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Assaying 2-HG's function

By Kai-Jye Lou, Staff Writer

Although 2-hydroxyglutarate is a known marker for various cancers, including leukemia,^{1,2} the metabolite's role in the disease remained unclear. Now, U.S. researchers have shown that the compound itself can drive leukemic transformation and that blocking its overproduction with a small molecule from **Agios Pharmaceuticals Inc.** reversed the effect.³

Isocitrate dehydrogenase 1 (IDH1) and IDH2 are critical metabolic enzymes that convert isocitrate to α -ketoglutarate, an essential cofactor for a number of enzymes. In 2009, Agios reported that a mutant form of IDH1 commonly found in gliomas gave the enzyme the additional ability to catalyze the formation of the (*R*) enantiomer of 2-hydroxyglutarate (2-HG) from α -ketoglutarate.^{4,5}

In 2010, Agios and its academic collaborators reported that acute myelogenous leukemia (AML) cells with mutations in *IDH1* and *IDH2* also produce 2-HG.^{1,2}

"The Agios group has previously shown that cells with mutations in *IDH1* can produce large quantities of 2-HG, though it was still unclear how 2-HG itself was affecting the cells because there was no cellular assay to study the metabolite's function with respect to promoting cancer," said William Kaelin Jr., a professor of medicine at the **Dana-Farber Cancer Institute** and an investigator at the **Howard Hughes Medical Institute**. "We thought it was important to prove that 2-HG was sufficient to induce leukemic transformation and was not just acting as a biomarker."

To do this, Kaelin's team developed cellular assays to enable the study of 2-HG's role in leukemia. The assays use a human erythroleukemia cell line transduced with lentiviral vectors that encode tagged versions of wild-type or oncogenic mutant *IDH1*. Cells transduced with oncogenic *IDH1* showed greater 2-HG production than those transduced with wild-type *IDH1*. Moreover, cells transduced with oncogenic *IDH1* also acquired two hallmarks of leukemogenesis: growth factor independence and impaired differentiation.

The group then used the assays to show that the (*R*) enantiomer of 2-HG drove leukemogenesis and that (*S*)-2-HG did not. A probe of downstream targets of 2-HG that were differentially regulated by the (*R*) and (*S*) enantiomers led to the identification of hypoxia-inducible factor prolyl hydroxylase 2 (EGLN1; HIF-PH2; PHD2) as a potential therapeutic target.

Finally, the researchers used a small molecule IDH1 inhibitor research reagent provided by Agios to confirm that inhibiting oncogenic IDH1-induced production of 2-HG reversed leukemogenesis.

The results were published in *Science*.

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Previous studies relied on *in vivo* phenotypic assays to assess the effects of targeting the IDH1 pathway, which are more labor-intensive and have lower throughput than *in vitro* cellular assays, said Ross Levine, an associate member in the Human Oncology & Pathogenesis Program and a physician in the leukemia service at **Memorial Sloan-Kettering Cancer Center**.

“This study is important from a biological and therapeutic standpoint because one could now test the effect of therapeutic candidates on leukemic transformation,” he told *SciBX*.

Levine added that phenotypic assays only allowed researchers to assess a compound's effects on the growth and proliferation of *IDH1*-mutant cancers. The assays did not show whether a molecule was actually targeting the mechanisms that drive disease.

“These researchers have created a model that will allow us to follow the biology of mutant *IDH1*,” added Katharine Yen, director of biology at Agios. “Before this study, nobody had proven that the 2-HG metabolite itself could be responsible for the downstream oncogenic effects of mutant *IDH1*.”

Yen added that the data also provide additional preclinical evidence to support the development of IDH1 inhibitors in cancer.

Agios has small molecules that inhibit either IDH1 or IDH2 in preclinical development for undisclosed cancer indications. CSO Scott Biller said the company hopes to take the compounds into Phase I testing in the next 12–24 months.

New research directions

The data reported in the paper open up new therapeutic avenues for *IDH1*-mutant cancers, such as targeting the transformation phenomenon, direct inhibition of 2-HG itself or going after the metabolite's downstream targets.

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“The researchers demonstrated that leukemic transformation was reversible, which is critical because it suggests that this transformation is not a one-way phenomenon,” said Levine. “The findings suggest one may be able to develop therapeutic compounds that work by reversing leukemic transformation.”

Kaelin thinks further probing the activity of the 2-HG enantiomers on downstream targets also could lead to the discovery of new therapeutic targets.

For example, he said, “we looked for proteins that are differentially regulated by the 2-HG enantiomers and came upon EGLN1, which was activated by (R)-2-HG but antagonized by (S)-2-HG.”

Kaelin said his group is now trying to translate the *in vitro* results into *in vivo* mouse models and trying to determine whether the targets of (R)-2-HG will vary by cancer type.

“We want to see if the results in leukemia also carry over to other types of cancers known to be driven by mutant *IDH1*, such as brain tumors and chondrosarcomas,” he told *SciBX*.

The work reported in *Science* is unpatented. Agios has multiple patent

applications filed covering mutant *IDH1* as a potential therapeutic target and 2-HG as a potential biomarker.

Celgene Corp. has an exclusive option from Agios to license rights to develop and commercialize an undisclosed number of preclinical compounds targeting cancer metabolism, which includes therapeutics targeting *IDH1*.⁶ Celgene's option kicks in after the compounds complete Phase I trials.

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COMPANIES AND INSTITUTIONS MENTIONED

Agios Pharmaceuticals Inc., Cambridge, Mass.
Celgene Corp. (NASDAQ:CELG), Summit, N.J.
Dana-Farber Cancer Institute, Boston, Mass.
Howard Hughes Medical Institute, Chevy Chase, Md.
Memorial Sloan-Kettering Cancer Center, New York, N.Y.

“We thought it was important to prove that 2-HG was sufficient to induce leukemic transformation and was not just acting as a biomarker.”

—William Kaelin Jr.,
Dana-Farber Cancer Institute

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Big brain science

By Lev Osherovich, Senior Writer

The Brain Activity Map, an academic consortium that aims to measure and model all the connections in living brains, has garnered mass media attention and comparisons to the Human Genome Project. However, unlike mapping the relatively well-defined human genome, visualizing the brain's complete wiring faces severe technical challenges. Also, it is unclear what the outcome of such a project would be and whether it would get new treatments to patients faster than more focused research.

The project's leaders have proposed a timeline of about 20 years for developing the technology to collect and interpret data from human brains. Popular press coverage of the Brain Activity Map (BAM) has focused on the idea of being able to image the activity of the entire brain in real time but has largely overlooked the project's massive technical challenges.

Debate about BAM within the neuroscience community has focused on the wisdom of channeling research funding for non-hypothesis-driven big science.

BAM consortium member Rafael Yuste, professor of biology at **Columbia University**, told *SciBX* that the project's goals coalesced from a series of meetings in 2011 and 2012 organized by **The Kavli Foundation**, the **Allen Institute for Brain Science** and **The Gatsby Charitable Foundation**. All three are private philanthropic organizations focused on basic neuroscience and nanotechnology research.

Over the course of these meetings, BAM evolved from a basic research technology wish list into an overarching plan for a great leap forward in brain imaging technology.

The project's framework was described in a conference white paper¹, a review in *Neuron* last summer² and in a perspective piece in *Science* this week.³

President Barack Obama mentioned the project in his State of the Union address as a grand scientific challenge akin to the Human Genome Project. Thereafter, comments on Twitter by NIH director Francis Collins about BAM sparked speculation about the NIH's involvement in the financing and administration of the project.

No official announcement by the White House or NIH about BAM has yet appeared, and there is no timeline for one.

Modeling the brain

Although proponents of the project are likening it to the Human Genome Project, both the scale and scope of the projects are different.

In the case of the Human Genome Project, the task was finite, with the genome initially thought to consist of about 25,000 genes. In addition, the technology to sequence those genes existed, even if it needed to be scaled up.

