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By *Chris Cain, Senior Writer*

**Regeneron Pharmaceuticals Inc.** has opened a new genetics center tasked with analyzing the genomes of at least 100,000 **Geisinger Health System** patients in the next 5 years. The company hopes the volume of data, diversity of the patient population and rapid validation in humanized mouse models will yield more actionable opportunities than earlier sequencing efforts.

Regeneron is the latest company to enhance in-house commitments to genomics-guided drug discovery as the cost of whole-genome sequencing falls and throughput improves. Another example is **Amgen Inc.**'s December 2012 acquisition of deCode genetics ehf for \$415 million in cash.<sup>1</sup>

"This is genomics the second time around," Regeneron CSO George Yancopoulos told *SciBX*. "During the genomics bubble of 2000, there was premature excitement and hype, but we emphasized the need for functional genetic studies in mice and did not think direct human sequencing would be a large tool for drug discovery."

Indeed, in a September 2000 interview with *BioCentury*,<sup>2</sup> he extolled the functional approach. "We are amazed at the amount of information that's been generated, but that is the easy part. The difficult part is translating that into valuable targets. There is no way of automating the scientific process. Traditional genomics has not yet led to a major scientific discovery that provides insight about a disease," he said.

"What has changed since then," Yancopoulos told *SciBX* last week, "is that the technology has improved exponentially." He also noted that low throughput genomics studies from academic teams have driven many drug discovery efforts, including two that were directly relevant for Regeneron.

An early genomics study identified and characterized mutations in *NLR family pyrin domain containing 3* (*NLRP3*; *NALP3*; *CIAS1*) as the cause of cryopyrin-associated periodic syndromes (CAPS). That finding led to the development of Regeneron's first marketed product, the IL-1 trap Arcalyst riloncept.

More recent academic studies linked proprotein convertase subtilisin/kexin type 9 (PCSK9) mutations to hypercholesterolemia and led to the development of PCSK9-targeting drugs.

At least 10 companies are developing inhibitors of the target, and Regeneron and partner **Sanofi** have the anti-PCSK9 mAb alirocumab in 12 Phase III studies.

Yancopoulos said that the ability to perform large-scale, whole-exome and whole-genome sequencing and automate the process was

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one reason that the time was right to reinvest in a genomics discovery effort. Indeed, the day after Regeneron and Geisinger launched their initiative, **Illumina Inc.** introduced the first system capable of sequencing whole human genomes for less than \$1,000.

Regeneron did not disclose the technology its sequencing center will use but did say it will use a combination of whole-exome and whole-genome technologies, as whole-exome sequencing is still substantially less expensive.

The center will be operated as a wholly owned subsidiary of Regeneron named Regeneron Genetics LLC. To lead its sequencing operations, the company hired John Overton, who previously was associate director of the **Yale University** Center for Genome Analysis.

To lead informatics, the company hired Jeffrey Reid, who was formerly an assistant professor at the Human Genome Sequencing Center at the **Baylor College of Medicine**.

Yancopoulos said that the partnership with Geisinger was another key to the new initiative. “We wanted to study a large population that had an outstanding commitment to electronic health records, long-term follow-up of individual patients and generations of data. We identified them as the best and perhaps only right collaborator for this effort—and they have about three million residents in their health system.”

Geisinger owns 41 hospitals and clinics in central and northeastern Pennsylvania and is also an insurer. The system has transitioned from a fee-for-service model to a performance-based accountable care model over the last several years, as described in an interview with Glenn Steele, president and CEO of Geisinger, on “*BioCentury This Week*.”<sup>3</sup>

Regeneron will obtain de-identified genetic data and health information through the collaboration and is covering the costs for Geisinger. “We are not paying them, and they are not profiting. This is two like-minded institutions working together at cost,” Yancopoulos said.

He said that the Geisinger patients will provide a much greater diversity of genetic information than prior population studies, such as those from deCode. “The Icelandic population is tapped, and it has limited genetic diversity due to founder effects,” he said.

He added that Regeneron has different goals than deCode. “We have enormous admiration for deCode; we think they were on the right track. But what differentiates us is a matter of focus and direction. Because they were not a therapeutics company, it was easy and exciting to publish academic publications. By combining the genomics approach with laboratory approaches, I think the number or fraction of actionable discoveries will increase,” said Yancopoulos.

He specifically highlighted Regeneron’s VelociGene knockout mouse platform as an example of how the company can rapidly test the effects of putative disease alleles.

Yancopoulos expects 100,000 patients to be sequenced within 5 years, but he did not disclose a timeline or specific benchmarks for when the results will inform Regeneron’s discovery stage pipeline.

**“We wanted to study a large population that had an outstanding commitment to electronic health records, long-term follow-up of individual patients and generations of data.”**

**—George Yancopoulos,  
Regeneron Pharmaceuticals Inc.**

According to Yancopoulos, the project is the largest planned sequencing effort to date in the U.S., and he noted that a U.K. plan to sequence and analyze the genome of 100,000 NHS patients is years away.

The Regeneron Genetics Center also has collaborations with the NIH and the **National Human Genome Research Institute** as part of the Undiagnosed Diseases Program and is open to additional collaborations.

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#### COMPANIES AND INSTITUTIONS MENTIONED

**Amgen Inc.** (NASDAQ:AMGN), Thousand Oaks, Calif.  
**Baylor College of Medicine**, Houston, Texas  
**Geisinger Health System**, Danville, Pa.  
**Illumina Inc.** (NASDAQ:ILMN), San Diego, Calif.  
**National Health Service**, London, U.K.  
**National Human Genome Research Institute**, Bethesda, Md.  
**National Institutes of Health**, Bethesda, Md.  
**Regeneron Pharmaceuticals Inc.** (NASDAQ:REGN), Tarrytown, N.Y.  
**Sanofi** (Euronext:SAN; NYSE:SNY), Paris, France  
**Yale University**, New Haven, Conn.

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# A new standard in reproducibility

By Michael J. Haas, Senior Writer

The **Global Biological Standards Institute** has determined that material and procedural standards are the key battleground for improving the reproducibility of preclinical studies—an area of growing concern among funding agencies and industry stakeholders.<sup>1-4</sup> This year the institute will form task forces that will begin developing standards in research areas in which the institute deems they are most needed, such as human cancer cell lines, antibody reagents and next-generation genome sequencing.

GBSI was founded in 2012 to catalyze the development and use of biological standards to enhance the reproducibility of basic and translational life sciences research. The organization's scientific advisory council (SAC) includes representatives from academia, industry, publishers and the NIH's **National Center for Advancing Translational Sciences** (NCATS).

Other groups are grappling with the reproducibility problem, albeit in a different way than GBSI's pursuit of standards. For example, in 2012, research service provider **Science Exchange**, publisher **PLOS** and the open-access data repository **figshare** launched the Reproducibility Initiative.<sup>5</sup>

The goal of the initiative is to enable academic researchers to have their studies replicated by a CRO or university lab facility. The entire validation study is carried out under a confidentiality agreement. The researchers are not obligated to make the new data public, although they are encouraged to publish the results in the *PLoS One* Reproducibility Collection and to post them on figshare.

Last month, GBSI released its first white paper, *The case for standards in life sciences research: seizing opportunities at a time of critical need*.<sup>6</sup> Based on input from nearly 60 stakeholders, the paper addressed the quality of research methodologies, identified areas of concern and recommended the use of standards to improve the reproducibility of preclinical research.

President Leonard Freedman said that each GBSI task force will ideally include key opinion leaders and stakeholders from academia, industry, the NIH, the NCATS, the **National Institute of Standards and Technology** and the **FDA**, who will focus on developing standards for one class of research reagents, materials or procedures.

Freedman previously was vice dean for research and a professor of biochemistry and molecular biology at the **Jefferson Medical College at Thomas Jefferson University**. Prior to that he was VP of women's health and musculoskeletal therapies at Wyeth (now part of **Pfizer Inc.**) and executive director and head of the Department of Endocrinology at **Merck & Co. Inc.**

On Jan. 22, the GBSI SAC was to have met for the first time to prioritize research areas for the new task forces and identify key

opinion leaders to include in them.

Key areas of interest to GBSI include authentication of human cancer cell lines, validation of antibody reagents and standardization of next-generation genome sequencing technologies, said Freedman.

"We want to follow up on ATCC's work on the human cell line authentication standard," which can confirm the origin of a human cell line but not identify its tissue type or cancer status, he said. An authentication standard for cancer cell lines "has obvious implications for drug screening and development and would complement what's already been done by ATCC."

Freedman is CSO of the **ATCC**, a not-for-profit organization that characterizes cell lines, microorganisms and other biological research materials, develops and evaluates techniques for validating those materials, preserves them and distributes the materials to the research community.

The organization published a human cell line authentication standard in 2011 after multiple studies suggested that up to 30% of cell lines used in research were misidentified.<sup>7</sup>

For antibodies used in research and diagnostics, Freedman said, "the key questions here are: what techniques should we use to standardize them? How do we cross-compare readouts from different antibodies against the same target? Everyone I talk to brings up this need because there are very few standards for the generation and use of antibodies" for those purposes.

