

## THIS WEEK

### ANALYSIS

#### COVER STORY

##### 1 Navigating the new road in psychiatry

The lack of predictive animal models for neuropsychiatric diseases is arguably the biggest single factor stifling early drug development in the field. To kick-start discovery for diseases such as autism, schizophrenia and depression, stakeholders will need to abandon traditional models, build on emerging genetic findings and capitalize on new capabilities in stem cell technology, imaging and computational modeling.

#### TRANSLATIONAL NOTES

##### 7 Translational tidbits

Astellas and Cancer Research UK team up to tackle autophagy in pancreatic cancer; the NIH bets big on bioelectronic therapeutics; a roundup of public-private partnerships.

#### TOOLS

##### 9 Liver, supercooled

Harvard Medical School scientists have reported a method that triples the time rat livers can be preserved for transplant and could thus increase the number of donor organs available for patients. Spinout Organ Solutions is licensing the technology, and the company and the medical school plan to submit to the FDA next year.

#### THE DISTILLERY

##### 11 This week in therapeutics

Inhibiting MFGE8 to prevent tumorigenic events promoting prostate cancer; DECTIN1 CAR-expressing T cells to treat opportunistic fungal infections; antibodies that stabilize SNCA to protect neurons in PD; and more...

##### 16 This week in techniques

EnPlex, a high throughput flow cytometry platform to assess potency and selectivity of small molecule enzyme inhibitors; Platypus, a reference genome-free algorithm that rapidly calls variants in clinical sequencing data; a two-gene signature that distinguishes between psoriasis and eczema; and more...

#### INDEXES

##### 19 Company and institution index

##### 20 Target and compound index

## Navigating the new road in psychiatry

By *C. Simone Fishburn, Executive Editor, and Lev Osherovich, Senior Writer*

The lack of predictive animal models for neuropsychiatric diseases is arguably the biggest single factor stifling drug development in the field. To kick-start discovery for diseases such as autism, schizophrenia and depression, stakeholders will need to abandon traditional models, build on emerging genetic findings and capitalize on new capabilities in stem cell technology, imaging and computational modeling.

Ultimately, drug developers will need to come together in precompetitive consortia, share data and find consensus for new standards, techniques and models.

After numerous clinical failures, the pipeline is thin and many pharmas have stepped away from the space. But progress in basic neurological science has given rise to a new theory of synaptic connectivity as a driver of neuropsychiatric disease.<sup>1</sup>

The hypothesis posits that disorders arise from abnormalities in synaptic connections between individual neurons and between entire brain regions involved in learning, cognition and emotion.

Recent genetic studies have associated mutations in synaptic genes with autism, schizophrenia and depression. Thus, many leaders in the field now view these seemingly diverse disorders as diseases driven by alterations in brain network activity—controlled by synaptic changes—and are discarding the classical view of them as neurotransmitter imbalances that can be corrected via specific receptors or transporters.

“There is a growing consensus on the study of neuropsychiatric disorders,” said Mriganka Sur. “There are about 400–500 genes that, when mutated, lead to similar clinical diagnoses of autism or schizophrenia. About 70% of the genes mutated in these disorders have some kind of synaptic function.” Sur is a professor of neuroscience and director of the Simons Center for the Social Brain at the **Massachusetts Institute of Technology**.

Although the receptor-and-transporter hypotheses of neuropsychiatric disease yielded flawed and only modestly effective drugs, they served as the premise of many animal models that became the standard for evaluation of new compounds.

For example, drugs such as L-dopa that were effective in alleviating symptoms in patients with Parkinson’s disease (PD) were introduced to animals to determine what effects they had on neurological pathways.<sup>2</sup> Those effects then became model behavioral readouts against which researchers measured future drugs. However, the standard rodent models of neuropsychiatric disorders have not provided good

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predictions of how a new compound will behave in humans and are now considered to be largely irrelevant for the new targets being explored.

As genetic studies have started to reveal new targets for neuropsychiatric diseases, knockout and transgenic mouse models have begun to offer alternative ways of testing compounds. However, these too are fraught with complexities that suggest they cannot simply supplant the older models.

At the SciBX Summit on Innovation in Drug Discovery and Development in Boston, and in discussions before and after, a panel of academic and industry experts discussed the obstacles and laid out a road map for stakeholders to counter the limitations of current animal models and advance drug discovery in the field.

The panelists included Sur, Daniela Brunner, Magali Haas, Kenneth Rhodes and Mustafa Sahin.

Brunner is SVP of behavioral R&D at **PsychoGenics Inc.**, Haas is founder and CEO of **Orion Bionetworks Inc.** and Sahin is an associate professor of neurology at **Boston Children's Hospital and Harvard University**. At the time of the summit, Rhodes was VP of neurology research at **Biogen Idec Inc.** He is currently establishing a new company focused on neurodegenerative diseases.

There was wholesale agreement among the panelists that the classical behavioral models for neuropsychiatric diseases no longer serve the industry's needs.

"The old idea of studying learned helplessness in a rat and looking for drugs that change the way they fight back will not actually lead to new therapeutics," said Sur.

The think tank identified four areas that require investment and focused research: genetic linkages for neuropsychiatric diseases; new cell-based and animal models built upon molecular pathology rather than on phenotypic similarity to human disease; imaging and other technologies to study the effects of compounds on multiple brain

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regions; and computer modeling and network systems to integrate the information from multiple sources.

Identifying the genes that underlie the three diseases is essential for making progress and will require collaborative efforts and computerized technology to fish out meaningful results from large-scale population genetics studies.

The field should move away from thinking about animal models of disease and using behavioral readouts that aim to mimic human phenotypes. Instead, it should use animal models with relevant genetic changes and molecular pathology and should measure behavioral and other responses that indicate the target in question has been engaged. In addition, focused investment is needed in stem cell technologies to develop functional synapses *in vitro*.

Because autism, schizophrenia and depression involve disrupted communication between neurons and between brain regions, new ways of measuring compounds that affect those systems in intact animal and human brains are needed. That includes new imaging technologies and other noninvasive methods that can be used in both preclinical and clinical studies.

Finally, the panel advocated for investment in computerized systems that can integrate information across the different lines of evidence. In particular, it called for more public-private collaborations not only to share data but also to develop standards for cell-based and animal models and to drive consensus for change.

