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NSD2 momentum

By Chris Cain, Senior Writer

Although NSD2 has been genetically linked to multiple myeloma for more than 15 years, drug discovery efforts against the target have lagged behind other histone methyltransferases including DOT1L and EZH2. Now, a **Novartis Institutes for BioMedical Research** and **Broad Institute of MIT and Harvard** collaboration and an independent **Northwestern University** team have identified activating mutations in NSD2 that drive a subset of leukemias,^{1,2} and a second Novartis team has made the best case to date that inhibiting the protein could help treat MM.³

DOT1L (histone methyltransferase DOT1L) and EZH2 (enhancer of zeste homolog 2) drive genetically defined subsets of leukemia. In the last year, **Epizyme Inc.** and its partners **Celgene Corp.** and **Eisai Co. Ltd.** have advanced inhibitors of the proteins into the clinic, and multiple companies have inhibitors of EZH2 in preclinical development.

Based largely on preclinical results and high expectations for these programs, Epizyme went public in June and now boasts a market cap of more than \$1 billion.

NSD2 (nuclear SET domain-containing protein 2; MMSET; WHSC1) also drives a genetically defined subset of blood cancers, but until recently comparatively little was known about its functional role in disease. About 20% of multiple myeloma (MM) cases are caused by the t(4;14) chromosomal translocation, one result of which is increased expression of NSD2.

However, the translocation also drives expression of *fibroblast growth factor receptor 3* (*FGFR3*; *CD333*), and for many years the contribution of NSD2 to tumor development in these patients remained unclear.

Recent studies have strengthened the case that NSD2 drives tumorigenesis by increasing histone H3K36 dimethylation,^{4,5} but the therapeutic potential of the target is relatively unexplored.

To build the case for targeting NSD2 in MM, a team of Shanghai-based Novartis researchers set out to detail the effect of inhibiting the target *in vivo* and confirm the mechanism by which it acts.

In bone marrow stromal adhesion assays, small hairpin RNA knockdown of *Nsd2* in multiple t(4;14)⁺ MM cell lines decreased adhesion and proliferation compared with no knockdown, and knockdown had no effect in t(4;14)⁻ lines. In mice injected with t(4;14)⁺ MM cells, shRNA knockdown of *Nsd2* delayed tumor formation and disease progression.

t(4;14)⁺ MM cells with *Nsd2* knockout did not form tumors in mice. Adding back wild-type *Nsd2* restored tumor formation, but adding

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back a catalytically dead mutant version of *Nsd2* did not. This strongly suggests that NSD2's methyltransferase activity is required to drive MM.

Finally, the team showed that the PHD2 domain of NSD2, which is one of many regions that mediate its binding to histones, also is required for oncogenic activity. The group thus suggested that disrupting the catalytic nuclear SET domain or the PHD2-substrate binding interface could effectively inhibit the target.

Results were published in *Cancer Research*. The team was led by Min Hu, an oncology investigator at the Shanghai campus of the Novartis Institutes for BioMedical Research (NIBR).

Activating NSD2

A separate collaboration between the Broad Institute and NIBR, as well as an independent team from the **Northwestern University Feinberg School of Medicine**, have bolstered the case for targeting NSD2 by uncovering a second genetically defined cancer driven by its activity.¹

The NIBR-Broad team made the discovery as part of a large-scale effort to catalog histone modifications in the **Cancer Cell Line Encyclopedia** (CCLE).

To accomplish this, the researchers turned to targeted mass spectrometry, which enabled them to measure 42 distinct combinations of histone H3 modifications in 115 cell lines.

"The key advantage of the global mass spectrometry profiling is that it overcomes the requirement for highly selective antibodies and allows for the monitoring of several combinatorial histone marks," Frank Stegmeier, director of oncology at NIBR and co-corresponding author of the work, told *SciBX*.

The team identified multiple clusters of cell lines with known

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mutations in histone-modifying enzymes. For example, one cluster had increased H3K27 trimethylation and decreased H3K27 mono- and dimethylation, a hallmark of *EZH2* mutation. As expected, this cluster was comprised entirely of B cell lymphomas with a mutation in *EZH2* that alters its histone substrate specificity.

A second cluster showed increased H3K36 dimethylation, but unexpectedly only 6 of the 13 lines in that cluster bore the t(4;14)⁺ translocation that drives *NSD2* overexpression. The team sought to explain the pattern in the other seven cell lines and thus analyzed their gene expression, copy number and mutational status.

Surprisingly, these seven lines all contained an E1099K mutation in *NSD2*, and six of the seven were acute lymphoblastic leukemia (ALL) lines that were primarily of pediatric origin. Additional sequence analysis of 1,021 pediatric cancer samples identified the mutation in 18 out of 239 B cell ALL cases and in no other pediatric cancer types.

The Northwestern team independently came to the same conclusion by analyzing the publically available database of genetic alterations in the CCLE and confirming increased H3K36 dimethylation and decreased H3K27 methylation in cells bearing the mutation.² Jonathan Licht, chief of the division of hematology/oncology at Feinberg and the **Robert H. Lurie Comprehensive Cancer Center of Northwestern University**, told *SciBX* that in their study his team also sequenced 200 adult patients with ALL and found no instances of the mutation.

Thus, he argued that it is largely confined to pediatric cases of ALL, though he noted that the mutation had been previously found in single cases of chronic lymphocytic leukemia (CLL) and lung and stomach cancer. Licht was a co-corresponding author on the study, which was published in *Leukemia*.

The NIBR-Broad team went a step further and characterized the effect of the mutation in detail. *In vitro* assays showed that the E1099K mutation increased the activity of *NSD2* on nucleosome substrates compared with wild-type *NSD2*.

Finally, the group sought to determine the therapeutic potential of inhibiting E1099K *NSD2* in ALL. In six cell lines carrying the mutation, shRNA knockdown decreased growth compared with no knockdown. In mice with a subcutaneously injected E1099K ALL cell line, shRNA knockdown reduced tumor growth.

Results from the Novartis-Broad team were published in *Nature Genetics*. The Broad group was led by Levi Garraway, who is an associate professor at **Harvard Medical School**, an assistant professor at the **Dana-Farber Cancer Institute** and a principal investigator at the Broad Institute.

“The data presented in this paper provide compelling evidence of a driver role for the E1099K mutant of *NSD2* in a subset of pediatric ALL,” said Epizyme EVP and CSO Robert Copeland.

He added that the approach used in the paper may have broad utility for target discovery. “I think the mass spectral method used here is quite elegant and may prove useful in broad efforts at target identification and target credentialing.”

NSD2 challenges

Although the evidence that inhibiting *NSD2* could have therapeutic benefit continues to build, the protein is still a challenging target.

Novartis is tight-lipped about any plans relating to *NSD2* inhibitors, and although at least two academic teams and two companies are pursuing the target, their results have not yet borne fruit.

Licht said that his team is attempting to discover inhibitors of *NSD2* using peptide-based screening and computational modeling. He suggested that progress in developing compounds that hit the target may be slow because it is hard to work with *in vitro*. “It is a difficult protein to work with, it seems to fold poorly *in vitro* and it is more active on assembled nucleosome substrates than on peptides,” he said.

Astex Pharmaceuticals Inc. president Harren Jhoti agreed. “Druggability of the histone methyltransferase protein family seems variable, and *NSD2* lies on the more challenging end of the spectrum. High throughput screening approaches are problematic because *NSD2* is a weakly active enzyme in the recombinant setting and requires whole nucleosomes as substrates,” he said.

He added, “Corporate compound collections may not contain the diversity required to find tractable hits. On the other hand, structure-based approaches are hampered by the lack of a crystal structure for *NSD2*, and although a structure is available for the close homolog *NSD1*, there are likely to be significant differences.”

Licht said that a crystal structure would help, although attempts to crystallize *NSD2* thus far have been unsuccessful.

In 2012, Astex began collaborating with **The Institute of Cancer Research** and **Cancer Research Technology Ltd.** to develop *NSD2* inhibitors.⁶ Astex is being acquired by **Otsuka Pharmaceutical Co. Ltd.**

Despite the challenges, Jhoti said that the clear next step “is to validate *NSD2* as a therapeutic target by testing the effects of a small molecule inhibitor in E1099K-mutant ALL and t(4;14) multiple myeloma tumor models.”

Irfan Asangani, a research investigator at the **University of Michigan Medical School**, told *SciBX* that it is only a matter of time before potent *NSD2* inhibitors are developed. “I predict we will see a great *NSD2* inhibitor within the next couple of years,” he said.

Asangani is named on a patent filed by the University of Michigan covering inhibitors of *NSD2*, but thus far no data for the compounds have been published. Earlier this year, Asangani published work showing that *NSD2* acts downstream of *EZH2* in some cancers.

OncoFusion Therapeutics Inc., a spinout of the University of Michigan Medical School founded by Asangani’s mentor, professor of pathology Arul Chinnaiyan, is developing *NSD2* inhibitors. The company did not return calls seeking comment.

Asangani said that his lab is continuing to develop *NSD2* inhibitors independently from the company. He added that *NSD2* is overexpressed in many cancer types, as is *EZH2*, so inhibitors of *NSD2* could have utility outside of these genetically defined populations.

Nevertheless, Copeland said that interest in *NSD2* as a drug target would largely be driven by the MM population. “While this is an interesting example of a genetic lesion conferring dependence of a specific cancer on a particular histone methyltransferase, I think that the unmet medical need and patient population size of t(4;14)⁺ multiple myeloma will remain the key driver for drug discovery and development of inhibitors of *NSD2*. If such compounds also inhibit

“Druggability of the histone methyltransferase protein family seems variable, and *NSD2* lies on the more challenging end of the spectrum.”

—Harren Jhoti,
Astex Pharmaceuticals Inc.

the E1099K mutant of NSD2, there would be opportunity to test the compounds as therapeutics for this pediatric indication.”

Copeland did not disclose whether Epizyme is developing inhibitors of NSD2.

