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ALS antisense oligonucleotides

By Lauren Martz, Staff Writer

Isis Pharmaceuticals Inc. has teamed up with a trio of academic groups to develop antisense therapeutics for the largest subset of patients with amyotrophic lateral sclerosis,¹⁻³ and all three teams have converged on a common mechanism of neurotoxicity caused by carrying hexanucleotide repeat expansions in the *C9orf72* gene. Antisense oligonucleotides targeting the repeats decreased the toxicity *in vitro*. The teams now need to determine whether the reduced toxicity correlates with decreased neurodegeneration in patients.

Amyotrophic lateral sclerosis (ALS) is a neurological disorder that involves muscle wasting, stiffness and spasticity due to loss of motor neurons. ALS often overlaps with frontotemporal lobar dementia (FTLD), a disease that involves neuronal degeneration in the frontal and temporal cortices.

Both diseases can occur as inherited familial disorders or sporadically with no known familial link.

The GGGGCC repeat expansion in the first intron of *C9orf72* (chromosome 9 open reading frame 72) is the most common genetic cause of ALS.^{4,5} It has been identified in more than 40% of familial ALS and FTLD cases and in at least 8% of sporadic cases.

Nevertheless, the mechanistic link between the expansion and neuronal toxicity remained a mystery.

To identify the root causes of neurotoxicity in *C9orf72* ALS and FTLD, Isis teamed up with three academic teams.

"Each lab is doing unique experiments, and we were fortunate that the results from the different labs triangulated. We have consistently seen that the antisense oligonucleotides reverse RNA foci formation and reverse the transcriptional problems seen in ALS," said C. Frank Bennett, SVP of research at Isis.

RNA foci are long RNA repeat expansions that have folded into stable structures. The foci sequester RNA-binding proteins required for normal cellular transcription and splicing. The result is disruption in normal gene expression and protein function.

"Each lab is doing unique experiments, and we were fortunate that the results from the different labs triangulated. We have consistently seen that the antisense oligonucleotides reverse RNA foci formation and reverse the transcriptional problems seen in ALS."

**—C. Frank Bennett,
Isis Pharmaceuticals Inc.**

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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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In a paper published in *Science Translational Medicine*, Robert Baloh and colleagues reported that RNA foci form in cells from patients with *C9orf72* ALS and that blocking the hexanucleotide repeats with antisense oligos decreased foci formation.

Baloh is director of neuromuscular medicine in the Department of Neurology and director of the ALS program at the Cedars-Sinai Medical Center. His team also included researchers from the University of California, Los Angeles, the Mayo Clinic, the University of California, San Diego, the Washington University in St. Louis School of Medicine and Isis.

The team studied motor neurons derived from ALS patient induced pluripotent stem (iPS) cells carrying the *C9orf72* hexanucleotide repeat expansions and found signs of RNA toxicity including RNA foci formation in the neurons.

The foci often colocalized with RNA-binding proteins including heterogeneous nuclear ribonucleoprotein A1 (HNRNPA1) and purine-rich element binding protein A (PURA). This colocalization altered expression of genes involved in cellular processes including cell adhesion, synaptic transmission and neuronal differentiation.

The patient-derived cells also had decreased electrical excitability when depolarized compared with cells from healthy controls.

The Cedars-Sinai group treated the patient-derived neurons with antisense oligos targeting either the *C9orf72* gene in general or the repeat region specifically. Both approaches prevented foci formation and partially corrected gene expression, and they increased electrical excitability compared with scrambled antisense oligos.

In a separate study published in *Neuron*, Jeffrey Rothstein, Rita Sattler and colleagues studied the effects of the repeat expansion using neurons derived from iPS cells from patients with *C9orf72* ALS as well as postmortem patient brain tissue.

Rothstein is director for the Brain Science Institute, a professor of neurology and neuroscience and director of the Robert Packard Center for ALS Research at The Johns Hopkins University School of Medicine. Sattler is an assistant professor in the Department of Neurology and a principal scientist in the NeuroTranslational Drug Discovery Program at the Johns Hopkins University School of Medicine.

The paper also included researchers from the University of Helsinki, the Mayo Clinic, the National Institute on Aging and Isis.

The Johns Hopkins team also found the presence of nuclear RNA foci. The foci colocalized with a different RNA-binding protein—adenosine deaminase RNA-specific B2 (ADARB2)—and the binding and sequestering of ADARB2 altered gene expression profiles in both the patient-derived iPS cells and the postmortem tissues.

The group also found that glutamate-induced excitotoxicity, a feature of ALS, was enhanced in the cells from patients but not in cells from healthy controls. In iPS cell-derived neurons from healthy controls, knockout of ADARB2 also elevated glutamate-induced excitotoxicity. These studies suggest that the sequestering of RNA-binding proteins by repeat-containing foci contributes to the toxic phenotype in patients with ALS.

In patient-derived neurons, antisense oligos targeting the repeat region decreased RNA foci formation and glutamate-induced toxicity compared with scrambled control antisense oligos and corrected dysregulated gene expression.

Finally, a team led by Don Cleveland and John Ravits at UCSD confirmed that RNA foci-mediated neurotoxicity occurred in cells from patients with *C9orf72* ALS.

Cleveland is chair of cellular and molecular medicine, a professor of medicine and of neurosciences and a member of the **Ludwig Institute for Cancer Research Ltd.** at UCSD. Ravits is a professor of clinical neuroscience at UCSD. The team also included researchers from the Cedars-Sinai Medical Center, the Washington University in St. Louis School of Medicine and Isis.

The foci were absent in tissues from patients with ALS who did not carry the expansions and from non-ALS controls.

In mice, intracerebroventricular injection of a mouse-specific antisense oligo was well tolerated and did not induce significant off-target changes in gene expression.

“Our next steps include screening for the best antisense molecules to take into the clinic to test for safety and efficacy. Once they are identified, we will perform the appropriate toxicology studies,” said Bennett.

Modeling efficacy

Bryan Traynor, investigator and chief of the neuromuscular disease research unit at the National Institute of Aging and an author on the *Neuron* paper, told *SciBX*, “It has just been two years since the *C9orf72* gene was published. We have been able to develop the oligonucleotides so quickly that the animal models for this genetic form of the disease do not exist yet.”

Mouse models for ALS are limited to *superoxide dismutase 1 (Sod1)*-mutant animals. *SOD1* mutations are the second most common cause of ALS and were first identified 10 years ago.^{6,7}

Bennett told *SciBX* that “it doesn’t make sense to test our antisense oligonucleotides in that model because we are dealing with a different genetic cause and different disease pathology. We need an animal model driven by this gene mutation. If one is identified, we will certainly test our molecules in it.”

Philip Van Damme, an associate professor of medicine in the laboratory for neurobiology at the **Catholic University Leuven**, added, “We are now confronted with a potential molecular therapy, but no animal disease models to test these therapies are available yet. It is thus unclear at present how the observations *in vitro* including reduced RNA foci, reduced toxicity and mitigation of transcriptional changes induced by repeat expansion will relate to neurodegeneration in patients.”

Frank Sieg, CSO of **CuroNZ Ltd.**, agreed that it would be worthwhile to develop an animal model “mimicking the *C9orf72* hexanucleotide repeat situation.”

CuroNZ’s NRP2945, a neural regeneration peptide, is in preclinical testing for severe, progressive multiple sclerosis (MS). The company said

that the peptide also enhances survival in a mouse model of *Sod1*-mutant ALS.

Traynor noted that it will likely take another few years to design suitable animal models for *C9orf72* ALS, but both he and Van Damme said that should not stop toxicity testing in animals and efficacy testing in iPSC cells.

Bennett said that Isis has a broad patent estate and actively files patents to cover all preclinical work. The company has filed for patents covering the *C9orf72* antisense molecules. In September, **Biogen Idec Inc.** received access to Isis’ antisense technology for neurological indications. The companies are not disclosing the specific projects.

Martz, L. *SciBX* 6(43); doi:10.1038/scibx.2013.1210
Published online Nov. 7, 2013

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COMPANIES AND INSTITUTIONS MENTIONED

Biogen Idec Inc. (NASDAQ:BIIB), Weston, Mass.
Catholic University Leuven, Leuven, Belgium
Cedars-Sinai Medical Center, Los Angeles, Calif.
CuroNZ Ltd., Auckland, New Zealand
Isis Pharmaceuticals Inc. (NASDAQ:ISIS), Carlsbad, Calif.
The Johns Hopkins University School of Medicine, Baltimore, Md.
Ludwig Institute for Cancer Research Ltd., La Jolla, Calif.
Mayo Clinic, Jacksonville, Fla.
National Institute on Aging, Bethesda, Md.
University of California, Los Angeles, Calif.
University of California, San Diego, La Jolla, Calif.
University of Helsinki, Helsinki, Finland
Washington University in St. Louis School of Medicine, St. Louis, Mo.

Translational tidbits

By Kai-Jye Lou & Lev Osherovich, Senior Writers

The **Cancer Prevention & Research Institute of Texas** is back in the grant-making business after a legislated time-out to rebuild its executive leadership and sort out perceived transparency problems.

Last week, Texas Gov. Rick Perry lifted an 11-month moratorium on the distribution of grants previously approved by the agency.

The Cancer Prevention & Research Institute of Texas (CPRIT), which distributes taxpayer money to Texas-based academic and industry cancer researchers, ran into problems last year when CSO Alfred Gilman accused the institute's executive leadership of tampering with the scientific peer review of grant proposals.¹

Gilman, an emeritus professor of pharmacology at **The University of Texas Southwestern Medical Center**, resigned in October 2012. His departure led to mass resignations of CPRIT's scientific staff and a political brouhaha that ultimately cost CPRIT executive director William Gimson his job.

