

THIS WEEK**ANALYSIS****COVER STORY****1 Personalized medicine gets personal**

Epithelial cancers are the most common malignancies, but immunotherapy development has been stymied because the low mutation frequency of these tumors elicits muted mutation-specific T cell responses. An NCI team has now used next-generation sequencing to identify such rare mutations in one patient and has developed an autologous cell therapy.

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By Tracey Baas, Senior Editor

Epithelial cancers are the most common malignancies, but immunotherapy development has been stymied because of the difficulty in identifying targets that are not expressed on normal tissues. A **National Cancer Institute** team has now used a next-generation sequencing approach to identify such rare mutations in one patient and determine which, if any, are recognized by the immune system. The team then developed an autologous cell therapy against one of the mutations that led to cancer regression and disease stabilization.¹

The researchers now need to show that the personalized method can provide similar results for unique mutations in other patients and that the approach can further be generalized to treat large numbers of patients.

"It isn't known at present how frequently actionable, i.e., immunogenic, mutations are to be found commonly in epithelial cancers," said Michel Sadelain, director of the **Memorial Sloan-Kettering Cancer Center's** Center for Cell Engineering and cofounding scientist of **Juno Therapeutics Inc.** "Methods to rapidly identify the relevant immunogenic mutations are direly needed."

The NCI team, led by Steven Rosenberg, set out to identify mutation-specific tumor-infiltrating lymphocytes (TILs) in epithelial cancers and characterize the TIL responses against the tumors.

Rosenberg is chief of surgery at the NCI and a professor of surgery at the **Uniformed Services University of the Health Sciences** and **George Washington University School of Medicine and Health Sciences**.

His group focused on one patient with widely metastatic cholangiocarcinoma—a rapid and incurable form of GI cancer that arises from mutated epithelial cells in the bile ducts.

The team obtained lung metastatic tissue to use for whole-exome sequencing and identified 26 mutations.

To determine if the patient's TILs could recognize and react to any of these mutations, the team transfected RNAs representing the 26 mutations into *ex vivo* antigen-presenting cells from the patient and cocultured them with the patient's TILs.

The researchers identified one set of CD4⁺ T cells that specifically recognized dendritic cells presenting an ErbB2 interacting protein (ERBB2IP) antigen containing an E805G mutation via the T cell receptor (TCR) Vβ22⁺.

The patient received adoptive cell therapy that used about 42 billion expanded TILs and included more than 10 billion of the CD4⁺,

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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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ERBB2IP^{E805G}-reactive T cells. The time from whole-exome sequencing to first cell therapy dosing was about six weeks.

The treatment resulted in up to 29% tumor regression in the patient's lung and liver lesions. Disease stabilization lasted for about 13 months, after which disease progressed in the lungs but not the liver.

Following relapse, the patient was treated with a T cell product consisting of a highly enriched population of Vβ22⁺, CD4⁺, ERBB2IP^{E805G}-reactive TILs. The patient showed more rapid tumor regression than that seen with the previous dosing, and tumors are still regressing at 7 months.

The results were published in *Science*.

“It isn’t known at present how frequently actionable, i.e., immunogenic, mutations are to be found commonly in epithelial cancers. Methods to rapidly identify the relevant immunogenic mutations are direly needed.”

—*Michel Sadelain,*
Memorial Sloan-Kettering
Cancer Center

Moving to prime time

Rosenberg cautioned that much more work is needed to turn the method into a therapy suitable for widespread use.

“Although our one-patient study demonstrates that low-frequency mutation-specific reactive T cells can be found and expanded from patient TILs to generate a T cell product to treat epithelial cancers, this strategy is not yet ready for prime time,” said Rosenberg. “We need more than an N of one.”

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“Although our one-patient study demonstrates that low-frequency mutation-specific, reactive T cells can be found and expanded from patient TILs to generate a T cell product to treat epithelial cancers, this strategy is not yet ready for prime time. We need more than an N of one.”

**—Steven Rosenberg,
National Cancer Institute**

populations will be easier in some patients than others, and it is not clear how broadly deployable this type of personalized therapy can be made to other cancer centers.”

Rosenberg agreed. “We have done some additional preliminary work with three other patients who have epithelial-derived colorectal cancers,” he told *SciBX*. “We used whole-exome sequencing to identify cancer-associated mutations in their metastatic tissues. When we used the cocultures of patient TILs and RNA-transfected APCs as described in our study, we found patient-specific T cells that were mutation reactive in two of the three patients.”

“Many mutations may not be targeted by a T cell population because the immune system might not process the antigen in a way that would

Michael Gladstone, an associate in the life sciences group at **Atlas Venture**, said that the strategy might be more practical if it were redirected to target frequent cancer mutations rather than patient-specific mutations.

“It would be helpful to see how readily and robustly mutation-specific tumor antigens can be identified from exome sequencing in different patients and different tumor types,” said Gladstone. “It is possible that identifying potent, mutation-specific T cell

be recognized by T cells,” continued Rosenberg. “Our method provides the opportunity to identify endogenous T cell populations that can be used for cell therapy but depends on the existence of an endogenous, patient-specific, mutation-reactive T cell population.”

Gladstone said that because of the complexity of the NCI’s cell therapy procedure, it would likely be reserved for the most severe and treatment-refractory patents. He did say it would be more scalable if patients were instead screened for a panel of relatively frequent mutations.

“In this way, cancer centers could establish master cell banks of relevant antigen-presenting cells for TIL expansion or could generate engineered TCRs or CARs [chimeric antigen receptors] that can be ectopically expressed in autologous or allogeneic T cells via viral transduction,” said Gladstone.

The NCI has filed for a patent application covering the findings.

Baas, T. *SciBX* 7(21); doi:10.1038/scibx.2014.602

Published online May 29, 2014

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New York's biotech beginnings

By C. Simone Fishburn, Senior Editor

New York has long produced top science but has struggled to retain and develop its own innovations. The city says it hopes a flurry of public-private partnerships, real estate developments and high-profile academic appointments will help establish it as a biotech hub. But VCs say New York will have to produce or attract experienced management in order to persuade them to seed local companies.

Unlike the translational hubs in the San Francisco Bay Area and Boston that sprouted spontaneously, the interest in New York is the result of city policies to grow the biotech industry in the region.

Maria Gotsch, president and CEO of the **Partnership Fund for New York City**, told *SciBX* that the desire to promote biotech dates to the early 2000s, as leaders of several city institutions noticed a mismatch between the amount and quality of life sciences research and the number of companies being created.

Gotsch noted that New York City contains nine of the country's top medical centers, and the state ranks in the top three for NIH awards. However, until recently, the majority of biotech innovations from many top New York institutions were used to launch companies in other cities.

"Keeping commercialization of biomedical sciences in New York is a problem we've been working on for the last decade," Gotsch told *SciBX*. "In the early days, a VC would fly in, go along First Avenue, stand outside Rockefeller and bring three things: a CEO, a bag of cash and a moving van to take it somewhere else."

There were myriad reasons that academic innovations ended up elsewhere, including insufficient lab space, a dearth of commercial interest and a lack of biotech-focused venture firms.

In the last four years, New York has addressed the first two issues by finding space and money for new labs and creating several significant early stage partnerships between academia and industry. By recruiting academic leaders with industry experience and launching commercially focused translational programs, the city hopes to attract venture funding and create a biotech ecosystem.

Landing biotech

According to Gotsch, one of the key challenges to starting companies in New York was the limited availability of affordable real estate for building wet labs.

"There was a disconnect between the academic science quality and the amount of land space," she said.

In 2003, she noted that Boston and New York received similar amounts of NIH funding—about \$1.5 billion and \$1.3 billion, respectively. At the time, she said, Boston had more than 12 million square feet in commercial lab space, whereas New York had only about 120,000.

"In the early days, a VC would fly in, go along First Avenue, stand outside Rockefeller and bring three things: a CEO, a bag of cash and a moving van to take it somewhere else."

—*Maria Gotsch, Partnership Fund for New York City*

That obstacle has largely been addressed, Gotsch said, with the opening in the last four years of the **Alexandria Center for Life Science**, the **Harlem Biospace** incubator and the **BioBAT** at the Brooklyn Army Terminal.

The Alexandria Center is a 15-story commercial facility with laboratory and office space located on 3.5 acres of city-owned land in Manhattan between **Bellevue Hospital** and **New York University**.

Eli Lilly and Co. signed up as the anchor tenant in 2010, and **Roche** inaugurated its Translational and Clinical Research Center (TCRC) in the Alexandria Center in October 2013.

Judith Dunn, global head of clinical development at Roche's Pharma Research and Early Development (pRED) unit, said that the company chose to set up in New York because it wanted access to external innovation via peer-to-peer interactions with teaching hospitals and medical schools.

The TCRC houses about 200 employees working on all aspects of development from drug discovery to regulatory science, and it serves as the U.S. operations base for the company's North American clinical trials.

Dunn said that in addition to the concentration and proximity of high-quality science, New York's multicultural population is a big advantage for the pharma's clinical operations. "In translational medicine you want bench scientists close to physicians. You also want a diverse population so that you can think about genomics in a macro way—New York is almost uniquely suited to this," she told *SciBX*.

In addition, she said, the fact that New York has attracted top talent with industry experience to lead some of its academic and medical centers was a significant draw.

Those high-profile appointments include Marc Tessier-Lavigne as president of **The Rockefeller University**, Louis Walcer as head of **Cornell University's** life science business incubator and Laurie Glimcher as dean of **Weill Cornell Medical College**, all in 2011.

Tessier-Lavigne was previously EVP and CSO at the **Genentech Inc.** unit of Roche; Walcer was senior commercialization officer at **Cleveland Clinic Innovations**, the technology commercialization arm of the **Cleveland Clinic**; and Glimcher was a professor at **Harvard Medical School** and a practicing rheumatologist at **Brigham and Women's Hospital**.

Pfizer Inc. also has leased space at the Alexandria Center for its Center for Therapeutic Innovation. Joel Marcus said that more than a dozen other life science companies have leased space, including small- and medium-sized biotechs.

Marcus is chairman, CEO and founder of **Alexandria Real Estate Equities Inc.**

The Harlem Biospace incubator is the brainchild of **Columbia University** professor Sam Sia, who cofounded it to provide academic entrepreneurs with low-cost lab space that is close to the university. The incubator has leased space to about 20 startups since it opened last November.