There also was broad consensus in the research and clinical communities that sequencing the genome would have broad and immediate utility. In practice, the human genome's organization and function proved far more complex than expected, but the output of the Human Genome Project proved a useful starting point for subsequent genomic studies.

In contrast, the connection map of the brain proposed by the BAM

project may not be consistent from one brain to another or even from one moment to the next.

Whether or not the analogy to the Human Genome Project is apt, BAM's goals and the technology to achieve them are not yet clearly defined.

BAM aims to build models of the brain in action from data gathered with a range of optical and electrophysiological technologies that do not yet exist. Because existing tools to study the brain capture only a fraction of its activity, BAM's first objective is to develop new technologies that can capture the full range of chemical and electrical activity of every neuron.

The consortium also wants to develop optogenetic and nanoelectronic methods to experimentally manipulate the activity of single neurons in living brains. The goal of this approach is to uncover the functional significance of every synaptic connection.

A third goal of BAM is to develop computational methods that model and eventually emulate the workings of the human brain.

"We're proposing a very massive project that could take a decade or two, on the scale of the Human Genome Project," said Yuste.

R. Clay Reid, senior investigator of neural coding at the Allen Institute, said the groundwork exists for the imaging technology but requires considerable scaling up.

"We've gone from being able to record from a handful of neurons to being able to routinely record from a thousand at a time. Now we're discussing going to 10,000 or 100,000 neurons," Reid said.

Yuste said the project will first test these imaging and recording technologies in small animals such as *Caenorhabditis elegans* and will work its way up to progressively larger and more complex organisms.

"We're proposing that in five years we might be able to reconstruct the nervous system of the worm and a significant portion of the nervous system of the fly. Maybe in 10 years you can do this on the scale of a million neurons, on the scale of the zebrafish brain or mouse retina," he said.

Yuste said it may eventually be possible to image and record the activity of the entire human brain and to externally manipulate complex neural circuits that influence behavior and perception.

He said a complete understanding of the brain's workings will help clinical researchers identify brain activity signatures of complex neurological diseases such as epilepsy and schizophrenia.

"You could have new types of diagnostics and therapeutics," said Yuste. "If you could map circuits in the brain with this level of detail, you could map the spread of epileptic seizures and observe which neurons are participating or not. If a brain region is involved in the spreading of seizures, you could stop that process" with external nanoelectronic manipulation.

Delivering insights

Even if BAM manages to build the technology needed to capture whole-brain data, not all neuroscientists are convinced the project will be able to deliver meaningful insights into the human brain's high-level functions, let alone reconstruct a nervous system.

Eve Marder, professor of biology at **Brandeis University**, said the proposed imaging technology could potentially be useful in studying larger numbers of neurons than is possible with current techniques but was uncertain whether the approach could scale up to the whole-brain level.

“Everyone agrees that there’s value to getting multiple recordings from brains during behavior and that some problems will not be solved by recording only from single neurons, one at a time,” said Marder.

However, she suspects the scale of activity in the whole human brain will defy interpretation. She said it is already difficult to interpret data from recordings of thousands of neurons, so piling on more data may not lead to greater insights.

“We already have the ability to collect more data than we know how to visualize or think about,” she added.

Marder said it was not clear what aspects of whole-brain activity are functionally relevant or pertain to specific behaviors, so large data sets of overall brain activity will likely be hard to interpret.

“If your goal is to understand the brain, we don’t have any consensus on what that even means,” said Marder. She said the theoretical framework for relating the brain’s electrophysiological activity to behavior is ill defined.

To address that concern, Yuste and Reid said BAM will use “big data” computational methods to identify hidden patterns of brain activity and correlate them with behavior. This will require developing new analytical methods and building massive computational facilities.

Even if BAM succeeds in capturing and analyzing the totality of brain activity, it is not clear whether this information would yield insights into high-level brain functions such as cognition and memory.

Partha Mitra, professor of neuroscience at **Cold Spring Harbor Laboratory**, argued in a *Scientific American* article⁴ that the complex functions of the brain are unlikely to arise merely from the sum of every neuron’s activity but

rather are influenced by external stimuli and prior history.

If so, BAM’s proposed high-resolution snapshot of the brain’s activity would not necessarily make it possible to reconstruct brain activity *in silico*.

Money woes

Another concern is how to fund the project during a period of shrinking basic research budgets. *The New York Times* estimated that the total cost of BAM will be in the range of \$3 billion.⁵ By comparison, the **National Institute of Neurological Disease and Stroke**’s budget for 2013 is \$1.6 billion.

Yuste said he expects the NIH, the White House’s **Office of Science and Technology Policy** and the U.S. **Department of Defense’s Defense Advanced Research Projects Agency** will announce how BAM will be funded this month.

Reid said private institutions like the Allen Institute and the **Howard Hughes Medical Institute** would provide some financial support, but the bulk of the funding would come from government agencies.

Cornelia Bargmann, professor and laboratory head at **The Rockefeller University** and a Howard Hughes Medical Institute investigator, is worried that concentrating neuroscience research money into BAM would reduce small grants to academic researchers.

“These are hard times for federal funding of research grants. I would want to be very, very sure that this was new funding and not resources that are taken away from a system that is already deeply stressed. An end around the normal scientific review process would be a mistake,” Bargmann told *SciBX*.

The BAM team wrote in a *Science* perspective that they want the project to be funded by new commitments from the government, not from existing neuroscience funds.

Even if BAM is ultimately paid for by new money, Bargmann is skeptical that funding large research centers is the best way to advance neuroscience.

“Are we talking about central planning inside the Beltway and the genome model of large ‘centers’? I would not be a fan even if that were new money; that’s not what the field needs,” said Bargmann.

Marder also was skeptical about launching another big science project.

“Neuroscience is at a moment where we could make tremendous advances in the next 10–15 years. This will require a mixture of larger- and smaller-scale projects, but there are a lot of good people who are being pushed out of the field because there isn’t enough money,” said Marder. “Diverting the meager resources that we have right now for bigger projects would be a mistake.”

Reid expects the funding will be distributed to a combination of large regional academic centers and smaller laboratories. He said it will take some time to build up the technology and imaging facilities ultimately envisioned by BAM, so for now the funding will go to smaller labs.

“I believe that neuroscience is ready for some of it being big science, but the majority of the work will be done in smaller groups for the foreseeable future,” said Reid.

Gone fishing

Pharmaceutical Research and Manufacturers of America (PhRMA) put out a general statement of support for BAM, but there are no authors from industry on either of the two papers the BAM team has published.

Douglas Williams, EVP of R&D at **Biogen Idec Inc.**, said BAM appears to be “a fundamental science project that is going to generate insights, but it’s hard to predict where and when the payoff will be.”

He added, “In a world of unlimited dollars, I’d love to see this done, but I think there are very pressing public health threats in neurology that are more important. It’s not that this isn’t a fascinating project to undertake, but public health considerations should garner more basic research funding.”

Although the project’s ultimate goal is to image the human brain, the most useful aspect of the work may be imaging the brains of mice to assist in preclinical studies.

Yuste said it may be possible to monitor the effects of drug candidates on whole-brain activity to gain insights into how they affect brain functions that go awry in disease.

“This technology will provide a new type of assay from brain-related pathology that could be used for drug discovery,” said Yuste. “You could image or record the effect of a drug on every neuron.”

Williams said another potential application could be the development of high-resolution brain imaging tools for clinical biomarker studies. “I see this project as a generator of new technologies,” he added.

(Continues on p. 6)

“We’ve gone from being able to record from a handful of neurons to being able to routinely record from a thousand at a time. Now we’re discussing going to 10,000 or 100,000 neurons.”