A third area of potential interest to GBSI—and the one that could be the most challenging—is standards for next-generation genome sequencing. "As the technology and procedures for sequencing the human genome get cheaper, all kinds of questions get raised about standards, such as the type of nucleic acid material used as controls and the lack of uniformity around instrumentation, informatics and software," Freedman said. "This area presents a tremendous opportunity for us, but it's also daunting because it's so vast."

## Calling for consensus

In conjunction with the release of the white paper, GBSI convened a panel in Washington, D.C., to discuss the development of standards that will improve the reproducibility of preclinical research. The take-home message was: follow the decades-old lead of clinical research, in which established processes for developing standards by consensus have changed the landscape.

The four panelists proposed specific steps that research institutions, funding agencies and journals could take to encourage researchers to adopt the standards once they have been developed.

"Clinical research began addressing the problem of reproducibility decades ago, and standards are now built into the system, but we don't have anything comparable in the preclinical arena," said panelist C. Glenn Begley. "Things that were acceptable in clinical trials in the 1970s aren't acceptable any longer."

As examples of standards now established in clinical research, Begley cited the use of control arms, double-blind experiments and all patients in the data analysis.

**"The process of developing and setting a consensus standard has to be dynamic. You have to think about this when you put a standard in place, so that newer, better methods can emerge."**

—Yvonne Reid, ATCC

Begley is CSO and SVP of **TetraLogic Pharmaceuticals Corp.** and a member of GBSI's SAC. He previously was a VP and global head of hematology/oncology research at **Amgen Inc.**, where he coauthored a *Nature* commentary stating that he and Amgen scientists had been able to replicate only 6 out of 53 'landmark' preclinical studies in the literature.<sup>1</sup>

Panelist Mary Lou Gantzer, immediate past president of the **Clinical and Laboratory Standards Institute (CLSI)**, said that it will be important to ensure that standards for preclinical research introduce greater conformity, control and reproducibility without stifling innovation.

CLSI is a not-for-profit organization that develops consensus standards for clinical research with input from academia, industry, government and healthcare professionals.

Because scientific research often requires the development of new methods, "the process of developing and setting a consensus standard has to be dynamic," said panel member Yvonne Reid, manager and scientist at ATCC. "You have to think about this when you put a standard in place, so that newer, better methods can emerge" as scientific knowledge and technology advance.

As an example, Reid said that most of the data used to establish the cell line authentication standard were based on eight genetic markers. "Now it is based on 18 markers," she said.

### Promoting adoption

Although GBSI's task forces will bring stakeholders together to develop consensus standards, the organization will not be involved in implementing those standards, Freedman said. Instead, that responsibility should fall to funding agencies, academic institutions and journals.

Begley said that funding agencies should take the lead in insisting on standards because they have the greatest influence over researchers. "Any grant would be contingent on the researcher's previous and ongoing use of standards and proper procedures. If the researcher doesn't use them, the agency shouldn't renew the grant or should think twice about funding that person again," he said.

Panelist and GBSI SAC member William Bentley added that funding agencies "could also provide more financial support for researchers interested in translating their work to industry," and academic institutions could also do more to educate researchers about translational science.

"Researchers who want to see their results translated to commercial settings would adhere to consensus standards because they would have a vested interest in making sure companies can replicate those findings," added Bentley, who is chair of bioengineering at the **University of Maryland, College Park**.

Academic institutions also could help to implement standards by having a researcher's findings independently validated before applying for a patent on them, Begley said.

"Most institutions spend hundreds of thousands of dollars on filing patent applications, many of which are not going to stand the test of

time" because the findings are not reproducible, he said.

If the institution validated the findings first, "this would have two immediate consequences: there would be a decrease in patents with little value, and the reputation of the institution would increase in the eyes of venture capitalists. This process could conceivably become self-sustaining for the institutions, with the savings from patent applications helping to pay for data validation," he said.

The panelists agreed that journals also could help implement consensus standards by publishing only studies that follow them, but Reid noted that "journals are sometimes still a little nervous about requiring adherence to a standard across all studies."

For example, she said, "if a scientist is using a human cell line as a positive control in an experiment, then it is just a tool, and he might not care whether the cell line" has been properly authenticated according to the ATCC-published standard. "But if that cell line is used as a model for a tumor type, then the identity of the cell is important, and misidentification can be a problem. Journals have difficulty in deciding when to insist on authentication of a cell line" because they perceive that a potential misidentification may not always affect the results.

"I take a harder stand and say that if the cell line has been misidentified—regardless of how it's used—then that's a problem"

because it may affect the reproducibility of that study and enable the use of the misidentified cell line in future studies, Reid said.

**"Researchers who want to see their results translated to commercial settings would adhere to consensus standards because they would have a vested interest in making sure companies can replicate those findings."**

—William Bentley,  
*University of Maryland, College Park*

### Back to basics

In addition to publishing only studies that adhere to established consensus standards, panelists said that journals could take several other steps to address the problem of irreproducibility—such as requiring researchers to provide extensive details on their methods and materials.

Begley cited the need for detailed information about methodologies and reagents in papers. This would avoid the confusion that can arise when authors cite an earlier paper that describes a method instead of spelling out exactly what they did in the new study, he said. "The researchers might have introduced small changes or differences that need to be reported in the new paper."

Begley also suggested that journals publish only studies that use basic scientific and procedural standards, such as blinded experiments, proper positive and negative controls and independently validated reagents.

Bentley agreed. "All of these are factors that enable reproducibility, and it is easy for the journal's reviewers to see whether or not the study used these procedures," he said. "Journals require some of these procedures but not all of them—and the requirement is not universal" across all journals.

Begley and Reid noted that these basic standards could be implemented quickly, without the need for prolonged discussion among stakeholders.

"I think the adoption of these basic standards would happen

(Continues on p. 6)

# Tables turning for TTOs

By C. Simone Fishburn, Senior Editor

A **Brookings Institution** report has helped quantify a problem that technology transfer offices have talked about for years—the inefficiency and expense associated with licensing university patents. The report advocates ramping up the decades-old practice of spinning out assets to newcos, although technology transfer offices contacted by *SciBX* were skeptical that focusing on newco creation is the best solution.

Although fostering startups remains part of their role, technology transfer offices (TTOs) are exploring other strategies beyond traditional licensing and startups to help more inventions see the light of day.

The Brookings report, written by Walter Valdivia, a fellow in the Center for Technology Innovation at Brookings, comes on the heels of increasing interest from Congress on how to promote entrepreneurship and was spurred by the Technology and Research Accelerating National Security and Future Economic Resiliency (TRANSFER) Act of 2013.

The TRANSFER Act is an amendment to the Small Business Act being debated in the U.S. House of Representatives that aims to accelerate the commercialization of federally funded research and technology by small businesses.

Valdivia's report concludes that although the TRANSFER Act is a step in the right direction, it does not go far enough, and that university TTOs should receive greater support from government and industry to help them spin out more companies.

## Low licensing rewards

The blockbuster deals originally envisaged when university TTOs were set up to commercialize academic discoveries have turned out to be few and far between. Only a handful of universities have managed to use licensing as a profit-generating strategy for translating their research

to the clinic.

Valdivia analyzed numbers from 155 TTOs that are members of the **Association of University Technology Managers (AUTM)** and found that although there is a slow increase in university-based startups, the majority of TTO activity is devoted to patent licensing, which brings low financial rewards.

Valdivia highlighted two cardinal problems with the majority of TTOs. First, the revenue raised by their licensing activities does not cover their costs. According to his data, less than 13% of universities generate enough revenue from licensing deals to cover their operating costs.<sup>1</sup> Second, TTOs focus on a few potentially high-value patents and thus pay little attention to the majority of inventions.

According to Valdivia, about 75% of licensing gross income went to only 10% (16) of the AUTM universities in 2003–2012.

Kevin Cullen, head of technology transfer at the **University of New South Wales (UNSW)**, also has analyzed AUTM data and agrees with Valdivia that licensing patents is rarely a cash cow for universities.

He said that about 5% of IP gets licensed and less than 0.5% will generate \$1 million in revenues per year.

Although licensing patents and spinning out companies has long been within the purview of TTOs, their role has broadened in recent years to include longer term co-development deals as pharma companies have sought out more academic alliances.

According to Cullen, the debate over the role of TTOs in the last few years has toggled between reaping value from IP to benefit the university, to being agents of economic development to help the local economy, to providing a bridge between academia and local industry.

The default setting is still IP, he said. Despite the very long odds of IP licensing yielding high returns, universities treat all IP as if it is million-dollar IP, Cullen told *SciBX*.

## Startup solution?

Valdivia's solution is for TTOs to receive more government support and to increase their focus on fostering startups from their research discoveries. He thinks that nurturing startups would be a more

(Continues on p. 7)

(Continued from "A new standard in reproducibility," p. 5)

overnight if funding agencies and journals said, "This is how it has to be done," Begley said.