### Starting with genes

The key opinion leaders agreed that the road to new models starts with identifying genes that cause synaptic dysfunction. “Genetics is the number-one stop,” said Haas. “The genetic evidence for overlap between diseases is highly compelling.” Indeed, one of the few areas of neuropsychiatric disease to see a surge of activity recently is large-scale genetic studies.

In July, the Psychiatric Genomics Consortium reported the results of a genomewide association study of about 37,000 schizophrenia cases and 113,000 controls.<sup>3</sup> The consortium identified 108 loci with single nucleotide polymorphisms associated with elevated schizophrenia risk. However, no individual single nucleotide polymorphism had a strong enough effect to cause schizophrenia by itself, and the data reinforce the growing consensus that in most cases these diseases will not reduce to single-gene mutations.

Along similar lines, a team led by Joseph Buxbaum, a professor of psychiatry, neuroscience, and genetics and genomic sciences at the **Icahn School of Medicine at Mount Sinai**, reported in July that more than 50% of autism cases arise from the additive effect of multiple common genetic variants throughout the genome.<sup>4</sup>

The next challenge will be to parse the information yielded by these studies and identify the genes or gene combinations involved. Haas said that the best way to do this will be to use a network approach and study

where mechanisms and pathways overlap and diverge. By looking at pathways disrupted in disease, researchers could reverse engineer the way back to molecules, she said.

Rhodes added that the genes identified might not be primary targets—in which the gene has a direct causal link to the disease—but could be modifier genes. Modifier genes are those found in patients who would normally get a disease but either fail to do so or develop it earlier or later than would be expected.

**“The idea that genetic alterations lead to a large number—perhaps a majority—of cases of neuropsychiatric disease is now widely accepted. The genetics of autism are unraveling more easily than for some other diseases. But even for Mendelian disorders, we don’t really have proof of principle that animal models work [like the disease] in people.”**

—Mustafa Sahin,  
Boston Children’s Hospital

“Modifier genes are the next generation of drug targets. Looking for outliers in a population is what can make this go forward,” said Rhodes.

Although the panelists agreed that the first step in building new models is to find the relevant targets, they also noted that using genetic information to create animal models is not straightforward. For example, Haas was skeptical that a piecemeal approach of knocking out and characterizing individual disease genes would be informative.

“These are emergent behavioral disorders with a broad range of symptoms that you won’t recreate in animals,” she said. “Making single point mutations and asking what happens to the animals is fun for basic scientists, but they won’t get anywhere because this is not a single-gene problem.”

“The idea that genetic alterations lead to a large number—perhaps a majority—of cases of neuropsychiatric disease is now widely accepted,” said Sahin. “The genetics of autism are unraveling more easily than for some other diseases. But even for Mendelian disorders, we don’t really have proof of principle that animal models work [like the disease] in people,” he added.

Brunner was concerned that neurophysiological differences between mice and humans could complicate the interpretation of purely genetic models. For example, she said, “there are several different mouse models with different variants of *Shank3* that show different behaviors and no clear rationale for choosing one model over another for drug development.” *SHANK3* (SH3 and multiple ankyrin repeat domains 3; *PROSAP2*; *SPANK-2*) is a postsynaptic scaffolding protein whose gene is mutated in some cases of autism.

In 2010, Buxbaum’s team showed that heterozygous loss-of-function mutations in *Shank3* seen in patients with autism produced only modest alterations in synaptic activity and behavior in mice.<sup>5</sup> But in 2011, a team from **Duke University** showed that mice with other *Shank3* mutations had severe neurological and behavioral symptoms, while a third team from **The Johns Hopkins University School of Medicine** showed that yet another *Shank3* knockout mouse had a different set of phenotypes.<sup>6,7</sup>

Thus, for interpreting disease mechanism, “if the gene in the mouse does something different than what it does in humans, then making the same mutation in mice doesn’t matter,” said Brunner.

### Face validity vs. construct validity

Nevertheless, the panelists said that the identification of disease-associated genes offers the best chance so far for moving beyond the face validity-based models that have held back drug development.

Face validity refers to models that use behaviors in animals to mimic disease-associated behavior in patients. The rationale is that if the rodent model exhibits patient-like behavior, the underlying pathological mechanisms are likely to be similar to those in humans. By contrast, construct validity refers to models based on an underlying molecular change that occurs in disease.

Sur said that excessive emphasis on face validity has misled researchers and drug makers into using models with poor predictive power. As an example, he cited anxiety disorders, which are modeled by frightening animals and testing for pharmacological interventions that alleviate fear.

“There may be some anxiety phenotypes in mice which may appear relevant to humans,” said Sur. “It’s likely that some complicated circuit involving the hippocampus, amygdala and frontal cortex are involved in anxiety. But many things could alter these circuits, so without construct validity from human mutations to back up the model, you have nothing.”

Brunner agreed. “There is no value for face validity,” she said. She had similar concerns about transgenic rodent models of autism that are based purely on behavioral abnormalities. “One popular assumption is that since people with autism have communication difficulty, we can study vocalization in mice as a model for the disease.”

But she outlined how the genetic information could be used to produce meaningful models. “The first step is to determine whether a model has construct validity,” she said. For cases in which a disease-linked mutation appears to alter protein function, “to achieve construct validity, you need to understand which parts of the mutated protein are affected and recapitulate that in animals. Then you need to see if the pathological processes in the mouse are homologous to what you see you in humans.”

However, she also said that existing behavioral assays should not be written off altogether. “There are 150 years of work on animal behavior that support many of these behavioral assays,” she said. “What’s important is the combination of an assay with a model that gives you predictive power.”

Sur added, “The role of an animal model is to link genotype to phenotype. You would want to establish at least some behavioral or cognitive deficit. Then you would have to ask what are the plausible cellular or network phenotypes that lead to the deficit.”

Rhodes said that animal behavior was useful primarily as a marker for whether a compound has affected a target.

“I agree that if you have a genetic defect, you have construct validity, but what do you measure? You still have to measure behavior, and that raises the question of whether it recapitulates what happens in people. In some ways that is not so important—as long as you have a phenotype to measure that is a readout of whether you have affected the target. We should not try to make models of disease. Instead we should look at behavior as a biomarker and not as a translational readout for what to expect in disease,” said Rhodes.

He added, “The translational value is slightly shifted—but it still sets you up to design clinical trials.” The data from behavioral assays “can provide tools such as pharmacokinetic/pharmacodynamic behavior that can help with clinical trial design. The most important investment you can make is in finding markers that help you know you have the right hypothesis.”