Novartis also did not disclose whether it is developing NSD2 inhibitors, but Stegmeier told *SciBX* that a patent has been filed by the NIBR-Broad team covering the discovery of oncogenic NSD2-E1099K mutations and molecular chromatin signatures that predict response to NSD2 inhibition.

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COMPANIES AND INSTITUTIONS MENTIONED

Astex Pharmaceuticals Inc. (NASDAQ:ASTX), Dublin, Calif.
Broad Institute of MIT and Harvard, Cambridge, Mass.
Cancer Research Technology Ltd., London, U.K.
Celgene Corp. (NASDAQ:CELG), Summit, N.J.
Dana-Farber Cancer Institute, Boston, Mass.
Eisai Co. Ltd. (Tokyo:4523; Osaka:4523), Tokyo, Japan
Epizyme Inc. (NASDAQ:EPZM), Cambridge, Mass.
Harvard Medical School, Boston, Mass.
The Institute of Cancer Research, Sutton, U.K.
Northwestern University, Evanston, Ill.
Northwestern University Feinberg School of Medicine, Chicago, Ill.
Novartis Institutes for BioMedical Research, Boston, Mass.
Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, Ill.
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Translational tidbits

By Kai-Jye Lou and Lev Osherovich, Senior Writers

Focusing the BRAIN

The NIH's BRAIN initiative has developed a road map for its near-term research priorities, chief among which is conducting a census of brain cells. Whether the ambitious, decades-long project will be funded at anticipated levels will depend on the outcome of Washington's stalled budget talks.

When BRAIN (Brain Research through Advancing Innovative Neurotechnologies) was announced in April, President Barack Obama and NIH director Francis Collins claimed that the project would yield technologies to image and model living human brains and techniques for manipulating brain activity in patients with neurological diseases.

Academic neuroscience researchers expressed mixed views on the initiative. Some liked the prospect for more funding, but others were concerned about the project's seemingly nebulous aims and the possible diversion of research dollars from traditionally focused research.¹

To address concerns about how to proceed with BRAIN, at the time of the project's announcement the NIH convened a working group of 15 prominent neuroscientists to define the project's overall aims and funding priorities.

The working group, which was cochaired by Cornelia Bargmann and William Newsome, published an [interim report on its recommendations](#) in September.

Bargmann is a professor and laboratory head at **The Rockefeller University** and a **Howard Hughes Medical Institute** (HHMI) investigator. Newsome is a professor of neurobiology at **Stanford University** and an HHMI investigator.

The most basic recommendation of the working group was to catalog all the different cell types found in the brain. In its interim report, the group argued that surveying the brains of animal models and human anatomical specimens to establish a census of neuronal and glial cells would help researchers develop standardized models and assays.

Variability in the cells and assays currently used by various laboratories complicates the head-to-head comparison of neuroscience data.

Next, the group recommended creating a large-scale structural map of the brain to uncover functional relationships between various circuits of interconnected neurons.

Toward that goal, the working group endorsed a slew of tool-building projects to enable better data gathering from the living brains of animals and humans, including development of instruments and techniques for recording and computational analysis of brain activity.

Likewise, the group recommended improving the resolution of existing brain imaging techniques such as functional MRI (fMRI) and PET imaging to zoom in on activity in smaller clusters of neurons than is currently possible.

Building tools to manipulate specific circuits of neurons *in vivo* is another priority for the BRAIN project. The working group suggested that a combination of optogenetic, pharmacological and electromagnetic tools should be developed to enable researchers to remotely turn individual neurons on or off.

The working group also recommended developing computational methods and models that integrate whole-brain imaging data with cellular and behavioral assays.

Finally, the working group highlighted the need to train neuroscientists in emerging techniques of brain imaging and manipulation as well as the computational and statistical methods used in the BRAIN project.

Although the scientific picture for BRAIN is becoming clearer, the project's funding prospects are clouded by Washington's budget stalemate.

For fiscal 2014, Obama proposed giving BRAIN about \$110 million from federal agencies, including about \$40 million from the NIH, \$50 million from the **Defense Advanced Research Projects Agency** and about \$20 million from the **National Science Foundation**.

Private organizations including HHMI, the **Allen Institute for Brain Science**, **The Kavli Foundation** and the **Salk Institute for Biological Sciences** planned to contribute at least \$158 million over the next 10 years.

With the NIH and National Science Foundation closed because of the government shutdown, and the possibility of reduced federal funding across the board for fiscal 2014, it is unclear how much new federal money BRAIN will receive.

The BRAIN working group will issue its final recommendations in June 2014.

CRISPR pairings

Less than a year after the initial deluge of results demonstrated the promise of CRISPR-Cas9-based genome editing for inducing site-specific mutations, research tool suppliers have taken notice and are starting to place their bets in the space.

In mid-September, cell line and assay supplier **Horizon Discovery Ltd.** acquired a nonexclusive license to IP from **Harvard University** that will allow the company to commercialize CRISPR (clustered, regularly interspaced short palindromic repeats)-Cas9 (CRISPR-associated protein 9)-based genome-editing technologies for research use.

One week later, rodent and rabbit model supplier **Sage Labs Inc.** augmented its technology portfolio by in-licensing CRISPR-Cas9 genome-editing technologies from **Caribou Biosciences Inc.**

Financial details of the deals are undisclosed.

Horizon and Sage announced the deals about a month after separate research groups from the **Broad Institute of MIT and Harvard**, **Harvard Medical School** and the **Wyss Institute for Biologically Inspired Engineering at Harvard University** published a pair of studies highlighting potential strategies to address the specificity concerns surrounding CRISPR-Cas9-based genome editing.²⁻⁴

The Harvard deal allows Horizon to add CRISPR to its Genesis gene-editing platform, which already includes recombinant adeno-associated virus (rAAV) and zinc finger nuclease (ZFN) technologies.

Horizon holds a nonexclusive license from **Sigma-Aldrich Corp.** to use Sigma's CompoZr ZFN technology. Sigma partnered with **Sangamo BioSciences Inc.** in 2007 to use ZFN technology to develop and commercialize research reagents.

Horizon said that it will use the trio of genome editing technologies in client-led projects and to expand the company's off-the-shelf cell line offerings and related products. Horizon said that it is planning for a near-term launch of a variety of rAAV, CRISPR, and hybrid rAAV and CRISPR gene-editing kits and associated reagents.

Under the Caribou deal, Sage has exclusive rights to use Caribou's CRISPR-Cas9 genome-editing technology to create and commercialize genetically engineered rat models and nonexclusive rights to use the technology to create and commercialize mouse and rabbit models.

Sage said that CRISPR technology will expand its portfolio of animal models and decrease turnaround times for its custom model creation service, SAGEspeed.

Sigma sold its Sage Labs unit for an undisclosed sum to an undisclosed private equity firm in March as part of a reorganization.

PPP roundup

Activity in the public-private partnership space ramped up in September following a relatively quiet August (*see* Table 1, “Selected public-private partnerships for September 2013”). Notable events last month include **AstraZeneca plc**’s announcement of a pair of early stage R&D collaborations covering a broad swath of disease areas, **Servier**’s quartet of collaborations with research institutes in Singapore and China, and the newly formed EpimiRNA consortium.

AstraZeneca’s **MedImmune LLC** unit partnered with the **University of Maryland, Baltimore** to pursue joint research projects relevant to the unit’s core therapeutic areas, including cancer and cardiovascular, metabolic,

respiratory, inflammatory, autoimmune and infectious diseases. Both parties will provide funding and scientists to work on joint projects, with MedImmune planning to contribute at least \$5 million and the university planning to contribute \$1 million over the 5-year collaboration.

MedImmune said that the deal is the first of several planned collaborations to bolster biomedical R&D activity within the state of Maryland.

AstraZeneca also announced a drug discovery alliance with **Hadassah University Hospitals** to discover and develop compounds to treat cancer, respiratory diseases and diabetes. Hadassah scientists will work with teams from AstraZeneca’s Innovative Medicines & Early Development organization for an initial period of three years.

AstraZeneca declined to disclose details.

Meanwhile, Servier signed a trio of research collaborations with the Singapore Immunology Network (SIGN) research unit of the **Agency for Science, Technology and Research (A*STAR)**. Two deals focus on dendritic cell biology in cancer, organ transplantation, inflammation

Table 1. Selected public-private partnerships for September 2013. After a quiet August, public-private partnership activity surged in September. Significant developments included a partnership between the Almac Discovery Ltd. unit of **Almac Group Ltd.** and **Queen’s University Belfast** to discover and develop new cancer treatments, and the newly formed EpimiRNA consortium to study molecular mechanisms and diagnostics for epilepsy and develop microRNA-based therapeutics. Notably, both **AstraZeneca plc** and **Servier** spent the month farming out R&D efforts. AstraZeneca did a pair of deals covering a broad swath of disease areas with academic institutes in the U.S. and Israel, and Servier announced four collaborations with research institutes in Singapore and China.