Last December, Perry and state legislators froze CPRIT's grant-giving authority until the agency created a new plan for vetting grant proposals. In June, the Texas legislature passed Senate Bill 149 (SB149), which dictates tighter terms for the composition of CPRIT's politically appointed oversight committee, and ordered the institute to tighten up its conflict-of-interest procedures.

Since then, CPRIT has appointed a new oversight committee, strengthened the role of scientifically qualified grant reviewers and clarified how it will report conflicts of interest. CPRIT also re-reviewed 118 grants awarded in FY12 and FY13 that had been frozen under the moratorium to make sure they conformed to its tighter ethical and scientific standards.

Perry's letter, co-signed by Lt. Gov. David Dewhurst and Speaker of the House Joe Strauss, noted that CPRIT has made good progress toward the reforms laid out in SB149 and ordered release of the frozen moneys even though not all of SB149's requirements have yet been met.

CPRIT spokeswoman Laura Kunz said that it is not yet clear when the grant recipients will receive their money.

Kunz said that the unfrozen funds include one of three grants flagged by state auditors earlier this year as having been improperly vetted. That grant, for \$11 million to **Peloton Therapeutics Inc.**, passed muster upon re-review.

The two grants that will not be funded are \$20 million to the Houston-Area Translational Research Consortium (HATRC), which is a biotech incubator at **Rice University** and **The University of Texas MD Anderson Cancer Center's** Institute for Applied Cancer Science, and a separate \$25.2 million grant primarily to MD Anderson for a now shuttered clinical trials consortium, the Statewide Clinical Trials Network of Texas (CTNet).

In a public meeting last week, the institute's new oversight committee endorsed promoting interim executive director Wayne Roberts to permanent executive director. Roberts must now formally apply for the job.

GSK discovers winners

GlaxoSmithKline plc announced the winners of its Discovery Fast Track contest, a program that aims to connect North American academics with

collaborators at the pharma to test drug discovery hypotheses.

The 8 academic teams, selected from 142 proposals, will work with GSK scientists to conduct preliminary drug screens in a range of therapeutic areas, although the majority of winning proposals focus on infectious disease.

Sarah Ades, an associate professor of biochemistry and molecular biology at **Pennsylvania State University**, will search for antimicrobial agents for Gram-negative bacteria. Rahul Kohli, an assistant professor of medicine and of biochemistry and biophysics at the **University of Pennsylvania**, will test a hypothesis for designing antibiotics to overcome drug resistance.

Myles Akabas, a professor of physiology and biophysics at the **Albert Einstein College of Medicine of Yeshiva University**, will screen for a new class of malaria therapeutics. A joint team led by **Boston University** research assistant professor Lauren Brown, Boston University associate professor of chemistry Scott Schaus and **University of California, San Francisco** pathology professor James McKerrow aims to identify new leishmaniasis therapies.

Three of the winning proposals focused on other diseases.

Richard Leduc, a professor in the Department of Pharmacology at the **University of Sherbrooke**, will test a new approach to treating iron overload disease. Deborah O'Brien, a professor of cell biology and physiology at **The University of North Carolina at Chapel Hill**, submitted a winning proposal concerning the regulation of male fertility. Another UNC team, led by pharmacology professor John Sondek, will screen for metastatic epithelial cancer therapeutics.

The contest winners submitted nonconfidential proposals outlining their screening strategies and how collaborating with GSK could be helpful.

Earlier this year, technology transfer officers at the **University of California, Los Angeles** raised concerns about whether participation in GSK's contest would undermine intellectual property claims by universities. In response, GSK modified the terms for contest participation to allow technology transfer offices to vet proposals for potential IP problems.²

Financial terms and the duration of the winning proposals are undisclosed. If any of the projects yield promising results after preliminary drug screens, the researchers will have the option to enter into a long-term collaboration with GSK.

PPP roundup

October public-private partnerships (PPPs) kicked off with the launch of **Tri-Institutional Therapeutics Discovery Institute Inc.** (Tri-I TDI) and its partnership with **Takeda Pharmaceutical Co. Ltd.** Other notable events last month included the announcement by **Evotec AG** of its fourth partnership with **Harvard University** and its affiliates this year, whereas **Debiopharm Group** moved into epigenetic regulators for cancer via a partnership with Singapore's **Agency for Science, Technology and Research (A*STAR)**.

Memorial Sloan-Kettering Cancer Center, **The Rockefeller University** and **Weill Cornell Medical College** launched Tri-I TDI as an independent, not-for-profit organization that will pool the resources of the institutions and form industry partnerships to help translate early stage research into diagnostics and therapeutics (see Table 1, "Selected public-private partnerships for October 2013").

It was founded with a \$15 million gift from Lewis and Ali Sanders and a \$5 million gift from Howard and Abby Milstein. The institute is funded through philanthropy, direct contributions from the institutions and a yearly \$1.5 million contribution from Takeda—Tri-TDI's first partner.

The institute initially will focus on small molecules, with medicinal chemistry activities taking place at Weill Cornell and Takeda helping to run research at the institute's laboratories.

Tri-I TDI eventually plans to expand into biologics and molecular imaging agents.

This month, Evotec announced its fourth deal for the year with Harvard and its affiliates—dubbed TargetEEM. The partners hope to identify new enteroendocrine mechanisms involved in insulin resistance and energy handling. Under the diabetes deal, Harvard is responsible for discovery research, while Evotec is responsible for development and will have rights to resulting products.

The partners will use animal models as well as transcriptional and proteomic profiling platforms from both parties and will share

commercialization profits. Financial details are undisclosed.

Including TargetEEM, Evotec has now disclosed six partnerships with Harvard and its affiliates. The biotech's other diabetes-focused partnership with the university is the CureBeta collaboration to jointly discover and develop therapies that target pancreatic β cell regeneration, which was announced in March 2011.

Last July, **Johnson & Johnson's** Janssen Pharmaceuticals Inc. unit in-licensed a portfolio of small molecules and biologics generated under the CureBeta collaboration for \$8 million up front and potential milestones of up to \$300 million per product, plus royalties.³

Finally, Debiopharm ventured into the epigenetics space this month via a partnership with the Experimental Therapeutics Centre research unit of A*STAR to exclusively develop oral small molecules targeting an undisclosed class of epigenetic modulators to treat tumors with genetic lesions.

Debiopharm and the center will cofund and participate in the discovery research. Debiopharm will be responsible for development and

Table 1. Selected public-private partnerships for October 2013. Two significant developments in the public-private partnership space this month include the launch of **Tri-Institutional Therapeutics Discovery Institute Inc.** and its partnership with **Takeda Pharmaceutical Co. Ltd.** to expedite early stage drug discovery, and the launch of the Canadian Alliance for Healthy Hearts and Minds project to identify early root causes of chronic diseases in the brain, heart and cardiovascular system. Notably, **Evotec AG** announced its fourth deal with **Harvard University** and its affiliates this year. Also, **Debiopharm Group** is making a move into epigenetics drug discovery in cancer with its partnership with the Experimental Therapeutics Centre at the **Agency for Science, Technology and Research (A*STAR)**.

Source: *BioCentury Archives*

Companies	Institutions	Business area	Disclosed value	Purpose
Takeda Pharmaceutical (Tokyo:4502)	Memorial Sloan-Kettering Cancer Center; The Rockefeller University; Weill Cornell Medical College	Pharmaceuticals	\$20 million + \$1.5 million/year	Launch of Tri-Institutional Therapeutics Discovery Institute to expedite early stage discovery into clinical treatments and therapies
Not applicable	Canadian Partnership Against Cancer; Heart and Stroke Foundation	Cancer; Cardiovascular disease; Neurology	C\$16 million (\$15.3 million)	Partnership to launch the Canadian Alliance for Healthy Hearts and Minds project to identify early root causes of chronic diseases of the brain, heart and cardiovascular system
EffRx Pharmaceuticals S.A.; Campbell Charles Associates Ltd.; Klifo A/S; RCTs; Sciprom S.a.r.l.; Sermes Planificacion S.L.U.	University of Liverpool; European Commission	Genitourinary disease	€5.9 million (\$8 million)	Metfizz consortium to develop EffRx's EX404 to treat polycystic ovarian syndrome (PCOS)
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK)	Bill & Melinda Gates Foundation	Infectious disease	\$1.8 million	Partnership to improve the thermostability of vaccine adjuvants, with an initial focus on the adjuvant AS01
Not applicable	Boston University; Medical Research Council	Cardiovascular disease; Inflammation	At least £577,000 (\$921,815)	Partnership to develop a humanized antibody against IL-16 to treat inflammatory diseases and ischemic reperfusion injury
Agilent Technologies Inc. (NYSE:A)	Seoul National University Hospital	Diagnostics	Undisclosed	Partnership to develop and verify biomarkers in areas such as narcotics and immunosuppressants
AstraZeneca plc (LSE:AZN; NYSE:AZN)	National Research Program for Biopharmaceuticals	Pharmaceuticals	Undisclosed	Partnership to allow researchers in Taiwan to conduct preclinical and clinical research on 20 small molecules and biologics developed and selected by AstraZeneca
AstraZeneca	Wyss Institute for Biologically Inspired Engineering at Harvard University	ADMET	Undisclosed	Partnership to develop and validate animal cell-based organs on chips for preclinical drug safety testing
Bayer AG (Xetra:BAYN)	RWTH Aachen University	Bioinformatics	Undisclosed	Partnership to form the Joint Research Center on Computational Biomedicine to develop new methods in computer-based modeling of complex biological processes

(Continues on p. 6)