Panelists agreed that there is a need for standardized methods for the construction and evaluation of genetic models. They said that there should be a battery of behavioral tests with standardized readouts and methods of validation.

One problem with defining behaviors for animal models of disease in psychiatry is that the human diseases are defined by behaviors described in the Diagnostic and Statistical Manual of Mental Disorders (DSM). The key opinion leaders agreed that DSM-defined behaviors are of limited value for drug discovery because the behaviors described in the DSM cannot be extrapolated directly to animals. Many of the definitions involve human behaviors or social interactions that have no direct parallels in animals.

“The DSM is a useful reference, but there are problems with using it to reach consensus about readouts for animal models,” said Brunner.

“Basing animal models on DSM-defined disease behaviors is a very slippery slope. It still means you are trying to make inferences from the animal’s state of mind to the human one. I’m not a big believer in that,” said Rhodes.

### iPSo facto

In addition to profiting from genomewide association studies, the field stands to benefit from new technologies that generate patient-derived induced pluripotent (iPS) cells, the panelists said. The problem is in deciding what phenotypic changes at the cellular level can be attributed to the cause of disease. In one notable case, Rett syndrome, there is good agreement between cell culture and rodent models that allows drug developers to rely on those systems for assaying candidate compounds.

Rett syndrome is a severe form of autism caused by loss-of-function mutations in methyl CpG binding protein 2 (MECP2; RTT), a DNA-binding protein. Because MECP2 affects the expression of a large number of genes and *Mecp2*-mutant mice display a broad range of abnormal phenotypes, it was initially difficult to determine which phenotypes to focus on for drug discovery.

But in 2010, a team from the **Salk Institute for Biological Studies** generated functional neurons from iPS cells derived from patients with Rett syndrome.<sup>8</sup> These neurons displayed a range of morphological and functional abnormalities including defects in synaptogenesis and intracellular signaling. Later studies showed that insulin-like growth factor-1 (IGF-1), which has abnormally low expression in patients and mouse models, partially restores synaptic outgrowth in cultured Rett neurons and corrects behavioral and electrophysiological defects in mouse models of the disease.<sup>9</sup>

Nonetheless, in the majority of cases in which multiple genes are involved, the absence of clear parallels between cellular and animal models makes it difficult to extrapolate from cellular abnormalities to behavioral and cognitive dysfunction.

“We have certain tests of some features of autism that work in mice, but even for the syndromic forms of disease there is still not enough validation of these models,” noted Sahin.

The panelists agreed that dedicated investment is needed to show that iPS cell-based neurons can form proper synapses in a dish. A collection of patient-derived cells with robust phenotypes *in vitro* is a realistic goal and could be a starting point for discovery screening.

“Can patient-derived iPS cells make the right type of synapse in a dish with the right type of neurons?” asked Sur. “Even organoids have not captured synapses properly, although they have recapitulated regions and reproduced action potential firing in neurons.”

Rhodes added, “It’s early days for iPS cells in psychiatric diseases. We have not yet been able to get mature plastic excitatory synapses. Getting a

synapse in a dish is still a key bottleneck. We need to find out what factors in the dish are needed.”

Sur suggested that it would be helpful to classify patient-specific cell culture models by their distinct patterns of cellular dysfunction. He expects that, irrespective of the underlying mutations, patient-derived neurons will show defects in either excitatory or inhibitory activity.

He added that multiple types of cell-based models will be needed. “We need to make cell-specific models, but we need to know which brain regions a gene is expressed in. Only certain brain regions are associated with disease behavior,” he said. “These are not disorders of just one brain system or neuron but rather of interconnectivity of brain regions. These are not behaviors that are going to be easy to model in a dish.”

### Regional connections

Indeed, looking at the effect of compounds on multiple brain regions is an important extension of the new way of viewing these diseases as synaptic disorders, said the panelists.

As the field’s focus shifts away from individual receptors and transporters toward viewing these as disorders of connectivity, it demands exploration not only of how disease affects components within synapses but also of how it affects the way neurons connect and transmit information between different regions of the brain. “We need to understand the connections between brain regions to help understand these diseases,” said Rhodes.

Sur said that it is impossible to predict how disease-associated changes to cellular physiology of affected neurons play out in the living brain but that starting with the phenotype makes it possible to come up with some educated guesses to guide the research.

“You would want to establish at least some behavioral or cognitive deficit. Then you would have to ask what are the plausible cellular or network phenotypes that lead to the deficit,” he said.

However, the panelists agreed that the problem in the field is in deciding where to look. In addition, the field badly needs new technologies that will make it possible to better visualize deep brain regions.

Several panelists noted that functional MRI (fMRI) provides a valuable noninvasive way to image the brain but that its capabilities are limited. fMRI measures brain activity by detecting changes in blood flow, specifically by comparing oxygen-rich blood with oxygen-poor blood, based on the premise that neuronal activity requires brain cells to use energy and alters oxygenation levels and cerebral blood flow.

Rhodes also said that researchers are starting to find markers for responses to drug therapy using arterial spin labeling fMRI, a modification of the technique that avoids the need for exogenous tracers by using arterial water as an endogenous tracer. In addition, he said, diffusion tensor imaging is being used in humans for fiber tracking—a method for highlighting neurons that shows their path between different brain regions.

Rhodes added that systems neuroscience is looking at how disease affects connections between brain regions using longitudinal

studies with fMRI or other imaging techniques. Brunner noted that electroencephalograms (EEGs) and some other technologies that have been around for a while have been underexploited preclinically.

In addition, there is increasing interest in drug discovery in the use of optogenetics, which uses light to activate neurons that have been engineered to express light-sensitive genes. Indeed, **Circuit Therapeutics Inc.** recently partnered with **Boehringer Ingelheim GmbH** to use the biotech’s optogenetics technology to screen for compounds to treat psychiatric disorders.<sup>10</sup>

But none of today’s techniques goes far enough, provides enough granularity or translates well between animals and humans, said the key opinion leaders.

“We need a more refined understanding of how synapses differ between brain regions and the subtle changes that occur in disease,” said Sur. Little is known about synaptic differences between brain regions in either animals or humans. However, although some techniques are making headway in studying this in animals, they cannot be used in humans and thus cannot help translate from preclinical to clinical studies.