Source: *BCIQ: BioCentury Online Intelligence*

Companies	Institutions	Business area	Disclosed value	Purpose
Almac Group	Invest Northern Ireland; Queen’s University Belfast	Cancer	£13 million (\$20.2 million)	Three-year deal to discover and develop cancer treatments, including ALM201
Bicoll Group; Biocomputing Platforms Ltd.; DIXI Microtechniques SAS; GABO:mi GmbH; InteRNA Technologies B.V.	Royal College of Surgeons in Ireland; Philipps University of Marburg; University Medical Center Utrecht; University College London; University of Verona; University of Erlangen-Nuremberg; Duke University; University of Campinas; Aarhus University; University of Southern Denmark; European Commission	Neurology	€11.5 million (\$15.4 million)	EpimiRNA consortium to investigate molecular mechanisms, diagnostics and treatments for epilepsy
Biotec Services International Ltd.; Oxford BioMedica plc (LSE:OXB)	Cell Therapy Catapult; Cranfield University; Heart of England NHS Foundation Trust	Gene and/or cell therapy	£7.7 million (\$12.1 million)	Consortium to develop a center of excellence for manufacturing gene-based therapies in the U.K. and improving supply chains
Illumina Inc. (NASDAQ:ILMN); Intel Corp. (NASDAQ:INTC)	Oregon Health & Science University; Leukemia & Lymphoma Society; Stanford University; The University of Texas Southwestern Medical Center; The University of Utah	Cancer	Over \$8.2 million	Acute myeloid leukemia (AML) research initiative to create a profile of possible genetic drivers
AstraZeneca (LSE:AZN; NYSE:AZN)	University of Maryland, Baltimore	Pharmaceuticals	At least \$6 million	Five-year research collaboration focused on disease areas that include cancer and cardiovascular, metabolic, respiratory, inflammation, autoimmune and infectious diseases
Genia Technologies Inc.	Columbia University; Harvard University; NIH	Genomics	\$5.3 million	Collaboration to develop Genia’s NanoTag sequencing technology
GlobeImmune Inc.	Colorado State University; NIH	Infectious disease	\$4 million	Deal to develop Tarmogen products to prevent drug-resistant tuberculosis
Roslin Cells Ltd.	Cell Therapy Catapult	Gene and/or cell therapy	£2 million (\$3.1 million)	Partnership to establish a source of clinical-grade induced pluripotent stem (iPS) cells according to GMP standards in the U.K.

(Continues on p. 7)

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

Companies	Institutions	Business area	Disclosed value	Purpose
OxThera AB; Cobra Biologics AB; SymbioPharm GmbH; Ergomed Clinical Research Ltd.; Galenica Ltd.; K.A.B.S. Laboratories; Bio- Images Research Ltd.	University Hospital Bonn; Civil Hospitals of Lyon; University College London Hospitals; Institute for Microecology; TNO; European Commission	Endocrine/metabolic disease	€2.2 million (\$3 million)	Elimox consortium to develop a bacterial pharmaceutical product using <i>Oxalobacter formigenes</i> to treat primary hyperoxaluria
BioVersys AG	University of Applied Sciences and Arts Northwestern Switzerland; University of Basel; University of Bern; University of Geneva; Zurich University of Applied Sciences; Commission for Technology and Innovation	Infectious disease	CHF2.1 million (\$2.3 million)	Consortium to develop a transcription regulator inhibitory compound that targets bacterial resistance mechanisms at a genetic level to restore efficacy of conventional antibiotics
BioHealth Innovation Inc.	The Johns Hopkins University	Other	Up to \$50,000 per company	Partnership to launch DreamIt Health Baltimore project to accelerate growth of early stage health IT companies
Anida Pharma Inc.	ALS TDI	Neurology	Undisclosed	Partnership to evaluate Anida's neuroprotectin D1 in superoxide dismutase 1 (SOD1) mice as a potential treatment for amyotrophic lateral sclerosis (ALS)
AstraZeneca	Hadassah University Hospitals	Cancer; endocrine/ metabolic disease; pulmonary disease	Undisclosed	Deal to discover and jointly develop compounds to treat cancer, respiratory diseases and diabetes
Bayer AG (Xetra: BAYN)	Broad Institute of MIT and Harvard	Cancer	Undisclosed	Five-year partnership to jointly discover and develop therapeutics that selectively target cancer genome alterations
C4X Discovery Ltd.	University of Southampton	Infectious disease	Undisclosed	Three-year partnership to develop HIV drug candidates derived from cyclic peptides
Evotec AG (Xetra:EVT)	Harvard University	Neurology	Undisclosed	CureMN collaboration to identify compounds that prevent or slow motor neuron loss
ImmunoGenes AG	Massachusetts General Hospital	Cancer	Undisclosed	Collaboration to identify key targets in hematological cancers and generate antibodies against them
Protea Biosciences Inc.	Virginia Commonwealth University	Cancer; Neurology	Unavailable	Partnership to develop methods to elucidate the molecular basis of diseases including cancer and Alzheimer's disease
Servier	Agency for Science, Technology and Research (A*STAR)	Cancer; autoimmune disease; transplantation	Undisclosed	Three collaborations to discover and develop compounds for indications that include cancer, autoimmune diseases and organ transplant
Servier	Chinese Academy of Sciences	Cancer	Undisclosed	Collaboration to develop cancer compound lucitanib (E-3810) in China
Teva Pharmaceutical Industries Ltd. (NYSE:TEVA); Cancer Research Technology Ltd.	Cancer Research UK	Cancer	Undisclosed	Three-year partnership to discover drugs that modulate DNA damage and repair response processes in cancer cells

and autoimmune diseases. The third focuses on identifying genetic predispositions in Asian patients related to drug-induced side effects.

SigN will be responsible for discovery research, whereas Servier will have rights to resulting compounds and will be responsible for development and commercialization. Financial details are undisclosed.

Servier also partnered with the **Chinese Academy of Sciences' Shanghai Institute of Materia Medica (SIMM)** to develop the cancer compound lucitanib (E-3810) in China. The partners will collaborate to run clinical trials, and SIMM also will conduct biomarker research. Servier said that clinical testing of lucitanib in China is scheduled to begin by mid-2014.

The current partnership includes a licensing agreement with SIMM, **Advenchen Laboratories LLC** and **SFFT Developing Co. Ltd.** that expands Servier rights to lucitanib to China.

Last October, Servier acquired exclusive rights to lucitanib outside of the U.S., Japan and China from **EOS S.p.A.** for €45 million (\$57.9 million) up front plus milestones and royalties.⁵ EOS has worldwide rights to lucitanib outside China from Advenchen.

Lucitanib, a small molecule inhibitor of fibroblast growth factor receptor 1 (FGFR1; CD331) and VEGF, is in a Phase I/IIa trial in solid tumors.

Finally, the newly formed EpimiRNA consortium received €11.5 million (\$15.4 million) in funding from the EU's Seventh Framework Program. The consortium is co-coordinated by the **Royal College of Surgeons in Ireland** and **Philipps University of Marburg** and comprised of 6 partners from industry and 10 from academia.

The consortium's focus is on investigating molecular mechanisms and diagnostics for epilepsy and developing microRNA-based treatments that could prevent epilepsy and seizures or reverse epilepsy once it is established.

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Agency for Science, Technology and Research, Singapore
Allen Institute for Brain Science, Seattle, Wash.
AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K.
Broad Institute of MIT and Harvard, Cambridge, Mass.
Caribou Biosciences Inc., Berkeley, Calif.
Chinese Academy of Sciences, Shanghai, China
Defense Advanced Research Projects Agency, Arlington, Va.
EOS S.p.A., Milan, Italy
Hadassah University Hospitals, Jerusalem, Israel
Harvard Medical School, Boston, Mass.
Harvard University, Cambridge, Mass.
Horizon Discovery Ltd., Cambridge, U.K.
Howard Hughes Medical Institute, Chevy Chase, Md.
The Kavli Foundation, Oxnard, Calif.
MedImmune LLC, Gaithersburg, Md.
National Institutes of Health, Bethesda, Md.
National Science Foundation, Arlington, Va.
Philipps University of Marburg, Marburg, Germany
The Rockefeller University, New York, N.Y.
Royal College of Surgeons in Ireland, Dublin, Ireland
Sage Labs Inc., St. Louis, Mo.
Salk Institute for Biological Sciences, San Diego, Calif.
Sangamo BioSciences Inc. (NASDAQ:SGMO), Richmond, Calif.
Servier, Neuilly-sur-Seine, France
SFFT Developing Co. Ltd., Hangzhou, China
Shanghai Institute of Materia Medica, Shanghai, China
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Stanford University, Stanford, Calif.
University of Maryland, Baltimore, Md.
Wyss Institute for Biologically Inspired Engineering at Harvard University, Cambridge, Mass.

KIM-1 driving chronic kidney disease

By Benjamin Boettner, Assistant Editor

Kidney injury molecule 1, a protein that helps overcome acute kidney injury, now has been shown by **Harvard Medical School** researchers to trigger the onset of chronic kidney disease.¹ Companies modulating the target thus need to scrutinize the therapeutic window of their molecules.

The body typically repairs nonfibrotic kidney damage inflicted by acute toxic or ischemic insults without long-term sequelae. However, some patients who recover from an acute kidney injury are left with an increased risk for developing chronic kidney disease (CKD), which manifests itself by fibrosis, impaired kidney parenchyma and cardiovascular malfunction.²

Kidney injury molecule 1 (KIM-1) is a cell surface receptor that is expressed on kidney epithelial cells and by distinct T cell populations and hepatocytes. In acutely injured kidneys, KIM-1 is thought to confer a phagocytic phenotype on kidney epithelial cells that contributes to recovery by removing debris from cells that died during the injury.³

In patients with CKD, on the other hand, elevated *KIM-1* expression has been shown to occur close to inflammatory cells and fibrotic tissue.⁴ However, whether KIM-1 actively promotes kidney fibrosis has not been resolved. The fibrotic reaction at the heart of CKD is triggered by inflammation-induced proliferation and recruitment of myofibroblasts that deposit extracellular matrix proteins. Those proteins, in turn, obstruct the kidney parenchyma.

To shed some light on the mechanistic role of KIM-1 in CKD, a team led by Benjamin Humphreys and Joseph Bonventre first used an established model of fibrosis to determine the dynamics of KIM-1 expression after acute injury in the absence of fibrosis. They showed that KIM-1 levels rapidly spike in surviving proximal epithelial cells, subside during recovery but, importantly, remain above normal thereafter.

Humphreys is an assistant professor in the department of medicine at Harvard Medical School and an associate physician of medicine at **Brigham and Women's Hospital**. Bonventre is a professor at Harvard Medical School and chief of the renal unit and director of the bioengineering division at Brigham and Women's Hospital.

Next, the researchers created a mouse model in which *Kim-1* was overexpressed in kidney epithelial cells. The animals developed tubulointerstitial inflammation and fibrosis six weeks after birth and died of progressive renal failure about five weeks later.