Sia is an associate professor of biomedical engineering at Columbia and cofounder of **Claros Diagnostics Inc.**, which was acquired by **Opko Health Inc.** for \$49 million in 2011.

Table 1. Boosting translation in New York academia. Select public-private partnerships (PPPs) and charitable donations involving New York City-based organizations since January 2013. The table includes only partnerships for translational programs in therapeutic areas or technologies and excludes partnerships to develop specific company products.

Source: BioCentury archives

Date	Companies or donors	Institutions	Disease/indication/tool	Description	Funding amount
PPPs and donations with disclosed funding					
September 2013	Genia Technologies Inc.	Columbia University; Harvard University; NIH	Genomics	Three-year grant from NIH's National Human Genome Research Institute to develop Genia's NanoTag sequencing technology, which combines technologies from the three institutes	\$5.3 million
October 2013	Takeda Pharmaceutical Co. Ltd. (Tokyo:4502); Lewis and Ali Sanders; Howard and Abby Milstein	Memorial Sloan-Kettering Cancer Center (MSKCC); The Rockefeller University; Weill Cornell Medical College	Multiple	Tri-Institutional Therapeutics Discovery Institute Inc. launched to expedite early stage discovery into clinical treatments and therapies	\$20 million + \$1.5 million/year
December 2013	Celgene Corp. (NASDAQ:CELG); Eli Lilly and Co. (NYSE:LLY); General Electric Co. (NYSE:GE)	New York City Economic Development Corp.	Multiple	City of New York Early-Stage Life Sciences Funding Initiative to invest at least \$100 million in early stage life science companies in the city	\$100 million
January 2014	Virginia and D.K. Ludwig Fund for Cancer Research	MSKCC; The Johns Hopkins University; Harvard University; Massachusetts Institute of Technology; Stanford University; The University of Chicago	Cancer	Funding for cancer research at six universities	\$540 million (including \$90 million for MSKCC)
March 2014	NIH's National Institute of Allergy and Infectious Diseases	Rockefeller University; Fred Hutchinson Cancer Research Center; NIH; Seattle Biomedical Research Institute; Seattle Children's Hospital; University of Washington	Infectious disease	Consortium to develop a vaccine to elicit broadly neutralizing antibodies against HIV-1	\$9.8 million
March 2014	Emergent BioSolutions Inc. (NYSE:EBS); Mapp Biopharmaceutical Inc.; Zalgen Labs LLC	Yeshiva University; Ben-Gurion University of the Negev; NIH; Public Health Agency of Canada; The Scripps Research Institute; Uganda Virus Research Institute; The University of Texas Medical Branch; University of Wisconsin System; U.S. Army Medical Research Institute of Infectious Diseases	Infectious disease	Consortium to develop immunotherapies for filoviruses and arenaviruses that cause severe hemorrhagic fever	Up to \$28 million
April 2014	UCB Group (Euronext:UCB)	Weill Cornell Medical College	Multiple	Advance translational research programs in bone disorders, metabolic disease and rare genetic variant analysis. UCB receives right to negotiate an exclusive license to develop and commercialize resulting products	\$8 million
May 2014	Marie-Josée and Henry R. Kravis Foundation	MSKCC	Cancer	Creation of the Marie-Josée and Henry R. Kravis Center for Molecular Oncology (CMO) to develop cancer treatments through genomic analysis of patient-derived tumors	\$100 million
PPPs with undisclosed or unavailable funding details					
February 2013	Genisphere LLC	Mount Sinai Hospital	Inflammation; diagnostics	Partnership to develop a high throughput, semiautomatic, peptide-based diagnostic to characterize food allergies	Undisclosed/unavailable
May 2013	Foundation Medicine Inc. (NASDAQ:FMI)	MSKCC	Diagnostics	Partnership to co-develop a molecular diagnostic product to match patients with hematologic cancers with targeted therapies or clinical trials based on patients' genomic profiles	Undisclosed/unavailable
July 2013	Johnson & Johnson (NYSE:JNJ)	Icahn School of Medicine at Mount Sinai	Inflammatory bowel disease (IBD)	Partnership to investigate triggers of IBD, identify new opportunities for therapeutic interventions and create diagnostics for therapeutics, and identify predictive biomarkers	Undisclosed/unavailable

(Continues on p. 6)

Table 1. Boosting translation in New York academia. (continued)

Date	Companies or donors	Institutions	Disease/indication/tool	Description	Funding amount
September 2013	Exosome Diagnostics Inc.	Icahn School of Medicine at Mount Sinai	Diagnostics	Partnership to develop real-time, nucleic acid-based body fluid diagnostics for research and biomarker discovery programs in oncology, inflammation and other disease areas	Undisclosed/unavailable
October 2013	Berg Pharma LLC	Icahn School of Medicine at Mount Sinai	Multiple	Partnership to discover and develop biologics, small molecules and diagnostic tools for cancer and CNS and endocrine disorders	Undisclosed/unavailable
October 2013	BioMotiv LLC	Alzheimer's Drug Discovery Foundation; University Hospitals Case Medical Center	Alzheimer's disease (AD)	Partnership to advance preclinical AD therapeutics in U.S. academic medical institutions	Undisclosed/unavailable
January 2014	Sutro Biopharma Inc.	MSKCC	Cancer	Partnership to produce bispecific antibodies developed by Sutro against targets discovered by MSKCC for treatment of neuroblastoma in children	Undisclosed/unavailable
March 2014	IBM (NYSE:IBM)	New York Genome Center	Pharmacogenetics	Partnership to evaluate a prototype of IBM's Watson cognitive system as a genomic research tool to help oncologists deliver personalized care initially for patients with glioblastoma	Undisclosed/unavailable

The Brooklyn BioBAT is a 500,000-square-foot facility founded by the **New York City Economic Development Corp.** (NYCEDC) together with **SUNY Downstate Medical Center**, with laboratory space currently available for lease.

Funding translation

The availability of commercial space has coincided with an influx of dollars dedicated to translational science. Since the start of 2013, city, commercial and philanthropic funds in New York City have committed more than \$300 million to public-private partnerships and academic centers for local translational programs (see **Table 1**, “Boosting translation in New York academia”).

In January, NYCEDC announced the largest of these—\$100 million for early stage life sciences. The goal of the funding initiative is to spur the creation of 15–20 new companies by 2020.

NYCEDC, **Celgene Corp.**, **Eli Lilly** and **GE Ventures** committed a joint \$50 million in anchor money and are seeking matching funds from VCs.

Eric Gertler, EVP of the NYCEDC, told *SciBX* that the initiative came on the heels of \$100 million committed by the city to help build the **Cornell Tech** applied sciences campus on Roosevelt Island and is part of the city's wider strategy to reap the benefits of its own intellectual assets.

“We want to ensure that the science that gets discovered here gets developed here,” he said.

“What's new is that now we're trying to retain the commercial value of our brains here,” added Geoffrey Smith, director of the Mount Sinai Institute of Technology and a professor of health evidence and policy at the **Icahn School of Medicine at Mount Sinai**. “The commercial

strength of our biology has been overlooked because of the strength of the financial services. We're in the conversation now as a place that this is happening.”

In addition, New York-based not-for-profit organizations and philanthropic funds are now backing local translational initiatives.

Two of these are directed toward oncology research at **Memorial Sloan-Kettering Cancer Center** (MSKCC).

In mid-May, MSKCC received \$100 million from the Marie-Josée and Henry R. Kravis Foundation to use genomic analysis of patient-derived tumors to advance personalized cancer treatments; in January, MSKCC received \$90 million from the Virginia and D.K. Ludwig Fund for Cancer Research. In total, the fund gave \$540 million to 6 institutions.

In October 2013, Lewis and Ali Sanders gave a \$15 million gift and Howard and Abby Milstein gave \$5 million to help found **Tri-Institutional Therapeutics Discovery Institute** Inc. The institute, which will develop small molecules from early discovery to clinical trials, is a consortium between MSKCC, Rockefeller University, Weill Cornell Medical

College and **Takeda Pharmaceutical Co. Ltd.**

The pharma is contributing \$1.5 million per year.

Capital gap

Although many parts of the ecosystem are now in place, there is still relatively little biotech VC activity in the region.

According to Gotsch, the next hurdle is to bring in capital for early stage companies. Although there has been some investment in companies with Phase II and later programs, hardly any money has gone into seeding new companies, she told *SciBX*.

“In translational medicine you want bench scientists close to physicians. You also want a diverse population so that you can think about genomics in a macro way—New York is almost uniquely suited to this.”

—*Judith Dunn, Roche*

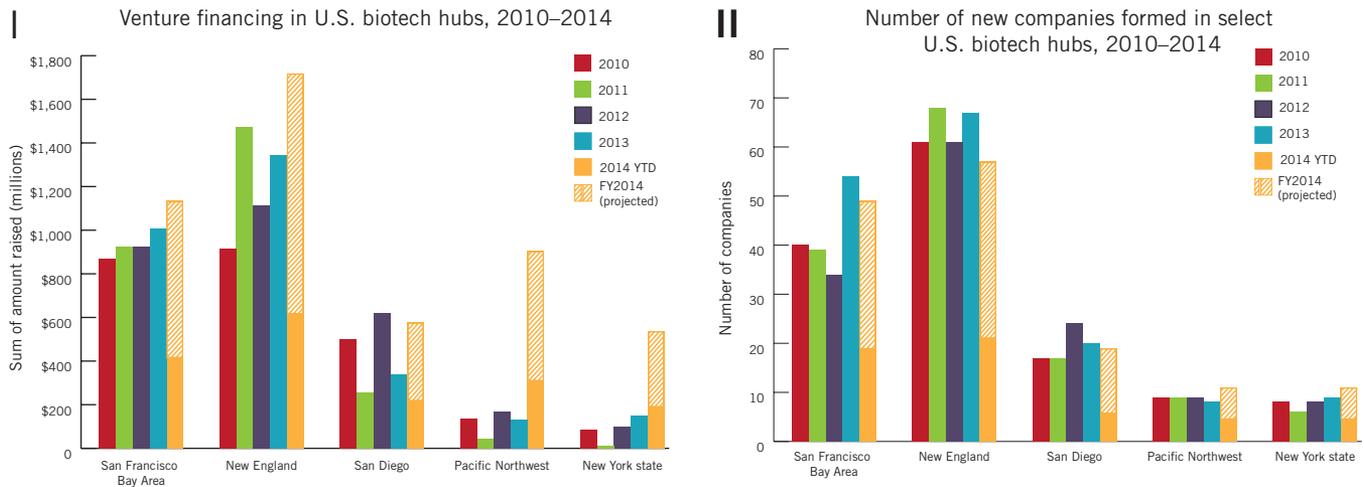


Figure 1. Slow to venture in New York. (I) Venture financing in U.S. biotech hubs, 2010–2014. Sum of amount raised in disclosed venture financing in select U.S. regions. (II) Number of new companies formed in select U.S. biotech hubs, 2010–2014. Data for 2014 is year to date (YTD). Stippled bars show projection for fiscal year 2014 (FY2014) based on YTD amounts. Source: BCIQ: BioCentury Online Intelligence

In the last four years, the total amount of venture funding in New York State has trailed even the smaller hubs of San Diego and the Pacific Northwest, and it is far behind the two biggest hubs in the San Francisco Bay Area and Boston–Cambridge. In all five regions, the amount raised to date in 2014 is outpacing prior years.