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## COMPANIES AND INSTITUTIONS MENTIONED

- Amgen Inc.** (NASDAQ:AMGN), Thousand Oaks, Calif.
- ATCC**, Manassas, Va.
- Clinical and Laboratory Standards Institute**, Wayne, Pa.
- figshare**, London, U.K.
- Food and Drug Administration**, Silver Spring, Md.
- Global Biological Standards Institute**, Washington, D.C.
- Jefferson Medical College at Thomas Jefferson University**, Philadelphia, Pa.
- Merck & Co. Inc.** (NYSE:MRK), Whitehouse Station, N.J.
- National Center for Advancing Translational Sciences**, Bethesda, Md.
- National Institute of Standards and Technology**, Gaithersburg, Md.
- National Institutes of Health**, Bethesda, Md.
- Pfizer Inc.** (NYSE:PFE), New York, N.Y.
- PLOS**, San Francisco, Calif.
- Science Exchange**, Palo Alto, Calif.
- TetraLogic Pharmaceuticals Corp.**, Malvern, Pa.
- University of Maryland, College Park**, Md.

economically beneficial way for universities to promote innovation than simply trying to patent discoveries.

Valdivia recommends three government actions to support the change: increased funding for Small Business Technology Transfer (STTR) programs designated for university startups, patent-use exemptions that would make it easier for not-for-profit organizations to use patented material in their research and an equity rule that would help less well-funded universities access government funding by apportioning part of the STTR funds based on the number of faculty.

But university technology transfer officers who spoke with *SciBX* were skeptical that spinouts are the answer, based on decades of experience in doing what Valdivia suggests, and indicated that the high investment of money and time in fostering startups is rarely profitable for the university.

Valdivia told *SciBX*, “A greater emphasis on entrepreneurship won’t bring income to universities necessarily, it could be a financial burden for them, but it will help them contribute to the local economy.”

“What I’m proposing is that universities need to leverage their resources, and since those resources are limited the government should be brought on board, and the private sector too,” he said.

Alicia Löffler agreed with Valdivia’s numbers and with the need for change but not with the idea of increasing government funding indiscriminately. She noted that his financial incentives might be more effective if targeted at spurring disruptive innovations or high-risk, high-reward research that leads to successful startups.

Löffler is associate VP and executive director of the Innovation and New Venture Office at **Northwestern University**.

According to Löffler, the mission of the Northwestern TTO is to move research to the public, and for most university TTOs being financially self-supporting is not—and should not be—part of the equation.

Northwestern ranks fifth in Valdivia’s table of top earners by licensing income.

That success, Löffler told *SciBX*, has largely been due to a few high-value patents, notably those behind **Pfizer Inc.**’s Lyrica pregabalin for epilepsy, pain and other neurological disorders.

The U.S. patent on Lyrica is set to expire in 2018. Despite that, the TTO has not been under pressure from the university to make a high-value licensing deal to compensate for the impending loss of revenue from Lyrica, Löffler told *SciBX*.

Nevertheless, the Northwestern TTO is expanding its activities beyond licensing, and it now places emphasis on co-development partnerships with biotechs and pharma that may lead to commercialization of more inventions in the long term. It also requires hiring university employees with skills and experience in business development, venture capital and program management.

Kirsten Leute, senior licensing associate in the Office of Technology Licensing at **Stanford University**, agreed that there has been a lot of internal debate at universities about changes within TTOs. “It’s not your grandfather’s TTO anymore. TTOs are being asked by governments, states and universities to do more and to have a broader job description,”

she told *SciBX*.

Universities are under pressure to show the fruits of public funding for research and to increase the efficiency of commercializing inventions. As TTOs take on new roles such as driving co-development partnerships, in addition to fostering startups and filing patents, they struggle with how to prioritize the different activities with their limited resources and how to access the necessary range of expertise.

Leute agreed that covering costs is not part of the mission, although Stanford is consistently one of the more successful universities at commercializing inventions.

Christian Suojanen and Morris Berrie, cofounders and chairmen of the Technology Transfer Summit (TTS) Global Initiative, think that the shift in TTO activities toward collaborations with industry is more a reaction to pharmas increasingly seeking external sources of innovation than to the fact that TTOs are not profit centers.

The TTS Global Initiative is an international network of technology licensing offices that brings together stakeholders at the academic-industry interface to help drive the commercialization of academic inventions.

Valdivia agreed that multiple factors are behind the change in TTOs.

“I don’t believe that TTOs not producing enough money is the main driver of change, but it is an element,” Valdivia told *SciBX*.

“TTOs must focus on whatever is the best way to take things forward, which may be licensing, startups or collaborations,

depending on the specific technology and situation,” Suojanen told *SciBX*. “Often the relationships start as collaborations and move to licensing and startups. Some institutes will have a greater emphasis on startups and spinouts, and some will be successful, but most people who have tried their hand at venture capital have not succeeded.”

Suojanen agreed with Löffler that to support startups and the shift in the pharma space toward academia-industry collaborations, TTOs will need to add skill sets they currently do not have. These include employees who understand biotech and have industry experience. He suggested that universities could tap into the pool of employees laid off from big pharma.

Berrie said that fostering startups is worthwhile but was not convinced that devoting more funds toward startup activities is a good idea.

“Throwing money at TTOs to make startups isn’t going to result in more or better startups,” Berrie told *SciBX*. “This won’t make them good, viable startups.” He added that startup success requires a number of factors not solved by money, including a good idea, an unmet need, an ability to execute and a host of market factors.

Valdivia responded that faculty members are the most likely to know the potential market value of their inventions. “Only a handful of companies recognize the true value of inventions at early stages of their maturity. If a faculty member can get the bare minimum of funding, he or she will have the energy necessary to take on the risk.”

Instead of increasing their focus on startups, Berrie told *SciBX* that TTOs from different universities should invest greater effort in collaborating with each other.

“Universities are still not open enough. There needs to be more

**“It’s not your grandfather’s TTO anymore. TTOs are being asked by governments, states and universities to do more and to have a broader job description.”**  
—Kirsten Leute, Stanford University

collaboration between universities to pool their thinking and help move products or other concepts forward,” he said.

UNSW’s TTO is pursuing an [Easy Access IP](#) strategy in which it gives away most of its IP licenses for free. This is because the cost of licensing IP, which includes staff, marketing and other activities, is greater than the received revenue.

The TTO makes an early decision on which inventions have the potential to make money. “If we can’t see a way to \$1 million, then we let it go,” Cullen told *SciBX*.

According to Cullen, the strategy has led to about 25 licenses and 3 **Australian Research Council** collaborations that would not otherwise have happened.

Easy Access IP also has helped the TTO at UNSW build relationships with new companies and institutions, according to Cullen. The number of academic researchers wanting to work with the TTO, and the number of companies making enquiries about research capabilities and IP, has increased tenfold since Easy Access IP was introduced in December 2011.

The licensing agreements are simple, one-page contracts in which the licensor commits to performing some activity related to the invention within three years, agrees to acknowledge the university if the IP is successfully exploited, and guarantees the licensee will not take action to prevent the university pursuing research in that area.

The strategy was first employed by Cullen in his previous position at the **University of Glasgow** and has now been adopted by about 25 universities in Europe, Canada and Australia. To date, he said, no U.S.-based university TTOs have adopted it.

Löffler told *SciBX* that at Northwestern, and most likely at many other U.S. universities, TTOs waive rights back to the inventor or the government for inventions they do not wish to pursue. It is then up to the inventor or government to decide what actions to take.

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Published online Jan. 23, 2014

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**Australian Research Council**, Canberra, Australian Capital Territory, Australia  
**Brookings Institution**, Washington, D.C.  
**Northwestern University**, Evanston, Ill.  
**Pfizer Inc.** (NYSE:PFE), New York, N.Y.  
**Stanford University**, Stanford, Calif.  
**University of Glasgow**, Glasgow, U.K.  
**University of New South Wales**, Sydney, New South Wales, Australia

# Diagnosing narcolepsy

By Lauren Martz, Staff Writer

A new way to diagnose narcolepsy using T cells<sup>1</sup> has piqued the interest of at least two companies—**Jazz Pharmaceuticals plc** and **GlaxoSmith-Kline plc**. The former could use the results to help diagnose patients eligible for its narcolepsy drug Xyrem sodium oxybate. The latter thinks the findings could help it develop influenza vaccines that lack the extremely rare side effect of inducing narcolepsy.

Narcolepsy causes excessive daytime sleepiness, cataplexy and disruptions in rapid eye movement (REM) sleep. The causes of narcolepsy are unknown but are thought to be a combination of environmental effects and a genetic immune predisposition that causes an autoimmune response against the neurotransmitter orexin (hypocretin; HCRT). The autoimmune attack, in turn, destroys the hypothalamic neurons that produce orexin.

About 98% of patients with narcolepsy who have an orexin deficiency express the human leukocyte antigen (HLA) molecule DQ0602, whereas only 18%–25% of the general population expresses the molecule.<sup>2,3</sup>

This suggests that antigen presentation by DQ0602 could be associated with an autoimmune response in patients.