"The genetic model does not require injury to trigger the pathogenic changes leading to CKD," noted Oxana Ibraghimov-Beskrovnyaya, VP of cell biology and distinguished scientific fellow at **Sanofi's Genzyme Corp.** unit. "The model should be uniquely useful for studying the role of a maladaptive KIM-1 response in kidney fibrosis as well as for testing novel therapeutic modalities."

Similar to human CKD, fibrotic disease in the mice was accompanied by cardiac remodeling and hypertension.

Mechanistically, overexpression of Kim-1 in epithelial cells induced proinflammatory cytokines, which triggered the recruitment of macrophages into the interstitial lumen and the initiation of the fibrotic process.

In a model of fibrosis, mice producing a partial loss-of-function version of Kim-1 did not develop the condition.

Humphreys told *SciBX* that the data show that "persistent KIM-1 expression clearly is harmful."

He thinks that the findings may help explain why humans, in particular the elderly, often develop CKD following an episode of acute kidney injury.

"We hypothesize that *KIM-1* induction after an episode of acute kidney injury is not downregulated in some patients, and this causes a simmering maladaptive repair response characterized by a proinflammatory environment that ultimately causes parenchymal loss, fibrosis and CKD," he said.

"The general notion of KIM-1 as a protective protein in the kidney has to be revised now, and in fact the study shows that KIM-1 exerts a bimodal function in a very organized fashion during disease progression in mice. It will have to be seen now whether this is also the case in humans," said Raghu Kalluri, chair of the Department of Cancer Biology at **The University of Texas MD Anderson Cancer Center**.

The findings were published in *Nature*.

All aKIMbo

Humphreys' team plans to use conditional models to overexpress Kim-1 exclusively in adult mice. He said that this should more closely emulate what happens in humans after an episode of acute injury and should help distinguish the beneficial effects of KIM-1 in the acute setting and its negative effects in the chronic arena.

Humphreys thinks that any attempts to target KIM-1 may be more complicated than simply

inhibiting all of its function.

"In acute kidney injury, KIM-1 function is good, in CKD it becomes bad—that is what makes drug development challenging," agreed Kalluri.

In addition, KIM-1 is expressed in other organs like the lung or liver. Thus, said Kalluri, "systemic inhibition of KIM-1 could cause unanticipated effects at these sites."

To validate KIM-1 as a viable target in CKD, Paul Rennert wanted to see "a study to show that kidney injury leading to fibrosis is reduced or ablated in *Kim-1* knockout mice. A similar study could be done using specific anti-mouse Kim-1 mAbs to block Kim-1 activity in normal mice subjected to acute kidney injury."

Such evidence would unequivocally show that KIM-1 is detrimental to regeneration in CKD. Rennert is CSO of **X-Rx Discovery Inc.** He previously was a principal investigator at **Biogen Idec Inc.**, where he studied the role of KIM-1 in immunity and infections.

Indeed, the expression of KIM-1 in immune cells could further complicate discovery efforts in kidney disease. "Since KIM-1 expressed by cells of the immune system can bind to KIM-1 expressed by the transgene,

"The general notion of KIM-1 as a protective protein in the kidney has to be revised now, and in fact the study shows that KIM-1 exerts a bimodal function in a very organized fashion during disease progression in mice. It will have to be seen now whether this is also the case in humans."

**—Raghu Kalluri,
The University of Texas
MD Anderson Cancer Center**

it becomes difficult to fully understand the role of the immune system in the presented mouse model,” said Rennert.

He suggested that strain-matched *Kim-1* knockout immune cells could be used in an adoptive transfer model to distinguish the immune system and the stromal effects of Kim-1 expression in renal injury and fibrosis models.

Such studies “could be complemented by mAb studies in wild-type rodents that would inhibit KIM-1 more broadly across different cell types,” he said.

The Harvard team holds issued patents on KIM-1 for diagnostics and therapeutics and has filed additional patent applications based on studies in mouse and zebrafish models of diabetic nephropathy kidney disease.

The findings are available for licensing, and KIM-1 patents have been licensed by **Johnson & Johnson**, Genzyme, Biogen Idec and undisclosed companies.

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Sanofi (Euronext:SAN; NYSE:SNY), Paris, France
The University of Texas MD Anderson Cancer Center, Houston, Texas
X-Rx Discovery Inc., Waltham, Mass.



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Seeing CCR5

By Tracey Baas, Senior Editor

Despite offering a new mechanism for inhibiting HIV, Selzentry maraviroc's sales have languished. **Pfizer Inc.**'s CC chemokine receptor 5 antagonist does not block viruses with tropism for another co-receptor, CXC chemokine receptor 4, and many physicians find tropism assays too costly and too slow.

Now, a Shanghai and La Jolla team has reported the crystal structure of human CC chemokine receptor 5 (CCR5; CD195) bound to Selzentry, which provides a better understanding of how HIV virions interact with co-receptors before gaining cellular entry.¹ The structural snapshot could be used to guide discovery of better versions of viral entry inhibitors.

Maraviroc is marketed by Pfizer in collaboration with **GlaxoSmithKline plc** for patients with CCR5-tropic HIV-1 infection. The small molecule posted combined sales of £96 million (\$126.5 million) in 2012.

HIV gains entry into immune cells when HIV gp120 binds to the cellular receptor CD4 and either of its co-receptors, CXC chemokine receptor 4 (CXCR4; NPY3R) or CCR5. Binding of HIV to CD4 and one of the co-receptors induces structural rearrangements in the gp120-containing trimeric virus envelope complexes, ultimately resulting in fusion of the virus with the cellular membrane and subsequent viral entry.

Most HIV infections occur initially via CCR5, but the virus often evolves to switch co-receptor usage from CCR5 to CXCR4, opening up more cell types to virus infection. This evolution also can lead to resistance against Selzentry.

Obtaining structural information for CCR5 and CXCR4 had been challenging because the two class A GPCRs are so structurally dynamic that they move easily through a range of conformations between active and inactive signaling states, making them difficult to crystallize.

In 2010, a team from **The Scripps Research Institute** led by professor of molecular biology Raymond Stevens was finally able to get CXCR4 crystals using stabilizing approaches, but CCR5 crystals remained elusive because of a host of technical challenges.²

The CXCR4 structure helped guide drug discovery and lead optimization. CXCR4 structure-based virtual ligand screening studies exhibited hit rates of 20%–70%.^{3–6}

Now, a member of Stevens' original team has used what she learned from the CXCR4 study to tackle CCR5. Beili Wu, a professor at the **Shanghai Institute of Materia Medica (SIMM)** of the **Chinese Academy of Sciences**, led her own team and determined the structure of CCR5.

The new team included researchers from SIMM and the Scripps Research Institute, including Stevens.

The first step was making the target less dynamic. Thus, the team engineered a human CCR5 construct with multiple modifications. These included taking out 33 amino acids from the C-terminus to increase thermostability, substituting 3 amino acids to increase both general stability and detergent solubility and substituting one more amino acid to help keep the protein in its inactive state.

To further stabilize the protein's inactive conformation, they focused on crystallizing CCR5 complexed with Selzentry.

The team determined the structure of the complex at 2.7 Å resolution and showed a number of similarities to CXCR4, such as the seven transmembrane α -helices bundling in a similar fashion.

One of the major differences was how the allosteric inverse agonist Selzentry interacted with CCR5 versus how a competitive antagonist, an isothiourea derivative, interacted with CXCR4. Selzentry penetrated more deeply into the CCR5 binding pocket than the competitive antagonist did within the CXCR4 binding pocket. Also, the CCR5 binding pocket was more open than the CXCR4 binding pocket.

Selzentry occupied the bottom of a deep binding pocket surrounded by helices, and the drug's phenyl group reached further down to form hydrophobic interactions with five aromatic residues. The triazole, tropane and cyclohexane moieties of the drug also fit into small subpockets to make individual hydrophobic contacts within the receptor.

These data further confirmed that Selzentry works by locking the receptor structure into an HIV-insensitive conformation rather than by physically blocking the virus from interacting with the receptor.

Results were published in *Science*.

"The CCR5-Selzentry structure reveals a chemokine binding site quite different from the CXCR4 structure. The CCR5 structure is thus a valuable new and different template for the homology modeling of potentially many other important receptors," said Jon Mason, senior research fellow at GPCR drug discovery company **Heptares Therapeutics Ltd.**

Per Johan Klasse, an associate professor of molecular biology and immunology at **Weill Cornell Medical College**, thinks that the CCR5-Selzentry complex structure will enable approaches to improve drug design. "The exact contacts of maraviroc with the receptor can be modified to increase drug potency and also alter the conformational effect of maraviroc binding, making it harder for the virus to overcome the block," he said.

"It might also be useful to use a peptide that represents the third variable region loop of HIV gp120—the binding portion of gp120—instead of inhibitors and solve the structure of CCR5 or CXCR4 with those. Then they could be compared with the inhibited forms," added Klasse.

This would provide multiple snapshots of the receptors and help create molecular dynamic simulations that could better guide drug development.

More snapshots

Wu's team will next undertake structural studies of CCR5 and CXCR4 in complex with HIV gp120 and CD4 to obtain more informative pictures of the process of viral infection.

"The structures of complexes between the co-receptors and gp120-CD4 are needed to fully understand mechanisms of HIV-1 infection. The structural information will help to identify key

"The team made slight changes to the receptor in order to be able to characterize its structure but in doing so might have made substantial functional alterations. Tiny changes in the structure of ligands for this type of receptor can produce large changes in protein functional character that cannot be predicted and will affect how one goes about designing therapeutics."

— Tony Wood, Pfizer Inc.

interactions between gp120 and the co-receptors, which will facilitate the development of new drugs that block the specific interactions,” she said.

Sam Williams, CEO of **C4X Discovery Ltd.**, said that dynamic modeling should be the next step. “X-ray co-crystallography can only provide a static picture of what a ligand looks like when bound to its target. Understanding the behavior of a ligand in solution in the unbound state demonstrates what transition the ligand has to make to bind the target and provides a fuller understanding of the relative binding affinities of different ligands from the same class,” he said.