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

Companies	Institutions	Business area	Disclosed value	Purpose
Berg Pharma LLC	Icahn School of Medicine at Mount Sinai	Cancer; Diagnostics; Endocrine/Metabolic disease; Neurology	Undisclosed	Partnership to discover and develop biologics, small molecules and diagnostic tools for cancer and CNS and endocrine disorders
BioMotiv LLC	Alzheimer's Drug Discovery Foundation; University Hospitals	Neurology	Unavailable	Partnership to advance preclinical Alzheimer's disease therapeutics in U.S. academic medical institutions
Charleston Laboratories Inc.	Stanford University	Gastrointestinal disease; Neurology	Unavailable	Partnership to evaluate antiemetic effects on opioid-induced hyperalgesia and physical dependence to prevent opiate withdrawal in patients on chronic opiates
DBV Technologies (Euronext:DBV)	Institut National de la Sante et de la Recherche Medicale (INSERM)	Hematology; Drug delivery	Undisclosed	One-year partnership to conduct preclinical testing of epicutaneous recombinant factor VIII (rFVIII) protein via DBV's Viaskin skin patch technology
Debiopharm	A*STAR	Cancer	Undisclosed	Partnership to develop oral small molecules targeting an undisclosed class of epigenetic modulators to treat tumors with genetic lesions
Eli Lilly and Co. (NYSE:LLY)	The University of Edinburgh	Cancer	Undisclosed	Partnership to study cancer mechanisms and mechanisms of action for undisclosed oncology compounds
Eli Lilly; Pfizer Inc. (NYSE:PFE)	Joslin Diabetes Center	Endocrine/Metabolic disease	Undisclosed	Partnership to conduct research to predict, treat and prevent kidney failure in patients who have type 2 diabetes
Evotec (Xetra:EVT)	Harvard University	Endocrine/Metabolic disease	Undisclosed	TargetEEM collaboration to identify enteroendocrine mechanisms for potential diabetes therapies
Not applicable	Alliance for Lupus Research; Lupus Research Institute	Autoimmune disease	Unavailable	Partnership to analyze a database of 70 drugs approved for other indications for potential use in lupus
Not applicable	Autism Speaks; Baylor College of Medicine; Boston Children's Hospital; University of California, Davis	Neurology	Unavailable	Preclinical Autism Consortium for Therapeutics to build and validate a platform of preclinical tests for new autism medications in rat and mouse models
Sanofi (Euronext:SAN; NYSE:SNY)	Bill & Melinda Gates Foundation	Infectious disease	Unavailable	Collaboration on platforms and methods for vaccine R&D
Sistemic Ltd.	Health Science Scotland; NHS Scotland	Diagnostics	Unavailable	Partnership to develop diagnostic biomarkers for the early detection of diabetic retinopathy and infective keratitis

will have rights to resulting compounds. Financial details are undisclosed.

Debiopharm has 10 disclosed oncology-focused programs in its pipeline in Phase III testing or earlier. The company already markets two oncology drugs: Eloxatin oxaliplatin to treat colorectal cancer and Pamorelin LA, a gonadotropin-releasing hormone (GnRH) agonist, to treat prostate cancer.

Lou, K.-J. & Osherovich, L. *SciBX* 6(43); doi:10.1038/scibx.2013.1211
Published online Nov. 7, 2013

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- McCallister, E. *BioCentury* 20(31), A9-A10; July 30, 2012

COMPANIES AND INSTITUTIONS

Agency for Science, Technology and Research, Singapore
Albert Einstein College of Medicine of Yeshiva University, New York, N.Y.
Boston University, Boston, Mass.
Cancer Prevention & Research Institute of Texas, Austin, Texas
Debiopharm Group, Lausanne, Switzerland

Evotec AG (Xetra:EVT), Hamburg, Germany
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Harvard University, Cambridge, Mass.
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Memorial Sloan-Kettering Cancer Center, New York, N.Y.
Peloton Therapeutics Inc., Dallas, Texas
Pennsylvania State University, College Station, Pa.
Rice University, Houston, Texas
The Rockefeller University, New York, N.Y.
Takeda Pharmaceutical Co. Ltd. (Tokyo:4502), Osaka, Japan
Tri-Institutional Therapeutics Discovery Institute Inc., New York, N.Y.
University of California, Los Angeles, Calif.
University of California, San Francisco, Calif.
The University of North Carolina at Chapel Hill, Chapel Hill, N.C.
University of Pennsylvania, Philadelphia, Pa.
University of Sherbrooke, Sherbrooke, Quebec, Canada
The University of Texas MD Anderson Cancer Center, Houston, Texas
The University of Texas Southwestern Medical Center, Dallas, Texas
Weill Cornell Medical College, New York, N.Y.

Pulse my heart

By Amy Donner, Senior Editor

Despite the potential for VEGF-A to limit or even repair post-myocardial infarction heart damage, the molecule has stumbled in the clinic because of issues with its delivery and therapeutic window. Now, a multinational team thinks it has solved these problems by using synthetic RNA.¹ The compound is partnered with **Moderna Therapeutics Inc.** and **Astra-Zeneca plc.**

Myocardial infarction (MI) patients typically receive β -blockers and blood thinners to protect the heart from a second infarct and restore blood flow. Some also receive angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers to limit damage to the heart.

Despite these treatments, “there is a compelling unmet need in repairing damage after heart attack,” said Kenneth Chien, a professor of cardiovascular research at the **Karolinska Institute**, a professor of stem cell and regenerative biology at **Harvard University** and a cofounder of Moderna.

An alternative approach using VEGF-A to promote neovascularization has also been tested to limit tissue damage after MI. However, multiple approaches for delivering VEGF-A, including injection of recombinant protein and gene therapy using naked DNA plasmids or engineered viruses, have been developed but then stumbled in the clinic.

Recombinant VEGF-A had limited stability in serum and was associated with hypotension and growth of atherosclerotic plaques.² DNA-mediated delivery of VEGF-A led to stable protein levels, but prolonged tissue exposure to the growth factor caused cases of excessive vascular permeability and edema.³

Chien and his team hypothesized that short, pulsed delivery of VEGF-A might circumvent these problems.

In addition, the group’s recent findings establishing that VEGF-A can mobilize cardiac progenitor cells to become endothelial cells and potentially help repair heart function provided one more reason to harness the therapeutic potential of the molecule by addressing the delivery challenges⁴ (see Figure 1, “VEGF-A promotes an endothelial cell fate in human cardiac progenitor cells”).

The researchers thus set out to develop an RNA-based platform with the ability to trigger a targeted but short-lived burst of protein expression in the heart.

The team chose to develop a modified RNA (modRNA) expressing VEGF-A. modRNAs are synthetic RNA molecules that contain chemical modifications at the 5’ guanine cap and incorporate 2-thiouridine (pseudouridine) in place of uridine and 5-methylcytosine in place of cytosine. The cap is essential to stabilize the RNA in cells and for recognition by the ribosome so the RNA is translated into protein.⁵

“Almost any cells can take up the modRNA—and immediately translate to the protein with an efficiency of over 90%,” said Chien.

In cultured primary cardiac cells from humans, mice and rats, VEGF-A modRNA transfection led to rapid, transient high levels of gene expression, whereas VEGF-A DNA vectors led to slow, stable high levels of gene expression. Thus, modRNA delivered a rapid pulse of VEGF-A to cells.

In mice, a single injection of modRNA into the heart resulted in tenfold more efficient gene expression than injection of DNA. Because

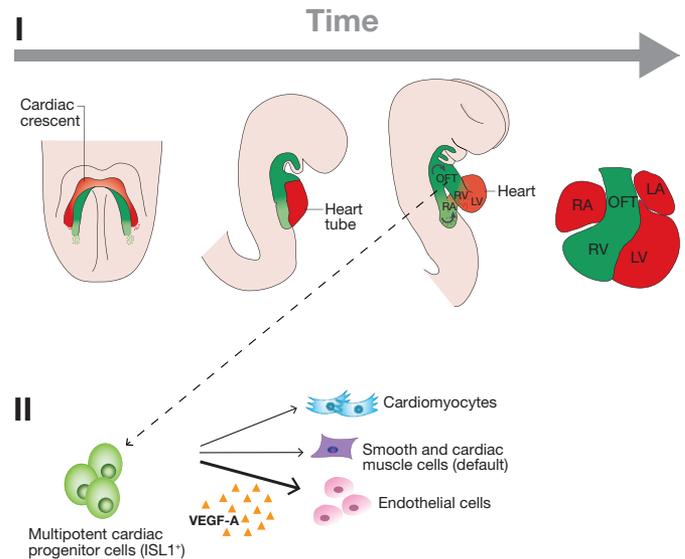


Figure 1. VEGF-A promotes an endothelial cell fate in human cardiac progenitor cells. Lui *et al.* identified VEGF-A as a paracrine factor that promotes endothelial cell differentiation from human cardiac progenitor cells. Endothelial cells contribute to the coronary artery and vein as well as endocardial compartments of the heart.

[I] Schematic representation of cardiac progenitor cell origins in the developing mouse embryo (pink). The first (red) and second (green) heart fields are shown at various stages of early embryonic development. The two fields make distinct regional and lineage contributions to the heart: right atrium (RA), left atrium (LA), right ventricle (RV) and left ventricle (LV). The second heart field makes major contributions to the outflow tract (OFT).

[II] ISL LIM homeobox 1 (ISL1)⁺ human cardiac progenitor cells can give rise to three cardiovascular cell lineages: cardiomyocytes, smooth muscle cells and endothelial cells. Lui *et al.* identified an intermediate population of endothelial cells, derived from the OFT of nine-week-old human fetal hearts (arrow), that resemble human embryonic stem cell (hESC)-derived ISL1⁺ endothelial cell progenitors. VEGF-A can promote *in vitro* differentiation of both types of multipotent progenitors (endogenous intermediate endothelial cells and ISL1⁺ cells derived from hESCs) toward an endothelial cell fate. In a mouse model, subcutaneous injection of human OFT-derived progenitor cells overexpressing VEGF-A from a synthetic modified RNA led to endothelial cell specification as well as the proliferation and survival of these cells *in vivo*.

(Figure based on Figure 3b in Buckingham, M. *et al.*, *Nat. Rev. Genet.* 6, 826–837; 2005.)

injection of VEGF-A modRNA led to pulse-like, high-level, localized gene expression, the team set out to test whether VEGF-A could function as a paracrine factor and promote tissue recovery after cardiac injury.