—R. Clay Reid,
Allen Institute for Brain Science

Funding breakthroughs

By Tracey Baas, Senior Editor

The \$33 million in prize money from the **Breakthrough Prize in Life Sciences Foundation** went to 11 deserving scientists. But it is worth debating whether, in an age of austerity, there are more efficient ways for the billionaire backers to put their money to work.

One line of thought holds that giving money to young researchers might be a better use of new funds than giving prize money to established researchers who already are well funded.

But at least two of the winners, as well as representatives from other philanthropies, think that essentially any form of large, long-term investigator award will give scientists more freedom than traditional grant-based research funding.

The Breakthrough Prize in Life Sciences Foundation was created by Art Levinson, Sergey Brin, Anne Wojcicki, Mark Zuckerberg, Priscilla Chan and Yuri Milner (see Table 1, “**Founders and awardees**”). Its stated goals are “advancing breakthrough research, celebrating scientists and generating excitement about the pursuit of science as a career,” according to the foundation’s website.

To achieve this, the foundation awarded \$3 million to each of 11 researchers. The awardees together cover a broad range of research activities, but the primary focus underlying much of the work is cancer. Recipients were selected by the foundation’s board, and next year’s recipients—of which

(Continued from “**Big brain science**,” p. 5)

Benjamin Matteo, cofounder and CEO of **Eos Neuroscience Inc.**, said methods developed by BAM could make it easier to evaluate the effect of therapeutics that stimulate specific neuronal activity. Eos is developing optogenetic gene therapies to treat blindness.

Eos’ most advanced candidate is EOS-13, an adeno-associated virus (AAV) vector that encodes channelrhodopsin-2 (ChR2), an algae-derived, light-activated ion channel protein. EOS-13 has completed preclinical testing for retinitis pigmentosa.

“We can now restore the ability of blind mice to navigate and can record populations of ganglion cells to show that these cells are firing normally in space and time,” said Matteo. “Right now we’re not at a stage [where] we can say what the animal is seeing, but we can tell that the mice are seeing something. More resolution in real time would give us more useful data” about the extent of vision restoration from EOS-13 therapy.

Regardless of the benefits of BAM’s proposed tool building, Matteo thinks the project could benefit from a more clear focus on disease.

“Better tools for recording and understanding circuits is only a part of the answer. Other pieces will come from hypothesis-driven work,” said Matteo. “If you ask me whether to spend \$3 billion on this purely basic work, I would say no; there needs to be more of a translational component.”

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there will be five—will be selected by a committee made up of this year’s winners.

The cash infusion clearly checks boxes two and three of the foundation’s goals, but whether breakthrough research will follow is anyone’s guess.

Three executives at research-supporting philanthropies say long-term awards to investigators of varying ages, rather than via prizes, are a good way to fund big ideas and drive innovation.

“We do not fund science through prizes. We find that our competitive investigator award schemes serve our goals and provide the flexibility and security that researchers need to tackle major scientific challenges,” said Kevin Moses, director of science funding at the **Wellcome Trust**.

Wellcome provides annual funding of up to £425,000 (\$640,000) to both new and senior investigators for up to 7 years.

In 2009, the organization announced it would stop offering project grants and instead offer the investigator awards. It has given 20 new investigator awards and 83 senior investigator awards at 27 different U.K. institutions and 1 overseas institution.

“To select candidates, we make an assessment of their potential and probability of doing significant science in the next-funded period, based on both their track record and their proposal,” said Moses. “We depend on help from outside scientists and clinicians for advice.”

Jack Dixon, VP and CSO of the **Howard Hughes Medical Institute**, noted that young blood was absent from the first round of the \$3 million prizes.

“The Breakthrough Prize in Life Sciences Foundation has selected an impressive group of people—terrific scientists—to give their awards to, but looking at the list, none of these individuals are beginners,” he said.

(Continues on p. 7)

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COMPANIES AND INSTITUTIONS MENTIONED

Allen Institute for Brain Science, Seattle, Wash.
Biogen Idec Inc. (NASDAQ:BIIB), Weston, Mass.
Brandeis University, Waltham, Mass.
Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y.
Columbia University, New York, N.Y.
Defense Advanced Research Projects Agency, Arlington, Va.
Eos Neuroscience Inc., San Francisco, Calif.
The Gatsby Charitable Foundation, London, U.K.
Howard Hughes Medical Institute, Chevy Chase, Md.
The Kavli Foundation, Oxnard, Calif.
National Institute of Neurological Disease and Stroke, Bethesda, Md.
National Institutes of Health, Bethesda, Md.
Office of Science and Technology Policy, Washington, D.C.
Pharmaceutical Research and Manufacturers of America, Washington, D.C.
The Rockefeller University, New York, N.Y.
U.S. Department of Defense, Washington, D.C.

“Shinya Yamanaka has already won a Nobel Prize, and three of their awardees—Cornelia Bargmann, Charles Sawyers and Bert Vogelstein—are Howard Hughes Medical Institute investigators.”

HHMI supports about 330 independent researchers as investigators at institutions throughout the U.S. By appointing scientists as HHMI investigators, rather than awarding them traditional grants for specific research projects, the researchers receive flexible funding for five years.

About 80% of the HHMI investigators are reappointed following a review process. HHMI also provides 6 years of funding to an additional 45

early career scientists—individuals who are 2–5 years into their tenure-track career.

The Paul G. Allen Family Foundation has been giving a growing portion of its awards to younger investigators. Of the 5 new Allen Distinguished Investigators awards announced last month, each ranging from \$1.4 million to \$1.6 million, none was given to a tenured professor.

“We are looking for the most innovative project proposals, and we’re not biased against a researcher’s CV, publication record or point in their career,” said VP Sue Coliton. “We have already seen progress come out

Table 1. Founders and awardees.

Founders	Title(s)	Science background
Sergey Brin	Cofounder of Google Inc.	Bachelor’s degree in mathematics and computer science from the University of Maryland, College Park and a master’s degree in computer science from Stanford University , where he is currently on leave from the PhD program
Priscilla Chan		Bachelor’s degree in biology from Harvard University and a medical degree from the University of California, San Francisco
Art Levinson	Chairman of Apple , chairman of Roche’s Genentech Inc. unit and member on the board of directors for Roche. Chairman of the board of directors for the Breakthrough Prize in Life Sciences Foundation	Bachelor’s degree in molecular biology from the University of Washington and a PhD in biochemical sciences from Princeton University
Yuri Milner	Founder of the internet company Mail.ru Group . Member of the board of directors for the Breakthrough Prize in Life Sciences Foundation	Advanced degree in theoretical physics from Lomonsov Moscow State University and subsequently conducted research at the Institute of Physics at the Russian Academy of Sciences
Anne Wojcicki	Cofounder of privately held personal genetics company 23andMe Inc. Member of the board of directors for the Breakthrough Prize in Life Sciences Foundation	Bachelor’s degree in biology from Yale University
Mark Zuckerberg	Founder, chairman and CEO of Facebook Inc. Member of the board of directors for The Breakthrough Prize in Life Sciences Foundation	Studied computer science at Harvard
Awardee	Title(s)	Research focus
Cornelia Bargmann	Professor and head of the Lulu and Anthony Wang Laboratory of Neural Circuits and Behavior at The Rockefeller University and a Howard Hughes Medical Institute (HHMI) investigator	Genetics of neural circuits and behavior, and synaptic guidepost molecules
David Botstein	Director of the Lewis-Sigler Institute for Integrative Genomics at Princeton University and professor of genomics at Princeton	Linkage mapping of Mendelian disease in humans using DNA polymorphisms
Lewis Cantley	Professor and director of the Cancer Center at Weill Cornell Medical College and New York–Presbyterian Hospital	Phosphoinositide 3-kinase (PI3K) and its role in cancer metabolism
Hans Clevers	Professor of molecular genetics at the Hubrecht Institute and president of the Royal Netherlands Academy of Arts and Sciences	Wingless-type MMTV integration site (WNT) signaling in tissue stem cells and cancer
Napoleone Ferrara	Professor of pathology and senior deputy director for basic sciences at the University of California, San Diego Moores Cancer Center	Mechanisms of angiogenesis that lead to therapies for cancer and eye diseases
Titia de Lange	Professor, head of the Laboratory of Cell Biology and Genetics and director of the Anderson Center for Cancer Research at The Rockefeller University	Telomeres—illuminating how they protect chromosome ends and their role in genome instability in cancer
Eric Lander	President and founding director of the Broad Institute of MIT and Harvard , professor of biology at the Massachusetts Institute of Technology (MIT) and professor of systems biology at Harvard Medical School	General principles for identifying human disease genes and enabling their application to medicine through the creation and analysis of genetic, physical and sequence maps of the human genome
Charles Sawyers	Chair of human oncology and the pathogenesis program at Memorial Sloan-Kettering Cancer Center and an HHMI investigator	Cancer genes and targeted therapy
Bert Vogelstein	Director of the Ludwig Institute for Cancer Research , professor of oncology and pathology at The Sidney Kimmel Comprehensive Cancer Center at The Johns Hopkins University School of Medicine and an HHMI investigator	Cancer genomics and tumor suppressor genes
Robert Weinberg	Professor for cancer research at MIT, director of MIT’s Ludwig Center for Molecular Oncology and a member of the Whitehead Institute for Biomedical Research	Characterization of human cancer genes
Shinya Yamanaka	Director of the Center for iPS Cell Research and Application at Kyoto University and senior investigator at The J. David Gladstone Institutes	Induced pluripotent stem cells