“Markers can be inserted into neurons in animals, for example, and then imaged using fMRI to light up specific individual neurons,” Sur said. But what is missing, he said, are ways to do this in humans, too. Thus, what are needed are noninvasive technologies that could work in humans. Better fMRI is one solution, but there are concrete limits to what any single technique can do, he said. “At this point, we can’t introduce extrinsic markers into humans—so we’re left with only intrinsic signals that can be measured.”

Brunner agreed that improved imaging technologies in nonhuman primates could help in looking for a signature that would define the response.

She noted that bioinformatics is already being used to look for behavioral signatures associated with drugs and mutations. For example, PsychoGenics has developed SmartCube, one of three proprietary behavioral systems used to phenotype models

of autism and other disorders. The ‘cubes’ are high throughput, *in vivo* platforms that involve computer vision to automatically capture rich behavioral datasets covering many different behavioral domains. These datasets are used to train machine-learning algorithms to define drug or mutant signatures.

### From imaging to the big picture

Bioinformatics, big data and large-scale collaborative projects are perhaps the cornerstones of the next phase in translational research for all areas of neurology.

For example, the **NIH BRAIN** (Brain Research through Advancing Innovative Neurotechnologies) initiative aims to use advanced microscopy to map functional circuits in the entire brain, starting with simple animal models such as flies and worms.<sup>11</sup>

But for neuropsychiatric diseases in particular, the panel was unanimous in calling for collaborative public-private initiatives to advance technologies, share information, create consensus for how animal models should be implemented and change accepted standards for what preclinical data are required to move to the clinic.

**“These are not disorders of just one brain system or neuron but rather of interconnectivity of brain regions. These are not behaviors that are going to be easy to model in a dish.”**

**—Mriganka Sur,  
Massachusetts Institute of Technology**

Haas noted that the **Institute of Medicine** has taken steps in this direction with a workshop held in 2012 on improving translation of animal models for nervous system disorders.<sup>12</sup>

She added that public-private partnerships using computational approaches will be needed to make sense of the volumes of genetic information coming out of genomewide association studies. In addition, she said, “what could help drive change would be to gather large amounts of human data via precompetitive consortia to serve as reference sets that could be used to inform animal models.”

Rhodes agreed. “Ultimately this is the only way that this will be done. The more partnerships for sharing data in an open and transparent way, the better off for everyone. We are making investments in large computational modeling [at Biogen Idec], but even there it is only looking at a small piece of the pie. People sharing data openly is key to success moving forward.”

The same is true for animal models, said Sahin. He noted that the not-for-profit organization **Autism Speaks** is forming a consortium of labs for unifying models across different laboratories. The need for not-for-profit organizations to drive this is huge, he said. “Without such support, there is little incentive for an academic lab to do this.”

Rhodes and Haas noted that companies could help—or even lead—rather than walking away from the field.

“Biotechs are pulling out rather than doubling down,” Rhodes said. “Some of the big players who have had a lot of revenue have pulled away. They haven’t just walked away; it’s been kind of an Olympic sprint.”

Haas added, “Industry needs to define the translational zone. The challenge is that academia has produced siloed endeavors. Pharma needs to rethink the investment model. Recently they have moved to external innovation, but they need to invest in precompetitive collaborations. So far industry has been more willing to move to a model of open science than academics.”

Haas proposed a Framingham-type study that would involve accumulation of observational data in longitudinal studies in a defined population. The study would be a modern-day version that would include deep and frequent genotyping of a group of people, in addition to characterizing elements such as cognitive performance, nutrition, environmental factors and microbiome status to find what factors correlate with the development of psychiatric disease in that population.

But she questioned whether the current approach should be rethought altogether. “The overreliance on models may be limiting us,” she said. “We need to take a new look at first in human studies and ask, ‘What evidence do we really need? Must it be an animal model?’”

Either way, the field needs to devise readouts that are clinically meaningful and to engage the **FDA** in the process, Rhodes said.

“Companies need to make every effort to work closely with regulators to develop novel and more meaningful endpoints, particularly in disease indications where it has been notoriously difficult to develop new therapies. Sometimes this means running expensive clinical studies using endpoints that are not well validated, which can be very challenging, and some companies have more of a stomach for it than others,” he said.

Ultimately, the panelists said, there is no alternative to finding new ways of measuring the effects of candidate compounds, and precompetitive consortia offer the best option for exploring the available possibilities and fleshing out the details. Investors, industry and regulators will need to get on board if those new ways are to translate to anything meaningful for patients.

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#### COMPANIES AND INSTITUTIONS MENTIONED

**Autism Speaks**, New York, N.Y.  
**Biogen Idec Inc.** (NASDAQ:BIIB), Weston, Mass.  
**Boehringer Ingelheim GmbH**, Ingelheim, Germany  
**Boston Children’s Hospital**, Boston, Mass.  
**Circuit Therapeutics Inc.**, Menlo Park, Calif.  
**Duke University**, Durham, N.C.  
**Food and Drug Administration**, Silver Spring, Md.  
**Harvard University**, Cambridge, Mass.  
**Icahn School of Medicine at Mount Sinai**, New York, N.Y.  
**Institute of Medicine**, Washington D.C.  
**The Johns Hopkins University School of Medicine**, Baltimore, Md.  
**Massachusetts Institute of Technology**, Cambridge, Mass.  
**National Institutes of Health**, Bethesda, Md.  
**Orion Bionetworks Inc.**, Cambridge, Mass.  
**PsychoGenics Inc.**, Tarrytown, N.Y.  
**Salk Institute for Biological Studies**, La Jolla, Calif.

# Translational tidbits

By Kai-Jye Lou, Senior Writer, and Lauren Martz, Staff Writer

## Astellas bites into autophagy

**Astellas Pharma Inc.** and **Cancer Research UK** announced a two-year research collaboration last week that will initially focus on identifying new drug targets that could block autophagy to treat pancreatic cancer. The collaboration builds upon recent work from U.K. scientists showing that the process plays a key role in the development of some pancreatic tumors.<sup>1</sup>

Autophagy is a process whereby cells maintain homeostasis by directing components of the cytoplasm to the lysosome to undergo degradation, freeing metabolites for use in other cellular processes. In the nutrient-deficient environment of tumors, autophagy can serve as an alternative energy source that helps cells survive and grow.

Astellas spokesperson Akiko Tanabe noted that recent studies have shown that autophagy activity is higher in pancreatic cancer than other cancers and that certain pancreatic cancers depend on autophagy to grow.