“Using NMR-based methods for accurate determination of ligand-solution structures would help to provide this dynamic picture and reveal novel routes forward for ligand optimization,” added Thorsten Nowak, senior medicinal chemist at C4X.

Tony Wood, SVP of medicinal chemistry at Pfizer and discoverer of Selzentry, agreed that molecular dynamics would provide a richer understanding of fundamental interactions between drug and receptor with which to guide drug research.

He also said that it is difficult to know if the modification used to stabilize the human CCR5 construct made substantial changes to the character of CCR5 without more functional evaluation. “The team made slight changes to the receptor in order to be able to characterize its structure but in doing so might have made substantial functional alterations,” he said. “Tiny changes in the structure of ligands for this type of receptor can produce large changes in protein character that cannot be predicted and will affect how one goes about designing therapeutics.”

“Another more complex question that is not entirely clear is does the field need another CCR5 agonist?” asked Wood. “If yes, CCR5-targeting therapeutics have to be developed with caution so that they are safe from a cardiovascular and hepatic point of view.”

Selzentry’s label includes a black box warning about hepatotoxicity, as well as warning language about an increased risk of cardiovascular events.

Nevertheless, the SIMM team already has performed structure-based drug design and has obtained several lead compounds with more potent antiviral effects than Selzentry.

The team’s CCR5 structure-based drug discovery project includes four SIMMs groups. Professor Hong Liu is leading compound synthesis, Deputy Director and Professor Hualiang Jiang is leading drug design, Professor Xin Xie is leading functional assays and Wu will continue to lead structural biology. Each scientist also played a role in the CCR5 structure project.

The findings from the study are not patented.

Other CCR5 inhibitors in development include **CytoDyn Inc.**’s PRO 140, which is in Phase II trials, and **Tobira Therapeutics Inc.**’s cenicriviroc, a dual CCR5 and CCR2 (CD192) antagonist, which is in Phase II development. Tobira plans to advance the compound to Phase III at the end of 2013.

Baas, T. *SciBX* **6**(39); doi:10.1038/scibx.2013.1086
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Chinese Academy of Sciences, Shanghai, China
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GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Heptares Therapeutics Ltd., Welwyn Garden City, U.K.
Pfizer Inc. (NYSE:PFE), New York, N.Y.
The Scripps Research Institute, La Jolla, Calif.
Shanghai Institute of Materia Medica, Shanghai, China
Tobira Therapeutics Inc., San Francisco, Calif.
Weill Cornell Medical College, New York, N.Y.

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				
Brain cancer	Solute carrier family 2 member 3 (SLC2A3; GLUT3)	Studies in patient samples, mice and cell culture suggest targeting GLUT3 could help treat brain cancer. In cultured brain tumor-initiating cells (BTICs), GLUT3 mRNA and protein expression were greater than that in non-BTICs. In BTICs, small hairpin RNA knockdown of <i>GLUT3</i> decreased cell growth and BTIC-mediated tumor propagation in mice compared with no knockdown. In patient brain tumor samples, high GLUT3 expression correlated with poor survival. Next steps could include design and synthesis of GLUT3 inhibitors for testing in preclinical models of brain cancer. SciBX 6(39); doi:10.1038/scibx.2013.1087 Published online Oct. 10, 2013	Patent and licensing status unavailable	Flavahan, W.A. <i>et al. Nat. Neurosci.</i> ; published online Sept. 1, 2013; doi:10.1038/nn.3510 Contact: Jeremy N. Rich, Cleveland Clinic, Cleveland, Ohio e-mail: richj@ccf.org
Cancer	CREB binding protein (CREBBP; CBP); E1A binding protein p300 (EP300; p300); hypoxia-inducible factor 1 α (HIF1A; HIF1 α)	<i>In vitro</i> and mouse studies suggest peptide inhibitors of HIF1A could help treat cancer. In human breast cancer cells, two stabilized peptide helix mimetics that block the interaction between HIF1A and its coactivators CBP or p300 decreased hypoxia-inducible transcription of target genes including <i>VEGF-A</i> compared with vehicle. In mouse xenograft models of human renal cell carcinoma, one of the mimetics decreased tumor volume compared with no treatment. Next steps could include testing the peptide mimetic in additional animal models. At least seven companies have HIF1A inhibitors in Phase II or earlier testing to treat various cancers. SciBX 6(39); doi:10.1038/scibx.2013.1088 Published online Oct. 10, 2013	Patent and licensing status unavailable	Kushal, S. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Sept. 9, 2013; doi:10.1073/pnas.1312473110 Contact: Paramjit S. Arora, New York University, New York, N.Y. e-mail: arora@nyu.edu Contact: Bogdan Z. Olenyuk, University of Southern California, Los Angeles, Calif. e-mail: bogdan@usc.edu
Cancer	Integrin-linked kinase (ILK); parvin- β (PARVB)	Mouse and cell culture studies suggest inhibiting ILK and PARVB signaling could help prevent tumor metastasis. In murine mammary carcinoma cell lines, small hairpin RNA knockdown of Ilk or Parvb decreased filopodium-like protrusion (FLP) formation and metastatic potential compared with no knockdown. In mice injected with metastatic mammary carcinoma cells, shRNA knockdown of Parvb or Ilk decreased the number of metastatic lesions in the lung compared with no knockdown. Next steps include using mouse models to determine whether and how blockade of this signaling pathway impedes metastasis and whether the blockade of this pathway has any therapeutic value. SciBX 6(39); doi:10.1038/scibx.2013.1089 Published online Oct. 10, 2013	Unpatented; licensing status not applicable	Shibue, T. <i>et al. Cancer Cell</i> ; published online Sept. 12, 2013; doi:10.1016/j.ccr.2013.08.012 Contact: Robert A. Weinberg, Whitehead Institute for Biomedical Research, Cambridge, Mass. e-mail: weinberg@wi.mit.edu

This week in therapeutics (continued)

Indication	Target/ marker/ pathway	Summary	Licensing status	Publication and contact information
Multiple myeloma (MM)	Nuclear SET domain-containing protein 2 (NSD2; MMSET; WHSC1)	<p>Mouse and cell culture studies suggest inhibiting NSD2 activity could help treat t(4;14)-translocated MM. t(4;14) translocations are found in about 10%–20% of MM cases and drive overexpression of NSD2 and fibroblast growth factor receptor 3 (FGFR3; CD333). In MM cell lines with the t(4;14) translocation, small hairpin RNA knockdown of NSD2 decreased proliferation on and adherence to bone marrow stroma compared with no knockdown. In mice injected with MM cells that had doxycycline-inducible NSD2 knockdown, doxycycline decreased tumorigenesis and disease progression compared with no treatment. Next steps could include developing inhibitors of NSD2 (<i>see NSD2 momentum</i>, page 1).</p> <p>SciBX 6(39); doi:10.1038/scibx.2013.1090 Published online Oct. 10, 2013</p>	Patent and licensing status undisclosed	<p>Huang, Z. <i>et al. Cancer Res.</i>; published online Aug. 26, 2013; doi:10.1158/0008-5472.CAN-13-1000 Contact: Min Hu, Novartis Institutes for BioMedical Research, Shanghai, China e-mail: min.hu@novartis.com</p>
Multiple myeloma (MM)	Signal transducer and activator of transcription 3 (STAT3)	<p>Studies in cell culture and patient samples identified STAT3 inhibitors that could help treat MM. In a panel of human MM cell lines, the compounds decreased cell proliferation compared with vehicle and had IC₅₀ values of 2.5–10 μM. In a human MM cell line with high expression of STAT3, the inhibitors decreased STAT3 phosphorylation and increased apoptosis compared with vehicle. In bone marrow samples from patients with MM, the inhibitors decreased tumor cell viability but had no effect on nonmalignant cells from the same patient samples. Next steps could include optimizing STAT3 selectivity and testing in xenograft mouse models of MM.</p> <p>Isis Pharmaceuticals Inc. and AstraZeneca plc have ISIS-STAT3Rx, an antisense inhibitor of STAT3, in Phase II for various cancers.</p> <p>At least three other companies have STAT3 inhibitors in preclinical development.</p> <p>SciBX 6(39); doi:10.1038/scibx.2013.1091 Published online Oct. 10, 2013</p>	Patent and licensing status unavailable	<p>Page, B.D.G. <i>et al. J. Med. Chem.</i>; published online Aug. 22, 2013; doi:10.1021/jm3017255 Contact: Patrick T. Gunning, University of Toronto Mississauga, Mississauga, Ontario, Canada e-mail: patrick.gunning@utoronto.ca Contact: Suzanne Trudel, Princess Margaret Hospital, Toronto, Ontario, Canada e-mail: strudel@uhnres.utoronto.ca</p>
Myelodysplastic syndrome (MDS)	p53	<p>Studies in cell culture and patients suggest antagonizing p53 could help treat the chromosome 5q deletion (del(5q)) subtype of MDS. Patients with MDS can develop anemia and require blood transfusions. In erythroid precursors from patients with del(5q) MDS, an antisense oligonucleotide that decreases p53 levels increased erythroid cell proliferation compared with a control oligonucleotide. In patients with Revlimid lenalidomide-resistant del(5q) MDS who are dependent on blood transfusions, Revlimid plus the p53 antagonist dexamethasone increased erythropoiesis compared with baseline and restored transfusion independence in five of eight patients. Next steps include starting a clinical trial this month in patients with lower-risk MDS.</p> <p>Celgene Corp. markets Revlimid to treat MDS, multiple myeloma (MM) and anemia.</p> <p>SciBX 6(39); doi:10.1038/scibx.2013.1092 Published online Oct. 10, 2013</p>	Provisional patent application filed; available for licensing	<p>Caceres, G. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Sept. 16, 2013; doi:10.1073/pnas.1311055110 Contact: Alan F. List, H. Lee Moffitt Cancer Center & Research Institute, Tampa, Fla. e-mail: alan.list@moffitt.org</p>