of our first cohort—including a spinoff company called **Inscopix Inc.** that came from a brain-imaging technology development from one of our investigators.”

The **NIH** has also been setting aside money to fund outside-the-box thinkers. It offers the NIH Director’s Pioneer Award, the NIH Director’s New Innovator Award, the NIH Director’s Transformative Research Award and the NIH Director’s Early Independence Award.

“The Pioneer Awards have been around for about 10 years, so we can see the award provides a pretty clear opportunity for groundbreaking research,” said NIH director Francis Collins. “We’ve had some exciting work come out of these awards but also some failures, which just goes to show that you can’t have interesting success stories without taking on some risk.”

Collins added, “One of the newly awarded Breakthrough Prize scientists—Titia de Lange—received one of our Pioneer Awards in 2005. It is encouraging to see that type of endorsement for a scientist and projects that are traditionally considered ‘too risky,’” he said.

The Pioneer Award provides scientists with up to \$750,000 in research and indirect costs per year for 5 years.

“I think it’s great that The Breakthrough Prizes in Life Sciences Foundation is providing such a large financial incentive to attract public attention and get young people interested in science,” Collins said. “I am delighted that they are able to provide that type of recognition, because we at the NIH wouldn’t be able to give an unrestricted personal prize of this magnitude with tax payers’ money.”

Prized fighters

Hans Clevers, a Breakthrough awardee who is professor of molecular genetics at the **Hubrecht Institute** and president of the **Royal Netherlands Academy of Arts and Sciences**, thinks a key advantage of awards versus grants is operating freedom.

Clevers has received multiple prizes and awards. To name a few, he is a past recipient of the Dutch Spinoza Award—a Dutch equivalent of the Nobel Prize—which provides €2.5 million (\$3.3 million) for research purposes; the Louis-Jeantet Prize, which provides €400,000 (\$520,000) for research and €75,000 (\$98,000) for personal use; and the Heineken Prize, which provides €150,000 (\$200,000) for personal use.

“There is no timeline for when you need to use the money,” he said. “I have felt secure in hiring people because I have money set aside to pay for salaries if fellowships don’t come through. I could never do this with a traditional grant because at the end of the grant, the money has to be used or you lose it. Also, unlike grants, the money can be used for expensive equipment, such as two-photon microscopes or gene arrayers, that my laboratory students and postdocs are interested in trying—just to see if it might further their research.”

Clevers also said that being free from the cycle of grant writing allows for more creative research. “The idea of exploration is what these types of awards foster. I have had about 30–40 manuscripts published in high-impact journals like *Nature*, *Cell* and *Science*,” he said. “Those publications have all come out of work that I never had to write a grant for. My breakthrough papers have come from awards—like Spinoza or Louis-Jeantet—that allowed me the freedom to explore. My work from aim-based grant proposals typically does not make the high-impact journals.”

Cornelia Bargmann, a Breakthrough awardee who is professor and laboratory head at **The Rockefeller University** and an HHMI investigator, agreed that freedom in research is what yields scientific advances. “I have had the huge privilege of being an HHMI investigator since 1995, and I understand how having that money provides you with the freedom to explore different aspects of your work,” she said. “Rockefeller has also contributed to that freedom, showing me that my work is valuable by providing me with funding and my graduate students with salaries.”

Traditionally, graduate student salaries are paid from grants received by their professor or from student fellowships that also are based on grant proposals.

“These types of awards are very important to provide support for basic research that seems to have no immediate or obvious payoff but in the long run contributes to medical breakthroughs,” said Bargmann. “When there is a clear lead or target to go after or treat disease, that is where big pharmas can take the lead—and they are very good at that. It is what they do. But academic scientists, exploring basic research problems—they are going to provide the information as to where or what those leads or targets may be. It is what we do best.”

Future funding

Ultimately, it will be up to the Breakthrough Prize’s selection committee to determine which scientists and what type of basic research problems should receive dollars.

Yuri Milner’s other big-money philanthropy—the **Fundamental Physics Prize Foundation**—provides a good case study. In its inaugural year of 2012, the Foundation awarded 9 Fundamental Physics Prizes, each at \$3 million.

This year, the foundation’s selection committee chose five laureates to receive the Physics Frontiers Prize, which recognizes transformative advances in the field, and three laureates to receive the New Horizons in Physics Prizes, which target promising junior researchers.

The New Horizon awardees will receive \$100,000. The Physics Frontiers Prize awardees will receive \$300,000 and will become nominees for the Fundamental Physics Prize.

Baas, T. *SciBX* 6(9); doi:10.1038/scibx.2013.207
Published online March 7, 2013

COMPANIES AND INSTITUTIONS MENTIONED

Breakthrough Prize in Life Sciences Foundation, no location provided

Fundamental Physics Prize Foundation, no location provided
Howard Hughes Medical Institute, Chevy Chase, Md.

Hubrecht Institute, Utrecht, the Netherlands

Inscopix Inc., Palo Alto, Calif.

National Institutes of Health, Bethesda, Md.

The Paul G. Allen Family Foundation, Seattle, Wash.

The Rockefeller University, New York, N.Y.

Royal Netherlands Academy of Arts and Sciences, Amsterdam, the Netherlands

Wellcome Trust, London, U.K.

“These types of awards are very important to provide support for basic research that seems to have no immediate or obvious payoff but in the long run contributes to medical breakthroughs.”

—Cornelia Bargmann,
The Rockefeller University

ALL emerges from relapse

By Lauren Martz, Staff Writer

Separate teams led by researchers from **New York University** and **Columbia University** have identified mutations in *5'-nucleotidase cytosolic II* that predict relapse, drug resistance and poor prognosis in acute lymphoblastic leukemia.^{1,2} Inhibiting the enzyme could improve disease outcomes and sensitize some relapsed patients to marketed acute lymphoblastic leukemia therapies.

Current treatment regimens for ALL involve first-line chemotherapy followed by maintenance therapy that includes the purine analogs 6-mercaptopurine (6-MP) and 6-thioguanine (6-TG).

Although the treatments are effective for many patients, about 10%–20% of pediatric patients and up to 50% of adult patients relapse. The relapsed disease often is resistant to drugs and has a cure rate of less than 40%.³

The two teams conducted genetic studies on patient samples to find the underlying mechanisms of ALL relapse. Both converged on overlapping sets of gain-of-function mutations in *5'-nucleotidase cytosolic II* (*NT5C2*), which were associated with disease relapse and could be causing drug resistance.