Meanwhile, twin studies suggest that the environment is a factor in narcolepsy, as there is only 25%–33% identical twin concordance in the condition.<sup>4</sup>

Another puzzle piece is that some bacterial and viral infections are associated with narcolepsy onset. In 2010, treatment with GSK's pandemic H1N1 influenza vaccine Pandemrix caused an increase in sudden onset narcolepsy in children and adolescents in Europe.<sup>5</sup> As a result, the EMA's Committee for Medicinal Products for Human Use restricted use of the vaccine in patients under 20.

In China, the H1N1 flu strain as well as seasonal flu infections also have been linked to new cases of narcolepsy.<sup>6</sup>

Not only is the cause of narcolepsy unclear but also the condition is difficult to diagnose. Current methods include sleep studies, which may be inaccurate, or an invasive procedure to detect orexin levels in cerebrospinal fluid. Diagnosis typically occurs years after symptom onset.

“Narcolepsy is a highly misdiagnosed and underdiagnosed condition,” said Jed Black, VP of sleep medicine and a consulting associate professor at the **Stanford University School of Medicine's** Stanford Center for Sleep Sciences and Medicine. It is estimated that more than 50% of individuals with narcolepsy have not been diagnosed, he added.

Now, Emmanuel Mignot, Elizabeth Mellins and colleagues may have found a new way to diagnose patients based on the presence of orexin-reactive T cells in the blood. The team also shed light on the role of autoimmunity in narcolepsy pathogenesis.

Mignot is a professor of sleep medicine and of psychiatry and behavior sciences at the Stanford University School of Medicine and director of the Stanford Center for Sleep Sciences and Medicine. Mellins is a professor of pediatrics at Stanford School of Medicine. The paper also included researchers from the **University of Bologna, Glostrup Hospital** and the **Mater Private Sleep Laboratory**.

The team first screened overlapping peptide segments of orexin to identify epitopes that bind to and may be presented as antigens by DQ0602. The team identified two epitopes, HCRT<sub>56-68</sub> and HCRT<sub>87-99</sub>, which bound the narcolepsy-associated HLA molecule and may serve as autoantigens.

The team then engineered antigen-presenting cells to contain only the DQ0602 antigen-presenting molecule and used those cells to present the orexin epitopes to T cells from patients with narcolepsy and healthy individuals with that HLA molecule.

The assay measured interferon- $\gamma$  (IFNG; IFN- $\gamma$ ) production in response to the antigen presentation and found that only the T cells from patients were activated by the orexin antigens.

T cells also reacted to the orexin epitopes from narcoleptic twins or siblings but not from DQ0602<sup>+</sup>, unaffected siblings. These findings suggest that the assay may be able to specifically diagnose patients with narcolepsy.

The researchers then took their work a step further to determine whether influenza vaccination induces a similar T cell response.

The team vaccinated 9 patients and 4 DQ0602<sup>+</sup> controls with a 2012 seasonal flu vaccine containing pandemic H1N1 antigens

and found that the vaccine increased the number of orexin-reactive T cells in patients but did not affect T cell reactivity in controls.

The vaccine did not increase narcolepsy symptoms in patients, possibly because orexin was depleted and could not be further decreased by the elevated T cell activity.

A screen of segments of the hemagglutinin, neuraminidase and polymerase PB1 H1N1-specific viral antigens within Pandemrix may have found the culprit within the vaccine that causes cross-reactivity with orexin-reactive T cells: an epitope of hemagglutinin. The epitope bound DQ0602 and increased the number of both hemagglutinin- and orexin-reactive T cells.

Results were published in *Science Translational Medicine*.

“A simple blood test would be much easier on the patient, simpler for the physician and a substantial reduction on the burden on the healthcare system,” said Black.

## Diagnostic design

Black said that new tools such as Stanford's immunoassay would allow physicians or sleep specialists to diagnose the disease more quickly and accurately, which would allow patients to get treatment sooner, although he thinks the Stanford group's diagnostic needs more work before commercialization.

“This data is a long way from a diagnostic product with suitable sensitivity and selectivity to avoid false negatives and false positives,” he said.

He added that the *Science Translational Medicine* paper only

**“A simple blood test would be much easier on the patient, simpler for the physician and a substantial reduction on the burden on the healthcare system.”**

—Jed Black,  
Stanford University  
School of Medicine

**“The research suggests a potential mechanism of action that was involved in the onset of narcolepsy in some individuals after vaccination with Pandemrix or infection with H1N1, but the association with Pandemrix remains to be fully explained.”**

—David Daley,  
GlaxoSmithKline plc

discussed narcolepsy patients with cataplexy. “More research would be needed to determine the viability of these diagnostic tools in patients who have narcolepsy without cataplexy,” said Black.

Adrian Howd, EVP and head of neurology and corporate development at **Evotec AG**, agreed that the Stanford team will likely need to improve the sensitivity and specificity of the test.

Evotec has histamine H3 receptor (HRH3) antagonists including EVT 501 in preclinical testing to treat narcolepsy.

Mignot said that his team’s next steps for diagnostic development include working on the sensitivity and specificity of the test. For example, he said, “designing an assay that measures two or three cytokines at the same time or using lower concentrations of the peptide may improve these parameters.”

He added that his team also plans to evaluate more samples to determine whether the test can pick up more mild forms of narcolepsy in patients without cataplexy.

Mignot said that “once narcolepsy symptoms develop, 80%–90% of the specific neurons are lost. Neurons are really not cells that recover, so when we detect the disease, it is already too late. If this test is able to detect disease in patients at risk or in milder stages of the disease, we may be able to find a way to stop neuron loss, but this application is a long way off.”

He added that identifying the disease with this type of assay could be more convenient and accurate than current diagnostic methods and could help patients who have had the disease for a long time get proper treatment.

Jazz Pharmaceuticals said that it is reviewing Mignot’s research, as well as research from other labs in the field, to assess the viability of a diagnostic. The company partially funded the work in the *Science Translational Medicine* paper but has not licensed any related IP.

### Influenza implications

The identification of the Pandemrix component that may trigger T cell cross-reactivity with self-antigens could lead to the design of safer vaccines.

GSK spokesperson David Daley said, “We are actively conducting research on the observed association between Pandemrix and narcolepsy and on the interaction this vaccine might have had with other risk factors in affected individuals. We hope these ongoing research efforts will enable us to provide more answers.”

He said that the new paper “confirms that narcolepsy is a complex disease involving a number of environmental and genetic factors and results from a sequence of these events that we don’t yet fully understand. The research suggests a potential mechanism of action that was involved in the onset of narcolepsy in some individuals after vaccination with Pandemrix or infection with H1N1, but the association with Pandemrix remains to be fully explained.”

**Stanford University** has filed a patent application covering the use of orexin epitopes for narcolepsy diagnosis and the modification of the 2009 H1N1 hemagglutinin epitope in influenza vaccines. The licensing status is under evaluation.

Martz, L. *SciBX* 7(3); doi:10.1038/scibx.2014.78  
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**Evotec AG** (Xetra:EVT), Hamburg, Germany  
**GlaxoSmithKline plc** (LSE:GSK; NYSE:GSK), London, U.K.  
**Glostrup Hospital**, Glostrup, Denmark  
**Jazz Pharmaceuticals plc** (NASDAQ:JAZZ), Dublin, Ireland  
**Mater Private Sleep Laboratory**, Dublin, Ireland  
**Stanford University**, Stanford, Calif.  
**Stanford University School of Medicine**, Stanford, Calif.  
**University of Bologna**, Bologna, Italy