In a mouse model of MI, VEGF-A modRNA and VEGF-A DNA injected into the ischemic region of the heart decreased infarct size and cell death and increased capillary density compared with no treatment.

However, the DNA version decreased survival, whereas the RNA

version increased survival. In addition, *VEGF-A* DNA-treated infarcted hearts had blood vessels with higher levels of permeability and edema than *VEGF-A* modRNA-treated hearts.

According to Chien, the group saw the same surprising expression kinetics and efficiency with the modRNA delivery system *in vivo* as *in vitro*. “Over 50% of the ventricle will express almost any protein, making a nice mimic of a paracrine signal. There was also no persistence of expression. The RNA was taken up quickly, made into protein and then degraded.”

To determine whether *VEGF-A* modRNA promoted regeneration after MI, the scientists tracked the fate of cardiac progenitor cells. In infarcted mice with epicardial progenitor cells and their descendants labeled with GFP, *VEGF-A* modRNA increased the number of progenitor cells fourfold and increased differentiation into endothelial cells compared with luciferase modRNA control.

Results were published in *Nature Biotechnology*.

The team on the *Cell Research* and *Nature Biotechnology* papers also included scientists from the **Boston Children’s Hospital,**

Harvard Medical School, The University of Hong Kong, Massachusetts General Hospital and the Icahn School of Medicine at Mount Sinai.

An RNA triangle

Moderna, AstraZeneca and Karolinska are collaborating through a pair of deals to take the modRNA-based VEGF-A strategy into the clinic.

In March, Moderna and AstraZeneca announced a deal to discover, develop and commercialize mRNA therapeutics to treat cardiovascular and metabolic diseases and cancer. AstraZeneca paid \$240 million up front for exclusive access to targets of choice in cardiometabolic disease and select cancer targets for a 5-year period and up to 40 products.

According to Stéphane Bancel, president and CEO of Moderna, “The chemical modifications used in the paper are older modifications. We have now improved many times on those nucleotide analogs.”

One of the programs that AstraZeneca is taking to the clinic through the partnership is the VEGF-A platform.

“Our initial interest is in heart failure as this is a major cause of

mortality worldwide, with a steady increase in prevalence,” said Marcus Schindler, head of AstraZeneca’s cardiovascular and metabolic disease innovative medicines unit.

In June, AstraZeneca and Karolinska formed a joint research center—the **Karolinska Institute/AstraZeneca Integrated Cardio Metabolic Centre**. According to Schindler, “The center’s aim is to identify and validate novel targets within cardiometabolic diseases. It will focus mainly on our three strategic research themes: cardiac regeneration, islet health (diabetes) and diabetic nephropathy.”

AstraZeneca will provide up to \$20 million per year for the first 5 years of the agreement. The center will feature up to 6 research groups, and 20–30 scientists from AstraZeneca and Karolinska will be full-time employees. The ongoing collaboration with Chien is one of the research programs at the institute.

According to Chien, the collaborators will follow up their mouse studies in a larger animal model, but he plans to move the VEGF-A project ahead to the first human studies in 18–24 months in collaboration with AstraZeneca and Moderna onsite at Karolinska.

Moderna has filed patent applications covering its mRNA platform, including chemistry, formulation, composition and dosing.

Donner, A. *SciBX* 6(43); doi:10.1038/scibx.2013.1212
Published online Nov. 7, 2013

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e-mail: kenneth.chien@ki.se
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5. Warren, L. *et al. Cell Stem Cell* **7**, 618–630 (2010)

COMPANIES AND INSTITUTIONS MENTIONED

AstraZeneca plc (LSE:AZN; NYE:AZN), London, U.K.
Boston Children’s Hospital, Boston, Mass.
Harvard Medical School, Boston, Mass.
Harvard University, Cambridge, Mass.
Icahn School of Medicine at Mount Sinai, New York, N.Y.
Karolinska Institute, Stockholm, Sweden
Karolinska Institute/AstraZeneca Integrated Cardio Metabolic Centre, Stockholm, Sweden
Massachusetts General Hospital, Boston, Mass.
Moderna Therapeutics Inc., Cambridge, Mass.
The University of Hong Kong, Hong Kong, China

“Our initial interest is in heart failure as this is a major cause of mortality worldwide, with a steady increase in prevalence.”

—Marcus Schindler,
AstraZeneca plc

Phenotypic screening on target

By Lev Osherovich, Senior Writer

U.S. researchers have used forward genetics, a combination of phenotypic screening and genetics, to identify a therapeutic for leukemia and its target, the metabolic enzyme nicotinamide phosphoribosyl transferase.¹ The platform plugs a gap in phenotypic screens that typically leave users guessing how their molecules work.

The strategy contrasts with the conventional approach to finding drug targets by biochemical methods or by selecting for mutations that affect drug response.

“One of the problems with phenotypic screens is that the target or mechanism of action is often unknown,” said Michael Wei, an instructor in the Department of Pediatrics at the **Stanford University School of Medicine** and a member of the team that reported on the new screening platform. “Applying forward genetics is a powerful approach to addressing this roadblock in phenotypic screen development.”

Unbiased search

The team started with a target-agnostic phenotypic screen of 115,000 molecules from a commercial library to identify com-

pounds that prevented growth of cultured acute lymphoblastic leukemia (ALL) cells at nanomolar concentrations. The most potent compound, STF-118804, decreased growth in a variety of ALL cell lines compared with vehicle.

In a mouse xenograft model of ALL, STF-118804 was well tolerated and improved survival.

To figure out how STF-118804 worked, the team transfected ALL cells with a small hairpin RNA library covering the entire genome and then exposed the transfected cells to STF-118804.

The team reasoned that cells expressing shRNAs against the actual target of STF-118804 would have a clear increase in death—from the combined effects of the small molecule and the shRNA—compared with cells expressing off-target shRNAs.

Indeed, high throughput sequencing of shRNA library-transfected cells showed those that underwent knockdown of nicotinamide phosphoribosyl transferase (NamPRT; NAMPT) were underrepresented in drug-treated vs. vehicle-treated populations.

Wei said that the shRNA library's high level of genomic coverage, with over 25 shRNA clones per gene, made it an ideal screening tool for target discovery.

“This library has very high coverage of shRNAs per gene, giving us confidence in the recovery of genes. This allowed us to home in right away on the target of the drug.”

The team went on to show that STF-118804 blocked NAMPT's catalytic activity *in vitro*. Results were reported in *Chemistry & Biology*. A pending patent on STF-118804 is available for licensing from **Stanford University**.

The shRNA library and the methods were developed by coauthors Jonathan Weissman, a professor of cellular and molecular pharmacology at the **University of California, San Francisco** and an investigator in the **Howard Hughes Medical Institute**, and Michael Bassik, acting assistant professor of genetics at Stanford's School of Medicine. UCSF has filed patents on the use of the shRNA platform for identifying drug targets.

The study was led by Michael Cleary, a professor of pediatric cancer biology and of pathology at Stanford's School of Medicine.

Amped about NAMPT

Despite the elegant proof of concept for matching a compound to its target, it is unclear whether STF-118804 is a good drug candidate or even whether NAMPT is a viable target.

NAMPT normally performs an enzymatic step in the synthesis of nicotine adenine dinucleotide (NAD⁺), an electron-ferrying small molecule that is critical for cellular metabolism.

Two previous NAMPT inhibitors—**Topotarget A/S's** APO866 and a molecule tested by the **EORTC**²—failed in clinical trials in various solid tumors.

In October, researchers at the **Genentech Inc.** unit of **Roche** reported preclinical biomarker studies with the company's own NAMPT inhibitors.³ Genentech spokeswoman Nadine Pinell said that the company and partner **Forma Therapeutics Holdings LLC** are now determining the next steps for the program.

The Stanford team showed that STF-118804 caused *in vitro* NAMPT inhibition comparable to that for Topotarget's APO866 but did not report cell culture or *in vivo* data comparing the two compounds.

Thus, it is unclear how STF-118804 measures up against previous NAMPT inhibitors. The new compound does have a distinct structure and was tested in the hematological cancer setting rather than in solid tumors.

“We have some hypotheses about why leukemia cells should be especially sensitive to NAMPT” vs. healthy bone marrow, said Wei. “We didn't see significant toxicity in mouse models and saw a good therapeutic index when we look at diseased vs. normal bone marrow progenitors.”

Wei thinks that bioavailability and toxicity issues will be easier to manage in hematological malignancies than in solid tumors.

“The Topotarget compound was tested in relapsed solid tumors, so we don't know if the indication is necessarily the best for NAMPT inhibition,” said Wei. “They had to administer the drug as a 96-hour infusion, so we might be able to improve on that.”

Wei said that his next step is to seek an industry partner to conduct detailed preclinical toxicity and efficacy studies with STF-118804.

Osherovich, L. *SciBX* 6(43); doi:10.1038/scibx.2013.1213
Published online Nov. 7, 2013

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Contact: Michael L. Cleary, Stanford University School of Medicine, Stanford, Calif.
e-mail: mcleary@stanford.edu

“One of the problems with phenotypic screens is that the target or mechanism of action is often unknown. Applying forward genetics is a powerful approach to addressing this roadblock in phenotypic screen development.”

—Michael Wei,
Stanford University
School of Medicine

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3. Shames, D.S. *et al. Clin. Cancer Res.*; published online Oct. 4, 2013; doi:10.1158/1078-0432.CCR-13-1186

COMPANIES AND INSTITUTIONS MENTIONED

EORTC, Brussels, Belgium

Forma Therapeutics Holdings LLC, Watertown, Mass.

Genentech Inc., South San Francisco, Calif.

Howard Hughes Medical Institute, Chevy Chase, Md.

Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland

Stanford University, Stanford, Calif.