“We think blocking the autophagy pathway may help stop some pancreatic cancers,” she added.

Last December, a Cancer Research UK (CRUK) research team led by Kevin Ryan of the **The Beatson Institute for Cancer Research** published mouse data in *Nature* showing that disruption of autophagy by knocking out *ATG5 autophagy related 5 homolog (Atg5)* or *Atg7* blocks the progression of premalignant pancreatic intraepithelial neoplasias into pancreatic ductal adenocarcinomas.<sup>1</sup> Ryan is a senior group leader at the institute and is participating in this new research partnership.

Researchers at multiple institutes already are evaluating the autophagy inhibitor hydroxychloroquine in investigator-led Phase I and Phase II trials to treat patients with pancreatic or other forms of cancer. Hydroxychloroquine inhibits autophagy by blocking autophagosome fusion and degradation.

CRUK researchers will screen for potential new targets and assess their druggability. Astellas will aid CRUK's efforts to identify potential targets and has an exclusive worldwide license to the targets identified under the collaboration that it can choose to advance. The pharma will be responsible for drug discovery and development on selected targets. CRUK's technology commercialization arm, **Cancer Research Technology Ltd.**, will be eligible for undisclosed milestones and royalties.

“The collaboration is building upon a mutual interest,” said CRUK and Cancer Research Technology spokesperson Emma Rigby. “Both Astellas and the Cancer Research UK researchers have had a strong interest in autophagy.”

The partners are not disclosing specific targets.

## NIH SPARCs bioelectronics research

The **NIH** has announced three new Common Fund programs, including a \$248 million initiative to build proof of concept for bioelectronic peripheral neuromodulation therapies that can regulate visceral organ functions. The program provides a major boost to research funding in an area that is attracting increased interest from industry.

Bioelectronics is an emerging therapeutic area in which nanoscale, implantable electrical circuits are used to modulate peripheral nerve networks that control visceral organs.

For example, an application for peripheral bioelectronics could be an implant that detects and blocks pulmonary nerve signals that contribute to airway hyperresponsiveness.

The Stimulating Peripheral Activity to Relieve Conditions (SPARC) program will support investigators working toward four primary research objectives: developing neural circuit maps for five organ systems, creating new electrode designs, outlining surgical procedures and creating stimulation protocols. The ultimate goal of the project is to develop new neuromodulatory therapies.

“The first phase of our program is to engage the very broad research community to determine which organs to study. We want to select the organ systems in which it is most feasible to make progress based on responses from investigators,” said James Anderson, director for program coordination, planning and strategic initiatives at the NIH. Another objective of the program, he said, is to coordinate storage and dissemination of the data that are collected to make them widely accessible.

Pending available funding, the NIH plans to allocate \$248 million to the SPARC program. The seven-year program will begin awarding grants in FY15, which begins this October.

At least one pharma company, **GlaxoSmithKline plc**, has also recently committed to the bioelectronics space. GSK's programs include a bioelectronics exploratory research program that is backing more than 30 academic projects, a \$50 million bioelectronics-focused venture fund and an innovation challenge to develop a rodent research platform involving a \$1 million prize.<sup>2,3</sup>

Kris Famm, VP of bioelectronics R&D at GSK, told *SciBX*, “Both GSK's and NIH's programs are dependent on further advances in research tools, an area in which GSK will seek to coordinate with NIH and other funding bodies over the next few months to ensure complementary schemes, accelerated development and effective access for the global research community.”

Anderson added, “The SPARC program was designed with knowledge of GSK's programs, and we have had discussions with device companies and academics in the area so that we have a good sense of what everyone is doing in the space.”

Famm said that the purpose of GSK's own programs is to lay the foundation for a new treatment modality for the pharma. The aim is to identify diseases that can be treated by precision modulation of signals in peripheral visceral nerves and research the technology that will enable modulation using miniature, implantable devices.

The NIH has not disclosed the amount of funding available to the two other Common Fund programs—the 4D Nucleome and the Glycoscience programs—that will also begin next fiscal year. The 4D Nucleome program is developing technologies to determine the temporal and spatial DNA arrangement in cells and how that arrangement affects cell functions. The Glycoscience program is developing methods and resources to study the impact of sugar modifications on protein function.

## Public-private partnership roundup

July was a quiet month for public-private partnerships, with the bulk of the activity happening outside the U.S. (See Table 1, “Selected public-private partnerships for July 2014.”)

**AstraZeneca plc** and the **Max Planck Institute of Molecular Physiology** partnered to establish a satellite for the pharma's Cardiovascular

**Table 1. Selected public-private partnerships for July 2014.** In July, **Intellimedix Inc.** and **Pfizer Inc.** (NYSE:PFE) partnered with the **Epilepsy Foundation** to develop drug discovery platforms for genetic forms of epilepsy, including Dravet syndrome. Separately, **AstraZeneca plc** (LSE:AZN; NYSE:AZN) partnered with the **Max Planck Institute of Molecular Physiology** to establish a cardiovascular and metabolic disease (CVMD) satellite unit to study new chemical modalities, including stabilized peptides, macrocycles and conjugation chemistry.

Source: *BioCentury Archives*

Companies	Institutions	Business area	Disclosed value	Purpose
AstraZeneca	Max Planck Institute of Molecular Physiology	Cardiovascular disease; chemistry; endocrine/metabolic disease	Undisclosed	Partnership to establish a CVMD satellite unit to study new chemistry modalities
AstraZeneca; <b>GlaxoSmithKline plc</b> (LSE:GSK; NYSE:GSK); <b>Johnson &amp; Johnson</b> (NYSE:JNJ); Pfizer; <b>Takeda Pharmaceutical Co. Ltd.</b> (Tokyo:4502); <b>UCB Group</b> (Euronext:UCB)	<b>Medical Research Council</b>	Pharmaceuticals	Undisclosed	Partnership to identify new uses for deprioritized compounds from pharma
<b>Bayer AG</b> (Xetra:BAYN)	<b>University of Oxford</b>	Genitourinary disease	Undisclosed	Partnership to discover and develop therapies to treat endometriosis and uterine fibroids
<b>Evotec AG</b> (Xetra:EVT)	<b>Fraunhofer Society</b>	Neurology; cancer	Undisclosed	Partnership to carry out drug discovery programs in CNS indications and oncology
<b>HD Biosciences Co. Ltd.</b>	<b>Marshall University</b>	Cancer	Unavailable	Partnership to develop drugs to treat cancer
<b>ImmunID S.A.S.</b>	<b>Agency for Science, Technology and Research (A*STAR)</b>	Autoimmune disease	Undisclosed	Partnership to use ImmunID's ImmunTraCkeR and ImmunIG tests to evaluate T and B cell immune repertoire diversity in the blood of patients
<b>Ono Pharmaceutical Co. Ltd.</b> (Tokyo:4528)	<b>The University of Tokyo</b>	Pharmaceuticals	Undisclosed	Partnership giving the university access to the pharma's compound library
Pfizer; Intellimedix	Epilepsy Foundation	Neurology	Undisclosed	Partnership to develop drug discovery platforms for genetic forms of epilepsy