In addition, the number of new companies founded in New York remains fairly static at under 10 per year (see Figure 1, “Slow to venture in New York”).

According to Gotsch, the lack of new company formation deprives the region of the supply of people with industry experience that new ventures need. “When you don’t have a track record of companies and exits, you don’t have a deep bench of experienced management. The scientist inventor is often not the best CEO,” she said.

Atlas Venture’s Jean-François Formela agreed and said that it is particularly difficult to establish a cluster in a city with other well-established industries that offer attractive alternatives for local talent.

“All the pluses in favor of New York are pretty obvious—academic excellence, clinical strength, translational centers. There’s also a lot of money in New York. But the key missing piece is the talent pool and the ability to recruit scientists and build companies in a setting that’s conducive to forming a cluster,” he said.

“The fact that New York is a cluster for so many other industries is a challenge. It has financial services, advertising, media and so many other industries,” he added.

“As a VC here in New York we’re at an extreme disadvantage, especially for early stage companies, because we’re not in the middle of an ecosystem,” said Martin Vogelbaum, partner at Rho Ventures.

He added that New York lacks an area like Cambridge’s Kendall Square, where coffee shops and hotels full of biotech executives and entrepreneurs lead to impromptu meetings and provide a good environment for deal making.

According to Polaris Partners’ Kevin Bitterman, the limited pool of experienced talent in New York is partly because the region has not had any significant home-grown, large companies to serve as feeders for new startups.

“If you look at companies [in the Bay Area and Boston] that were started and successful in the last few years, the management team will have folks from the big companies—Millennium, Genentech, Genzyme—these are phenomenal training grounds for growing talent,” he said.

Millennium is now part of Takeda, Genentech is part of Roche and Genzyme is owned by Sanofi.

The recruitment of Roche and Eli Lilly to New York, and Pfizer’s expansion of its translational research activities there, could help catalyze change.

“When pharma put down its roots in Boston, that really helped trigger the growth in that region,” Formela said. He cautioned that a pharma footprint does not replace the need for people with startup experience. “The talent pool that you need for a biotech hub is different from pharma,” noted Formela.

Indeed, Scott Friedman, dean for therapeutic discovery and a professor of medicine at the Icahn School of Medicine, said that the academics in the region still have precious little experience with starting companies.

“You need a cultural change for an innovation ecosystem,” he said. “You need to have both the appetite and the infrastructure for change.”

Smith said that they are bringing about that change at Sinai and other institutions by creating programs to teach translational science and having senior faculty directly involved with industry.

Those strategies—together with the city’s investment in the sector—are starting to pay off among scientists, he told *SciBX*.

“Now there is a concerted effort being made in New York to build biotech here by local government and academic centers, and it’s

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“We want to ensure that the science that gets discovered here gets developed here.”

—Eric Gertler,
New York City Economic
Development Corp.

A conversation with Aled Edwards

By Amy Donner, Senior Editor

As the **Structural Genomics Consortium** enters its second decade, the challenge has shifted from showing that its model of providing open access to biological data is sustainable to expanding intellectual and geographic reach. Thus, the consortium now is looking to engage clinical scientists and add a site in South America.

The SGC is a not-for-profit public-private partnership (PPP) that produces 3D structures of biomedically relevant proteins as well as chemical tools that enable drug discovery. Outputs from the consortium are placed in the public domain without IP restrictions.

When the SGC was formed 10 years ago by **GlaxoSmithKline plc**, the **Wellcome Trust** and Canadian funders, there were doubts about the attractiveness and sustainability of the model because of its no-IP policy.

The SGC received an initial investment of \$95 million. CEO Aled Edwards was tasked with building a partnership that could deliver structures for 350 new human proteins by July 2007 and hiring team leaders and staff for sites in Oxford and Toronto.

Edwards is a professor of medical research at the **University of Toronto** and a visiting professor of chemical biology at the **University of Oxford**.

To date, the SGC has produced structures for over 1,500 proteins—about 15% of the human proteome—and has ongoing collaborations with more than 300 groups.

“Leveraged funding, huge academic network, no TTOs [technology transfer offices] in the way, pioneering science, reproducible results and, soon, open access to patient-derived cells—it makes sense to many companies.”

—Aled Edwards,
Structural Genomics Consortium

The consortium has expanded from the original 6 founding organizations to a total of 13 members, including 9 pharma companies.

SciBX talked with Edwards about how the consortium has continued to grow and evolve and about the future for open-access partnerships in biomedical research.

SciBX: What was the motivation for founding the SGC?

Al Edwards: Rob Cooke and others at GSK came up with the idea to pool resources to solve the protein structures that each company was working on individually. Because the Wellcome Trust was involved in building a synchrotron and was motivated to seed research activity around it, there was a nexus of interest from pharma and Wellcome to build a SNP-like consortium [the Single Nucleotide Polymorphism Consortium] for protein structures in Oxford.

SciBX: What were the early days like?

AE: In 2003, we were in hunker-down mode. There were 2 of us, empty labs and a \$100 million check. Our goal was to solve 350 human protein structures by mid-2007. And

we had to solve them from a list provided by the funders. There were a lot of doubts that we could meet our goal. We solved 465 structures.

In 2007, we proposed structures as our goal again, this time committing to solve 650 with some membrane proteins. By 2011, we had solved 692 structures.

SciBX: What was the initial perception of the SGC and its open-access research model?

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(Continued from “**New York's biotech beginnings**,” p. 7)

happening on the grass roots side too. People have started to believe you can be entrepreneurial.”

Fishburn, C.S. *SciBX* 7(21); doi:10.1038/scibx.2014.603

Published online May 29, 2014

COMPANIES AND INSTITUTIONS MENTIONED

Alexandria Center for Life Science, New York, N.Y.
Alexandria Real Estate Equities Inc., Pasadena, Calif.
Atlas Venture, Cambridge, Mass.
Bellevue Hospital, New York, N.Y.
BioBAT, New York, N.Y.
Brigham and Women's Hospital, Boston, Mass.
Celgene Corp. (NASDAQ: CELG), Summit, N.J.
Cleveland Clinic, Cleveland, Ohio
Cleveland Clinic Innovations, Cleveland, Ohio
Columbia University, New York, N.Y.
Cornell Tech, New York, N.Y.
Cornell University, New York, N.Y.
Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.

GE Ventures, Menlo Park, Calif.
Genentech Inc., South San Francisco, Calif.
Harlem Biospace, New York, N.Y.
Harvard Medical School, Boston, Mass.
Icahn School of Medicine at Mount Sinai, New York, N.Y.
Memorial Sloan-Kettering Cancer Center, New York, N.Y.
New York City Economic Development Corp., New York, N.Y.
New York University, New York, N.Y.
Opko Health Inc. (NYSE:OPK; Tel Aviv:OPK), Miami, Fla.
Partnership Fund for New York City, New York, N.Y.
Pfizer Inc. (NYSE:PFE), New York, N.Y.
Polaris Partners, Boston, Mass.
Rho Ventures, New York, N.Y.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
The Rockefeller University, New York, N.Y.
Sanofi (Euronext:SAN; NYSE:SNY), Paris, France
SUNY Downstate Medical Center, Brooklyn, N.Y.
Takeda Pharmaceutical Co. Ltd. (Tokyo:4502), Osaka, Japan
Tri-Institutional Therapeutics Discovery Institute Inc., New York, N.Y.
Weill Cornell Medical College, New York, N.Y.

AE: One bias from the academic world was that the effort constituted a nonscience-driven factory that was simply taking money away from the funding base. A second bias was that we were doing industry's business with the public purse. This bias was mitigated somewhat by the involvement of respected organizations like the Canadian funders and the Wellcome Trust.

Pharmaceutical companies had different biases. First, and one that remains today, is that consortia involving academics cannot be successful. The second was that their internal structural biologists could tackle any problem without help. This, of course, was true. The third view was that any donation to the public good only served to support their competitors—the free-rider argument. Of course, there is some truth to this as well.

SciBX: Has this perception changed among academia?

AE: Ten years later, there is more acceptance of the idea that this project serves the public good. We have hundreds of collaborators in academia and have published with 150 different institutions in the past 3 years alone.

Our structures have a reputation of high quality, and our work is known for being reproducible. So yes, I believe it has changed.

SciBX: And among pharma?

AE: Yes, I think the perception changed because the SGC as a precompetitive consortium delivers what it says it will, and produces high-quality, reproducible science. The perception change has also been helped by the ever-increasing squeeze on research dollars. Companies can spend \$1 to get \$1 of research internally or spend \$1 to get \$10 of research or more in the SGC and its collaborative network.

Leveraged funding, huge academic network, no TTOs [technology transfer offices] in the way, pioneering science, reproducible results and, soon, open access to patient-derived cells—it makes sense to many companies.

SciBX: How did the SGC get interested in chemical probes?

AE: In 2004, we started to build chemistry capabilities. We knew then that we ultimately wanted to make inhibitors, but we were only funded for structures. We knew that having a small molecule that bound a protein could improve the probability of getting crystals and showed this using hundreds of examples with the thermal shift assay.¹

Thus, we made the argument that we needed to build small molecule libraries in order to identify small molecules that stabilized proteins and increased the efficiency of solving structures. And so we were into chemical biology.