## 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
<b>Autoimmune disease</b>				
Multiple sclerosis (MS)	Platelet derived growth factor receptor (PDGFR)	<i>In vitro</i> and human sample studies suggest activating PDGFR could help treat primary progressive MS (PPMS). In patients with PPMS, transcranial magnetic stimulation showed that long-term potentiation (LTP), which can protect against clinical symptoms of neuronal loss, was lower than that in patients with relapsing remitting MS (RRMS) or healthy controls. In mouse hippocampal slices, PDGF increased LTP compared with vehicle. In cerebrospinal fluid samples from patients with PPMS or RRMS with active relapse, PDGF levels were lower than those in healthy controls and patients with clinically silent RRMS. Next steps include correlating PDGF levels and LTP amplitude in patients with PPMS.	Unpatented; unavailable for licensing	Mori, F. <i>et al. J. Neurosci.</i> ; published online Dec. 4, 2013; doi:10.1523/JNEUROSCI.2536-13.2013 <b>Contact:</b> Diego Centonze, University of Rome Tor Vergata, Rome, Italy e-mail: <a href="mailto:centonze@uniroma2.it">centonze@uniroma2.it</a>
<b>SciBX 7(3); doi:10.1038/scibx.2014.79</b> <b>Published online Jan. 23, 2014</b>				
<b>Cancer</b>				
Acute lymphoblastic leukemia (ALL)	Protein kinase B (PKB; PKBA; AKT; AKT1)	Studies in cell culture and mice suggest AKT inhibitors could be useful for treating glucocorticoid-resistant ALL. Glucocorticoids are a standard component of first-line therapy for ALL. In cultured T ALL (T-ALL) cells, forced activation of AKT inhibited the ability of glucocorticoids to promote apoptosis, whereas normal AKT activity did not. In a xenograft mouse model of T-ALL, the AKT inhibitor MK-2206 restored tumor sensitivity to glucocorticoids and increased survival compared with vehicle. Next steps could include clinical testing of AKT inhibitors as an adjunct to T-ALL therapy. Merck & Co. Inc.'s MK-2206 is in Phase I and Phase II testing in a range of solid tumors.	Patent and licensing status undisclosed	Piovan, E. <i>et al. Cancer Cell</i> ; published online Nov. 27, 2013; doi:10.1016/j.ccr.2013.10.022 <b>Contact:</b> Adolfo A. Ferrando, Columbia University, New York, N.Y. e-mail: <a href="mailto:af2196@columbia.edu">af2196@columbia.edu</a> <b>Contact:</b> Andrea Califano, same affiliation as above e-mail: <a href="mailto:ac2248@columbia.edu">ac2248@columbia.edu</a>
<b>SciBX 7(3); doi:10.1038/scibx.2014.80</b> <b>Published online Jan. 23, 2014</b>				
Cancer	Euchromatic histone-lysine N-methyltransferase 2 (EHMT2; G9A)	<i>In vitro</i> and mouse studies suggest inhibiting G9A-mediated serine-glycine synthesis could help treat cancer. G9A is overexpressed in multiple human cancers and correlates with disease progression. In mouse xenograft tumor models, G9A overexpression was sufficient to promote tumor growth. In multiple cancer cell lines, shRNA knockdown or small molecule inhibition of G9A decreased H3K9 monomethylation of genes encoding enzymes of the serine-glycine biosynthetic pathway, which lowered enzyme levels and serine-dependent cell proliferation compared with control shRNA or no treatment. Next steps include determining how G9A is targeted to genes encoding enzymes in the serine-glycine pathway and testing G9A inhibitors in preclinical cancer models.	Unpatented; licensing status not applicable	Ding, J. <i>et al. Cell Metab.</i> ; published online Dec. 3, 2013; doi:10.1016/j.cmet.2013.11.004 <b>Contact:</b> Han-Fei Ding, Georgia Regents University, Augusta, Ga. e-mail: <a href="mailto:hding@gru.edu">hding@gru.edu</a>
<b>SciBX 7(3); doi:10.1038/scibx.2014.81</b> <b>Published online Jan. 23, 2014</b>				