and Metabolic Diseases Innovative Medicines Unit. The unit will study new chemistry modalities and be located at the institute. Focus areas will include stabilized peptides, macrocycles and conjugation chemistry. AstraZeneca will be responsible for staffing, and the institute will manage and provide the facilities. Members from both parties will be part of a committee that will select, manage and oversee research projects.

AstraZeneca said that the partnership will help identify targets for cardiac regeneration, islet health and diabetic nephropathy. Financial details were not disclosed.

One of AstraZeneca's most significant public-private partnerships last year was a deal with the **Karolinska Institute** to create a similar satellite unit focused on the same therapeutic areas. The pharma is providing up to \$20 million to that center per year.

In the U.S., **Intellimedix Inc.**, **Pfizer Inc.** and the **Epilepsy Foundation** announced a three-way partnership to develop a drug discovery platform for genetic forms of epilepsy such as Dravet syndrome, a rare form of pediatric-onset epilepsy.

Intellimedix will perform gene sequencing and systems biology analysis, personalized zebrafish line development and zebrafish drug screening. Pfizer will provide its induced pluripotent stem (iPS) cell harvesting and screening capabilities through its Neusentis research unit. The foundation is providing scientific expertise and bringing in patient perspectives.

Intellimedix president and CEO Daniel Fischer said that the company has already identified several FDA-approved drugs that appear to decrease seizure activity in models of Dravet syndrome. "Two of these drugs are currently being considered for clinical trials," he added.

Lou, K.-J. & Martz, L. *SciBX* 7(31); doi:10.1038/scibx.2014.914  
Published online Aug. 14, 2014

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- Osherovich, L. *SciBX* **6**(14); doi:10.1038/scibx.2013.327
- Flanagan, M. *BioCentury* **21**(32), A15; Aug. 19, 2014

## COMPANIES AND INSTITUTIONS MENTIONED

**Astellas Pharma Inc.** (Tokyo:4503), Tokyo, Japan  
**AstraZeneca plc** (LSE:AZN; NYSE:AZN), London, U.K.  
**The Beatson Institute for Cancer Research**, Glasgow, U.K.  
**Cancer Research UK**, London, U.K.  
**Cancer Research Technology Ltd.**, London, U.K.  
**Epilepsy Foundation**, Landover, Md.  
**GlaxoSmithKline plc** (LSE:GSK; NYSE:GSK), London, U.K.  
**Intellimedix Inc.**, Atlanta, Ga.  
**Karolinska Institute**, Stockholm, Sweden  
**Max Planck Institute of Molecular Physiology**, Dortmund, Germany  
**National Institutes of Health**, Bethesda, Md.  
**Pfizer Inc.** (NYSE:PFE), New York, N.Y.

# Liver, supercooled

By Amy Donner, Senior Editor

A new supercooling technique that triples the time livers can be preserved for transplant could make more livers available for patients and increase the usability of donated organs for developing regenerative therapies.<sup>1</sup> **Harvard Medical School** and spinout **Organ Solutions LLC** are extending the studies from rats to larger species and scaling up the method in preparation for an FDA submission next year.

Korkut Uygun, the lead scientist on the study, founded Organ Solutions to help drive the studies and commercialize the technology. Uygun is an assistant professor of surgery at Harvard Medical School.

Liver availability is the main roadblock limiting the number of transplants each year. Thus, finding a way to prolong liver viability could expand the geographical region the organs can be sent to and hence the number of eligible recipients.

In addition, human hepatocytes from livers not healthy enough for transplant are needed for developing alternatives to transplantation, but those cells are also in short supply.

“The shortage of human livers is probably our biggest challenge in clinical liver transplantation and cell therapies for liver disease, such as bioartificial liver,” said Scott Nyberg, who is a professor of surgery and director of the Artificial Liver Program at the **Mayo Clinic**. He is also founder of **Liver Cell Therapies Inc.**, which is developing a bioartificial liver.

“Current organ storage technologies have become the major bottleneck for organ transplantation today and the tissue-engineered replacements of tomorrow. We are hoping this method will provide an important step in moving from practical but limited current storage techniques to functional organ preservation,” said Uygun.

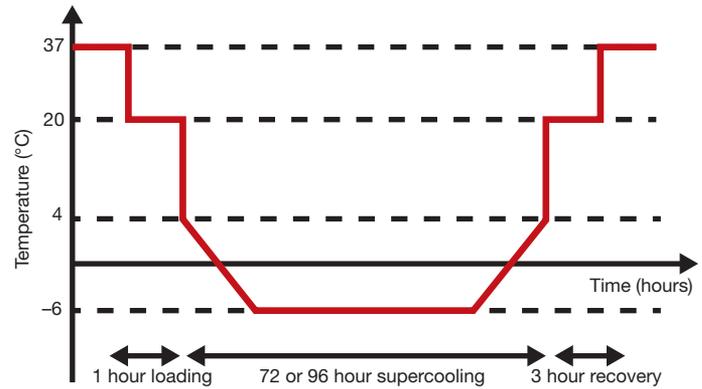
Although there is a centralized national network to link organ donors with patients, the distance between donor and recipient is an important factor in assigning organs. According to Paul Magnin, interim CEO of Organ Solutions, matches are typically made within small geographic regions such as the six states of New England.

## Staying cool

When organs are recovered from donors, they are stored in a cold organ-preservation solution and transported to the recipient hospital. Although cryopreservation has been attempted as a way to extend organ viability, the extreme temperatures involved cause too much tissue damage to organs intended for transplantation. Machine perfusion, which involves *ex vivo* artificial circulation, is used routinely for kidneys and short-term organ recovery after injury.