In a paper published in *Nature Genetics*, William Carroll and colleagues at NYU sequenced RNA samples from pediatric patients with B lymphoblastic leukemia, the most common form of ALL. Carroll is a professor of pediatrics and director of the NYU Cancer Institute.

The team found 20 missense mutations in samples from 10 relapse patients that were absent in matched samples from patients at diagnosis or during remission, including two mutations in the coding region of *NT5C2*.

In a follow-up analysis of samples from another 61 relapse patients, full exon sequencing of *NT5C2* identified additional mutations in 5 more patient samples, suggesting the gene is mutated about 10% of the time. Moreover, every patient who expressed the *NT5C2* mutations relapsed within 36 months of initial diagnosis.

Mechanistic studies showed that expression of the *NT5C2* mutants in *Escherichia coli* led to greater *5'-nucleotidase* activity than expression of wild-type *NT5C2*. In cultured B lymphoblastic leukemia cells, lentivirus-mediated expression of mutant *NT5C2* rendered the cells resistant to apoptosis by 6-MP and 6-TG compared with expression of the wild-type gene.

The paper also included researchers from **St. Jude Children's Research Hospital**, the **Memorial Sloan-Kettering Cancer Center**, **Weill Cornell Medical College**, the **University of Colorado Denver School of Medicine** and **Children's Hospital Colorado**.

In a paper published in *Nature Medicine*, a Columbia University team led by Adolfo Ferrando published similar findings for patients with a highly aggressive ALL subtype—T cell ALL. Ferrando is an

associate professor of pathology and pediatrics at Columbia's Institute for Cancer Genetics.

Ferrando's group used matched whole-exome sequencing on samples from five patients with T-ALL at diagnosis, remission and relapse and identified a relapse-associated mutation in *NT5C2* in one of the patients.

The group then studied a panel of 98 relapsed T-ALL and 35 relapsed B precursor ALL samples. *NT5C2* was mutated in 1 additional patient with B-ALL and 19 additional patients with T-ALL. The mutations were absent in matched samples from the time of diagnosis.

In a *5'-nucleotidase* assay, the mutant enzymes had up to 48-fold greater activity than wild-type enzyme. In T-ALL cells, vector-mediated expression of the mutant genes increased cell viability with increasing concentrations of 6-MP or 6-TG compared with expression of wild-type *NT5C2* or an empty vector control.

The paper also included researchers from the **Albert Einstein College of Medicine of Yeshiva University**, **Charité-University Hospital Berlin**, **Cancer Institute Padua**, the **Technion-Israel Institute of Technology**, **Memorial Sloan-Kettering**, the **Shaare Zedek Medical Center** and the **University of Padua**.

Carroll, corresponding author of the *Nature Genetics* paper, told *SciBX* that his team was encouraged by the results of the *Nature Medicine* paper “because we found the relapse-associated mutation in the B cell subset of ALL, and they have found it in the other form, T-ALL. These are different biological

subtypes, and it is interesting that regardless of the type of cancer, common treatments may lead to the emergence of the same resistance mechanisms due to the selective pressure. This is a form of convergent evolution. To us, this means that other cancers, particularly adult forms of ALL, may also be affected by the same resistance mechanisms.”

“If one were to target *NT5C2*, the potential danger would lie in inhibiting the normal function of *NT5C2* in purine metabolism.”

—Josef Vormoor,
Cancer Research UK

NT5C2 inhibitors

Both teams told *SciBX* that their next steps included designing *NT5C2* inhibitors. The molecules likely would be used to resensitize resistant ALL to standard therapies like 6-MP and 6-TG.

“If one were to target *NT5C2*, the potential danger would lie in inhibiting the normal function of *NT5C2* in purine metabolism,” noted Josef Vormoor, a **Cancer Research UK** childhood leukemia expert and professor of child health at **Newcastle University**.

Carroll and colleagues hope to avoid that problem by designing inhibitors that selectively bind the mutant form of the enzyme.

“Our ultimate goal is to design inhibitors specific for the mutant forms of the enzymes to spare the wild-type enzyme function. We have not yet seen if this is possible, and designing selective compounds has been challenging, but these studies are underway,” said Carroll.

“The cellular function of *NT5C2* is to clear purine nucleoside intermediates out of the cell in conditions of high energy. At this point, it is unclear what would be the systemic effects of *NT5C2* inhibition,” added corresponding author Ferrando.

In addition to therapeutic discovery, Ferrando told *SciBX* that his team is developing diagnostic assays to identify *NT5C2* mutations as biomarkers of prognosis and drug resistance.

He noted that there are alternative therapeutics for patients with leukemia who do not respond to 6-MP or other purine drugs, so it would be beneficial to be able to predict response.

For example, Ferrando's team showed that nelarabine, an approved drug in the purine pathway, was active against *NT5C2*-mutated cancer cell lines. He added that other antileukemic drugs with different mechanisms of action including glucocorticoids and methotrexate also are active in *NT5C2*-mutated leukemias.

GlaxoSmithKline plc markets Arranon nelarabine to treat ALL and lymphoma.

Carroll said a key goal for his team is to prevent global resistance before it begins. "Once frank relapse occurs, other mutations have likely emerged, causing pan-resistance. The chances that restoring sensitivity to purine analogs will be sufficient to cure the cancer alone are reduced," he said. "We are now looking into whether we can use next-generation sequencing of patient samples throughout disease remission to see whether we can catch these mutations early as they emerge to alter the therapeutic regimen before full relapse occurs."

Carroll said NYU has filed a patent application covering the mutations and that the IP is available for licensing.

Ferrando told *SciBX* that Columbia has filed a patent application for the *NT5C2* mutations for diagnostic and therapeutic applications. The IP is available for licensing.

Martz, L. *SciBX* 6(9); doi:10.1038/scibx.2013.208
Published online March 7, 2013

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Contact: William L. Carroll, NYU Cancer Institute, New York, N.Y.
e-mail: william.carroll@nyumc.org
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Contact: Adolfo Ferrando, Columbia University, New York, N.Y.
e-mail: af2196@columbia.edu
3. Pui, C.-H. & Evans, W.E. *et al. N. Engl. J. Med.* **354**, 166–178 (2006)

COMPANIES AND INSTITUTIONS MENTIONED

Albert Einstein College of Medicine of Yeshiva University, New York, N.Y.
Cancer Institute Padua, Padua, Italy
Cancer Research UK, London, U.K.
Charité–University Hospital Berlin, Berlin, Germany
Children's Hospital Colorado, Aurora, Colo.
Columbia University, New York, N.Y.
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Memorial Sloan-Kettering Cancer Center, New York, N.Y.
Newcastle University, Newcastle upon Tyne, U.K.
New York University, New York, N.Y.
Shaare Zedek Medical Center, Jerusalem, Israel
St. Jude Children's Research Hospital, Memphis, Tenn.
Technion–Israel Institute of Technology, Haifa, Israel
University of Colorado Denver School of Medicine, Aurora, Colo.
University of Padua, Padua, Italy
Weill Cornell Medical College, New York, N.Y.