In 2009, we published our open-access model for chemical probes.² GSK, led by Tim Willson and others, took the plunge and engaged with us to make tool compounds against epigenetic targets and put them in the public domain. This was an enormous inflection point.

“I think in the coming years, you are going to see greater scrutiny of PPPs in terms of value created. And by value I mean scientific, economic and social. Perhaps when those analyses are done, the advantages of the open-access model will become more starkly apparent.”

—Aled Edwards,
Structural Genomics Consortium

Fast forward to 2014—we have many chemical libraries in house, and we occasionally put out a chemical probe. The consortium is also helping to raise the bar for how a chemical probe is defined and validated. With industry's help, we're making high-quality molecules. This is a significant contribution. Every chemical probe costs over \$2 million to make, and after we make them, we simply give them away.

In 2013 alone, over 1,500 samples were distributed. The success of this project, which focuses on proteins implicated in epigenetic signaling, has encouraged us to expand the remit. Thus—again with the leadership of GSK—we are soon launching a project to generate chemical probes to protein kinases implicated in the regulation of epigenetics and also RNA biology.³

This project will involve a new laboratory at the **University of Campinas** in Brazil, and we are excited that the open-access model is expanding beyond Canada and Europe.

SciBX: What will the next phase look like for the SGC?

AE: We have noticed that when the tools we generate are used by clinicians in patient-

derived samples, there is much more rapid uptake of the probes by other academic scientists and much more interest generated in industry. So the path is obvious—continue to make tools, but organize networks of clinical institutions that agree to use the tools in patient-derived samples and make the data available without restriction.

We have already established very focused collaborations, knowledge-based collaborations, with three hospitals. Making sure that these are successful and expanding the number of collaborators is our vision for the next five years.

SciBX: What makes the SGC unique?

AE: I think we are unique from an organizational point of view. To my knowledge, no other PPP of this scale has an explicit no-IP policy. We are also more like a company within academia.

It is hard to gather a group of independent academics toward common objectives. We hire scientists—PIs [principal investigators]—to do the work of the SGC rather than pulling together professors who each have their own research objectives. Consortia generally bring together professors because they have the right skill sets and expect them to perform like a well-oiled machine.

The other advantage is that decisions can be made about what projects to pursue without necessarily achieving consensus. As such, we have the freedom to work on proteins that may be less fashionable. Indeed, we spend most of our time working on the proteins less studied by the traditional granting system.

In our view, the popular proteins already receive massive investment. Our relatively small effort will have more impact if we exclusively try to focus where others do not.

SciBX: How do you compare the productivity of the SGC to other PPPs?

AE: There are no good measures for this. To my knowledge, PPPs set objectives but don't advertise them, or they set fuzzy objectives. They are rarely held to account. In some cases, the partnership rather than the outcome is viewed as the end goal.

At the SGC, if we don't meet our objectives, people lose their jobs. There is a greater sense of urgency for us, and a four- to five-year funding cycle keeps the fear of failure real.

But meeting our milestones is not enough. The unwritten objectives have included creating a culture of transparency in sharing our data and the impact of our papers. I'm starting to hear about the need for job creation, but no one will give me target numbers.

SciBX: What are the biggest challenges for the open-access model?

AE: Balancing the expectations of the various funders is the hardest aspect of what I do. Academics and public-sector funders respect papers, and companies care about the impact, as well as quantitative metrics to ensure that there is no mission drift. There is always some internal tension.

Maintaining public funding is a humongous challenge. Our only public funders have been the Canadian and Ontario governments. And we increasingly face the question—if industry sees the value in funding the SGC, why are we needed? Of course, when I go to industry, the question is why should we fund the SGC if the project generates basic science. Therein lies the challenge.

Of course, the real reason to have both sectors supporting us goes beyond economics. The involvement of the public sector assures our collaborators that our mission is to serve the public good—and this has allowed us to collaborate with anybody without involving TTOs and without the need for MTAs. If we were funded exclusively by pharma, I am sure that many scientists would not collaborate with us.

If the private sector were absent, then there would be a natural tendency to slow down and chase some of the fascinating scientific stories we have uncovered. Their most important contribution is their expertise—access to their medicinal chemists is priceless.

SciBX: There is an abundance of PPPs now. Why do you think the IP-free model for open innovation remains rare?

AE: It remains hard for people to wrap their heads around the fact that the misuse of patents and the opportunity cost of filing patents at the early stages of any business can have a detrimental effect on innovation. And there is also the lottery ticket mentality, where on rare occasions, one can get lucky and generate a result of enormous commercial benefit.

I think in the coming years, you are going to see greater scrutiny of PPPs in terms of value created. And by value I mean scientific, economic and social. Perhaps when those analyses are done, the advantages of the open-access model will become more starkly apparent.

SciBX: After 10 years, what are the biggest benefits you have seen come from the open-access research model?

AE: This is an interesting question. I could point to the dozens of high-profile papers that have emerged from our work, but to be honest if you took the funding we received and distributed it among a dozen top scientists, I'm sure that they'd publish good papers too.

I think the real benefits come from the fact that on top of the papers we publish, we make enabling tools available. And the unrestricted availability of these tools has proven a powerful accelerant to science. Second, the open-access framework and the willingness to share our output is what allows us to focus resources on areas of the proteome that would be very difficult to fund in any other way.

SciBX: Thank you very much for your time.

Donner, A. *SciBX* 7(21); doi:10.1038/scibx.2014.604
Published online May 29, 2014

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COMPANIES AND INSTITUTIONS MENTIONED

GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Structural Genomics Consortium, Oxford, U.K.
University of Campinas, São Paulo, Brazil
University of Toronto, Toronto, Ontario, Canada
University of Oxford, Oxford, U.K.
Wellcome Trust, London, U.K.

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S100A9—clot not, bleed not

By Michael J. Haas, Senior Writer

Although the new generation of antithrombotic drugs provides marked improvements over warfarin, they all still carry bleeding risk. S100 calcium binding protein A9 could represent a new target that, when blocked, prevents thrombosis without increasing that risk.¹

The new findings from U.S. researchers may hand a new indication to at least two companies—**InflammatoRx Inc.** and **Active Biotech AB**—developing inhibitors of this S100 protein to treat cancer, autoimmune diseases and inflammation.

S100 proteins are a family of signaling molecules whose individual members play multiple roles in many cells and tissue types. S100 calcium binding protein A9 (S100A9; calgranulin B; MRP14) is expressed by neutrophils and monocytes and is activated by endothelial, epithelial and synovial cells.

Although its intracellular functions are poorly understood, secreted S100A9 can stimulate the production of proinflammatory cytokines by monocytes and promote the migration and adhesion of neutrophils and monocytes to sites of inflammation.

S100A9 frequently occurs as a heterodimer with S100A8 (calgranulin A; MRP8), whose function requires S100A9 to bind and stabilize it.

In 2006 and 2008, teams led by Daniel Simon identified an S100A8/S100A9 heterodimer expressed by platelets as a risk marker for acute ST-segment elevation myocardial infarction (STEMI)—a type of heart attack involving abnormal cardiac electrophysiology—in previously healthy individuals.² The heterodimer also was a marker for the recurrence of cardiovascular events such as MI, stroke and death in patients with acute coronary syndrome (ACS).³

Simon is chief of cardiovascular medicine and director of the Harrington Heart & Vascular Institute at **University Hospitals Case Medical Center** and a professor of cardiovascular research at **Case Western Reserve University School of Medicine**.

In 2009, another Simon-led team showed that S100A9 regulates vascular inflammation and responses to vascular injury in mouse models of atherosclerosis, vascular inflammation and restenosis by promoting leukocyte recruitment to vascular lesions.⁴

For the new study, Simon's team set out to determine whether platelet-expressed S100A8/S100A9 played a causal role in arterial thrombosis and thus might be a therapeutic target to prevent or treat thrombotic events.

In wild-type mouse models of arterial thrombosis, S100A8/S100A9 expression in platelets was upregulated and platelets secreted S100A8/A100A9 in response to clot-stimulating thrombin (factor IIa; F2). Also in the models, *S100a9* deficiency decreased thrombin-induced platelet

activation and accumulation on arterial walls, thereby increasing the time to thrombus formation, compared with unmodified *S100a9* expression.

Moreover, there was no difference in tail vein bleeding time—a measure of hemostasis and bleeding risk—between the *S100a9* knockout and wild-type mice.

Next, the team conducted thrombosis assays in whole blood from the *S100a9*-deficient mice and normal human blood pretreated with a research antibody against S100A9. The time to thrombus formation was longer than that for blood from wild-type mice or human blood pretreated with an inactive control antibody.

Additional experiments in mice confirmed that signaling between S100a9 secreted specifically by platelets and Cd36 (Gpiv) on other platelets drove thrombosis in the models.

Lastly, the team found platelet-derived S100A9 in arterial thrombi from patients with STEMI—a finding that further supported a causal role for S100A9 in thrombotic events in patients.

“Our paper shows that you can inhibit arterial thrombosis in mice without prolonging bleeding time or affecting parameters that influence hemostasis” by blocking S100A9, Simon told *SciBX*. “Targeting S100A9 would thus be useful in preventing and/or treating thrombosis in patients” with ACS, stroke and other conditions involving thrombosis.

Simon's team included researchers from **Brigham and Women's Hospital, Harvard Medical School, the Medical College of Wisconsin, Cancer Research UK's London Research Institute and Portola Pharmaceuticals Inc.**, which conducted the thrombosis assays in human blood.

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

Francisc Mitjans, CSO of **Lykera Biomed S.A.**, said, “Inhibiting S100A9 appears to be a potential strategy to prevent or treat thrombosis.”

S100 possibilities

Mitjans said that the study raises the question of whether other members of the S100 family of proteins—some of which have been implicated in atherosclerosis⁵ and cardiac fibrosis⁶—might also be involved in thrombotic processes.

Thus, he wanted to see head-to-head comparisons between inhibitors of different S100 proteins and whether the targets synergize with approved antithrombotic drugs.

Marketed antithrombotic therapies include inhibitors of factor Xa, inhibitors of thrombin and formulations of low molecular weight heparin (LMWH) that inhibit both factors Xa and IIa. All of the therapies have better safety profiles than warfarin and other coumarins—which inhibit vitamin K-dependent synthesis of multiple clotting factors and the proteins that regulate them—but still carry a risk of GI bleeding.