This week in therapeutics (continued)

Indication	Target/ marker/ pathway	Summary	Licensing status	Publication and contact information
Ovarian cancer	Fibroblast growth factor 18 (FGF18)	<p>Studies in patient samples and mice suggest inhibiting FGF18 signaling could help treat ovarian cancer. In patient samples, FGF18 upregulation correlated with increased tumor aggressiveness and poor overall survival. In a mouse xenograft model of ovarian cancer, small hairpin RNA knockdown of <i>FGF18</i> decreased tumor angiogenesis and macrophage infiltration compared with no knockdown. In the same model, an FGF receptor (FGFR) inhibitor significantly decreased tumor burden compared with vehicle ($p=0.006$). Next steps include assessing the relevance of FGF18 in orthotopic mouse models of ovarian cancer with FGF ligand trap molecules and FGFR inhibitors. Five Prime Therapeutics Inc. and GlaxoSmithKline plc have GSK2052230, an FGF ligand trap, in Phase I testing to treat solid tumors.</p> <p>At least 15 companies have compounds that inhibit FGFRs in Phase III testing or earlier development to treat various cancers.</p> <p>SciBX 6(39); doi:10.1038/scibx.2013.1093 Published online Oct. 10, 2013</p>	Patent applications filed by Harvard University; available for licensing	<p>Wei, W. <i>et al. J. Clin. Invest.</i>; published online Sept. 9, 2013; doi:10.1172/JCI70625</p> <p>Contact: Michael J. Birrer, Massachusetts General Hospital, Boston, Mass. e-mail: mbirrer@partners.org</p>
Pancreatic cancer	ADAM10; amyloid precursor protein (APP)	<p>Cell culture studies suggest inhibiting ADAM10 or secreted APP could increase the efficacy of Gemzar gemcitabine in pancreatic cancer. In human pancreatic cancer cell lines, pharmacological inhibition of ADAM10, which is frequently overexpressed in pancreatic cancer, was shown to prevent the generation of secreted APP. In human pancreatic cancer cell lines, small interfering RNA against ADAM10 increased Gemzar sensitivity compared with control siRNA. Next steps include evaluating the safety and additive or synergistic effects of the combination in mouse pancreatic cancer models.</p> <p>Eli Lilly and Co. markets the nucleoside analog Gemzar to treat pancreatic and other cancers.</p> <p>SciBX 6(39); doi:10.1038/scibx.2013.1094 Published online Oct. 10, 2013</p>	Unpatented; licensing status not applicable	<p>Woods, N.K. & Padmanabhan, J. <i>J. Biol. Chem.</i>; published online Sept. 10, 2013; doi:10.1074/jbc.M113.459255</p> <p>Contact: Jaya Padmanabhan, University of South Florida, Tampa, Fla. e-mail: jpadmana@health.usf.edu</p>
Skin cancer	Not applicable	<p><i>In vitro</i> and mouse studies suggest treating skin inflammation could help treat or prevent skin squamous cell carcinoma (SCC). In mice, inducible overexpression of c-fos in keratinocytes led to recruitment of CD4⁺ T cells, inflammation and development of preneoplastic lesions. In this mouse model, a topical carcinogen accelerated development of invasive SCCs. In this mouse model, the generic anti-inflammatory drug sulindac decreased tumor size and frequency compared with no treatment. Next steps could include testing anti-inflammatory agents in models of established SCC.</p> <p>SciBX 6(39); doi:10.1038/scibx.2013.1095 Published online Oct. 10, 2013</p>	Patent and licensing status unavailable	<p>Briso, E.M. <i>et al. Genes Dev.</i>; published online Sept. 12, 2013; doi:10.1101/gad.223339.113</p> <p>Contact: Erwin F. Wagner, Spanish National Cancer Research Center (CNIO), Madrid, Spain e-mail: ewagner@cnio.es</p>

This week in therapeutics (continued)

Indication	Target/ marker/ pathway	Summary	Licensing status	Publication and contact information
Cardiovascular disease				
Atherosclerosis	Gremlin 1 (GREM1); macrophage migration inhibitory factor (MIF)	<i>In vitro</i> and mouse studies suggest a GREM1 fusion protein could be used to antagonize MIF and treat atherosclerosis. In an <i>apolipoprotein E (APOE)</i> -deficient mouse model of atherosclerosis, Grem1 and Mif colocalized to atherosclerotic lesions, and <i>in vitro</i> binding assays showed that GREM1 binds to MIF. In <i>ApoE</i> -deficient mice fed a cholesterol-rich diet, a Grem1 fusion protein with better pharmacokinetics than native Grem1 decreased levels of Mif, numbers of macrophages in atherosclerotic lesions and formation of lesions compared with a control fusion protein. Next steps include identifying GREM1-MIF interaction sites. SciBX 6(39); doi:10.1038/scibx.2013.1096 Published online Oct. 10, 2013	Patented application filed; available for licensing	Muller, I. <i>et al. J. Biol. Chem.</i> ; published online Sept. 3, 2013; doi:10.1074/jbc.M113.477745 Contact: Meinrad Gawaz, Eberhard Karls University of Tuebingen, Tuebingen, Germany e-mail: meinrad.gawaz@med.uni-tuebingen.de
Endocrine/metabolic disease				
Hypercholesterolemia; hyperlipidemia	ATP-binding cassette sub-family A member 1 (ABCA1); microsomal triglyceride transfer protein (MTTP; MTP)	Mouse studies suggest inhibiting MTP and ABCA1 in the intestines could help treat hypercholesterolemia and hyperlipidemia. In mice, combined, intestine-specific knockout of <i>Mtp</i> and <i>Abca1</i> decreased acute cholesterol absorption and plasma cholesterol concentrations compared with single knockouts or no knockout. Next steps include designing an agent that inhibits both MTP and ABCA1. Aegerion Pharmaceuticals Inc. and Catalent Pharma Solutions Inc. market the MTP inhibitor Juxtapid lomitapide to treat hypercholesterolemia. Nano Terra Inc. and Kadmon Corp. LLC have KD026, an enterocyte-selective MTP inhibitor, in Phase II testing to treat diabetes and obesity. SciBX 6(39); doi:10.1038/scibx.2013.1097 Published online Oct. 10, 2013	Findings unpatented; unavailable for licensing	Iqbal, J. <i>et al. J. Biol. Chem.</i> ; published online Sept. 9, 2013; doi:10.1074/jbc.M113.501247 Contact: M. Mahmood Hussain, SUNY Downstate Medical Center, Brooklyn, N.Y. e-mail: mahmood.hussain@downstate.edu
Hepatic disease				
Liver disease	Proteasome activator subunit 3 (PSME3)	Mouse studies suggest inhibition of the proteasome activator PSME3 could help treat and prevent liver steatosis. In mice fed a high-fat diet, deletion of <i>Psme3</i> prevented lipid accumulation and onset of liver steatosis. Next steps include analyzing the effects of <i>Psme3</i> loss in other mouse models of obesity. SciBX 6(39); doi:10.1038/scibx.2013.1098 Published online Oct. 10, 2013	Unpatented; licensing status not applicable	Dong, S. <i>et al. Cell Metab.</i> ; published online Sept. 3, 2013; doi:10.1016/j.cmet.2013.08.012 Contact: Chuangui Wang, Institute of Biomedical Sciences, Shanghai, China e-mail: cgwang@bio.ednu.edu.cn Contact: Xiaotao Li, same affiliation as above e-mail: xiaotaol@bcm.edu

This week in therapeutics (continued)

Indication	Target/ marker/ pathway	Summary	Licensing status	Publication and contact information
Infectious disease				
HIV/AIDS	Not applicable	<p>Macaque studies suggest vector-based cytomegalovirus (CMV) vaccines could limit the extent of initial HIV infection and eventually eliminate it. In normal macaques challenged with simian immunodeficiency virus (SIV), preimmunization with a CMV-based vaccine expressing SIV proteins decreased the extent of initial infection in lymph nodes, spleen, bone marrow and other tissues compared with preimmunization using empty vector. During follow-on studies in the immunized macaques that exhibited this limited initial infection, viral loads in plasma and tissue remained below detectable levels with only infrequent, transient episodes of viremia. At the end of the 3.5-year follow-up period, multiple tissues from these macaques exhibited low viral DNA or RNA levels that were indistinguishable from vaccinated, unchallenged macaques. Planned work by TomegaVax Inc. includes testing whether the CMV-based vaccine can control and clear virus in macaques with established SIV infection.</p> <p>SciBX 6(39); doi:10.1038/scibx.2013.1099 Published online Oct. 10, 2013</p>	Patented by Oregon Health & Science University; licensed to TomegaVax	<p>Hansen, S.G. <i>et al. Nature</i>; published online Sept. 11, 2013; doi:10.1038/nature12519 Contact: Louis J. Picker, Oregon Health & Science University, Portland, Ore. e-mail: pickerl@ohsu.edu Contact: Jeffrey D. Lifson, SAIC Frederick Inc., Frederick, Md. e-mail: lifsonj@mail.nih.gov</p>
Tuberculosis	<i>Mycobacterium tuberculosis</i> probable ATP-dependent protease ATP-binding subunit ClpC1 (ClpC1)	<p><i>In vitro</i> studies identified ClpC1 as the target of antituberculosis compound cyclomarin A (CymA), which could guide the design of new ClpC1 inhibitors to treat tuberculosis. CymA has activity against both replicating and nonreplicating tuberculosis, but the 848-amino-acid protein has poor pharmacokinetics. Cocrystallization of CymA in complex with ClpC1 showed that the compound bound the N-terminal domain of ClpC1. Next steps include designing ClpC1 inhibitors with improved therapeutic properties.</p> <p>SciBX 6(39); doi:10.1038/scibx.2013.1100 Published online Oct. 10, 2013</p>	Findings unpatented; licensing status not applicable	<p>Vasudevan, D. <i>et al. J. Biol. Chem.</i>; published online Sept. 10, 2013; doi:10.1074/jbc.M113.493767 Contact: Christian G. Noble, Novartis Institute for Tropical Diseases, Chromos, Singapore e-mail: christian.noble@novartis.com</p>
Musculoskeletal disease				
Osteoporosis	Hypoxia-inducible factor 1 α (HIF1A; HIF1 α)	<p>Mouse studies suggest HIF1A inhibitors could help prevent postmenopausal osteoporosis. In the ovariectomized mouse model of osteoporosis, compared with sham-operated animals, estrogen deficiency increased Hif1a levels in osteoclasts. In the same model, a HIF1A inhibitor decreased osteoclast activation and increased bone mineral density compared with vehicle. Next steps could include determining mechanisms of estrogen-mediated HIF1A regulation.</p> <p>At least seven companies have HIF1A inhibitors in Phase II or earlier testing to treat various cancers.</p> <p>SciBX 6(39); doi:10.1038/scibx.2013.1101 Published online Oct. 10, 2013</p>	Patent application filed; licensing details available from Keio University	<p>Miyauchi, Y. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Sept. 10, 2013; doi:10.1073/pnas.1308755110 Contact: Takeshi Miyamoto, Keio University, Tokyo, Japan e-mail: miyamoto@z5.keio.jp</p>
Neurology				
Nerve damage	Neurotrophic tyrosine kinase receptor 2 (NTRK2; TrkB)	<p>Mouse studies suggest two TrkB agonists could be applied topically to treat nerve damage. In a mouse model of peripheral nerve injury, topical or systemic treatment with either of two previously described TrkB agonists—7,8 dihydroxyflavone and deoxygedunin—both increased axon regeneration compared with controls that did not receive either compound. Next steps include testing the effects of the TrkB agonists on nerve function in mice and other animal models of nerve injury.</p> <p>SciBX 6(39); doi:10.1038/scibx.2013.1102 Published online Oct. 10, 2013</p>	Patent pending; available for licensing	<p>English, A.W. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Sept. 16, 2013; doi:10.1073/pnas.1303646110 Contact: Arthur W. English, Emory University School of Medicine, Atlanta, Ga. e-mail: medae@emory.edu</p>