Stanford University School of Medicine, Stanford, Calif.

Topotarget A/S (CSE:TOPO), Copenhagen, Denmark

University of California, San Francisco, Calif.



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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				
Multiple sclerosis (MS)	Muscarinic acetylcholine receptor (CHRM; HM)	<i>In vitro</i> and mouse studies suggest CHRM antagonists could help treat MS. In rat oligodendrocyte precursor cells, benzotropine induced differentiation into cells expressing oligodendrocyte markers and increased remyelination of axons when cocultured with neurons compared with vehicle. In a mouse model of experimental autoimmune encephalomyelitis (EAE), benzotropine prevented relapse and decreased disease severity compared with vehicle, and its effects were similar to those of the immunosuppressant MS treatments interferon- β (IFN β) and Gilenya fingolimod. In a mouse model of remyelination, benzotropine accelerated remyelination, whereas vehicle did not. Next steps include testing benzotropine in patients with MS. Generic benzotropine is marketed to treat symptoms of Parkinson's disease (PD). Novartis AG markets the sphingosine 1-phosphate receptor agonist Gilenya to treat relapsing forms of MS.	Patent application filed; available for licensing	Deshmukh, V.A. <i>et al. Nature</i> ; published online Oct. 9, 2013; doi:10.1038/nature12647 Contact: Peter G. Schultz, The Scripps Research Institute, La Jolla, Calif. e-mail: schultz@scripps.edu
SciBX 6(43); doi:10.1038/scibx.2013.1214 Published online Nov. 7, 2013				
Cancer				
Brain cancer	Aurora kinases; polo-like kinase 1 (PLK1; STPK13)	Mouse and cell culture studies suggest inhibiting aurora kinases or PLK1 could help treat sonic hedgehog homolog (SHH)-associated medulloblastoma. In mouse tumor cells with enhanced SHH signaling, aurora kinase and PLK1 inhibitors decreased proliferation and increased apoptosis compared with vehicle. In a mouse model of SHH-associated medulloblastoma, a PLK1 inhibitor increased tumor cell apoptosis and decreased tumor growth compared with vehicle. Next steps include clinical testing of aurora kinase and PLK1 inhibitors in medulloblastoma. At least 21 companies have aurora kinase or PLK1 inhibitors in Phase III testing or earlier to treat various cancers.	Unpatented; licensing status not applicable	Markant, S.L. <i>et al. Cancer Res.</i> ; published online Sept. 25, 2013; doi:10.1158/0008-5472.CAN-12-4258 Contact: Robert J. Wechsler-Reya, Sanford-Burnham Medical Research Institute, La Jolla, Calif. e-mail: rwreya@sanfordburnham.org
SciBX 6(43); doi:10.1038/scibx.2013.1215 Published online Nov. 7, 2013				
Breast cancer	Solute carrier family 7 member 11 cystine glutamate transporter (SLC7A11; xCT)	<i>In vitro</i> and mouse studies suggest xCT inhibitors could help treat a subset of triple-negative breast cancers. In a panel of 46 breast cancer cell lines, metabolic analysis identified a subset of triple-negative cells that were dependent on glutamine. In cultured breast cancer cells, inhibition of the glutamine-dependent xCT by small interfering RNA knockdown or Azulfidine sulfasalazine increased oxidative stress compared with no inhibition. In glutamine-dependent breast cancer cells and in mouse xenograft models, sulfasalazine decreased growth compared with saline. Next steps could include developing improved xCT inhibitors derived from sulfasalazine. Pfizer Inc. markets Azulfidine sulfasalazine to treat inflammatory bowel disease (IBD) and rheumatoid arthritis (RA).	Patent and licensing status unavailable	Timmerman, L.A. <i>et al. Cancer Cell</i> ; published online Oct. 3, 2013; doi:10.1016/j.ccr.2013.08.020 Contact: Luika A. Timmerman, University of California, San Francisco, Calif. e-mail: timmerma@cc.ucsf.edu
SciBX 6(43); doi:10.1038/scibx.2013.1216 Published online Nov. 7, 2013				

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cancer	Checkpoint kinase 1 (CHK1); protein CIP2A (KIAA1524; CIP2A)	<p>Studies in human tumor samples and cell lines suggest CIP2A levels could help predict the efficacy of CHK1 inhibitors in cancer. In human tumor samples, elevated expression of CIP2A and the DNA damage response protein CHK1 was associated with decreased patient survival. In two human cancer cell lines, a CHK1 inhibitor decreased CIP2A expression and viability in the sensitive cell line but not in the resistant cell line. Next steps include evaluating CIP2A and CIP2A-regulated targets as predictors of response to CHK1 inhibitors in clinical trials.</p> <p>SciBX 6(43); doi:10.1038/scibx.2013.1217 Published online Nov. 7, 2013</p>	Patent applications filed covering inhibition of CIP2A; available for licensing	<p>Khanna, A. <i>et al. Cancer Res.</i>; published Sept. 26, 2013; doi:10.1158/0008-5472.CAN-13-1002 Contact: Jukka Westermarck, University of Turku, Turku, Finland e-mail: jukwes@utu.fi</p>
Cancer	Heparan sulfate glycosaminoglycan (HSGAG)	<p>Cell culture studies suggest inhibiting HSGAG-dependent exosome uptake by noncancerous cells could help prevent exosome-mediated tumor development. Exosome-mediated trafficking of signaling molecules and other tumorigenic factors has recently been linked to cancer proliferation. In cell culture, fluorescently labeled exosomes derived from a glioblastoma multiforme (GBM) cell line bound to HSGAGs. In HSGAG-deficient cell lines or cells treated with the HSGAG antagonist heparin, exosome uptake was lower than that in wild-type cells or cells given no treatment. Next steps could include screening for small molecule inhibitors of exosome binding.</p> <p>SciBX 6(43); doi:10.1038/scibx.2013.1218 Published online Nov. 7, 2013</p>	Patent and licensing status unavailable	<p>Christianson, H.C. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Oct. 7, 2013; doi:10.1073/pnas.1304266110 Contact: Mattias Belting, Lund University, Lund, Sweden e-mail: mattias.belting@med.lu.se</p>
Cancer	Topoisomerase I (TOP1)	<p><i>In vitro</i> and mouse studies suggest fluorinated camptothecin could be used to treat cancer. α-Fluoroether-modified camptothecins had greater stability in phosphate buffered saline than unmodified camptothecin and maintained inhibitory activity against TOP1. In human lung, breast and colon cancer cells, the fluorinated camptothecins decreased proliferation compared with vehicle. In mouse xenograft models of human lung cancer, one of the compounds had antitumor activity comparable to that of the camptothecin topotecan. Next steps include optimizing a clinical candidate from the series.</p> <p>SciBX 6(43); doi:10.1038/scibx.2013.1219 Published online Nov. 7, 2013</p>	Patent application filed; available for licensing	<p>Miao, Z. <i>et al. J. Med. Chem.</i>; published online Sept. 26, 2013; doi:10.1021/jm400906z Contact: Wannian Zhang, Second Military Medical University, Shanghai, China e-mail: zhangwnk@hotmail.com Contact: Chunquan Sheng, same affiliation as above e-mail: shengcq@hotmail.com Contact: Zhenyuan Miao, same affiliation as above e-mail: miaozhenyuan@hotmail.com</p>

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Chronic myelogenous leukemia (CML)	β -Catenin (CTNNB1); interferon regulatory factor 8 (IRF8)	<i>In vitro</i> and mouse studies suggest simultaneously increasing <i>IRF8</i> expression and inhibiting CTNNB1 could help treat CML. In <i>Irf8</i> ^{-/-} mice, which develop CML, enhanced activation of Ctnnb1 caused disease progression to fatal blast crisis. In a BCR-ABL tyrosine kinase mouse model of CML, combined <i>Irf8</i> knockout and Ctnnb1 activation increased Gleevec imatinib resistance compared with wild-type <i>Irf8</i> expression and normal Ctnnb1 activation. Next steps include testing Gleevec in combination with <i>Irf8</i> activation and Ctnnb1 inhibition as a triple therapy at the initiation of blast crisis in models of CML. Novartis AG markets Gleevec, a BCR-ABL tyrosine kinase inhibitor, to treat gastrointestinal stromal tumors (GISTs), acute lymphoblastic leukemia (ALL) and CML. Prism Pharma Co. Ltd. and Eisai Co. Ltd. have the CTNNB1 inhibitor PRI-724 in Phase I/II testing to treat CML and other cancers. Marina Biotech Inc.'s CEQ508, an oral RNAi targeting CTNNB1, is in Phase I/II testing to treat colorectal cancer. SciBX 6(43); doi:10.1038/scibx.2013.1220 Published online Nov. 7, 2013	Patent and licensing status not applicable	Scheller, M. <i>et al. J. Exp. Med.</i> ; published online Oct. 7, 2013; doi:10.1084/jem.20130706 Contact: Achim Leutz, Max Delbrueck Center for Molecular Medicine, Berlin, Germany e-mail: aleutz@mdc-berlin.de Contact: Marina Scheller, same affiliation as above e-mail: m.scheller@uke.de
Non-Hodgkin's lymphoma (NHL); mantle cell lymphoma (MCL)	Histone deacetylase 6 (HDAC6); microRNA-548m (miR-548m); c-Myc (MYC)	<i>In vitro</i> and mouse studies suggest inhibiting HDAC6 and MYC could help treat MCL and other NHLs. In MCL or other lymphoma cells cocultured with stromal cells, overexpression of miR-548m or inhibition of its target, HDAC6, prevented stromal adhesion-induced resistance to mitoxantrone chemotherapy. In mouse xenograft models of lymphoma, inhibiting MYC using the reagent JQ1 plus mitoxantrone or an HDAC6 inhibitor was more effective than single agents. Next steps could include testing the combination therapy in animal models of additional types of NHL. Acetylon Pharmaceuticals Inc. has the HDAC6 inhibitor ACY-1215 in Phase I/II testing to treat multiple myeloma (MM). At least two other companies have HDAC6 inhibitors in preclinical testing. SciBX 6(43); doi:10.1038/scibx.2013.1221 Published online Nov. 7, 2013	Patent and licensing status unavailable	Lwin, T. <i>et al. J. Clin. Invest.</i> ; published online Oct. 8, 2013; doi:10.1172/JCI64210 Contact: Jianguo Tao, H. Lee Moffitt Cancer Center & Research Institute, Tampa, Fla. e-mail: jianguo.tao@moffitt.org
Prostate cancer	Prostate-specific membrane antigen (PSMA; FOLH1; GCPII); CD3	<i>In vitro</i> and mouse studies suggest PSMA-targeting small molecule-antibody conjugates could help treat prostate cancer. The conjugate was made by linking 2-[3-(1,2-dicarboxy propyl)-ureido] pentanedioic acid (DUPA) to a modified α CD3 antibody fragment. DUPA binds to PSMA on cancer cells, whereas the antibody fragment binds CD3-expressing T cells to recruit them to prostate cancer tumors. In immunodeficient mice injected with both human PSMA-expressing prostate cancer and peripheral blood mononuclear cells, the conjugate prevented tumor growth and caused regression of established tumors, whereas an unconjugated mixture or vehicle did not. Next steps include testing the conjugate in humans. Northwest Biotherapeutics Inc. has DCVax-Prostate, therapeutic autologous dendritic cells treated with PSMA <i>ex vivo</i> , in Phase III testing to treat prostate cancer. At least seven other companies have PSMA-targeting therapeutics in Phase II or earlier testing to treat prostate cancer. SciBX 6(43); doi:10.1038/scibx.2013.1222 Published online Nov. 7, 2013	Patent application filed covering the small molecule-antibody conjugate and synthesis strategy; available for licensing	Kim, C.H. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Oct. 14, 2013; doi:10.1073/pnas.1316026110 Contact: Peter G. Schultz, The Scripps Research Institute, La Jolla, Calif. e-mail: schultz@scripps.edu Contact: Chan Hyuk Kim, California Institute for Biomedical Research, La Jolla, Calif. e-mail: chkim@calibr.org