Philippe Tessier, president and CSO of **InflammatoRx**, was less sanguine about the prospects of inhibiting S100A9 to prevent or treat thrombosis.

“Our paper shows that you can inhibit arterial thrombosis in mice without prolonging bleeding time or affecting parameters that influence hemostasis. Targeting S100A9 would thus be useful in preventing and/or treating thrombosis in patients.”

—Daniel Simon,
Case Western Reserve University
School of Medicine

“While this is an interesting study, the antithrombotic effect of blocking S100A9 does not seem very drastic, so I do not see an anti-S100A9 therapy as a first-line treatment in cardiovascular patients at high risk of thrombosis,” he said.

Instead, he said, anti-S100A9 therapy might help prevent thrombosis in a different patient population—those with autoimmune diseases.

“High concentrations of S100A9 are found in the serum and at sites of inflammation in patients with diseases like rheumatoid arthritis, psoriasis and Crohn’s disease, and we know that patients with autoimmune diseases are at risk for cardiovascular disease,” he said. “The *JCI* study indicates that the presence of S100A9 in serum might enhance thrombosis and thus explain the risk of thrombotic events” in patients with these autoimmune diseases.

In turn, “the study suggests that targeting S100A9 to reduce inflammation in patients with autoimmune disease might have the added benefit of preventing thrombosis,” he said.

InflammatRx has a humanized antibody against S100A9 in preclinical development to treat undisclosed inflammatory indications.

Tessier said that the *JCI* study “indicates that our antibody might reduce both inflammation and the risk of thrombosis in patients with autoimmune disease” and thus might differentiate InflammatRx’s product from other autoimmune therapies.

Mitjans and Tessier agreed that inhibiting S100A9 to prevent or treat thrombosis would probably have few—if any—side effects.

“Under normal physiological conditions, there are no reports of secreted S100 proteins, indicating they maintain only intracellular roles,” Mitjans said. “S100 proteins appear to be secreted and released into the extracellular milieu only under pathological conditions.”

Tessier said that unpublished preclinical safety studies by InflammatRx found that prolonged treatment with an anti-S100A9 antibody had no obvious side effects in mice, and “mice deficient in *S100a9* or treated with the antibody can still develop normal immune responses during infection.”

Thus, an anti-S100A9 antibody could have the desired antithrombotic effect without blocking the protein’s intracellular functions, he said. “But, of course, there are a few instances—such as wound healing and menstruation—where thrombus formation is part of the normal process,” and the safety of anti-S100A9 therapy would have to be closely scrutinized.

Tessier said that an antibody against S100A9 would be preferable to a small molecule inhibitor because S100A9 binds to multiple receptors—among them CD36, receptor for advanced glycation endproducts (RAGE) and toll-like receptor 4 (TLR4). A small molecule would be unlikely to block S100A9’s interactions with all of them.

Lykera has three antibodies against S100 proteins in preclinical development to treat solid tumors: LK-1, a humanized mAb against S100A4; LK-3, a humanized mAb against S100 calcium binding protein P (S100P); and LK-5, a mAb against S100A7 (psoriasis).

Knockout technicality

A significant gap in the *JCI* study was that the team only tested the antithrombotic effects of *S100a9* knockout—not an actual S100A9 inhibitor—in the mouse models.

Although the team was unable to test its anti-S100A9 antibody in the models because it did not target the mouse protein, “there are other possible options, such as tasquinimod” for testing S100A9 inhibition *in vivo*, said Mitjans.

Active Biotech and **Ipsen Group** have tasquinimod (ABR-215050; TASQ), an oral quinoline-3-carboxamide derivative that binds S100A9, in Phase III testing to treat prostate cancer and in Phase II testing to treat gastric, liver, ovarian and renal cancers.

In addition, Active Biotech and **Teva Pharmaceutical Industries Ltd.** have Nerventra laquinimod, an oral quinoline-3-carboxamide immunomodulator that targets S100A9, in registration to treat multiple sclerosis (MS) and in Phase II testing to treat Crohn’s disease and lupus. Active Biotech also has the compound in Phase II testing to treat Huntington’s disease (HD).

Active Biotech’s paquinimod (ABR-215757), a small molecule quinoline-3-carboxamide immunomodulator that targets S100A9, is in Phase II testing to treat lupus.

Simon said that his team had not yet contacted Active Biotech but was thinking about doing so. Active Biotech did not respond to requests for comment.

Simon’s team is now investigating whether levels of S100A8/S100A9 in platelets can predict differing risks of coronary artery disease (CAD) events in patients with ACS versus those with stable CAD.

“We have preliminary data showing that platelet expression of the heterodimer is increased in ACS compared with CAD,” suggesting that S100A8/S100A9 levels could help identify patients with ACS in whom anti-S100A9 or anti-platelet therapy might reduce the risk of a cardiovascular event, Simon said. This is an important finding because “we currently have no markers to predict the risk of plaque rupture and future myocardial infarction or stroke.”

The team is also investigating the role of S100A9 in venous thrombosis and—with collaborators at the **University of Michigan**—conducting genomewide association studies to identify the genes involved in regulating plasma levels of S100A8/S100A9.

Simon noted that although levels of the heterodimer predict first and recurrent heart attacks, the team’s studies in arterial thrombi from patients with STEMI showed that not all platelets expressed S100A8/S100A9, for reasons that were unclear.

However, “we know from preliminary data that plasma levels of S100A8/S100A9 are inheritable—meaning that approximately 40% of the variability in those levels is genetically controlled,” he said. “The genomewide studies will give us insights into which genes are responsible for this variability” and might reveal potential antithrombotic targets upstream of S100A9.

He added that it was unlikely that those upstream targets would have the same therapeutic potential as S100A9 because the prothrombotic role of S100A9-CD36 signaling between platelets is distinct from the pro-clotting role of platelets in response to injury.

“The study suggests that targeting S100A9 to reduce inflammation in patients with autoimmune disease might have the added benefit of preventing thrombosis.”

—Philippe Tessier,
InflammatRx Inc.

According to Simon, **Case Western Reserve University** has patented the findings reported in *JCI*, and the IP is unlicensed.

Haas, M.J. *SciBX* 7(21); doi:10.1038/scibx.2014.605
Published online May 29, 2014

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Case Western Reserve University School of Medicine, Cleveland, Ohio
Harvard Medical School, Boston, Mass.
InflammatoRx Inc., Quebec City, Quebec, Canada
Ipsen Group (Euronext:IPN; Pink:IPSEY), Boulogne-Billancourt, France
London Research Institute, London, U.K.
Lykera Biomed S.A., Barcelona, Spain
Medical College of Wisconsin, Milwaukee, Wis.
Portola Pharmaceuticals Inc. (NASDAQ:PTLA), South San Francisco, Calif.
Teva Pharmaceutical Industries Ltd. (NYSE:TEVA), Petah Tikva, Israel
University Hospitals Case Medical Center, Cleveland, Ohio
University of Michigan, Ann Arbor, Mich.



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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
Cancer				
Breast cancer	Eyes absent homolog 2 (EYA2)	<i>In vitro</i> studies suggest selective allosteric inhibitors of EYA2 could help treat breast cancer. A phosphatase assay was used to identify <i>N</i> -arylidenebenzohydrazide-based compounds that noncompetitively and reversibly blocked the phosphatase activity of EYA2, which has been associated with increased oncogenic transformation, invasion, migration and metastasis in breast cancer. In human breast cancer cells, one of the EYA2 inhibitors decreased migration compared with vehicle. Next steps include additional efficacy and medicinal chemistry studies on the identified EYA2 inhibitors. Coauthors on the study are scientific founders of SixOne Solutions LLC, which is discovering EYA2 inhibitors to treat breast cancer. SciBX 7(21); doi:10.1038/scibx.2014.606 Published online May 29, 2014	Patent applications pending; licensed to SixOne Solutions; available for partnerships	Krueger, A.B. <i>et al. J. Biol. Chem.</i> ; published online April 22, 2014; doi:10.1074/jbc.M114.566729 Contact: Rui Zhao, University of Colorado Denver School of Medicine, Denver, Colo. e-mail: rui.zhao@ucdenver.edu Contact: Heide Ford, same affiliation as above e-mail: heide.ford@ucdenver.edu Contact: Juan Marugan, National Institutes of Health, Bethesda, Md. e-mail: maruganj@mail.nih.gov
Cancer	<i>Isocitrate dehydrogenase 1 (IDH1)</i>	<i>In vitro</i> studies suggest inhibiting oxidative metabolism could help treat <i>IDH1</i> -mutant cancers. In human colon cancer cell lines, heterozygous expression of a loss-of-function <i>IDH1</i> mutant resulted in greater metabolic impairment under hypoxic conditions than expression of either wild-type <i>IDH1</i> or an <i>IDH2</i> mutant. In cultured <i>IDH1</i> mutant-expressing cells, pharmacological inhibition of oxidative metabolism resulted in more potent growth inhibition than that seen in parental cells. Next steps could include testing therapeutic candidates that block oxidative metabolism in animal cancer models. Agios Pharmaceuticals Inc. has the <i>IDH1</i> inhibitor AG-120 in Phase I testing to treat cancer. SciBX 7(21); doi:10.1038/scibx.2014.607 Published online May 29, 2014	Patent and licensing status unavailable	Grassian, A.R. <i>et al. Cancer Res.</i> ; published online April 22, 2014; doi:10.1158/0008-5472.CAN-14-0772-T Contact: Christian M. Metallo, University of California, San Diego, La Jolla, Calif. e-mail: cmetallo@ucsd.edu
Cancer	<i>K-Ras (KRAS)</i> ; tankyrase TRF1-interacting ankyrin-related ADP-ribose polymerase (TNKS); MEK; keratinocyte growth factor receptor (KGFR; FGFR2; CD332)	Cell culture and mouse studies suggest a MEK inhibitor plus a TNKS inhibitor could be used to treat <i>KRAS</i> -mutant cancers. In 138 cancer cell lines, a large-scale compound screen determined that combinations of MEK and TNKS inhibitors synergistically blocked growth and induced apoptosis in colorectal and <i>KRAS</i> -mutant cancer cell lines. In a human colorectal cancer cell line and in mice bearing xenograft tumors, the MEK inhibitor selumetinib (AZD6244) plus the TNKS inhibitor TNKS656 blocked MEK-induced FGFR2 signaling and decreased cancer cell growth and tumor regression compared with either inhibitor alone. Next steps could include assessing the efficacy of the combination treatment in mouse xenograft models of primary tumors derived from individuals with <i>KRAS</i> -mutant colorectal cancer tumors. Array BioPharma Inc. and AstraZeneca plc's selumetinib (AZD6224) is in Phase III trials for non-small cell lung cancer (NSCLC) and Phase II testing for various cancer indications. At least six additional companies have MEK inhibitors in preclinical to Phase III development to treat cancer. The development status of Novartis AG's TNKS656 was not disclosed. SciBX 7(21); doi:10.1038/scibx.2014.608 Published online May 29, 2014	Patent and licensing status undisclosed	Schoumacher, M. <i>et al. Cancer Res.</i> ; published online April 18, 2014; doi:10.1158/0008-5472.CAN-14-0138-T Contact: Wenlin Shao, Novartis Institutes for BioMedical Research, Cambridge, Mass. e-mail: wenlin.shao@novartis.com