Livers for transplantation can be preserved for 12–24 hours after recovery. Uygun and colleagues came up with the idea that by combining supercooling with machine perfusion, they could overcome problems associated with cryopreservation and extend the time livers can be preserved prior to transplant.

Supercooling is a method for tissue preservation that involves maintaining the tissue at subzero temperatures without allowing it to freeze. By supercooling the tissue, the team wanted to slow down metabolism as far as possible without causing damage. However, there were three problems associated with supercooling that the researchers needed to preempt: ice



**Figure 1. Liver preservation protocol.** The liver preservation protocol reported by Berendsen *et al.* combined subnormothermic machine perfusion (SNMP) with supercooling and enabled rat livers to be cryopreserved for up to four days prior to successful transplant.

The protocol included three major steps; loading, supercooling and recovery. Prior to supercooling, livers were loaded by SNMP with cryopreservation medium that was supplemented with 3-O-methyl-D-glucose. During loading, livers were cooled to 4 °C at a rate of 1 °C per minute. After loading, the livers were flushed with UW solution containing 5% 35 kDa polyethylene glycol and submerged in the same solution.

For supercooling, livers were placed inside a controlled-rate freezer and cooled to –6 °C at a rate of 0.1 °C per minute. The supercooling phase was maintained for 72 or 96 hours.

To recover the livers for transplant, the temperature was gradually increased to 4 °C when livers were flushed with medium and subjected to SNMP for 3 hours. Livers were transplanted into healthy syngeneic rats. (Figure based on Figure 1a in ref. 1.)

formation, irreversible injury to plasma membranes, and oxidative damage from the cold temperature and the subsequent warming when the tissue is revived.

The researchers modified the standard preservation solution to protect against those effects. Because polyethylene glycol polymers protect plasma membranes in epithelial cells and glucose can protect internal membranes, 35 kDa polyethylene glycol and the nonmetabolizable glucose derivative 3-O-methyl-D-glucose were added to the solution.

The team turned to machine perfusion to reduce ischemic damage because it can minimize hypothermic endothelial injury, help reinitialize metabolic activity, replenish ATP and prime the vasculature for reperfusion.

Earlier studies from Uygun’s lab showed that function can be preserved in livers deemed unsuitable for transplantation if the organs are cooled to subphysiological temperatures before initiating *ex vivo* circulation, in a process dubbed subnormothermic machine perfusion (SNMP).<sup>2</sup>

The team thus created a protocol for testing the method in rats that involved stepwise lowering of the temperature and perfusion with the modified preservation solution (*see* Figure 1, “Liver preservation protocol”).

All rats that received livers preserved for three days using the combination protocol survived for three months after transplant with no detectable signs of organ failure. By contrast, all rats that received livers preserved with the standard protocol for three days died within two days of transplant.

When livers were preserved for 4 days in the combined protocol, 58% of the recipient rats survived for 3 months. Rats that survived 30 days with 4-day preserved livers had greater hepatic resistance—resistance to circulation during the recovery phase—than animals that did not survive that long. In addition, bile production was increased in the survivors. The reasons for the link between positive transplant outcome and increased hepatic resistance and bile production are not clear.

Uygun said that hepatic resistance and bile production during recovery could be used as markers to distinguish transplantable from nontransplantable organs. “ATP is also a good marker,” he said. “We are looking for even more practical markers—perhaps oxygen uptake.”

Because the scientists tested numerous permutations of their methodology, Uygun was confident that every component of the protocol contributed to the prolonged preservation. “The preservative was necessary, SNMP was necessary and supercooling was necessary,” he said.

The work was published in *Nature Medicine*. Scientists from the **University Medical Center Utrecht** and **Rutgers University** also contributed to the study.

“The lower temperature attained reduces the rate of energy consumption and prolongs the maximum storage time compared to ‘normal’ cold storage at ice temperature. The ability to preserve organs for three days would improve the logistics of liver transplantation. For example, liver transplantation might become a less urgent procedure. Alternatively, it would enable livers to be transported for greater distances to the best recipient,” said Peter Friend, a professor of transplantation at the **University of Oxford**.

“However,” he added, “the technology still results in an organ that is becoming progressively energy depleted, and the direct effect of cooling on cell membranes would, if anything, be more severe. Therefore, it is not yet clear if this technology would improve the ability to transplant successfully the very marginal organs for which conventional cold preservation is inadequate.”

In the short term, Uygun’s team hopes to adapt the method for marginal livers. In the longer term, the team hopes to increase the number of healthy livers that are available. “We would like to abolish waiting lists,” said Uygun.

Uygun told *SciBX* that his team is addressing two goals in parallel: scaling up the procedure for *ex vivo* application to human livers and applying the method to a pig transplant model.

“With the two, we think we’ll be ready for an FDA application in a year or so if all goes well,” said Uygun. “First, we will scale up to human livers to ensure the supercooling protocol works, and then we’ll move to pigs for transplant,” he told *SciBX*.

Because there are potential complications that are not well modeled in the rat, the team wants to test the system on larger animals. One such complication is the amount of free water in livers larger than those of rats. Uygun said that there is a higher likelihood of ice formation during preservation that can damage larger livers. He believes the team has not reached the limit of the method and that the technique can be further optimized for the larger organs if necessary.

### Bioartificial livers

The team also plans to use the supercooling SNMP technology to increase the number of human hepatocytes that can be used both in research and for developing bioartificial livers—bioreactors that perform the functions of a normal liver.

“Livers have an amazing ability to regenerate,” said Nyberg. Bioartificial livers can provide temporary support to allow liver regeneration and avoid a liver transplant altogether or bridge a patient to a successful transplant. He added, “Most patients with acute liver failure are healthy and in the prime of life, so the impact of successful bioartificial liver therapy can be quite significant.”

“If it is unburdened from the load of cleaning the blood for a while, there is a lot of evidence that the liver can heal itself,” said Magnin.

According to Nyberg, acute liver failure occurs in about 2,500 patients in the U.S. each year. Another 100,000 patients in the U.S. develop acute-on-chronic liver failure, for example, from conditions such as cirrhosis. Global numbers are 50- to 100-fold greater.

He said that the major limitations impeding the development of human hepatocyte-based bioartificial livers are the availability and functionality of hepatocytes obtained either from cell lines or human stem cells.

Magnin told *SciBX* that Organ Solutions could provide human hepatocytes for scientists developing such technologies.