## This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Castration-resistant prostate cancer (CRPC)	MEK	<p>Human tissue studies suggest a combination of Src and MEK family inhibitors could be useful for treating metastatic CRPC. Proteomic analysis of phosphoproteins from 41 CRPC metastases in 17 patients identified patterns of phosphorylation across multiple metastatic lesions from individual patients. In a subset of 16 metastatic lesions, kinase activation predicted sensitivity to combined Src and MEK family inhibition in about 69% of patients. Next steps could include clinical testing of a combination of Src and MEK inhibitors.</p> <p>GlaxoSmithKline plc and Japan Tobacco Inc. market the MAP kinase kinase 1 (MAP2K1; MEK1) and MEK2 (MAP2K2) inhibitor Mekinist trametinib (GSK1120212) for melanoma.</p> <p>At least six other MEK inhibitors are in Phase II or Phase III testing for various cancers.</p> <p>Bristol-Myers Squibb Co. and Otsuka Pharmaceutical Co. Ltd.'s Sprycel dasatinib and Pfizer Inc.'s Bosulif bosutinib, which inhibit Src as well as BCR-ABL tyrosine kinase, are marketed for hematological malignancies.</p> <p>At least four other kinase inhibitors targeting Src are in Phase I and Phase II testing for various cancers.</p> <p><b>SciBX 7(3); doi:10.1038/scibx.2014.82</b>  <b>Published online Jan. 23, 2014</b></p>	Patent and licensing status undisclosed	<p>Drake, J.M. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Nov. 18, 2013; doi:10.1073/pnas.1319948110</p> <p><b>Contact:</b> Owen N. Witte, University of California, Los Angeles, Calif.  e-mail: <a href="mailto:owenwitte@mednet.ucla.edu">owenwitte@mednet.ucla.edu</a></p>
Colon cancer	BMI1 polycomb ring finger oncogene (BMI1)	<p><i>In vitro</i> and mouse studies suggest inhibiting BMI1 expression could help treat colon cancer. In cultured cancer-initiating cells from human colon tumors, shRNA knockdown of <i>BMI1</i> prevented both cell self-renewal and the formation of tumors when cells were implanted into mice. In mouse xenograft models with established human colon cancer, PTC-209, a small molecule inhibitor of BMI1 expression, decreased cancer-initiating tumor cells and irreversibly decreased tumor volume compared with vehicle. Next steps include optimizing the BMI1 inhibitor series.</p> <p>PTC Therapeutics Inc. has BMI1-expression inhibitors including PTC-596 and PTC-209 in preclinical testing for cancer.</p> <p><b>SciBX 7(3); doi:10.1038/scibx.2014.83</b>  <b>Published online Jan. 23, 2014</b></p>	Patent application filed by PTC Therapeutics; available for licensing	<p>Kreso, A. <i>et al. Nat. Med.</i>; published online Dec. 1, 2013; doi:10.1038/nm.3418</p> <p><b>Contact:</b> John E. Dick, University Health Network, Toronto, Ontario, Canada  e-mail: <a href="mailto:jdick@uhnres.utoronto.ca">jdick@uhnres.utoronto.ca</a></p>
Lymphoma	Killer cell immunoglobulin-like receptor three domains long cytoplasmic tail 1 (KIR3DL1; CD158E1); CD20	<p><i>In vitro</i> and mouse studies suggest combining anti-KIR3DL1 and anti-CD20 antibodies could help treat lymphomas. KIR3DL1 inhibits NK cells. In cultures of NK cells or human CD20-expressing mouse lymphoma cells, an antibody blocking the mouse homolog of KIR3DL1 increased cytotoxicity induced by the anti-CD20 antibody Rituxan rituximab compared with that seen in cultures treated only with Rituxan. In transgenic mice expressing human KIR3DL1, the anti-KIR3DL1 antibody lirilumab plus Rituxan led to increased antitumor effects and survival following challenge with human B cell lymphoma compared with either treatment alone. Next steps could include testing the antibody combination in additional animal models and clinical lymphoma isolates.</p> <p>Innate Pharma S.A.'s lirilumab is in Phase II testing to treat acute myelogenous leukemia (AML) and preclinical testing to treat lymphoma.</p> <p>Rituxan/MabThera, from Biogen Idec Inc. and the Genentech Inc. unit of Roche, is marketed for a variety of autoimmune diseases and hematological cancers.</p> <p><b>SciBX 7(3); doi:10.1038/scibx.2014.84</b>  <b>Published online Jan. 23, 2014</b></p>	Patent and licensing status unavailable	<p>Kohrt, H.E. <i>et al. Blood</i>; published online Dec. 10, 2013; doi:10.1182/blood-2013-08-519199</p> <p><b>Contact:</b> Holbrook E. Kohrt, Stanford University, Stanford, Calif.  e-mail: <a href="mailto:kohrt@stanford.edu">kohrt@stanford.edu</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Melanoma	Programmed cell death 1 (PDCD1; PD-1; CD279); hepatitis A virus cellular receptor 2 (HAVCR2; TIM3)	<p><i>In vitro</i> studies suggest combining antibodies against PD-1 and TIM3 could increase patient response to melanoma vaccines. In peripheral blood mononuclear cells (PBMCs) taken from patients with metastatic melanoma vaccinated with tumor-associated cancer/testis antigen 1B (CTAG1B; NY-ESO-1) peptide, antigen-specific T cell expression of PD-1 and TIM3 was upregulated in about 73% and 18% of cases. In the PBMCs, the NY-ESO-1 peptide plus both anti-PD-1 and anti-TIM3 antibodies showed an additive effect in expanding tumor antigen-specific T cells. Next steps could include testing the antibody combination with cancer vaccines in patients.</p> <p>Bristol-Myers Squibb Co. and Ono Pharmaceutical Co. Ltd. have the PD-1 antibody nivolumab in Phase III trials to treat melanoma.</p> <p>Merck &amp; Co. Inc. has the PD-1 antibody lambrolizumab in Phase III testing for the indication.</p> <p>At least four other companies have antibodies against PD-1 in Phase II or earlier testing to treat cancers.</p> <p><b>SciBX 7(3); doi:10.1038/scibx.2014.85</b>  <b>Published online Jan. 23, 2014</b></p>	Patent and licensing status unavailable	<p>Fourcade, J. <i>et al. Cancer Res.</i>; published online Dec. 16, 2013; doi:10.1158/0008-5472.CAN-13-2908  <b>Contact:</b> Hassane M. Zarour, University of Pittsburgh School of Medicine, Pittsburgh, Pa.  e-mail: <a href="mailto:zarourhm@upmc.edu">zarourhm@upmc.edu</a></p>
Non-small cell lung cancer (NSCLC)	Peroxisome proliferation-activated receptor- $\alpha$ (PPARA; PPAR $\alpha$ )	<p>Mouse studies suggest PPAR<math>\alpha</math> agonists could help treat NSCLC. In transgenic mice that develop spontaneous NSCLC tumors, a PPAR<math>\alpha</math> ligand decreased tumor size, number and vascularization by decreasing the expression and activity of cytochrome P450 family 2 subfamily C polypeptide 44 (Cyp2c44) and levels of proangiogenic epoxyeicosatrienoic acids (EETs) compared with vehicle. Also in mice, PPAR<math>\alpha</math>-activating ligands including bezafibrate decreased primary tumor growth and metastasis of human NSCLC cells injected into the lung parenchyma. Next steps could include testing bezafibrate in additional models of NSCLC. Bezafibrate and other generic PPAR<math>\alpha</math> agonists are marketed to treat dyslipidemia.</p> <p><b>SciBX 7(3); doi:10.1038/scibx.2014.86</b>  <b>Published online Jan. 23, 2014</b></p>	Patent and licensing status unavailable	<p>Skrypnik, N. <i>et al. Cancer Res.</i>; published online Dec. 3, 2013; doi:10.1158/0008-5472.CAN-13-1928  <b>Contact:</b> Ambra Pozzi, Vanderbilt University School of Medicine, Nashville, Tenn.  e-mail: <a href="mailto:ambra.pozzi@vanderbilt.edu">ambra.pozzi@vanderbilt.edu</a></p>
<b>Endocrine/metabolic disease</b>				
Gaucher's disease	Glucocerebrosidase (GBA; GCase)	<p><i>In vitro</i> studies suggest the natural compound celastrol could help treat Gaucher's disease, which is caused by loss-of-function mutations in GCase. In fibroblasts from patients with Gaucher's disease with the two most common GCase mutations, celastrol increased both GCase activity and its levels compared with no treatment. The compound functioned by inhibiting heat shock protein 90 (Hsp90)-mediated degradation of GCase. In cultured cells, celastrol increased expression of chaperone proteins that promote stability of mutant GCase compared with vehicle. Next steps could include testing celastrol in animal models of Gaucher's disease.</p> <p>Shire plc markets Vpriv velaglycerase alfa, a recombinant GCase, to treat Gaucher's disease.</p> <p>Sanofi markets Cerezyme imiglucerase and Ceredase, a recombinant GCase and alglucerase, to treat the disease.</p> <p>Pfizer Inc. markets Protalix BioTherapeutics Inc.'s Elelyso alfatriglycerase, a recombinant GCase, for Gaucher's disease.</p> <p>Several companies have compounds targeting the GCase system in Phase III or earlier development for Gaucher's disease.</p> <p><b>SciBX 7(3); doi:10.1038/scibx.2014.87</b>  <b>Published online Jan. 23, 2014</b></p>	Patent and licensing status unavailable	<p>Yang, C. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Dec. 18, 2013; doi:10.1073/pnas.1321341111  <b>Contact:</b> Zhengping Zhuang, National Institutes of Health, Bethesda, Md.  e-mail: <a href="mailto:zhuangp@ninds.nih.gov">zhuangp@ninds.nih.gov</a>  <b>Contact:</b> Roscoe O. Brady, same affiliation as above  e-mail: <a href="mailto:bradyr@ninds.nih.gov">bradyr@ninds.nih.gov</a>  <b>Contact:</b> Chunzhang Yang, same affiliation as above  e-mail: <a href="mailto:yangc2@ninds.nih.gov">yangc2@ninds.nih.gov</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
<b>Gastrointestinal disease</b>				
Pancreatitis	Toll-like receptor 4 (TLR4)	<p>Mouse studies suggest CO-based therapeutics could help treat acute pancreatitis. In two mouse models of acute pancreatitis, a CO-releasing molecule or adoptive transfer of macrophages primed with the molecule decreased mortality, pancreatic damage, systemic inflammation and Tlr4 activation compared with vehicle or an inactive form of the molecule. In mice engrafted with Tlr4-deficient bone marrow cells, compared with those given wild-type bone marrow, pancreatic injury was decreased and CO had no further protective effect. Next steps could include investigating how CO inhibits TLR4 activation and testing the effects of the CO-releasing molecule in larger animal models of pancreatic injury.</p> <p>At least six companies have TLR4-targeted compounds in Phase III or earlier testing for various indications.</p> <p><b>SciBX 7(3); doi:10.1038/scibx.2014.88</b> Published online Jan. 23, 2014</p>	Patent application filed; unlicensed	<p>Xue, J. &amp; Habtezion, A. <i>J. Clin. Invest.</i>; published online Dec. 16, 2013; doi:10.1172/JCI71362</p> <p><b>Contact:</b> Aida Habtezion, Stanford University, Stanford, Calif. e-mail: <a href="mailto:aidah@stanford.edu">aidah@stanford.edu</a></p>
<b>Hematology</b>				
Myeloproliferative disorder	<i>Calreticulin (CALR)</i>	<p>Genetic studies suggest neutralizing <i>CALR</i> mutations associated with myeloproliferative neoplasms could help treat the disease. Mutations in <i>Janus kinase-2 (JAK-2)</i> and other genes cause the majority of myeloproliferative neoplasms, but genetic causes for about 30%–45% of cases are unknown. In the first study, exome sequencing identified frameshift mutations in <i>CALR</i> that altered the C-terminal peptide in all six patients lacking known mutations. The <i>CALR</i> mutations were confirmed in 67% of patients with thrombocythemia and 88% of patients with myelofibrosis in a validation cohort. In the second study, exome sequencing identified <i>CALR</i> mutations in 70%–84% of samples from 151 patients with myeloproliferative neoplasms that lacked <i>JAK-2</i> mutations but not in patients with other cancers. In mouse B cells, expression of the most common <i>Calr</i> mutant increased cell proliferation compared with wild-type <i>Calr</i> expression. Next steps include designing mAbs targeting the new C-terminal peptide sequence of mutant <i>CALR</i>. Authors from the first study plan to start a company to develop anti-<i>CALR</i> antibodies.</p> <p><b>SciBX 7(3); doi:10.1038/scibx.2014.89</b> Published online Jan. 23, 2014</p>	<p>For findings in first study, patent application filed for diagnostic applications and for mutant <i>CALR</i> as a therapeutic target; diagnostic applications available for licensing</p> <p>Patent and licensing status unavailable for findings in second study</p>	<p>Klampfl, T. <i>et al. N. Eng. J. Med.</i>; published online Dec. 10, 2013; doi:10.1056/NEJMoa1311347</p> <p><b>Contact:</b> Robert Kralovics, Research Center for Molecular Medicine of the Austrian Academy of Sciences, Vienna, Austria e-mail: <a href="mailto:robert.kralovics@cemm.oeaw.ac.at">robert.kralovics@cemm.oeaw.ac.at</a></p> <p>Nangalia, J. <i>et al. N. Eng. J. Med.</i>; published online Dec. 10, 2013; doi:10.1056/NEJMoa1312542</p> <p><b>Contact:</b> Anthony R. Green, Cambridge Institute for Medical Research, Cambridge, U.K. e-mail: <a href="mailto:arg1000@cam.ac.uk">arg1000@cam.ac.uk</a></p>
<b>Infectious disease</b>				
HIV/AIDS	Caspase-1 (CASP1)	<p>Human tissue culture studies suggest CASP1 inhibitors could help treat HIV infection. In cultures of normal human lymphoid tissue, HIV predominantly infected quiescent CD4<sup>+</sup> T cells, upregulated CASP1 and led to CASP1-activated pyroptosis, which was not observed in HIV-infected, activated CD4<sup>+</sup> T cells. Also in the HIV-infected tissue cultures, CASP1-targeting shRNA or the small molecule CASP1 inhibitor VX-765 decreased CASP1 levels and the number of pyroptotic CD4<sup>+</sup> T cells compared with scrambled shRNA or no treatment. Ongoing work in collaboration with Vertex Pharmaceuticals Inc. may include a Phase II trial of the company's VX-765 in combination with antiretroviral therapies in patients with HIV infection. VX-765 is in Phase II testing to treat epilepsy.</p> <p><b>SciBX 7(3); doi:10.1038/scibx.2014.90</b> Published online Jan. 23, 2014</p>	<p>Patent application filed by the Gladstone Institutes; licensing status undisclosed</p>	<p>Doitsh, G. <i>et al. Nature</i>; published online Dec. 19, 2013; doi:10.1038/nature12940</p> <p><b>Contact:</b> Warner C. Greene, Gladstone Institute of Virology and Immunology, San Francisco, Calif. e-mail: <a href="mailto:wgreene@gladstone.ucsf.edu">wgreene@gladstone.ucsf.edu</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
<b>Inflammation</b>				
Asthma; allergy	Oxoecosanoid receptor 1 (OXER1; GPR170)	<i>In vitro</i> studies identified OXER1 antagonists that could help treat asthma and allergic diseases. Compounds that incorporated an indole scaffold and structural components of 5-oxo-eicosatetraenoic acid (ETE) antagonized OXER1 with IC <sub>50</sub> values of about 30 nM. In cell culture, pretreatment with either of the two most potent compounds inhibited actin polymerization and chemotaxis of neutrophils and eosinophils induced by 5-oxo-ETE. Next steps include testing the antagonists in animal models of asthma or other allergic diseases.  <b>SciBX 7(3); doi:10.1038/scibx.2014.91</b> <b>Published online Jan. 23, 2014</b>	Patent application filed covering antagonists; licensed by AmorChem Holdings Inc.; available for licensing	Gore, V. <i>et al. J. Med. Chem.</i> ; published online Dec. 18, 2013; doi:10.1021/jm401292m <b>Contact:</b> William S. Powell, McGill University, Montreal, Quebec, Canada e-mail: <a href="mailto:william.powell@mcgill.ca">william.powell@mcgill.ca</a> <b>Contact:</b> Pranav Patel, Navinta LLC, Ewing, N.J. e-mail: <a href="mailto:pranav.patel@navinta.com">pranav.patel@navinta.com</a> <b>Contact:</b> Vivek Gore, same affiliation as above e-mail: <a href="mailto:vivek.gore@navinta.com">vivek.gore@navinta.com</a>
<b>Neurology</b>				
Alzheimer's disease (AD)	Microtubule-associated protein- $\tau$ (MAPT; tau; FTDP-17)	Mouse imaging studies suggest insoluble tau aggregates may be a side effect rather than a cause in AD. In the visual cortex of mice overexpressing a human mutant form of tau (P301L), neurofibrillary tangle (NFT)-bearing neurons were functionally intact and indistinguishable from non-NFT-bearing neurons. Next steps could include assessing the impact of NFTs on neurons at distinct locations in the brain or at later time points during disease. At least four companies have compounds or antibodies that target tau in Phase I or earlier development to treat AD.  <b>SciBX 7(3); doi:10.1038/scibx.2014.92</b> <b>Published online Jan. 23, 2014</b>	Patent and licensing status unavailable	Kuchibhotla, K.V. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Dec. 24, 2013; doi:10.1073/pnas.1318807111 <b>Contact:</b> Bradley T. Hyman, Harvard Medical School, Charlestown, Mass. e-mail: <a href="mailto:bhyman@partners.org">bhyman@partners.org</a>
Alzheimer's disease (AD)	Rho-associated coiled-coil containing protein kinase 2 (ROCK2)	Studies in cell culture and mice suggest ROCK2 inhibitors could be useful for treating AD. In cultured human neuroblastoma cells and mouse brain slices, a small molecule ROCK2 inhibitor lowered activity of $\beta$ -site APP-cleaving enzyme 1 (BACE1) and decreased levels of $\beta$ -amyloid (A $\beta$ ) compared with vehicle. In a mouse model of AD, the ROCK2 inhibitor lowered A $\beta$ levels compared with mock injection. Next steps could include testing the effect of ROCK2 inhibitors on behavioral and cognitive functioning in AD mouse models. KD025, a ROCK2 inhibitor from Kadmon Corp. LLC, has completed Phase I testing in autoimmune indications.  <b>SciBX 7(3); doi:10.1038/scibx.2014.93</b> <b>Published online Jan. 23, 2014</b>	Patent and licensing status undisclosed	Herskowitz, J.H. <i>et al. J. Neurosci.</i> ; published online Dec. 4, 2013; doi:10.1523/JNEUROSCI.2508-13.2013 <b>Contact:</b> James J. Lah, Emory University School of Medicine Center for Neurodegenerative Disease, Atlanta, Ga. e-mail: <a href="mailto:jlal@emory.edu">jlal@emory.edu</a>
Amyotrophic lateral sclerosis (ALS)	Eukaryotic translation initiation factor 2 $\alpha$ kinase 3 (EIF2AK3; PERK); TAR DNA binding protein 43 (TDP-43; TARDBP)	Studies in flies and primary rat neurons suggest inhibiting EIF2AK3 could help treat ALS. In a tdp-43-expressing fly model of ALS, siRNA-mediated or pharmacological inhibition of PERK decreased deficits in climbing ability and increased eif2a phosphorylation compared with no inhibition. In rat primary cortical neurons expressing Tdp-43, a PERK inhibitor decreased Tdp-43-associated toxicity compared with vehicle. Next steps include using the ALS fly model to identify other cellular pathways that play a role in EIF2A phosphorylation and TDP-43 toxicity.  <b>SciBX 7(3); doi:10.1038/scibx.2014.94</b> <b>Published online Jan. 23, 2014</b>	Patented; licensed by FoldRx Pharmaceuticals Inc., which Pfizer Inc. acquired in 2010	Kim, H.-J. <i>et al. Nat. Genet.</i> ; published online Dec. 15, 2013; doi:10.1038/ng.2853 <b>Contact:</b> Nancy M. Bonini, University of Pennsylvania, Philadelphia, Pa. e-mail: <a href="mailto:nbonini@sas.upenn.edu">nbonini@sas.upenn.edu</a>