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cardiovascular disease				
Cardiomyopathy	Myosin heavy chain 7 cardiac muscle- β (MYH7)	Mouse studies suggest RNAi that targets a disease-causing mutation in MYH7 could help prevent hypertrophic cardiomyopathy (HCM). The R403Q mutation in MYH7, which encodes the myosin heavy chain, causes progressive and early onset HCM. In mice with a heterozygous, homologous mutation, injection of an adenoviral vector encoding RNAi that specifically targets the mutant gene under a cardiac-specific promoter prevented both hypertrophy and fibrosis, whereas injection of a vector encoding control RNAi did not. Next steps include designing a modified adenoviral vector for delivery to the human heart.	Patent application filed; unavailable for licensing	Jiang, J. <i>et al. Science</i> ; published online Oct. 4, 2013; doi:10.1126/science.1236921 Contact: Christine E. Seidman, Harvard Medical School, Boston, Mass. e-mail: cseidman@genetics.med.harvard.edu
SciBX 6(43); doi:10.1038/scibx.2013.1223 Published online Nov. 7, 2013				
Gastrointestinal disease				
Colitis	ST3 β -galactoside α -2,3-sialyltransferase 4 (ST3GAL4)	Mouse studies suggest removing oligosaccharide sialyl(α 2,3)lactose (3SL) from breast milk could help prevent colitis in susceptible infants. In a mouse model of spontaneous colitis, homozygous knockout of <i>St3gal4</i> , which encodes the enzyme that synthesizes 3SL in breast milk, delayed disease onset and decreased disease severity compared with no knockout. In colitis-susceptible newborn mice, 3SL-depleted milk decreased leukocyte infiltration and inflammation in the intestines compared with nondepleted milk. In these susceptible mice, supplementation with 3SL increased intestinal inflammation compared with lactose or water. Next steps could include developing agents or filters to remove 3SL from breast milk and evaluating the resulting milk in colitis-susceptible animals.	Patent and licensing status unavailable	Kurakevich, E. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Oct. 7, 2013; doi:10.1073/pnas.1306322110 Contact: Lubor Borsig, University of Zurich, Zurich, Switzerland e-mail: lborsig@access.uzh.ch
SciBX 6(43); doi:10.1038/scibx.2013.1224 Published online Nov. 7, 2013				
Infectious disease				
Bacterial infection; infectious disease	Unknown	<i>In vitro</i> and mouse studies identified 5-nitroimidazole (5-NI) derivatives that could help treat drug-resistant bacterial and protozoan infections. In growth and survival assays for <i>Giardia lamblia</i> , <i>Trichomonas vaginalis</i> , <i>Helicobacter pylori</i> and <i>Clostridium difficile</i> , 44 of the 378 tested 5-NI derivatives were more effective against all 4 organisms than the parent compound metronidazole. In these assays, the 5-NI derivatives showed antimicrobial activity against multiple clinical isolates, including those resistant to metronidazole. In mouse models of giardiasis, 7 of 16 tested 5-NI derivatives showed greater antimicrobial activity against the parasite than metronidazole. Next steps include selecting specific indications for testing individual compounds.	Patent pending; available for licensing	Miyamoto, Y. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Oct. 7, 2013; doi:10.1073/pnas.1302664110 Contact: Lars Eckmann, University of California, San Diego, La Jolla, Calif. e-mail: leckmann@ucsd.edu
SciBX 6(43); doi:10.1038/scibx.2013.1225 Published online Nov. 7, 2013				

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Infectious disease	Transforming growth factor- β (TGFB; TGF- β); integrin $\alpha_v\beta_8$	<p>Mouse studies suggest inhibiting TGF-β or integrin $\alpha_v\beta_8$ could help prevent chronic helminth infection. In <i>Trichuris muris</i> egg-infected mouse models of helminth infection, Tgf-β signaling on Cd4⁺ T cells was higher than that in uninfected controls. In these models, an anti-TGF-β antibody decreased worm burden—a marker of chronic infection—compared with an inactive control antibody. Also in these models, an integrin $\alpha_v\beta_8$ deficiency on dendritic cells decreased Tgf-β signaling in Cd4⁺ T cells compared with normal expression of integrin $\alpha_v\beta_8$ and led to a consequent reduction in worm burden. Ongoing work includes investigating whether the integrin $\alpha_v\beta_8$-TGF-β pathway is involved in other infectious diseases.</p> <p>Acceleron Pharma Inc. and Celgene Corp. have ACE-536, a modified activin receptor type 2A (ACVR2A) fusion protein that inhibits several ligands in the TGF-β superfamily, in Phase II testing to treat anemia and thalassemia.</p> <p>BTG plc has Pleneva (BGC20-0134), an oral TGFB1 immunomodulator, in Phase II testing to treat multiple sclerosis (MS).</p> <p>Eli Lilly and Co.'s LY2382770, a neutralizing mAb against TGFB1, is in Phase II testing to treat diabetic nephropathy and renal disease.</p> <p>SciBX 6(43); doi:10.1038/scibx.2013.1226 Published online Nov. 7, 2013</p>	Unpatented; unlicensed	<p>Worthington, J.J. <i>et al. PLoS Pathog.</i>; published online Oct. 3, 2013; doi:10.1371/journal.ppat.1003675</p> <p>Contact: Mark A. Travis, The University of Manchester, Manchester, U.K. e-mail: mark.travis-2@manchester.ac.uk</p>
Tuberculosis	DNA gyrase	<p><i>In vitro</i> and mouse studies identified thiazolopyridine urea DNA gyrase inhibitors that could be useful for treating tuberculosis. In <i>Mycobacterium tuberculosis</i> culture, thiazolopyridine urea-based compounds showed time- and concentration-dependent bactericidal activity. In a mouse model of <i>M. tuberculosis</i> infection, a lead member of the series caused dose-dependent decreases in lung bacterial counts compared with vehicle. Next steps could include optimizing and evaluating the lead inhibitor in additional models of <i>M. tuberculosis</i> infection.</p> <p>SciBX 6(43); doi:10.1038/scibx.2013.1227 Published online Nov. 7, 2013</p>	Patent and licensing status unavailable	<p>Kale, M.G. <i>et al. J. Med. Chem.</i>; published online Oct. 3, 2013; doi:10.1021/jm401268f</p> <p>Contact: Sandeep R. Ghorpade, AstraZeneca India Pvt. Ltd., Bangalore, India e-mail: sandeep.ghorpade@astrazeneca.com</p>
Tuberculosis	<i>Mycobacterium tuberculosis</i> transmembrane transport protein 3 (mmpL3)	<p><i>In vitro</i> and mouse studies identified indol-2-carboxamides that could help treat tuberculosis. <i>In vitro</i>, two carboxamide analogs with indol and cyclohexyl ring modifications had activity against <i>M. tuberculosis</i> but not human monocytes or hepatocytes. In mice, the two compounds decreased <i>M. tuberculosis</i> colony formation in the lung compared with no treatment or the generic compound ethambutol. Next steps could include further optimization of the compounds for potency and solubility and publication of further details of how the compounds inhibit their proposed target, mmpL3.</p> <p>SciBX 6(43); doi:10.1038/scibx.2013.1228 Published online Nov. 7, 2013</p>	Patent and licensing status unavailable	<p>Kondreddi, R.R. <i>et al. J. Med. Chem.</i>; published online Oct. 3, 2013; doi:10.1021/jm4012774</p> <p>Contact: Ravinder Reddy Kondreddi, Novartis Institute for Tropical Diseases, Chromos, Singapore e-mail: ravinder.kondreddi@novartis.com</p>