This week in therapeutics (continued)

Indication	Target/ marker/ pathway	Summary	Licensing status	Publication and contact information
Pulmonary disease				
Cystic fibrosis (CF)	Diacylglycerol kinase- ι (DGKI); epithelial sodium channel (ENaC)	<i>In vitro</i> and cell culture studies suggest DGKI inhibition could help treat CF. An RNAi screen on airway epithelial cells identified DGKI and ciliary neurotrophic factor receptor as activators of ENaC, which is upregulated in CF. In human airway cells and <i>ex vivo</i> mouse tracheas, pharmacological inhibition of DGKI decreased ENaC levels and activity compared with no inhibition. In human airway epithelial cells from patients with CF, inhibition of DGKI decreased both ENaC activity to levels seen in healthy cells and fluid absorption compared with no inhibition. Next steps could include testing DGKI inhibition in animal models of CF. Parion Sciences Inc. has the ENaC inhibitor P-552 in Phase II testing to treat CF and xerostomia. SciBX 6(39); doi:10.1038/scibx.2013.1103 Published online Oct. 10, 2013	Patent application filed; available for exclusive licensing	Almaça, J. <i>et al. Cell</i> ; published online Sept. 12, 2013; doi:10.1016/j.cell.2013.08.045 Contact: Margarida D. Amaral, University of Lisboa, Lisboa, Portugal e-mail: mdamaral@fc.ul.pt



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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			
Bacterial cytological profiling (BCP) to identify the mechanism of action for antibacterial compounds	Fluorescence imaging-based BCP can help identify the mechanism of action for antibacterial compounds. BCP distinguished between inhibitors of five major biological pathways including translation, transcription, DNA replication, membrane synthesis and peptidoglycan synthesis. BCP also distinguished subclasses of inhibitors within each of the five classes. In <i>Escherichia coli</i> grown in the presence of compounds at five times minimum inhibitory concentration, BCP revealed that spirohexenolide A—a compound with an unknown mechanism of action—caused a collapse in proton motive force and induced a phenotype similar to that initiated by the antibacterial peptide nisin. Next steps include using BCP to screen for new antibacterial compounds and developing BCP for use in other pathogens. SciBX 6(39); doi:10.1038/scibx.2013.1104 Published online Oct. 10, 2013	Patent application filed; licensed to Linnaeus Bioscience Inc.	Nonejuie, P. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Sept. 17, 2013; doi:10.1073/pnas.1311066110 Contact: Joe Pogliano, University of California, San Diego, La Jolla, Calif. e-mail: jpogliano@ucsd.edu
Mass spectrometry profiling of histone modifications	Mass spectrometry profiling of histone modifications could be used to discover new cancer targets that modify chromatin. Mass spectrometry analysis of 42 combinations of histone H3 modifications across 115 cancer cell lines enabled partitioning of cell subsets by chromatin state. Further DNA sequence analysis and gene expression profiling led to the identification of a subgroup of acute lymphoblastic leukemia (ALL) cells carrying E1099K activating mutations in the <i>nuclear SET domain-containing protein 2 (NSD2; MMSET; WHSC1)</i> methyltransferase. In cell culture and mouse xenograft models carrying this mutation, small hairpin RNA knockdown of <i>NSD2</i> decreased growth compared with no knockdown. Next steps include expanding the method for use in patient stratification and selection (<i>see NSD2 momentum, page 1</i>). SciBX 6(39); doi:10.1038/scibx.2013.1105 Published online Oct. 10, 2013	Patent application filed covering discovery of oncogenic <i>NSD2-E1099K</i> mutations and molecular chromatin signatures that predict response to <i>NSD2</i> inhibition; licensing status undisclosed	Jaffe, J.D. <i>et al. Nat. Genet.</i> ; published online Sept. 29, 2013; doi:10.1038/ng.2777 Contact: Frank Stegmeier, Novartis Institutes for BioMedical Research, Cambridge, Mass. e-mail: frank.stegmeier@novartis.com Contact: Levi A. Garraway, Broad Institute of MIT and Harvard, Cambridge, Mass. e-mail: levi_garraway@dfci.harvard.edu
Method for expressing large genes in cardiomyocytes	A method for expressing large genes in cardiomyocytes could be useful for creating new models and assays. It is challenging to use conventional viral vectors to transfect cells with genes larger than 6 kb because of limits in the vector's packaging capacity. The new method, called split-intein protein transsplicing, involves splitting the sequence that encodes a large protein into two smaller parts that incorporate an intein, which is a protein-splicing element that promotes the joining of two polypeptide fragments. In human cardiomyocytes, adenovirus-mediated transduction of two halves of the 6.6 kb calcium channel L-type $\alpha 1c$ subunit resulted in expression of the full-length subunit and functional L-type calcium channels. Next steps include testing the method with other large proteins. SciBX 6(39); doi:10.1038/scibx.2013.1106 Published online Oct. 10, 2013	Unpatented; available for licensing	Subramanyam, P. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Sept. 3, 2013; doi:10.1073/pnas.1308161110 Contact: Henry M. Colecraft, Columbia University, New York, N.Y. e-mail: hc2405@columbia.edu
Computational models			
Web-based platform to identify cancer driver mutations across tumor types based on new and existing sequencing data	A computational model called IntOGen-mutations could help to identify mutations that drive tumor formation. The platform integrates sequencing data from tumor genomes and genome analyzers to a scale of hundreds of thousands of genomes. The platform predicts the functional impact of nonsynonymous somatic tumor mutations on protein and pathway function. Next steps include updating the platform with more somatic mutation datasets from tumor genomes and enriching it with data on protein-drug interactions. SciBX 6(39); doi:10.1038/scibx.2013.1107 Published online Oct. 10, 2013	Unpatented; available for licensing through the Pompeu Fabra University Technology Transfer Office; platform accessible at http://www.gitools.org/datasets/	Gonzalez-Perez, A. <i>et al. Nat. Methods</i> ; published online Sept. 15, 2013; doi:10.1038/nmeth.2642 Contact: Nuria Lopez-Bigas, Pompeu Fabra University, Barcelona, Spain e-mail: nuria.lopez@upf.edu