## This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Autism	Not applicable	<p>Mouse studies suggest correcting GI barrier defects could help treat autism spectrum disorders. In a mouse model of autism that also displays GI barrier abnormalities, treatment with the commensal human bacteria <i>Bacteroides fragilis</i> decreased gut permeability compared with saline and improved communication and behavioral deficits and restored normal serum metabolite levels. In mice, 4-ethylphenylsulfate potassium salt, a serum metabolite upregulated in the autism model and downregulated by <i>B. fragilis</i>, induced behavioral abnormalities consistent with autism. Next steps could include testing the effects of commensal bacteria in other autism models.</p> <p><b>SciBX 7(3); doi:10.1038/scibx.2014.95</b>  <b>Published online Jan. 23, 2014</b></p>	Patent and licensing status unavailable	<p>Hsiao, E.Y. <i>et al. Cell</i>; published online Dec. 5, 2013; doi:10.1016/j.cell.2013.11.024  <b>Contact:</b> Sarkis K. Mazmanian, California Institute of Technology, Pasadena, Calif.  e-mail: <a href="mailto:sarkis@caltech.edu">sarkis@caltech.edu</a>  <b>Contact:</b> Paul H. Patterson, same affiliation as above  e-mail: <a href="mailto:php@caltech.edu">php@caltech.edu</a>  <b>Contact:</b> Elaine Y. Hsiao, same affiliation as above  e-mail: <a href="mailto:ehsiao@caltech.edu">ehsiao@caltech.edu</a></p>
Neurology	Epidermal growth factor receptor (EGFR)	<p>Mouse studies suggest activating EGFR could improve outcomes following neonatal brain injury. Chronic hypoxia is a clinically relevant model of premature brain injury caused by insufficient gas exchange due to poor lung development. In mice with chronic hypoxia, oligodendrocyte-specific overexpression of EGFR after brain injury induced oligodendrocyte functional recovery and decreased oligodendrocyte death and white matter-dependent behavioral deficits compared with no overexpression. In the hypoxic mice, intranasal administration of an activating EGFR ligand, heparin-binding EGF, led to similar results. Next steps could include testing intranasally delivered heparin-binding EGF in additional brain injury models.</p> <p><b>SciBX 7(3); doi:10.1038/scibx.2014.96</b>  <b>Published online Jan. 23, 2014</b></p>	Patent and licensing status unavailable	<p>Scafidi, J. <i>et al. Nature</i>; published online Dec. 25, 2013; doi:10.1038/nature12880  <b>Contact:</b> Vittorio Gallo, Children's National Medical Center, Washington, D.C.  e-mail: <a href="mailto:vgallo@cnmcresearch.org">vgallo@cnmcresearch.org</a></p>
<b>Ophthalmic disease</b>				
Age-related macular degeneration (AMD)	Fibromodulin (FMOD)	<p><i>In vitro</i> and mouse studies suggest inhibiting FMOD could help treat AMD and other angiogenesis-dependent diseases. Comparative microarray analysis showed that FMOD was more highly expressed in nonpigmented than pigmented melanocytes. In a coculture system, human dermal microvascular endothelial cells (HMVECs) migrated in conditioned media from nonpigmented cells but did not migrate in media from pigmented melanocytes. In cultured mouse choroidal melanocytes, a neutralizing FMOD antibody or <i>Fmod</i>-targeting siRNA decreased proliferation and HMVEC migration compared with no treatment. Next steps could include identifying therapeutic targets in the FMOD angiogenic pathway.</p> <p><b>SciBX 7(3); doi:10.1038/scibx.2014.97</b>  <b>Published online Jan. 23, 2014</b></p>	Patent and licensing status unavailable	<p>Adini, I. <i>et al. J. Clin. Invest.</i>; published online Dec. 20, 2013; doi:10.1172/JCI69404  <b>Contact:</b> Irit Adini, Boston Children's Hospital and Harvard Medical School, Boston, Mass.  e-mail: <a href="mailto:irit.adini@childrens.harvard.edu">irit.adini@childrens.harvard.edu</a></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
<b>Assays &amp; screens</b>			
Clustered, regularly interspaced short palindromic repeats (CRISPR)-based genome-wide screening platform	<i>In vitro</i> studies suggest CRISPR could be used for large-scale genetic screens in mammalian cells. Pools of lentivirus expressing Cas9 nuclease, a single guide DNA and a selection marker were used to generate a library of knockout cells. In a CRISPR library targeting 18,080 genes, a negative selection screen identified genes required for melanoma cell survival, and a positive selection screen identified genes, including those not found through shRNA screening, whose knockout resulted in resistance to BRAF inhibition. In both haploid and diploid human leukemia cells, positive and negative selection screens with a CRISPR library targeting 7,114 genes also identified genes whose loss caused resistance to drug-induced cell death. Next steps include using the screens to identify new therapeutic targets.  <b>SciBX 7(3); doi:10.1038/scibx.2014.98</b> <b>Published online Jan. 23, 2014</b>	Patent application filed for findings in first study; available for licensing  Patent and licensing status unavailable for findings in second study	Shalem, O. <i>et al. Science</i> ; published online Dec. 12, 2013; doi:10.1126/science.1247005 <b>Contact:</b> Feng Zhang, Broad Institute of MIT and Harvard, Cambridge, Mass. e-mail: <a href="mailto:zhang@broadinstitute.org">zhang@broadinstitute.org</a>  Wang, T. <i>et al. Science</i> ; published online Dec. 12, 2013; doi:10.1126/science.1246981 <b>Contact:</b> Eric S. Lander, Broad Institute of MIT and Harvard, Cambridge, Mass. e-mail: <a href="mailto:lander@broadinstitute.org">lander@broadinstitute.org</a> <b>Contact:</b> David M. Sabatini, Massachusetts Institute of Technology, Cambridge, Mass. e-mail: <a href="mailto:sabatini@wi.mit.edu">sabatini@wi.mit.edu</a>
Orexin (hypocretin; HCRT)-based immunoassays to diagnose narcolepsy	Immunoassays to determine T cell reactivity to two HCRT epitopes could be used to diagnose narcolepsy. Narcolepsy has been associated with human leukocyte antigen (HLA) DQ0602, but no molecular diagnostics for the condition exist. In coculture with an HLA DQ0602-specific T-B fusion cell line treated with HCRT <sub>56-68</sub> or HCRT <sub>87-99</sub> , T cells obtained from narcoleptic individuals showed strong HCRT peptide-specific CD4 <sup>+</sup> T cell reactivity. Statistical analysis of the assay identified 19 of 23 patients with narcolepsy and 24 of 24 unaffected individuals. Next steps could include using the assay on larger patient cohorts and evaluating association of T cell reactivity with HCRT levels in patient spinal fluid ( <i>see Diagnosing narcolepsy, page 9</i> ).  <b>SciBX 7(3); doi:10.1038/scibx.2014.99</b> <b>Published online Jan. 23, 2014</b>	Patent application filed by Stanford University for HCRT epitopes for narcolepsy diagnosis; licensing status unavailable	De la Herrán-Arita, A.K. <i>et al. Sci. Transl. Med.</i> ; published online Dec. 18, 2013; doi:10.1126/scitranslmed.3007762 <b>Contact:</b> Emmanuel Mignot, Stanford University School of Medicine, Stanford, Calif. e-mail: <a href="mailto:mignot@stanford.edu">mignot@stanford.edu</a> <b>Contact:</b> Elizabeth D. Mellins, same affiliation as above e-mail: <a href="mailto:mellins@stanford.edu">mellins@stanford.edu</a>
<b>Computational models</b>			
An algorithm to predict drug combinations to treat genetically heterogeneous tumors	A computational model could help predict drug combinations for genetically heterogeneous tumors. Using published data on drug-genotype interactions, an algorithm predicted effective two-drug combinations. In a model of tumor genetic diversity consisting of mixed cultures of parental and shRNA-expressing subpopulations of lymphoma cells, combinations predicted by the algorithm decreased growth of subpopulations compared with three other drug combinations selected by alternative criteria. In a mouse model of genetically heterogeneous lymphoma, the algorithm-predicted drug combination minimized the emergence of any tumor subpopulation and increased tumor-free survival compared with another differently selected drug combination. Next steps could include testing the algorithm in additional tumor models.  <b>SciBX 7(3); doi:10.1038/scibx.2014.100</b> <b>Published online Jan. 23, 2014</b>	Patent and licensing status unavailable	Zhao, B. <i>et al. Cancer Discov.</i> ; published online Dec. 6, 2013; doi:10.1158/2159-8290.CD-13-0465 <b>Contact:</b> Michael T. Hemann, Massachusetts Institute of Technology, Cambridge, Mass. e-mail: <a href="mailto:hemann@mit.edu">hemann@mit.edu</a>