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Viral infection	Dihydroorotate dehydrogenase (DHODH)	Cell culture studies suggest inhibiting pyrimidine synthesis could help prevent or treat RNA viral infections. A chemical screen for inducers of an <i>interferon-β</i> (<i>IFNB</i> ; <i>IFN-β</i>) reporter gene identified a compound with potent antiviral activity against multiple RNA viruses. In a human epithelial cell line, the compound inhibited pyrimidine synthesis and amplified expression of antiviral innate immune response genes. The cell line studies also suggested the compound inhibits pyrimidine synthesis by inhibiting a key enzyme in the pyrimidine biosynthesis pathway, DHODH. Next steps include genomewide analysis to identify genes induced by pyrimidine synthesis inhibitors and development of more active inhibitors. SciBX 6(43); doi:10.1038/scibx.2013.1229 Published online Nov. 7, 2013	Unpatented; licensing status not applicable	Lucas-Hourani, M. <i>et al. PLoS Pathog.</i> ; published online Oct. 3, 2013; doi:10.1371/journal.ppat.1003678 Contact: H�el�ene Munier-Lehmann, Pasteur Institute, Paris, France e-mail: helene.munier-lehmann@pasteur.fr Contact: Fr�ed�eric Tangy, same affiliation as above e-mail: frederic.tangy@pasteur.fr Contact: Pierre-Olivier Vidalain, same affiliation as above e-mail: pierre-olivier.vidalain@pasteur.fr
Viral infection	IL-29 (IFNL1)	Studies in patient samples suggest IL-29 could help treat the viral infections that frequently accompany atopic dermatitis. In skin biopsies, IL-29 expression was associated with the production of antiviral proteins. In a 3D model of human epidermis and in explanted skin biopsies from healthy individuals, IL-29 increased expression of antiviral proteins compared with no IL-29. Next steps could include testing IL-29 in models of atopic dermatitis. Bristol-Myers Squibb Co. has recombinant IL-29 in Phase III testing to treat HCV. SciBX 6(43); doi:10.1038/scibx.2013.1230 Published online Nov. 7, 2013	Patent and licensing status unavailable	Wolk, K. <i>et al. Sci. Transl. Med.</i> ; published online Sept. 25, 2013; doi:10.1126/scitranslmed.3006245 Contact: Robert Sabat, Charit�e–University Hospital Berlin, Berlin, Germany e-mail: robert.sabat@charite.de Contact: Kerstin Wolk, same affiliation as above e-mail: kerstin.wolk@charite.de
Inflammation				
Allergy	IgE	<i>In vitro</i> and mouse studies suggest inhibiting weak affinity allergen–IgE interactions could help prevent allergies. In a rat cell culture model, tetravalent allergens were shown to bind IgE and induce mast cell degranulation, an initial step in triggering allergic reactions. A bivalent inhibitor that targets both the antigen- and nucleotide-binding sites on IgE inhibited mast cell degranulation induced by a tetravalent allergen, whereas inhibitors that only target one of the two sites did not. In a mouse model of allergy, the bivalent inhibitor decreased tetravalent allergen–induced ear swelling compared with no treatment. Next steps could include testing the bivalent inhibitor in additional models of allergy. SciBX 6(43); doi:10.1038/scibx.2013.1231 Published online Nov. 7, 2013	Patent and licensing status unavailable	Handlogten, M.W. <i>et al. Nat. Chem. Biol.</i> ; published online Oct. 6, 2013; doi:10.1038/nchembio.1358 Contact: Basar Bilgicer, University of Notre Dame, Notre Dame, Ind. e-mail: bbilgicer@nd.edu
Neurology				
Neurology	Eukaryotic translation initiation factor 2α kinase 3 (EIF2AK3; PERK)	Mouse studies suggest inhibiting PERK could help treat prion-associated diseases. Misfolded prion proteins in the brain activate PERK to trigger the unfolded protein response, which shuts down the normal translation process required for neuron function and survival. In mice infected with prions, the oral PERK inhibitor GSK2606414 prevented further neurodegeneration and the associated behavioral and memory symptoms. In the brains of treated mice, normal protein translation was restored. Next steps could include testing PERK inhibitors in additional models of prion-associated diseases. GlaxoSmithKline plc collaborated on the study. The pharma has no disclosed PERK inhibitors in development. GSK2606414 is a research reagent. SciBX 6(43); doi:10.1038/scibx.2013.1232 Published online Nov. 7, 2013	Patent application filed by GlaxoSmithKline covering GSK2606414 and other PERK inhibitors; licensing status unavailable	Moreno, J.A. <i>et al. Sci. Transl. Med.</i> ; published online Oct. 9, 2013; doi:10.1126/scitranslmed.3006767 Contact: Giovanna R. Mallucci, University of Leicester, Leicester, U.K. e-mail: grm7@le.ac.uk

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Pain	Solute carrier family 12 potassium-chloride transporter member 5 (SLC12A5; KCC2)	<i>In vitro</i> and rat studies suggest stimulating chloride extrusion through KCC2 activation could help treat pain. A high throughput screen of a library of 92,500 drug-like compounds identified KCC2-enhancing agonists. In spinal slices from rats with peripheral nerve injury, the screening hits stimulated KCC2 activity and increased chloride extrusion by 46%. In a rat model of neuropathic pain, the lead KCC2 agonist had analgesic effects comparable to those of Lyrica pregabalin but did not also dampen motor function. Next steps include testing the lead screening hits and their derivatives in models of pain. Pfizer Inc. markets Lyrica pregabalin to treat multiple neurological conditions including neuropathic pain. SciBX 6(43); doi:10.1038/scibx.2013.1233 Published online Nov. 7, 2013	Patents for the lead compound and new, undisclosed compounds owned by Laval University; licensing status undisclosed	Gagnon, M. <i>et al. Nat. Med.</i> ; published online Oct. 6, 2013; doi:10.1038/nm.3356 Contact: Yves De Koninck, Laval University, Quebec City, Quebec, Canada e-mail: yves.dekoninck@crulrg.ulaval.ca
Pain	Toll-like receptor 4 (TLR4)	Rat studies suggest antagonizing TLR4 in the ventrolateral periaqueductal gray (vlPAG) region of the brain could help prevent morphine tolerance. TLR4 has previously been shown to mediate a neuroinflammatory response that can counteract the antinociceptive effects of opioids. In rats, injection of a TLR4 antagonist into the vlPAG region prevented morphine tolerance, whereas injection of TLR4 agonists caused morphine tolerance. In a rat model of persistent inflammatory pain, systemic TLR4 antagonism increased the effect of morphine compared with vehicle control. Next steps could include combination studies in additional models of pain. At least four companies have TLR4 antagonists in Phase II or earlier testing. SciBX 6(43); doi:10.1038/scibx.2013.1234 Published online Nov. 7, 2013	Unpatented; licensing status unavailable	Eidson, L.N. & Murphy, A.Z. <i>J. Neurosci.</i> ; published online Oct. 2, 2013; doi:10.1523/JNEUROSCI.1609-13.2013 Contact: Anne Z. Murphy, Georgia State University, Atlanta, Ga. e-mail: amurphy@gsu.edu
Various				
Sepsis; shock/trauma	Cold-inducible RNA-binding protein (CIRP)	<i>In vitro</i> and rodent studies suggest decreasing CIRP levels could help treat hemorrhagic shock and sepsis. In hemorrhaged human patients and in a rat model of hemorrhagic shock, serum CIRP levels were greater than those in healthy controls. In mouse and rat models of hemorrhagic shock and sepsis, <i>Cirp</i> knockout or a Cirp-neutralizing antibody decreased the inflammatory response and mortality compared with no knockout or an IgG control. Next steps include testing therapeutic peptide fragments of human CIRP that interfere with its function in animal models of sepsis. SciBX 6(43); doi:10.1038/scibx.2013.1235 Published online Nov. 7, 2013	Patent applications filed; TheraSource LLC has an option to license the IP; available for licensing from The Feinstein Institute for Medical Research and TheraSource	Qiang, X. <i>et al. Nat. Med.</i> ; published online Oct. 6, 2013; doi:10.1038/nm.3368 Contact: Ping Wang, The Feinstein Institute for Medical Research, Manhasset, N.Y. e-mail: pwang@nshs.edu