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Disease models			
Induced neuronal (iN) cells from mouse embryonic fibroblasts to model neurological diseases	<i>In vitro</i> studies suggest iN cells could be useful for developing neurological disease models. In culture with primary mouse neurons, iN cells created from wild-type or autism-associated, <i>neuroligin 3 (Nlgn3)</i> -mutant mouse embryonic fibroblasts formed normal synaptic connections with neighboring neurons. In the <i>Nlgn3</i> -mutant iN cells, both GABA _A receptor- and AMPA-type glutamate receptor-mediated synaptic transmission was lower than that seen in iN cells from wild-type mice, which recapitulates the phenotype of hippocampal neurons in <i>Nlgn3</i> -mutant mice. Next steps could include using iN cells to model neurological diseases. SciBX 6(39); doi:10.1038/scibx.2013.1108 Published online Oct. 10, 2013	Patent and licensing status unavailable	Chanda, S. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Sept. 17, 2013; doi:10.1073/pnas.1316240110 Contact: Thomas C. Südhof, Stanford University School of Medicine, Stanford, Calif. e-mail: tcs1@stanford.edu Contact: Marius Wernig, same affiliation as above e-mail: wernig@stanford.edu
Drug platforms			
Crystal structure of the dopamine transporter in complex with a tricyclic antidepressant	The crystal structure of the dopamine transporter in complex with the tricyclic antidepressant nortriptyline could help guide the design of new antidepressants. Analysis of the crystal structure of the <i>Drosophila</i> dopamine transporter, which shares homology with the human transporter, in complex with Pamelor nortriptyline showed that the drug blocks substrate binding and locks the transporter in an outward-open conformation. The structure also revealed a binding site for cholesterol that helps stabilize the outward-open confirmation. Next steps could include using the structural information to rationally design new antidepressants. Mallinckrodt plc markets Pamelor to treat depression. SciBX 6(39); doi:10.1038/scibx.2013.1109 Published online Oct. 10, 2013	Patent and licensing status unavailable	Penmatsa, A. <i>et al. Nature</i> ; published online Sept. 15, 2013; doi:10.1038/nature12533 Contact: Eric Gouaux, Oregon Health & Science University, Portland, Ore. e-mail: gouaux@ohsu.edu
Crystal structure of Selzentry maraviroc-bound HIV-1 co-receptor CC chemokine receptor 5 (CCR5; CD195)	The crystal structure of HIV-1 co-receptor CCR5 bound by the allosteric inhibitor Selzentry maraviroc could help to guide design of therapies for HIV-1 infection. The crystal structure of the complex was determined at 2.7 Å resolution and showed Selzentry bound at a site distinct from proposed recognition sites for chemokines and HIV gp120. Crystal structure-based modeling showed that different charge distributions and steric hindrances in the co-receptor ligand-binding pocket could be major determinants for HIV-1 co-receptor selectivity. Next steps include structural studies of CCR5 and CXCR4 chemokine receptor 4 (CXCR4; NPY3R) in complex with the HIV envelope protein gp120 and CD4 to obtain more insight into the process of viral infection. Selzentry is marketed by Pfizer Inc. to treat HIV/AIDS. CytoDyn Inc.'s CCR5 inhibitor, PRO 140, is in Phase II trials. Tobira Therapeutics Inc. has the dual CCR5 and CCR2 (CD192) antagonist cenicriviroc in Phase II trials to treat HIV/AIDS. (<i>see Seeing CCR5, page 11</i>) SciBX 6(39); doi:10.1038/scibx.2013.1110 Published online Oct. 10, 2013	Unpatented; licensing status not applicable	Tan, Q. <i>et al. Science</i> ; published online Sept. 12, 2013; doi:10.1126/science.1241475 Contact: Beili Wu, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, China e-mail: beiliwu@simm.ac.cn
Integrated approach to accelerate biomimetic material engineering	An integrated platform that combines RNA-seq with standard proteomics and materials science approaches could accelerate the development of new biomimetic materials. The platform involves generating a transcriptome database for a tissue of interest using RNA-seq and then using proteomics tools to identify the sequence and structure of relevant proteins that have a desired function or property. The approach was used to identify a shock-absorbing elastomer protein from the egg capsule of a marine snail, an underwater adhesive protein from the byssal complex of a mussel and a silk-like protein from squid sucker ring teeth. Recombinant forms of the silk-like protein were generated and used to build surfaces and films with elastic moduli and stiffness superior to those of many other engineered polymers. Next steps include testing the engineered biomaterials as scaffolds in cell and tissue cultures and evaluating their <i>in vivo</i> biocompatibility and degradation rates. SciBX 6(39); doi:10.1038/scibx.2013.1111 Published online Oct. 10, 2013	Patent and licensing status undisclosed	Guerette, P.A. <i>et al. Nat. Biotechnol.</i> ; published online Sept. 8, 2013; doi:10.1038/nbt.2671 Contact: Ali Miserez, Nanyang Technological University, Singapore e-mail: ali.miserez@ntu.edu.sg

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
MicroRNA and small interfering RNA combination therapy for cancer	<p>Mouse and cell culture studies suggest combined use of miRNA and siRNA against a target could be useful for treating cancer. In human ovarian cancer cell lines, miR-520d-3p was shown to be tumor suppressive and decrease EPH receptor A2 (EPHA2) and EPHB2 expression compared with no treatment. In two mouse xenograft models of ovarian cancer, liposomes loaded with miR-520d-3p and siRNA against EPHA2 inhibited growth more potently than liposomes loaded with one of the two RNAs. Next steps could include testing the siRNA and miRNA combination in other tumor models with elevated EPHA2 expression.</p> <p>SciBX 6(39); doi:10.1038/scibx.2013.1112 Published online Oct. 10, 2013</p>	Patent and licensing status unavailable	<p>Nishimura, M. <i>et al. Cancer Discov.</i>; published online Sept. 3, 2013; doi:10.1158/2159-8290.CD-13-0159 Contact: George A. Calin, The University of Texas MD Anderson Cancer Center, Houston, Texas e-mail: gcalin@mdanderson.org</p>
Protease-resistant cytotoxic antibodies	<p>Engineered, protease-resistant, cytotoxic, therapeutic antibodies could have better efficacy than nonresistant counterparts. In protease incubation assays, combined mutations in the C_H2 and hinge region of an IgG1 increased stability compared with that of the parent antibody. In peripheral blood mononuclear cells, opsonized human lymphoma and adenocarcinoma cell lines, IgG1 antibodies that have mutations in the C_H2 and hinge regions showed greater antibody-mediated cytotoxicity or antibody-dependent macrophage killing than IgG1 antibodies that have mutations in just one of the two regions. In nonhuman primates, the two-region mutant antibodies increased B cell depletion compared with saline. Next steps include testing the protease-resistant antibodies in preclinical models of cancer and autoimmune diseases.</p> <p>SciBX 6(39); doi:10.1038/scibx.2013.1113 Published online Oct. 10, 2013</p>	Patent and licensing status undisclosed	<p>Kinder, M. <i>et al. J. Biol. Chem.</i>; published online Aug. 28, 2013; doi:10.1074/jbc.M113.486142 Contact: Randall J. Brezski, Janssen R&D LLC, Spring House, Pa. e-mail: rbrezski@its.jnj.com</p>
Treating inflammation using mesenchymal stem cells (MSCs) overexpressing <i>P selectin glycoprotein ligand-1 (PSGL-1; CD162; SELPLG)</i> , <i>Sialyl-LewisX (SLeX)</i> and <i>IL-10</i>	<p>MSCs overexpressing <i>PSGL-1</i>, <i>SLeX</i> and <i>IL-10</i> could be used to treat inflammation. In mice with lipopolysaccharide (LPS)-induced ear inflammation, retro-orbitally injected MSCs transfected with <i>Psgl-1</i> and <i>SLeX</i>-synthesizing $\alpha(1,3)$ fucosyltransferase (<i>Fut7</i>) mRNA had stronger interactions with the inflamed endothelium than unmodified MSCs. In the same model, systemically injected MSCs transfected with <i>Psgl-1</i>, <i>Fut7</i> and <i>IL-10</i> mRNA increased IL-10 levels in the ear and decreased inflammation by about 50% compared with injected MSCs transfected with <i>Psgl-1</i> and <i>Fut7</i> mRNA. Next steps include testing the MSCs in several preclinical animal models.</p> <p>Wibi + Works LLC has Antimunocel, an anti-inflammatory, MSC-based product, in Phase I testing to treat rheumatoid arthritis (RA).</p> <p>SciBX 6(39); doi:10.1038/scibx.2013.1114 Published online Oct. 10, 2013</p>	Cell engineering approaches patented; available for licensing	<p>Levy, O. <i>et al. Blood</i>; published online Aug. 26, 2013; doi:10.1182/blood-2013-04-495119 Contact: Jeffrey M. Karp, Harvard Medical School, Boston, Mass. e-mail: jeffkarp.bwh@gmail.com</p>
Imaging			
Heat shock protein 90 (Hsp90) inhibitors tethered to radioiodinated or optical probes for noninvasive breast cancer imaging	<p><i>In vitro</i> and mouse studies suggest Hsp90 inhibitors tethered to optical and radioiodinated probes could help detect and treat breast cancers. In breast cancer cells with ectopic expression of Hsp90, fluorophore-tethered Hsp90 inhibitors specifically bound surface-exposed Hsp90 and were internalized. In mice with breast cancer xenografts, radioiodinated Hsp90 inhibitors specifically accumulated in breast cancer cells and enabled noninvasive tumor imaging. Next steps include demonstrating that the probes selectively target the tumors over healthy tissues in microdosing trials in humans and exploring therapeutic approaches using tethered Hsp90 inhibitors.</p> <p>Synta Pharmaceuticals Corp.'s Hsp90 inhibitor, ganetespib, is in Phase III testing to treat non-small cell lung cancer (NSCLC). The company has Hsp90 inhibitor–drug conjugates designed for tumor cell delivery in preclinical testing.</p> <p>At least 13 other companies have Hsp90 inhibitors in Phase II or earlier testing to treat cancers.</p> <p>SciBX 6(39); doi:10.1038/scibx.2013.1115 Published online Oct. 10, 2013</p>	Patent application filed; available for licensing	<p>Barrott, J.J. <i>et al. Chem. Biol.</i>; published online Sept. 12, 2013; doi:10.1016/j.chembiol.2013.08.004 Contact: Timothy A. Haystead, Duke University, Durham, N.C. e-mail: hayst001@dm.duke.edu</p>

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Stimulated Raman scattering (SMS) microscopy for label-free imaging of tumor-infiltrated brain tissues during surgery	<p>Mouse studies suggest SRS microscopy could help detect tumor margins during brain cancer surgery without using a molecular label. In mice with human glioblastoma multiforme xenografts, SRS imaging was able to differentiate tumor tissue from normal brain tissue <i>ex vivo</i> and during surgery and was comparable to microscopy using the hematoxylin and eosin (H&E) stain. In brain samples from patients with glioblastoma, SRS imaging results corresponded with tumor margins identified with H&E staining. Next steps include developing a clinical system for the technology and establishing safety and efficacy.</p> <p>SciBX 6(39); doi:10.1038/scibx.2013.1116 Published online Oct. 10, 2013</p>	<p>Findings patented; Leica Microsystems GmbH has co-exclusive rights for research microscopy; Invenio Imaging Inc. has an option for a co-exclusive research microscopy license and an exclusive license in all other fields; unavailable for licensing</p>	<p>Ji, M. <i>et al. Sci. Transl. Med.</i>; published online Sept. 4, 2013; doi:10.1126/scitranslmed.3005954 Contact: X. Sunney Xie, Harvard University, Cambridge, Mass. e-mail: xie@chemistry.harvard.edu</p>

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