## This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
<b>Drug platforms</b>			
Asymmetrical Fc engineering to enhance antibody-dependent cellular cytotoxicity (ADCC)	Antibodies engineered to asymmetrically interact with Fc $\gamma$ -receptor IIIa (CD16a; FCGR3A; Fc $\gamma$ RIIIa) could enhance ADCC. ADCC is mediated through contact of antibody Fc chains with FCGR3A on NK cells upon binding of tumor or viral antigen. In a heterodimeric Fc library, screening of 9,000 individual antibody clones identified heterodimeric human IgG1 antibodies containing asymmetrical Fc mutations that increased binding to FCGR3A and ADCC activity compared with wild-type human IgG1. In multiple mouse xenograft models of cancer, heterodimeric IgG1 variants decreased tumor size compared with normal IgG1. Next steps include enhancing ADCC activities of therapeutic antibodies that are based on Fc heterodimers such as bispecific antibodies.	Patent application filed; licensing status undisclosed	Liu, Z. <i>et al. J. Biol. Chem.</i> ; published online Dec. 5, 2013; doi:10.1074/jbc.M113.513366 <b>Contact:</b> Wei Yan, Amgen Inc., Seattle, Wash. e-mail: <a href="mailto:ywei@amgen.com">ywei@amgen.com</a> <b>Contact:</b> Zhi Liu, same affiliation as above e-mail: <a href="mailto:liuz@amgen.com">liuz@amgen.com</a>
	<b>SciBX 7(3); doi:10.1038/scibx.2014.101</b> Published online Jan. 23, 2014		
Pluripotent cell-derived nephron progenitor cells and self-organizing 3D structures	Differentiation of pluripotent cells into nephron progenitors could help model and treat renal diseases. A three-step, <i>ex vivo</i> differentiation protocol involving culture in growth factors including activin A and bone morphogenetic protein 4 (BMP4) or a wingless-type MMTV integration site (WNT) agonist followed by fibroblast growth factor 9 (FGF9; GAF) converted human embryonic stem cells (hESCs) into nephron progenitor cells. Differentiated hESCs self-organized into nephron-forming structures <i>ex vivo</i> . The process was similar to what occurs with dissociated then reaggregated mouse embryonic kidneys. Next steps could include developing the system for nephrotoxicity screens, <i>ex vivo</i> disease modeling and the generation of transplantable organoids.	Patent and licensing status unavailable	Takasato, M. <i>et al. Nat. Cell Biol.</i> ; published online Dec. 15, 2013; doi:10.1038/ncb2894 <b>Contact:</b> M.H. Little, The University of Queensland, Brisbane, Queensland, Australia e-mail: <a href="mailto:m.little@imb.uq.edu.au">m.little@imb.uq.edu.au</a>
	<b>SciBX 7(3); doi:10.1038/scibx.2014.102</b> Published online Jan. 23, 2014		
<b>Imaging</b>			
Magnetic resonance spectroscopy (MRS) of hyperpolarized ( $^2\text{H}$ , $^{13}\text{C}$ )-labeled glucose to detect tumor response to drug treatment	Mouse studies suggest MRS using a hyperpolarized ( $^2\text{H}$ , $^{13}\text{C}$ )-labeled glucose probe could help detect tumor responses to drug treatment. In mouse models of T cell lymphoma and lung cancer, MRS using the probe detected the glycolysis product ( $^2\text{H}$ , $^{13}\text{C}$ )-labeled lactate in tumors within 15 seconds but not in normal tissues. In chemotherapy-treated mouse models of T cell lymphoma, MRS using the probe showed that the intratumoral ratio of lactate to glucose signals decreased by 62% 24 hours after treatment compared with no treatment. Planned work includes comparing the sensitivity of the method and $^{18}\text{F}$ -labeled fluorodeoxyglucose PET imaging in tumor models.	Unpatented; unlicensed	Rodrigues, T.B. <i>et al. Nat. Med.</i> ; published online Dec. 8, 2013; doi:10.1038/nm.3416 <b>Contact:</b> Kevin M. Brindle, University of Cambridge, Cambridge, U.K. e-mail: <a href="mailto:kmb1001@cam.ac.uk">kmb1001@cam.ac.uk</a>
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<b>R</b>		Sodium oxybate	9	TIM3	13	
Rho-associated coiled-coil containing protein kinase 2	15	Sprycel	12	TLR4	14	<b>W</b>
Rilonacept	1	Src	12	Toll-like receptor 4	14	Wingless-type MMTV integration site
Rituxan	12	<b>T</b>	Trametinib	12	WNT	18
Rituximab	12	TAR DNA binding protein 43	15	<b>V</b>		
ROCK2	15	TARDBP	15	Velaglucerase alfa	13	<b>X</b>
		Tau	15	Vpriv	13	Xyrem
						9