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This week in therapeutics

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

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

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Autoimmune disease				
Autoimmune disease	Protein kinase C θ (PRKCQ)	<p>Mouse and <i>in vitro</i> studies identified pyrazolo-[3,4-<i>b</i>]pyridine-based PRKCQ inhibitors that could help treat autoimmune diseases. <i>In vitro</i>, the lead compound inhibited PRKCQ with an IC₅₀ value of 0.08 nM and 75-fold selectivity over related protein kinase C (PKC) isoforms. In mice, the lead compound decreased serum levels of the proinflammatory cytokine Il-2 compared with vehicle. Next steps include testing the class of inhibitors in models of autoimmune disease and evaluating their toxicity.</p> <p>SciBX 6(9); doi:10.1038/scibx.2013.209 Published online March 7, 2013</p>	Patent application filed; licensing status undisclosed	<p>Jimenez, J.-M. <i>et al. J. Med. Chem.</i>; published online Feb. 11, 2013; doi:10.1021/jm301465a</p> <p>Contact: Juan-Miguel Jimenez, Vertex Pharmaceuticals Inc., Oxfordshire, U.K. e-mail: juan-miguel_jimenez@vrtx.com</p>
Rheumatoid arthritis (RA)	Heat shock protein 60 (Hsp60)	<p>Mouse studies suggest T_{reg} cells targeting Hsp60 could help treat RA. In a collagen-induced arthritis mouse model for RA, infusion of CD8⁺ T_{reg} cells that recognized a peptide fragment of Hsp60 decreased disease progression compared with vehicle infusion and eliminated autoreactive T helper type 17 (Th17) and follicular helper T cells. In the mouse model, methotrexate plus T_{reg} cell infusion synergistically decreased disease severity compared with either treatment alone. Next steps include testing the strategy in a humanized mouse model for arthritis. The generic methotrexate is marketed to treat cancer and autoimmune diseases.</p> <p>SciBX 6(9); doi:10.1038/scibx.2013.210 Published online March 7, 2013</p>	Patent application filed; available for licensing	<p>Leavenworth, J.W. <i>et al. J. Clin. Invest.</i>; published online Feb. 8, 2013; doi:10.1172/JCI66938</p> <p>Contact: Harvey Cantor, Dana-Farber Cancer Institute, Boston, Mass. e-mail: harvey_cantor@dfci.harvard.edu</p>
Cancer				
Breast cancer	Plasminogen activator urokinase receptor (PLAUR; uPAR; suPAR)	<p>Mouse studies suggest anti-uPAR antibodies could help treat aggressive breast cancer. In a mouse xenograft model for triple-negative breast cancer, two different anti-uPAR human antibodies inhibited tumor growth. In the same mouse model, a radiotherapeutic-conjugated variant of one of the antibodies caused tumor regression. Next steps include generating sufficient quantities of GMP material for a clinical trial.</p> <p>SciBX 6(9); doi:10.1038/scibx.2013.211 Published online March 7, 2013</p>	Patent applications filed covering uPAR-binding agents and their methods of use; available for licensing from the University of California, San Francisco Office of Technology Management	<p>LeBeau, A.M. <i>et al. Cancer Res.</i>; published online Feb. 11, 2013; doi:10.1158/0008-5472.CAN-12-3526</p> <p>Contact: Charles S. Craik, University of California, San Francisco, Calif. e-mail: charles.craik@ucsf.edu</p>

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cancer	Hedgehog acyltransferase (HHAT); sonic hedgehog homolog (SHH); smoothened (SMO)	<p><i>In vitro</i> studies identified HHAT inhibitors that could help treat SHH-driven cancers. HHAT acts upstream of SMO in the hedgehog signaling pathway, potentially providing an alternative way to target the cancer-associated pathway. A high throughput screen identified hits that inhibited HHAT activity with low or submicromolar IC₅₀ values. In cell lines, the lead inhibitor decreased SHH signaling compared with vehicle. Next steps include testing the HHAT inhibitors in preclinical models of SHH-driven cancers such as pancreatic cancer.</p> <p>Erivedge vismodegib, a SMO inhibitor from Roche's Genentech Inc. unit and partners Chugai Pharmaceutical Co. Ltd. and Curis Inc., is marketed to treat basal cell carcinoma (BCC) and is in Phase II testing or earlier to treat other types of cancer.</p> <p>At least four other companies have SMO inhibitors in Phase III testing or earlier to treat various cancers.</p> <p>SciBX 6(9); doi:10.1038/scibx.2013.212 Published online March 7, 2013</p>	Patent application filed; available for licensing	<p>Petrova, E. <i>et al. Nat. Chem. Biol.</i>; published online Feb. 17, 2013; doi:10.1038/nchembio.1184</p> <p>Contact: Marilyn D. Resh, Memorial Sloan-Kettering Cancer Center, New York, N.Y. e-mail: reshm@mskcc.org</p>
Cancer	Mammalian target of rapamycin complex 1 (mTORC1); mTORC2	<p>An SAR study suggests dual-specificity inhibitors of mTORC1 and mTORC2 could help treat cancer. <i>In vitro</i> lead optimization studies identified benzoxazepine-based compounds that were nanomolar inhibitors of both mTORC1 and mTORC2 but not of phosphoinositide 3-kinase (PI3K). In a mouse xenograft model, the lead compound, XL388, decreased tumor growth compared with vehicle control. Next steps could include further optimization or IND-enabling studies.</p> <p>Exelixis Inc.'s XL388 is in preclinical development for cancer indications.</p> <p>Takeda Pharmaceutical Co. Ltd.'s INK128, an inhibitor of mTORC1 and mTORC2, is in Phase I testing for various cancers.</p> <p>SciBX 6(9); doi:10.1038/scibx.2013.213 Published online March 7, 2013</p>	Patented by Exelixis; available for partnering or licensing	<p>Takeuchi, C.S. <i>et al. J. Med. Chem.</i>; published online Feb. 8, 2013; doi:10.1021/jm3007933</p> <p>Contact: James W. Leahy, University of South Florida, Tampa, Fla. e-mail: jwleahy@usf.edu</p> <p>Contact: Byung Gyu Kim, Asan Institute for Life Science, Seoul, South Korea e-mail: byunggyu72kim@gmail.com</p>
Cancer	Phosphatase and tensin homolog pseudogene 1 (PTENP1; PTENpg1); PTEN (MMAC1; TEP1)	<p>Cell culture studies suggest inhibiting <i>PTENpg1</i>-encoded antisense RNA could help treat cancer. <i>PTENpg1</i> is a nonfunctional homolog of <i>PTEN</i> that positively regulates <i>PTEN</i> translation by binding and depleting microRNAs. In a panel of cell lines, a <i>PTENpg1</i> antisense RNA was detected and its expression inversely correlated with <i>PTEN</i> expression. In cultured cells treated with the generic chemotherapeutic doxorubicin, small interfering RNA against <i>PTENpg1</i> antisense RNA increased cell death compared with control siRNA. Next steps include inhibiting the <i>PTENpg1</i> antisense RNA in disease models.</p> <p>SciBX 6(9); doi:10.1038/scibx.2013.214 Published online March 7, 2013</p>	Patent application filed; available for licensing	<p>Johnsson, P. <i>et al. Nat. Struct. Mol. Biol.</i>; published online Feb. 24, 2013; doi:10.1038/nsmb.2516</p> <p>Contact: Kevin V. Morris, The Scripps Research Institute, La Jolla, Calif. e-mail: kmorris@scripps.edu</p> <p>Contact: Dan Grandér, Karolinska Institute, Stockholm, Sweden e-mail: dan.grander@ki.se</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Solid tumors	<i>Phosphatidylinositol glycan anchor biosynthesis class N (PIGN)</i> ; <i>mex-3 homolog C (MEX3C)</i> ; <i>zinc finger protein 516 (ZNF516)</i>	Patient sample and cell culture studies suggest nucleoside supplementation could help treat solid tumors. In 26 colorectal tumor samples and 20 cell lines showing chromosomal instability, <i>PIGN</i> , <i>MEX3C</i> and <i>ZNF516</i> were identified as suppressors of chromosomal instability and were frequently deleted in tumors. In a colorectal cancer cell line lacking <i>PIGN</i> , <i>MEX3C</i> or <i>ZNF516</i> , nucleoside supplementation decreased markers of chromosome instability compared with no treatment. Next steps include determining the role of <i>PIGN</i> , <i>MEX3C</i> and <i>ZNF516</i> in normal cells. SciBX 6(9); doi:10.1038/scibx.2013.215 Published online March 7, 2013	Unpatented; licensing details available from Cancer Research Technology Ltd.	Burrell, R.A. <i>et al. Nature</i> ; published online Feb. 27, 2013; doi:10.1038/nature11935 Contact: Charles Swanton, Cancer Research UK London Research Institute, London, U.K. e-mail: charles.swanton@cancer.org.uk
Endocrine/metabolic disease				
Diabetes; obesity	Inhibitor of κ -light polypeptide gene enhancer in B cells kinase- ϵ (IKBKE; IKK- ι); TANK-binding kinase 1 (TBK1)	Mouse and <i>in vitro</i> studies suggest the generic drug amlexanox could help treat obesity and obesity-related metabolic disorders such as diabetes. In mice fed a high-fat diet, <i>Ikbke</i> and <i>Tbk1</i> expression was greater than that in mice fed a normal diet. <i>In vitro</i> dose-response studies showed that amlexanox inhibited IKBKE and TBK1 with IC ₅₀ values of 1–2 μ M. In mouse models for diet-induced obesity, amlexanox increased insulin sensitivity and decreased both hepatic steatosis and adipose tissue inflammation compared with vehicle. Next steps could include clinical trials to evaluate amlexanox in patients. Amlexanox is a generic drug marketed to treat aphthous ulcers and asthma. SciBX 6(9); doi:10.1038/scibx.2013.216 Published online March 7, 2013	Patent and licensing status unavailable	Reilly, S.M. <i>et al. Nat. Med.</i> ; published online Feb. 10, 2013; doi:10.1038/nm.3082 Contact: Alan R. Saltiel, University of Michigan, Ann Arbor, Mich. e-mail: saltiel@umich.edu
Hematology				
Hemophilia	Factor VIII	Mouse and nonhuman primate studies suggest an adeno-associated virus (AAV) encoding an optimized recombinant human factor VIII could help treat hemophilia A. In wild-type mice, tail vein injection of an AAV encoding the optimized factor VIII led to 10-fold higher expression of the factor than injection of vectors encoding a nonoptimized factor VIII variant. In a mouse model for hemophilia A, injection of the optimized vector decreased tail clip-induced blood loss compared with saline injection. In nonhuman primates, peripheral vein delivery of the vector resulted in stable expression of the factor. Next steps could include evaluating the vector in nonhuman primate models for hemophilia. SciBX 6(9); doi:10.1038/scibx.2013.217 Published online March 7, 2013	Patent and licensing status unavailable	McIntosh, J. <i>et al. Blood</i> ; published online Feb. 20, 2013; doi:10.1182/blood-2012-10-462200 Contact: Amit C. Nathwani, UCL Cancer Institute, University College London, London, U.K. e-mail: a.nathwani@ucl.ac.uk

