therapy was used to eradicate tumors, cytokine analysis of skin samples showed Il-6 and Vegf were elevated specifically at the time when latent tumor cells initiated tumor recurrence but not prior to recurrence or after the formation of larger tumors. In mice with different primary tumors, VEGF treatment induced early recurrence of tumors from latent tumor cells that had not yet acquired resistance, and these recurrent tumors were sensitive to therapy. Next steps include developing a blood or urine test to detect early immune markers of recurrence. SciBX 6(48); doi:10.1038/scibx.2013.1411 Published online Dec. 19, 2013	Patented; available for licensing	Kottke, T. <i>et al. Nat. Med.</i> ; published online Nov. 17, 2013; doi:10.1038/nm.3397 Contact: Richard Vile, Mayo Clinic, Rochester, Minn. e-mail: vile.richard@mayo.edu

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