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Cancer	Presequence translocase-associated motor 16 homolog (PAM16; MAGMAS)	Cell culture studies identified a small molecule MAGMAS inhibitor that could help sensitize cancer cells to chemotherapy. In a human medullary thyroid carcinoma cell line, the lead inhibitor did not decrease cell viability, suggesting the compound itself is not cytotoxic. In this cell line, the lead inhibitor plus the cytotoxic natural product staurosporine increased apoptosis compared with staurosporine alone. Next steps include conducting a focused SAR study on the aliphatic part of the lead MAGMAS inhibitor and evaluating the compound in combination with antitumor agents such as cisplatin or doxorubicin. SciBX 7(21); doi:10.1038/scibx.2014.609 Published online May 29, 2014	Patent application filed; available for licensing	Zatelli, M.C. <i>et al. J. Med. Chem.</i> ; published online April 24, 2014; doi:10.1021/jm5000535 Contact: Claudio Trapella, University of Ferrara, Ferrara, Italy e-mail: claudio.trapella@unife.it
Glioma	V-region immunoglobulin-containing suppressor of T cell activation (VISTA)	Mouse studies suggest antagonizing VISTA could help treat glioma. In mice, <i>Vista</i> knockout increased the number of CD4 ⁺ T cells in the liver compared with no alteration. In CD4 ⁺ T cells isolated from the knockout mice, compared with T cells from wild-type mice, an anti-CD3 mAb increased T cell proliferation and cytokine production. In a mouse model of glioma, <i>Vista</i> knockout increased survival compared with no alteration. Next steps could include identification of a counter-receptor for VISTA. SciBX 7(21); doi:10.1038/scibx.2014.610 Published online May 29, 2014	Patent and licensing status unavailable	Flies, D.B. <i>et al. J. Clin. Invest.</i> ; published online April 17, 2014; doi:10.1172/JCI74589 Contact: Lieping Chen, Yale School of Medicine, New Haven, Conn. e-mail: lieping.chen@yale.edu
Liver cancer	Long noncoding RNA (lncRNA); transforming growth factor β 1 (TGFB1)	Studies in patient samples and mice suggest depleting TGFB1-activated lncRNAs could help prevent cancer metastasis. In samples from patients with hepatocellular carcinoma (HCC), TGFB1-induced lncRNAs were upregulated and correlated with poor prognosis. In a mouse model of metastatic HCC, shRNA against the TGFB1-induced lncRNAs decreased cancer invasiveness and metastasis compared with control shRNA. Next steps could include evaluating the inhibition of TGFB1-induced lncRNAs in additional cancer models. SciBX 7(21); doi:10.1038/scibx.2014.611 Published online May 29, 2014	Patent and licensing status unavailable	Yuan, J.-h. <i>et al. Cancer Cell</i> ; published online April 24, 2014; doi:10.1016/j.ccr.2014.03.010 Contact: Shu-han Sun, Second Military Medical University, Shanghai, China e-mail: shsun@vip.sina.com
Ovarian cancer	Notch 3 (NOTCH3)	<i>In vitro</i> and mouse studies suggest NOTCH3 inhibitors could help treat ovarian cancer. In patients with ovarian cancer, amplification and upregulation of <i>NOTCH3</i> were associated with poor survival. In human ovarian cancer cell lines, an indirect NOTCH inhibitor increased apoptosis in NOTCH3 ⁺ cells compared with NOTCH3 ⁻ cells, and <i>NOTCH3</i> siRNA increased sensitivity to paclitaxel compared with scrambled control siRNA. In mice bearing NOTCH3 ⁺ xenograft ovarian tumors, systemic delivery of a <i>NOTCH3</i> siRNA and paclitaxel decreased tumor growth compared with delivery of either agent alone. Ongoing work includes testing NOTCH3 inhibitors in the models. OncoMed Pharmaceuticals Inc. has OMP-59R5 (Anti-Notch2/3), a HuCAL mAb that binds NOTCH2 and NOTCH3, in Phase I/II testing to treat pancreatic and small lung cell cancers and Phase I trials to treat solid tumors. SciBX 7(21); doi:10.1038/scibx.2014.612 Published online May 29, 2014	siRNA delivery method patented by The University of Texas System Board of Regents; unlicensed	Hu, W. <i>et al. Cancer Res.</i> ; published online April 17, 2014; doi:10.1158/0008-5472.CAN-13-2066 Contact: Anil K. Sood, The University of Texas MD Anderson Cancer Center, Houston, Texas e-mail: asood@mdanderson.org

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Prostate cancer	Signal transducer and activator of transcription 3 (STAT3)	<p><i>In vitro</i> studies suggest inhibiting STAT3 with galiellalactone could be useful for treating prostate cancer. Previous studies identified galiellalactone as a small molecule inhibitor of <i>STAT3</i>-driven prostate cancer growth, but its mechanism of action was undefined. <i>In vitro</i>, a biotinylated analog of galiellalactone bound covalently to STAT3 and blocked its binding to DNA. Next steps include animal studies to optimize galiellalactone dosing alone and in combination with other therapies for castration-resistant prostate cancer caused by excessive STAT3 activity.</p> <p>Glactone Pharma AB has galiellalactone analogs in preclinical development for prostate cancer. Isis Pharmaceuticals Inc. and AstraZeneca plc have AZD9150, an antisense oligonucleotide targeting <i>STAT3</i>, in Phase I/II testing for various cancers. Otsuka Pharmaceutical Co. Ltd. has the small molecule STAT3 inhibitor OPB-31121 in Phase I trials for solid tumors.</p> <p>SciBX 7(21); doi:10.1038/scibx.2014.613 Published online May 29, 2014</p>	Patented; licensed to Glactone Pharma	Don-Doncow, N. <i>et al. J. Biol. Chem.</i> ; published online April 22, 2014; doi:10.1074/jbc.M114.564252 Contact: Rebecka Hellsten, Lund University, Lund, Sweden e-mail: rebecka.hellsten@med.lu.se
Renal cancer	NADPH oxidase 4 (NOX4)	<p>Cell culture and mouse studies suggest NOX4 inhibition could help treat renal cell carcinoma (RCC). In human RCC cell lines, the superoxide scavenger 4-hydroxy-2,2,6,6-tetramethyl-1-piperidin-1-oxyl (TEMPOL) or shRNA against the superoxide-producing <i>NOX4</i> decreased invasion and levels of a known RCC marker compared with no treatment or scrambled shRNA. In a mouse xenograft model of RCC, <i>NOX4</i> knockdown delayed early tumor growth compared with no alteration. Ongoing work includes investigating a NOX4 inhibitor by Genkyotex S.A. and TEMPOL variants.</p> <p>Genkyotex is investigating the dual NOX1 and NOX4 small molecule inhibitor GKT137831 in Phase II trials to treat diabetic nephropathy.</p> <p>SciBX 7(21); doi:10.1038/scibx.2014.614 Published online May 29, 2014</p>	Unpatented; licensing status not applicable	Gregg, J.L. <i>et al. Cancer Res.</i> ; published online April 22, 2014; doi:10.1158/0008-5472.CAN-13-2979 Contact: Jodi K. Maranchie, University of Pittsburgh, Pittsburgh, Pa. e-mail: maranchiej@upmc.edu
Cardiovascular disease				
Cardiomyopathy	Apolipoprotein O (APOO)	<p><i>In vitro</i> and mouse studies suggest inhibiting cardiac APOO could help treat diabetes-associated cardiomyopathy. <i>APOO</i> is elevated in hearts of patients with diabetes. In mice overexpressing human <i>APOO</i> and fed a high-fat diet, ventricular function was decreased compared with that in wild-type mice. In cultured rat cardiac myoblasts, overexpression of <i>ApoO</i> increased respiration and mitochondrial uncoupling compared with wild-type <i>ApoO</i> expression and led to reactive oxygen species generation, lipotoxicity and cell death. Next steps could include developing an APOO inhibitor.</p> <p>SciBX 7(21); doi:10.1038/scibx.2014.615 Published online May 29, 2014</p>	Findings patented; available for licensing	Turkieh, A. <i>et al. J. Clin. Invest.</i> ; published online April 17, 2014; doi:10.1172/JCI74668 Contact: Fatima Smith, Institut National de la Santé et de la Recherche Médicale (INSERM), Toulouse, France e-mail: fatima.smith-rouet@inserm.fr