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Infectious diseases				
Gram-positive bacterial infection; <i>Staphylococcus</i>	Lipoteichoic acid synthase (LtaS)	A study <i>in vitro</i> and in mice suggests inhibiting LtaS could help treat infections of <i>Staphylococcus aureus</i> and other Gram-positive bacteria. A high throughput screen identified a compound that blocked LtaS <i>in vitro</i> and inhibited the growth and altered the cell wall morphology of <i>S. aureus</i> , methicillin-resistant <i>S. aureus</i> and other Gram-positive bacteria at single-digit micromolar concentrations. In a mouse model for <i>Staphylococcus</i> sepsis, the compound increased survival compared with vehicle. Next steps include improving the <i>in vivo</i> stability and efficacy of inhibitors in animal models.	Patent application filed; available for licensing	Richter, S.G. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Feb. 11, 2013; doi:10.1073/pnas.1217337110 Contact: Dominique Missiakas, The University of Chicago, Chicago, Ill. e-mail: dmissiak@bsd.uchicago.edu
SciBX 6(9); doi:10.1038/scibx.2013.218 Published online March 7, 2013				
Inflammation				
Inflammation	Not applicable	Mouse and human studies suggest some mouse models for inflammatory disease may be less relevant than previously thought. In mouse models for inflammation caused by burns, trauma, endotoxemia and sepsis, a comparison of gene expression profiles showed poor correlation with corresponding expression profiles from human tissues undergoing similar insults. Next steps could include developing mouse models for inflammatory diseases with gene expression patterns that more closely match those seen in human tissue.	Patent and licensing status undisclosed	Seok, J. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Feb. 11, 2013; doi:10.1073/pnas.1222878110 Contact: Ronald W. Davis, Stanford University, Palo Alto, Calif. e-mail: dbowe@stanford.edu
SciBX 6(9); doi:10.1038/scibx.2013.219 Published online March 7, 2013				
Neurology				
Addiction	Muscarinic acetylcholine receptor 5 (CHRM5; HM5)	<i>In vitro</i> studies identified HM5-selective antagonists that could help treat drug addiction. In mammalian cells expressing muscarinic acetylcholine receptors, a highly selective derivative of 1,2,5,6-tetrahydropyridine-3-carboxylic acid had 11-fold selectivity for HM5 over other muscarinic receptors. In striatal slices from wild-type rats, the compound inhibited dopamine release as effectively as genetic knockout of Hm5. Computational studies of the HM5 receptor identified the binding mode of the new compound. Next steps include testing the compound in animal models for drug abuse.	Findings unpatented; unavailable for licensing	Zheng, G. <i>et al. J. Med. Chem.</i> ; published online Feb. 4, 2013; doi:10.1021/jm301774u Contact: Guangrong Zheng, University of Arkansas for Medical Sciences, Little Rock, Ark. e-mail: gzheng@uams.edu
SciBX 6(9); doi:10.1038/scibx.2013.220 Published online March 7, 2013				