This week in techniques

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

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

Approach	Summary	Licensing status	Publication and contact information
Assays & screens			
Metabolite suppression profiling to understand the mechanism of action for antibacterial compounds	Metabolite suppression profiles can help define the mechanism of action for antibacterial compounds. In limited nutrient conditions in which bacteria rely on biosynthetic pathways to survive and grow, supplementation with primary metabolites can suppress the antibacterial activity of compounds acting in the same or related pathways. In <i>Escherichia coli</i> , the metabolite suppression profiles of 22 known antibacterial compounds were consistent with their known mechanisms of action. In a chemical screen, metabolite suppression profiling led to the discovery and mechanistic characterization of three new antibacterial compounds. Next steps include performing screens with larger compound collections and evaluating the three identified compounds in animal models of bacterial infection.	Patent application filed covering the three lead compounds; available for licensing	Zlitni, S. <i>et al. Nat. Chem. Biol.</i> ; published online Oct. 13, 2013; doi:10.1038/nchembio.1361 Contact: Eric D. Brown, McMaster University, Hamilton, Ontario, Canada e-mail: ebrown@mcmaster.ca
	SciBX 6(43); doi:10.1038/scibx.2013.1236 Published online Nov. 7, 2013		
Computational models			
Bioinformatics-based approach to identify combined microRNA- and mRNA-derived cancer signatures	A bioinformatics approach to predict mRNA and miRNA connectivity in transcriptional networks could help identify genetic vulnerabilities in cancer cells. The method analyzes mRNA and miRNA expression data based on transcript abundance and fold changes. The method was used to generate a thermodynamic signature comprised of about 100 genes that could distinguish tumor cells from normal cells. The signature highlighted a network of connected mRNAs and miRNAs that is strengthened in cancer cells but not in normal cells. Next steps include using the approach to predict patient-specific tumor differences.	Patent status undisclosed; licensing status not applicable	Zadran, S. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Oct. 7, 2013; doi:10.1073/pnas.1316991110 Contact: R.D. Levine, The Hebrew University of Jerusalem, Jerusalem, Israel e-mail: rafi@fh.huji.ac.il
	SciBX 6(43); doi:10.1038/scibx.2013.1237 Published online Nov. 7, 2013		
Disease models			
Fibrillin 1 (Fbn1)-mutant mouse models of systemic scleroderma	Mice harboring mutations in the integrin-binding domain of Fbn1 could help model systemic scleroderma. The mice exhibited multiple disease features seen in patients with systemic scleroderma or patient fibroblasts, including high levels of collagen, activated integrin β_3 (GPIIIa; CD61) in the skin and high levels of antinuclear antibodies in circulation. Compared with control IgG, an integrin β_1 (CD29)-activating antibody decreased CD61 activity and collagen expression in patient fibroblasts, skin fibrosis and levels of circulating antinuclear antibodies in the mice. Future studies could include using the models to compare the efficacy and safety of CD29-activating and CD61-inhibiting antibodies. Mitsubishi Tanabe Pharma Corp.'s Venoglobulin IH (GB-0998), a liquid human IgG preparation derived from donated plasma, is in Phase III testing to treat systemic scleroderma. arGentis Pharmaceuticals LLC's ARG201, a solubilized type I native bovine collagen, is in Phase II testing to treat systemic scleroderma.	Patent and licensing status unavailable	Gerber, E.E. <i>et al. Nature</i> ; published online Oct. 9, 2013; doi:10.1038/nature12614 Contact: Harry C. Dietz, The Johns Hopkins University School of Medicine, Baltimore, Md. e-mail: hdietz@jhmi.edu
	SciBX 6(43); doi:10.1038/scibx.2013.1238 Published online Nov. 7, 2013		

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
<i>In vitro</i> model to predict pharmacokinetic parameters important to antimalarial drug efficacy	An <i>in vitro</i> model to predict pharmacokinetic parameters important for antimalarial drug efficacy could help improve drug dosing. In a glass cartridge system, the ability of chloroquine to inhibit <i>Plasmodium falciparum</i> growth depended on minimum inhibitory concentration, whereas the ability of artemisinin to inhibit parasite growth depended on peak concentration (C_{max}) of the drug. In a mouse model of malarial infection, the relationship between C_{max} and the antimalarial activity of artemisinin was confirmed. Next steps include studying drug-resistant parasites and studying two drugs with different pharmacokinetic profiles at the same time. Chloroquine and artemisinin are generic drugs used to treat malaria infection.	Patent status undisclosed; licensing status not applicable	Bakshi, R.P. <i>et al. Sci. Transl. Med.</i> ; published online Oct. 2, 2013; doi:10.1126/scitranslmed.3006684 Contact: Theresa A. Shapiro, The Johns Hopkins University, Baltimore, Md. e-mail: tshapiro@jhmi.edu
Drug delivery			
Cyclodextrin-modified dendritic polyamine (DexAM) construct for delivery of stem cell differentiation factors	DexAM constructs that simultaneously deliver small interfering RNA and small molecules could be used to control stem cell differentiation. The dendritic polyamine portion of the construct is in complex with a negatively charged siRNA, whereas the cyclodextrin portion of the construct is loaded with a hydrophobic small molecule. In neuronal stem cells, DexAM carrying the small molecule retinoic acid and siRNA targeting SRY (sex determining region Y)-box 9 (SOX9) led to about 71% of the stem cells differentiating into neurons, whereas DexAM carrying either component alone achieved about 50% differentiation. Next steps include testing the delivery vehicle in other types of stem cells and in animal models.	Patent application filed; unavailable for licensing	Shah, S. <i>et al. J. Am. Chem. Soc.</i> ; published online Oct. 9, 2013; doi:10.1021/ja4071738 Contact: Ki-Bum Lee, Rutgers University, Piscataway, N.J. e-mail: kblee@rutgers.edu
Drug platforms			
Gene-specific transcriptional activation using DNA (cytosine-5-)-methyltransferase 1 (DNMT1)-RNA interactions	Suppression of DNMT1-mediated gene methylation using gene-specific RNAs could provide a mechanism for activating gene expression. A DNMT1-binding, noncoding RNA sequence was identified at the <i>CCAAT enhancer binding protein-α</i> (<i>CEBPA</i>) gene that suppressed local DNA methylation and increased <i>CEBPA</i> transcription. In a genome-wide survey, thousands of DNMT1-RNA interactions were discovered, suggesting this could be a previously unknown, gene-specific activating mechanism. Next steps include using clustered, regularly interspaced short palindromic repeats (CRISPR) technology to guide noncoding RNA-derived oligonucleotides to disease-suppressing genes to increase their activation.	Patent applications filed; available for licensing	Di Ruscio, A. <i>et al. Nature</i> ; published online Oct. 9, 2013; doi:10.1038/nature12598 Contact: Daniel G. Tenen, Harvard Medical School and Beth Israel Deaconess Medical Center, Boston, Mass. e-mail: daniel.tenen@nus.edu.sg
Site-directed mRNA editing to correct genetic diseases	A method to site-specifically edit mRNA could be used to correct genetic mutations associated with inherited diseases. A human adenosine deaminase catalytic domain was fused to an RNA-binding protein and then expressed in cells in conjunction with an antisense RNA that the fusion protein recruits to the target mRNA sequence. In <i>Xenopus</i> extracts, injection of RNA encoding the fusion protein and an antisense RNA that targets a mutant form of the cystic fibrosis transmembrane conductance regulator (CFTR) corrected 20% of the transcripts on average. In human cells, transfection of multiple vectors encoding the system enabled the correction of a mutant form of GFP. Next steps include increasing the efficiency of the approach and testing it in zebrafish and mouse models. The study is funded by a 2013 NIH transformative R01 award.	Patent application filed; licensing status undisclosed	Montiel-Gonzalez, M.F. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Oct. 9, 2013; doi:10.1073/pnas.1306243110 Contact: Joshua J.C. Rosenthal, University of Puerto Rico–Medical Sciences Campus, San Juan, Puerto Rico e-mail: joshua.rosenthal@upr.edu

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Markers			
Genomic rearrangements in the androgen receptor (AR) as an androgen-independent prostate cancer resistance mechanism	<i>In vitro</i> studies suggest genomic rearrangements in the <i>AR</i> gene driving androgen-independent prostate cancer growth could help predict drug response. In castration-resistant prostate cancer tissue samples, X-chromosomal rearrangements were identified that led to the exclusive production of truncated AR variants lacking the ligand-binding domain. In prostate cancer cells, genomic rearrangements introduced into the wild-type <i>AR</i> gene by transcription activator-like effector nuclease (TALEN)-based genome editing caused androgen-independent cell growth. Next steps include validating and qualifying the resistance mechanism as a biomarker. SciBX 6(43); doi:10.1038/scibx.2013.1243 Published online Nov. 7, 2013	Patent applications filed covering the TALEN method and AR isoforms in prostate cancer; TALEN method licensed; additional methods, receptor isoforms and genome-edited prostate cancer cell lines available for licensing	Nyquist, M.D. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Oct. 7, 2013; doi:10.1073/pnas.1308587110 Contact: Scott M. Dehm, University of Minnesota, Minneapolis, Minn. e-mail: dehm@umn.edu Contact: Daniel F. Voytas, same affiliation as above e-mail: voytas@umn.edu

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H		L		Polo-like kinase 1	11	STPK13	11
HDAC6	13	LY2382770	15	Pregabalin	17	Sulfasalazine	11
Heparan sulfate glycosaminoglycan	12	Lyrca	17	PRI-724	13	<i>Superoxide dismutase 1</i>	3
Heparin	12	M		Prostate-specific membrane antigen	13	T	
Heterogeneous nuclear ribonucleoprotein A1	2	Metronidazole	14	Protein CIP2A	12	TALEN	20
Histone deacetylase 6	13	MicroRNA-548m	13	Pseudouridine	7	TGFB	15
HM	11	MiR-548m	13	PSMA	13	TGFB1	15
HNRNPA1	2	Mitoxantrone	13	PURA	2	TGF- β	15
HSGAG	12	Mmpl3	15	Purine-rich element binding protein A	2	Thiazolopyridine urea	15
I		Morphine	17	R		TLR4	17
IFNB	11,16	Muscarinic acetylcholine receptor	11	Recombinant factor VIII	6	Toll-like receptor 4	17
IFN- β	11,16	MYC	13	Retinoic acid	19	TOP1	12
IFNL1	16	<i>Mycobacterium tuberculosis</i> transmembrane transport protein 3	15	RFVIII	6	Topoisomerase I	12
IgE	16	MYH7	14	S		Topotecan	12
IgG	17,18	Myosin heavy chain 7 cardiac muscle- β	14	SHH	11	Transcription activator-like effector nuclease	20
IL-16	5	N		Sialyl(α 2,3)lactose	14	Transforming growth factor- β	15
IL-29	16	NAD ⁺	9	SLC7A11	11	U	
Imatinib	13	NamPRT	9	SLC12A5	17	Uridine	7
Indol-2-carboxamide	15	NAMPT	9	<i>Sod1</i>	3	V	
Integrin $\alpha_v\beta_8$	15	Nicotinamide phosphoribosyl transferase	9	Solute carrier family 7 member 11 cystine glutamate transporter	11	VEGF-A	7
Integrin β_1	18	Nicotine adenine dinucleotide	9	Solute carrier family 12 potassium-chloride transporter member 5	17	Venoglobulin IH	18
Integrin β_3	18	NRP2945	3	Sonic hedgehog homolog	11	Viaskin	6
Interferon- β	11,16					X	
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