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Heart failure	MicroRNA-21 (miR-21)	<i>In vitro</i> and mouse studies suggest antagonizing the miR-21 passenger strand could help treat cardiac hypertrophy. Passenger strand miRNAs result from the processing of precursor miRNAs and are generally believed to be inactive. In cardiac fibroblasts and cardiomyocyte cocultures, increasing miR-21 passenger strand levels resulted in larger cardiomyocytes than increasing miR-21 itself. In a mouse model of cardiac hypertrophy, miR-21 passenger strand levels were greater than those in healthy control mice. Next steps include developing strategies to target the miR-21 passenger strand and evaluating them in mice and large-animal models of pathological cardiac remodeling. SciBX 7(21); doi:10.1038/scibx.2014.616 Published online May 29, 2014	Patent application filed; licensing status undisclosed	Bang, C. <i>et al. Neuron</i> ; published online April 17, 2014; doi:10.1172/JCI70577 Contact: Thomas Thum, Hannover Medical School, Hannover, Germany e-mail: thum.thomas@mh-hannover.de
Inflammation				
Asthma	Programmed cell death 1 ligand 2 (PDCD1LG2; B7-DC; PD-L2); repulsive guidance molecule family member b (RGMB)	<i>In vitro</i> and mouse studies suggest promoting the PD-L2-RGMB co-inhibitory interaction could help treat asthma. <i>In vitro</i> and in cellular assays, RGMB bound to PD-L2 but not PD-L1 (CD274; B7-H1) or other related ligands. In a mouse model of intranasal antigen-induced respiratory tolerance, <i>Pd-l2</i> knockout or intranasal administration of an anti- <i>Pd-l2</i> mAb or anti-Rgmb mAb prevented respiratory tolerance and expansion of CD4 ⁺ T cell numbers. In a mouse model of intranasal antigen-induced asthma, both antibodies prevented the development of respiratory tolerance, resulting in severe airway hyperactivity and lung inflammation upon rechallenge with antigen. Next steps could include determining whether the PD-L2-RGMB interaction can be targeted for cancer immunotherapy. AstraZeneca plc has AMP-224, a fusion protein containing the extracellular domain of PD-L2 and the Fc portion of IgG, in Phase I trials to treat cancer. SciBX 7(21); doi:10.1038/scibx.2014.617 Published online May 29, 2014	Patent and licensing status unavailable	Xiao, Y. <i>et al. J. Exp. Med.</i> ; published online April 21, 2014; doi:10.1084/jem.20130790 Contact: Gordon J. Freeman, Harvard Medical School, Boston, Mass. e-mail: gordon_freeman@dfci.harvard.edu
Neurology				
Alzheimer's disease (AD)	Prion protein (PRNP; PrP; CD230)	Rat studies suggest the humanized anti-PrP antibody PRN100 could help treat AD. In rats, intracardiac injection of PRN100 decreased β -amyloid-associated disruption of long-term potentiation in neurons compared with injection of an isotype control antibody. Next steps include clinical trials of PRN100 in patients with sporadic Creutzfeldt-Jakob disease (CJD), which is caused by abnormal PrP. SciBX 7(21); doi:10.1038/scibx.2014.618 Published online May 29, 2014	Antibodies and use of ligands binding to the helix-1 region of PrP patented by D-Gen Ltd.; nonexclusively licensed to the Medical Research Council for development of PRN100 to treat prion diseases including CJD and AD; available for licensing	Klyubin, I. <i>et al. J. Neurosci.</i> ; published online April 30, 2014; doi:10.1523/JNEUROSCI.3526-13.2014 Contact: John Collinge, UCL Institute of Neurology, London, U.K. e-mail: j.collinge@prion.ucl.ac.uk Contact: Michael J. Rowan, Trinity College Dublin, Dublin, Ireland e-mail: mrowan@tcd.ie

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Alzheimer's disease (AD)	Tumor necrosis factor receptor superfamily member 21 (TNFRSF21; DR6)	<p>Mouse studies suggest antagonizing DR6 may not be useful for treating AD. Previous cell culture studies suggested DR6 promoted neuronal apoptosis by interacting with AD-associated amyloid precursor protein (APP) (see Osherovich, L., <i>SciBX</i> 2(8); doi:10.1038/scibx.2009.300). In two new studies, deletion of Dr6 in mouse models of AD did not improve cellular, cognitive or behavioral deficits. Next steps include identifying other potential AD targets. Roche's Genentech Inc. unit has discontinued its discovery stage programs targeting DR6 in AD.</p> <p>SciBX 7(21); doi:10.1038/scibx.2014.619 Published online May 29, 2014</p>	Patents on modulating DR6 in AD previously filed by Genentech; licensing status undisclosed	<p>Kallop, D.Y. <i>et al. J. Neurosci.</i>; published online May 7, 2014; doi:10.1523/JNEUROSCI.4963-13.2014 Contact: Robby M. Weimer, Genentech Inc., South San Francisco, Calif. e-mail: weimer.robby@gene.com</p> <p>Olsen, O. <i>et al. J. Neurosci.</i>; published online May 7, 2014; doi:10.1523/JNEUROSCI.3522-13.2014 Contact: Marc Tessier-Lavigne, The Rockefeller University, New York, N.Y. e-mail: marctl@rockefeller.edu Contact: Robby M. Weimer, Genentech Inc., South San Francisco, Calif. e-mail: weimer.robby@gene.com</p>
Pain	Bradykinin receptor	<p>Rat and <i>in vitro</i> studies identified dynorphin A analogs that antagonize bradykinin receptors and could be useful for treating chronic pain. <i>In vitro</i>, the lead analog bound to bradykinin receptors with higher affinity than bradykinin and inhibited bradykinin receptors with nanomolar IC₅₀ values. In a rat model of neuropathic pain, the lead analog decreased sensitivity to thermal and mechanical pain compared with vehicle. Next steps could include optimizing the dynorphin A analogs.</p> <p>SciBX 7(21); doi:10.1038/scibx.2014.620 Published online May 29, 2014</p>	Patent and licensing status unavailable	<p>Lee, Y.S. <i>et al. J. Am. Chem. Soc.</i>; published online April 17, 2014; doi:10.1021/ja501677q Contact: Victor J. Hruby, The University of Arizona, Tucson, Ariz. e-mail: hruby@email.arizona.edu</p>
Transplantation				
Bone marrow transplant (BMT)	Granzyme B (GrB; GZMB)	<p>Mouse studies suggest inhibiting GZMB could help improve bone marrow reconstitution following hematopoietic stem cell (HSC) transplantation. In mice, transplanted HSCs lacking <i>Gzmb</i> showed greater engraftment and proliferative capacity than wild-type HSCs. In <i>Gzmb</i> knockout mice, resistance to toxicity and death from serial challenge with 5-fluorouracil was increased compared with what was seen in wild-type mice. Next steps could include developing inhibitors of GZMB and evaluating their use in animal models.</p> <p>SciBX 7(21); doi:10.1038/scibx.2014.621 Published online May 29, 2014</p>	Patent and licensing status unavailable	<p>Carnevali, L.S. <i>et al. J. Exp. Med.</i>; published online April 21, 2014; doi:10.1084/jem.20131072 Contact: Andreas Trumpp, Heidelberg Institute for Stem Cell Technology and Experimental Medicine, Heidelberg, Germany e-mail: a.trumpp@dkfz.de</p>

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
Disease models			
Human embryonic stem cells (hESCs) generated from somatic cell nuclear transfer (SCNT) using postnatal somatic cells	SCNT could be useful for creating patient-matched hESCs for disease modeling and therapeutic applications. Previous efforts to reliably generate hESCs with nuclear transfer protocols have been limited to using nuclei from fetal as opposed to postnatal somatic cells. Fibroblasts from a 32-year-old female with type 1 diabetes or a newborn male were fused to enucleated donor human oocytes and activated with an oocyte activation protocol. A subset of the oocytes bearing the diploid genome of the donor fibroblasts developed into blastocysts, which were used to establish stable hESC lines. Next steps include comparing induced pluripotent stem (iPS) cell lines to nuclear transfer cell lines of the same genetic makeup to understand key differences between the two types of cells.	Patent application filed; licensing status undisclosed	Yamada, M. <i>et al. Nature</i> ; published online April 28, 2014; doi:10.1038/nature13287 Contact: Dieter Egli, The New York Stem Cell Foundation, New York, N.Y. e-mail: d.egli@nyscf.org
	SciBX 7(21); doi:10.1038/scibx.2014.622 Published online May 29, 2014		
Modeling effects of mutant huntingtin (HTT)–associated pathology with a conditional transgenic mouse model	Understanding how mutant HTT expression in different cell populations affects Huntington's disease (HD) pathology could provide new therapeutic insights on how to treat HD. In a conditional transgenic mouse model of HD, selectively decreasing mutant Htt expression in cortical neurons led to less severe HD-associated motor and behavioral deficits compared with baseline but did not attenuate neurodegeneration. In the mouse model, decreasing mutant Htt expression in both cortical and striatal neurons resulted in less neurodegeneration and less severe HD-associated motor and behavioral deficits compared with baseline. Next steps include studying cell-autonomous mechanisms of mutant HTT toxicities in the cortical and striatal neuronal cell types and elucidating the molecular basis of non–cell-autonomous interactions between the two neurons that result in toxicity.	Model unpatented; licensed to CHDI Foundation Inc. and several undisclosed companies	Wang, N. <i>et al. Nat. Med.</i> ; published online April 28, 2014; doi:10.1038/nm.3514 Contact: X. William Yang, University of California, Los Angeles, Calif. e-mail: xwyang@mednet.ucla.edu
	SciBX 7(21); doi:10.1038/scibx.2014.623 Published online May 29, 2014		
Mouse models of lung squamous cell carcinoma with inactivated <i>serine/threonine kinase 11</i> (<i>Stk11</i> ; <i>Lkb1</i>) and <i>Pten</i> (<i>Mmac1</i> ; <i>Tep1</i>)	Mice with lung-specific inactivation of <i>Lkb1</i> and <i>Pten</i> could be useful as models to evaluate therapeutic candidates for lung squamous cell carcinoma. The mice developed malignant nodules in the lung that showed squamous characteristics 30–40 weeks after inactivation of <i>Lkb1</i> and <i>Pten</i> . In these mice, the histological and gene expression profile of the tumors recapitulated multiple hallmarks of human squamous cell carcinoma. Next steps could include evaluating the effect of various cancer therapies in the mouse model.	Patent and licensing status unavailable	Xu, C. <i>et al. Cancer Cell</i> ; published online May 1, 2014; doi:10.1016/j.ccr.2014.03.033 Contact: Kwok-Kin Wong, Harvard Medical School, Boston, Mass. e-mail: kwong1@partners.org Contact: Carla F. Kim, Boston Children's Hospital, Boston, Mass. e-mail: carla.kim@childrens.harvard.edu Contact: Peter S. Hammerman, Dana-Farber Cancer Institute, Boston, Mass. e-mail: phammerman@partners.org
	SciBX 7(21); doi:10.1038/scibx.2014.624 Published online May 29, 2014		