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cognitive dysfunction	GABA _A receptor α 5 (GABRA5)	<p>Mouse studies suggest selective GABRA5 negative allosteric modulators could help treat cognitive dysfunction in Down syndrome. In a transgenic mouse model for Down syndrome, the GABRA5 negative allosteric modulator RO4938581 increased spatial learning, memory and attention compared with vehicle. In these mice, RO4938581 did not induce anxiety-like behaviors or convulsions. Next steps include additional preclinical studies with RO4938581. Roche has RG1662 in Phase I testing to treat Alzheimer's disease (AD) and cognitive dysfunction associated with Down syndrome.</p> <p>SciBX 6(9); doi:10.1038/scibx.2013.221 Published online March 7, 2013</p>	Patented; unavailable for licensing	<p>Martínez-Cué, C. <i>et al. J. Neurosci.</i>; published online Feb. 27, 2013; doi:10.1523/JNEUROSCI.1203-12.2013 Contact: Maria-Clemencia Hernández, Roche, Basel, Switzerland e-mail: maria-clemencia.hernandez@roche.com</p>
Depression	Annexin A2 (ANXA2); helicase-like transcription factor (HLTF; SMARCA3); S100 calcium binding protein A10 (S100A10; P11)	<p>Mouse and <i>in vitro</i> studies suggest targeting SMARCA3 signaling could help treat depression. A series of <i>in vitro</i> and mouse studies identified SMARCA3 as a binding partner of the P11-ANXA2 complex, which regulates response to serotonin-specific reuptake inhibitor (SSRI) antidepressants. In <i>Smarca3</i> knockout mice, Prozac-induced neuronal and behavioral responses were lower than those seen in wild-type controls. Next steps include identifying the genes targeted by the P11-ANXA2 complex in neuronal cells and determining how those genes contribute to the effects of SSRI drugs. Eli Lilly and Co. markets Prozac fluoxetine to treat major depressive disorder, obsessive-compulsive disorder (OCD), bulimia nervosa and panic disorder.</p> <p>SciBX 6(9); doi:10.1038/scibx.2013.222 Published online March 7, 2013</p>	Patent and licensing status undisclosed	<p>Oh, Y.-S. <i>et al. Cell</i>; published online Feb. 14, 2013; doi:10.1016/j.cell.2013.01.014 Contact: Paul Greengard, The Rockefeller University, New York, N.Y. e-mail: greengard@rockefeller.edu Contact: Yong Kim, same affiliation as above e-mail: kimyo@rockefeller.edu</p>
Ophthalmic disease				
Glaucoma	MAP kinase kinase kinase 12 (MAP3K12; DLK)	<p>Rodent studies suggest inhibiting DLK could have neuroprotective effects that help treat glaucoma. In a mouse model for optic nerve damage, deletion of <i>Dlk</i> in retinal ganglion cells decreased the loss of those cells by 75% compared with no deletion. In a rat model for intraocular pressure-induced glaucoma, pretreatment with tozasertib, an inhibitor of multiple kinases including DLK, prevented disease progression. Next steps could include developing more selective DLK inhibitors. Tozasertib is a research reagent.</p> <p>SciBX 6(9); doi:10.1038/scibx.2013.223 Published online March 7, 2013</p>	Patent and licensing status unavailable	<p>Welsbie, D.S. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Feb. 19, 2013; doi:10.1073/pnas.1211284110 Contact: Donald J. Zack, The Johns Hopkins University School of Medicine, Baltimore, Md. e-mail: dzack@jhmi.edu</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Pulmonary disease				
Acute lung injury	IL-6; IL-6 receptor (IL-6R; CD126); IL-6 signal transducer (IL-6ST; gp130; CD130)	<p>Human plasma and mouse studies suggest inhibiting IL-6 trans-signaling could help treat pancreatitis-associated acute lung injury. In patients with acute pancreatitis who progressed to lung or other organ failure, plasma taken at disease onset showed significantly higher IL-6 and IL-6R levels than plasma from individuals with mild acute pancreatitis ($p < 0.001$). In a mouse model for acute pancreatitis-induced lethal acute lung injury, a fusion protein called sgp130Fc that inhibits IL-6 trans-signaling decreased lung injury and increased survival compared with no treatment. Next steps include testing sgp130Fc or the anti-IL-6 mAb Actemra tocilizumab in patients with acute pancreatitis-associated acute lung injury and as a prophylactic in patients undergoing pancreatic endoscopy, which increases the risk of pancreatitis. Roche and partner Chugai Pharmaceutical Co. Ltd. have Actemra in Phase III testing to treat ankylosing spondylitis and Phase II testing to treat scleroderma.</p> <p>Regeneron Pharmaceuticals Inc. and partner Sanofi have sarilumab, an anti-IL-6R human mAb, in Phase III testing to treat rheumatoid arthritis (RA).</p> <p>Ablynx N.V.'s ALX-0061, an anti-IL-6R nanobody, is in Phase II testing to treat RA.</p> <p>SciBX 6(9); doi:10.1038/scibx.2013.224 Published online March 7, 2013</p>	Sgp130Fc patented; licensed to the Conaris Research Institute AG; protein out-licensed to Ferring Pharmaceuticals A/S for use in inflammatory bowel disease (IBD)	Zhang, H. <i>et al. J. Clin. Invest.</i> ; published online Feb. 15, 2013; doi:10.1172/JCI64931 Contact: Hana Algül, Technical University Munich, Munich, Germany e-mail: hana.alguel@lrz.tum.de
Various				
Cancer; viral infections	Cell division cycle 42 (CDC42)	<p><i>In vitro</i> and cell culture studies identified a selective inhibitor of the GTPase CDC42 that could help treat cancer or viral infections. High throughput screening identified compounds that inhibited CDC42 selectively over four other GTPases. In an ovarian cancer cell line-based migration assay, low micromolar concentrations of the lead inhibitor decreased migration compared with vehicle. In hantavirus-infected cells, incubation with inhibitor 60–75 minutes postinfection decreased viral replication compared with vehicle incubation. Next steps include optimizing the CDC42 inhibitor and testing its effects in cell-based models for disease.</p> <p>SciBX 6(9); doi:10.1038/scibx.2013.225 Published online March 7, 2013</p>	Screening technology patented; patent application filed covering the CDC42 inhibitors; available for licensing	Hong, L. <i>et al. J. Biol. Chem.</i> ; published online Feb. 4, 2013; doi:10.1074/jbc.M112.435941 Contact: Angela Wandinger-Ness, The University of New Mexico, Albuquerque, N.M. e-mail: wness@unm.edu Contact: Larry A. Sklar, same affiliation as above e-mail: lsklar@salud.unm.edu

This week in techniques

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

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

Approach	Summary	Licensing status	Publication and contact information
Disease models			
Inducible mouse model for Alzheimer's disease (AD)	Mice with inducible expression of Alzheimer-type β -amyloid (A β) could be useful for studying AD pathology. The mice developed amyloid pathology and showed impairment of short- and long-term memory at about 12 months. In this model, acute doxycycline-induced suppression of amyloid production partially rescued deficits in short-term spatial memory, whereas longer-term suppression also led to improvements in long-term spatial memory and working memory. Next steps could include using the mice to evaluate AD therapeutics. SciBX 6(9); doi:10.1038/scibx.2013.226 Published online March 7, 2013	Patent and licensing status unavailable	Melnikova, T. <i>et al. J. Neurosci.</i> ; published online Feb. 27, 2013; doi:10.1523/JNEUROSCI.4251-12.2013 Contact: David R. Borchelt, University of Florida, Gainesville, Fla. e-mail: drb1@ufl.edu Contact: Alena Savonenko, The Johns Hopkins University School of Medicine, Baltimore, Md. e-mail: asavone1@jhmi.edu
Drug platforms			
Nonembryonic stem cells for cardiac repair	Nonembryonic stem cells could be used to generate cardiomyocytes for cardiac repair. Nontransgenic blastocysts from mice were used to generate 12 stem cell lines that had properties comparable to those of embryonic, induced pluripotent and germline-derived pluripotent stem cells. A cell differentiation protocol generated cardiomyocytes from one of those stem cell lines. In a mouse model of myocardial infarction, a graft of engineered heart muscle produced from the cardiomyocytes led to greater anterior wall thickness in diastole and a greater anterior wall thickening fraction than no graft. Next steps include creating engineered heart muscle from similar stem cells taken from nonhuman primates and humans. SciBX 6(9); doi:10.1038/scibx.2013.227 Published online March 7, 2013	Covered by issued and pending patents; some patents licensed to Myriamed GmbH; additional licensing details available from Tissue Science Holding GmbH	Didié, M. <i>et al. J. Clin. Invest.</i> ; published online Feb. 22, 2013; doi:10.1172/JCI66854 Contact: Wolfram-Hubertus Zimmermann, University Medical Center Goettingen, Goettingen, Germany e-mail: w.zimmermann@med.uni-goettingen.de
Markers			
N-Acetytyramine-O, β -glucuronide (NATOG) as a biomarker for <i>Onchocerca volvulus</i> infection	Studies in human samples suggest NATOG could be a biomarker of onchocerciasis infection. In urine samples from African patients infected with the <i>O. volvulus</i> parasite that causes river blindness, liquid chromatography-mass spectrometry (LCMS)-based analysis of the urine metabolome showed that levels of NATOG, a neurotransmitter-derived metabolite from <i>O. volvulus</i> , were six times higher than levels in samples from healthy controls. Next steps include designing antibodies against the biomarker. SciBX 6(9); doi:10.1038/scibx.2013.228 Published online March 7, 2013	Unpatented; available for licensing	Globisch, D. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Feb. 25, 2013; doi:10.1073/pnas.1221969110 Contact: Kim D. Janda, The Scripps Research Institute, La Jolla, Calif. e-mail: kdjanda@scripps.edu

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