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Drug delivery			
Paired liposomes for intracellular, ATP-inducible drug release	<p>A paired liposome system for ATP-induced chemotherapy release could help treat cancers. The system uses a cell-penetrating, ATP-containing liposome plus a membrane fusion-promoting liposome containing an ATP-responsive DNA scaffold loaded with doxorubicin. In a mouse xenograft model of human breast cancer, intratumoral injection of both liposomes increased tumor growth inhibition compared with injection of the doxorubicin-containing liposome alone or free doxorubicin. Next steps include testing the liposome delivery system on larger animals and adapting it for the delivery of other drugs.</p> <p>SciBX 7(21); doi:10.1038/scibx.2014.625 Published online May 29, 2014</p>	Patent application filed; available for licensing	<p>Mo, R. <i>et al. Angew. Chem. Int. Ed.</i>; published online April 24, 2014; doi:10.1002/anie.201400268 Contact: Zhen Gu, The University of North Carolina at Chapel Hill and North Carolina State University, Raleigh, N.C. e-mail: zgu@email.unc.edu Contact: Ran Mo, same affiliation as above e-mail: rmo@ncsu.edu</p>
Drug platforms			
Genome editing with dimeric, RNA-guided FokI-Cas9 nucleases	<p><i>In vitro</i> studies suggest dimerization-dependent nucleases could improve the specificity of clustered, regularly interspaced short palindromic repeats (CRISPR)-based genome editing for research and therapeutic applications. FokI nuclease, which requires dimerization for DNA cleavage, was fused to a catalytically inactive version of Cas9. In cultured human cells, expression of the dimeric editing tool and guide RNAs cleaved the enhanced GFP reporter target and 11 of 12 target genes without affecting any of 5 previously identified off-target sites for wild-type Cas9. Also in cultured cells, expression of a distinct FokI-Cas9 dimeric nuclease with guide RNAs allowed targeting of 14 genomic sites with lower efficiency but higher specificity than wild-type Cas9 or monomeric Cas9 nickases. Next steps include modifications to other aspects of CRISPR-based technology including delivery and toxicity.</p> <p>SciBX 7(21); doi:10.1038/scibx.2014.626 Published online May 29, 2014</p>	<p>Patent and licensing status unavailable for findings from first study</p> <p>For findings from second study, patent application filed by Harvard University, which is in negotiations with Editas Medicine for licensing a variety of CRISPR-related IP</p>	<p>Tsai, S.Q. <i>et al. Nat. Biotechnol.</i>; published online April 25, 2014; doi:10.1038/nbt.2908 Contact: J. Keith Joung, Massachusetts General Hospital, Boston, Mass. e-mail: jjoung@mgh.harvard.edu</p> <p>Guilinger, J.P. <i>et al. Nat. Biotechnol.</i>; published online April 25, 2014; doi:10.1038/nbt.2909 Contact: David R. Liu, Harvard University, Cambridge, Mass. e-mail: drliu@fas.harvard.edu</p>
Hematopoietic stem cells (HSCs) generated via <i>ex vivo</i> dedifferentiation for transplant applications	<p>A study in mice suggests HSCs generated <i>ex vivo</i> could be useful for transplantation. <i>Ex vivo</i> viral expression of a cocktail of transcription factors in myeloid or lymphoid progenitor cells caused dedifferentiation into an HSC-like state. After transplantation into myelo-ablated mice, HSCs engrafted into bone, spleen and thymus and differentiated into the full range of blood cells. Next steps could include repeating the experiment with human cells in a humanized mouse model and testing the ability of induced HSCs to restore bone marrow and immune function in disease models.</p> <p>SciBX 7(21); doi:10.1038/scibx.2014.627 Published online May 29, 2014</p>	Patent pending; available for licensing	<p>Riddell, J. <i>et al. Cell</i>; published online April 24, 2014; doi:10.1016/j.cell.2014.04.006 Contact: Derrick J. Rossi, Harvard University, Cambridge, Mass. e-mail: derrick.rossi@childrens.harvard.edu</p>
Human embryonic stem cell-derived cardiomyocytes (hESC-CMs) to treat ischemia/reperfusion injury	<p>Nonhuman primate studies suggest hESC-CM transplantation could be used to treat ischemia/reperfusion injury. In a nonhuman primate model of ischemia/reperfusion injury, delivery of one billion hESC-CMs to the infarct site resulted in their engraftment in the host animal heart and subsequent maturation and perfusion by blood vessels over a period of three months. In animals that received the transplant, the grafts showed electromechanical coupling with the heart, but ventricular arrhythmias were observed for the first two weeks after the transplant. Next steps could include conducting studies using larger numbers of animals to determine the mechanisms leading to the arrhythmias and doing a more detailed assessment of cardiac function.</p> <p>SciBX 7(21); doi:10.1038/scibx.2014.628 Published online May 29, 2014</p>	Patent and licensing status unavailable	<p>Chong, J.J.H. <i>et al. Nature</i>; published online April 30, 2014; doi:10.1038/nature13233 Contact: Charles E. Murry, University of Washington, Seattle, Wash. e-mail: murry@uw.edu</p>

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Human neutralizing mAbs against Middle East respiratory syndrome coronavirus (MERS-CoV)	Human neutralizing mAbs against MERS-CoV could aid the development of new therapeutics to treat or prevent infection. A screen of a single-chain variable domain fragment (scFv) phage library yielded seven unique fragments that bind to the MERS-CoV spike protein. In a nonhuman primate cell line, the most potent human mAbs generated from the identified scFvs neutralized the MERS-CoV with IC ₅₀ values ranging from 1.25 to 2 µg/mL. Next steps could include optimizing the lead neutralizing mAb and evaluating it in models of MERS-CoV infection. SciBX 7(21); doi:10.1038/scibx.2014.629 Published online May 29, 2014	Patent and licensing status unavailable	Tang, X.-C. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online April 28, 2014; doi:10.1073/pnas.1402074111 Contact: Wayne A. Marasco, Dana-Farber Cancer Institute, Boston, Mass. e-mail: wayne_marasco@dfci.harvard.edu
Imaging			
Self-assembling fluorescent small molecule probe to image tumor response to chemotherapy <i>in vivo</i>	Cell culture and mouse studies have identified an apoptosis-sensing molecular probe that could be used to image tumor response to treatment <i>in vivo</i> . A biocompatible, caspase-sensitive fluorescent probe that self-assembles within cells after caspase cleavage and thiol-mediated cyclization was identified. In cultured tumor cell lines, staurosporine- or doxorubicin-induced apoptosis led to a dose- and time-dependent increase in probe fluorescence within cells compared with no treatment. In a mouse xenograft model of cervical cancer, i.v. infusion of the probe plus doxorubicin led to greater fluorescence within tumor cells than either infusion of the probe plus saline or doxorubicin alone. Next steps include adapting the probe for PET or MRI imaging. Staurosporine is a research reagent that acts as a pan-kinase inhibitor. Doxorubicin is a generic chemotherapy drug. SciBX 7(21); doi:10.1038/scibx.2014.630 Published online May 29, 2014	Patented; available for licensing	Ye, D. <i>et al. Nat. Chem.</i> ; published online April 28, 2014; doi:10.1038/nchem.1920 Contact: Jianghong Rao, Stanford University, Stanford, Calif. e-mail: jrao@stanford.edu

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APP	18
ATP	20
AZD6244	14
AZD9150	16

B

β-Amyloid	17
B7-DC	17
B7-H1	17
Bradykinin receptor	18

C

Calgranulin A	11
Calgranulin B	11
Cas9	20
CD230	17

CD274	17
CD3	15
CD332	14
Cd36	11
CD4	1,15,17
Cisplatin	15
Clustered, regularly interspaced short palindromic repeats	20
Coumarin	11
CRISPR	20

D

Doxorubicin	15,20,21
DR6	18
Dynorphin A	18

E

ErbB2 interacting protein	1
ERBB2IP	1
EYA2	14
Eyes absent homolog 2	14

F

F2	11
Factor IIa	11
Factor Xa	11
FGFR2	14

G

Galiellalactone	16
GKT137831	16
Gpiv	11
Granzyme B	18
GrB	18
GZMB	18

H

Heparin	11
HTT	19
Huntingtin	19

I

IDH1	14
IDH2	14
Isocitrate dehydrogenase 1	14

K

K-Ras	14
Keratinocyte growth factor receptor	14
KGFR	14
KRAS	14

L

Laquinimod	12
LK-1	12
LK-3	12
LK-5	12
Lkb1	19

M

MAGMAS	15
MEK	14
MicroRNA-21	17
miR-21	17
Mmac1	19
MRP14	11
MRP8	11

N

NADPH oxidase 4	16
NanoTag	5

Nerventra	12	PRNP	17	S100A7	12	TGFB1	15
Notch 3	15	Programmed cell death 1		S100A8	11	Thrombin	11
NOTCH	15	ligand 2	17	S100A9	11	TLR4	12
NOTCH2	15	PrP	17	S100P	12	TNFRSF21	18
NOTCH3	15	Psoriasis	12	Selumetinib	14	TNKS	14
NOX1	16	<i>Pten</i>	19	<i>Serine/threonine kinase 11</i>	19	TNKS656	14
NOX4	16			Signal transducer and activator of transcription 3	16	Toll-like receptor 4	12
O		Q		STAT3	16	Transforming growth factor β 1	15
OMP-59R5	15	Quinoline-3-carboxamide	12	Staurosporine	15,21	Tumor necrosis factor receptor superfamily member 21	18
OPB-31121	16			<i>Stk11</i>	19		
P		R				V	
Paclitaxel	15	RAGE	12	T		V-region immunoglobulin-containing suppressor of T cell activation	15
PAM16	15	Receptor for advanced glycation endproducts	12	T cell receptor	1	V β 22 ⁺	1
Paquinimod	12	Repulsive guidance molecule family member b	17	Tankyrase TRF1-interacting ankyrin-related ADP-ribose polymerase	14	VISTA	15
PD-L1	17	RGMB	17	TASQ	12	Vitamin K	11
PD-L2	17			Tasquinimod	12		
PDCD1LG2	17	S		TCR	1	W	
Presequence translocase-associated motor 16 homolog	15	S100 calcium binding protein A9	11	TEMPOL	16	Warfarin	11
Prion protein	17	S100 calcium binding protein P	12	<i>Tep1</i>	19		
PRN100	17	S100A4	12				