“Akin to dialysis for the kidney, we could provide cartridges containing human liver cells for a bioartificial liver that can allow the liver to recover,” he said. For example, he said, “patients could use the bioartificial liver for six months, replacing the cartridge every two weeks. Certain patients could then dispose of the artificial liver, return to their native liver and live a healthy life.”

There are no FDA-approved bioartificial liver devices. At least two companies are developing bioartificial livers. **Vital Therapies Inc.** has ELAD, a bioartificial liver based on a human cell line, in Phase III trials to treat acute liver failure. Liver Cell Therapies is preparing a spheroid reservoir bioartificial liver (SRBAL) for a Phase I trial. SRBAL is based on primary hepatocytes and contains a semipermeable membrane that separates the cells from the patient’s circulation as an immune barrier and an added safety feature.

**Partners HealthCare** has filed three patent applications covering supercooled preservation, machine perfusion recovery and quality assessment of the livers prior to transplant. The IP will be licensed to Organ Solutions.

Donner, A. *SciBX* 7(31); doi:10.1038/scibx.2014.915  
Published online Aug. 14, 2014

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e-mail: [uygun.korkut@mgh.harvard.edu](mailto:uygun.korkut@mgh.harvard.edu)  
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- Bruinsma, B.G. *et al. Am. J. Transplant.* **14**, 1400–1409 (2014)

### COMPANIES AND INSTITUTIONS MENTIONED

**Food and Drug Administration**, Silver Spring, Md.  
**Harvard Medical School**, Boston, Mass.  
**Liver Cell Therapies Inc.**, Rochester, Minn.  
**Mayo Clinic**, Rochester, Minn.  
**Organ Solutions LLC**, Wilmington, Del.  
**Partners HealthCare**, Boston, Mass.  
**Rutgers University**, Piscataway, N.J.  
**University Medical Center Utrecht**, Utrecht, the Netherlands  
**University of Oxford**, Oxford, U.K.  
**Vital Therapies Inc.** (NASDAQ:VTL), San Diego, Calif.

## 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>Cancer</b>				
Cancer	DNA	<i>In vitro</i> and rat studies have identified mitochondria-targeted nanoparticle formulations of cisplatin that could help treat cisplatin-resistant cancers. Cisplatin resistance is enhanced by nucleotide excision repair mechanisms that are absent in mitochondria. A cisplatin prodrug, platin-M, was engineered to target the mitochondria and encapsulated in a biodegradable nanoparticle to promote its half-life and mitochondrial release. In cisplatin-resistant cancer cell lines, the formulation showed greater cytotoxicity than unmodified cisplatin. In rats, i.v. injection of the formulation led to blood brain barrier penetration of the nanoparticles. Next steps include testing the safety and efficacy of the formulation in larger animal models.  <b>SciBX 7(31); doi:10.1038/scibx.2014.916</b> <b>Published online Aug. 14, 2014</b>	Provisional patent filed; licensed by Partikula LLC; available for licensing for applications other than cancer	Marrache, S. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online July 7, 2014; doi:10.1073/pnas.1405244111 <b>Contact:</b> Shanta Dhar, University of Georgia, Athens, Ga. e-mail: <a href="mailto:shanta@uga.edu">shanta@uga.edu</a>
Cancer	Not applicable	Mouse studies suggest short, ultrahigh pulses of radiation therapy could help treat cancer with less damage to healthy tissue than continuous irradiation. In mouse xenograft models of breast tumors and head and neck tumors, short, ultrahigh pulses of radiation showed comparable potency to a continuous irradiation protocol. In an orthotopic mouse model of lung cancer, pulsed radiation at 28 gray doses increased survival and tumor regression compared with a continuous 15 gray dose and did not cause radiotherapy-associated lung fibrosis. Next steps include Phase I testing of a pulsed irradiation regimen.  <b>SciBX 7(31); doi:10.1038/scibx.2014.917</b> <b>Published online Aug. 14, 2014</b>	Unpatented; licensing status not applicable	Favaudon, V. <i>et al. Sci. Transl. Med.</i> ; published online July 16, 2014; doi:10.1126/scitranslmed.3008973 <b>Contact:</b> Vincent Favaudon, Curie Institute, Orsay, France e-mail: <a href="mailto:vincent.favaudon@curie.fr">vincent.favaudon@curie.fr</a>
Chronic lymphocytic leukemia (CLL)	Protein kinase C $\beta$ (PRKCB)	<i>In vitro</i> and mouse studies suggest inhibiting PRKCB with sotrastaurin could help treat CLL. In primary CLL cells, the PRKCB inhibitor sotrastaurin decreased proliferation compared with no treatment and did not affect B cells from healthy subjects. In a mouse model of CLL, sotrastaurin decreased spleen size and circulating levels of CLL cells compared with vehicle. Next steps include collaborating with Novartis AG to evaluate sotrastaurin in a Phase II trial to treat CLL and mantle cell lymphoma (MCL). Novartis has sotrastaurin (AEB071) in Phase I testing for diffuse B cell lymphoma (DBCL) and other undisclosed cancers.  <b>SciBX 7(31); doi:10.1038/scibx.2014.918</b> <b>Published online Aug. 14, 2014</b>	Unpatented; licensing status undisclosed	El-Gamal, D. <i>et al. Blood</i> ; published online July 7, 2014; doi:10.1182/blood-2014-05-574830 <b>Contact:</b> John C. Byrd, The Ohio State University, Columbus, Ohio e-mail: <a href="mailto:john.byrd@osumc.edu">john.byrd@osumc.edu</a>
Prostate cancer	Lactadherin (MFGE8; HMFG)	Studies in patient samples and cell culture suggest inhibiting MFGE8 could help treat prostate cancer. In samples from patients, MFGE8 levels were higher on the surface of prostate cancer cells and blood exosomes than levels in healthy controls. In cocultures of apoptotic human prostate cancer cells with bone marrow macrophages, an MFGE8-neutralizing antibody decreased protumorigenic polarization of macrophages compared with IgG control. Next steps include delineating the contribution of MFGE8 to prostate tumor growth in mouse models and designing clinically relevant MFGE8-neutralizing antibodies.  <b>SciBX 7(31); doi:10.1038/scibx.2014.919</b> <b>Published online Aug. 14, 2014</b>	Unpatented; licensing status not applicable	Soki, F.N. <i>et al. J. Biol. Chem.</i> ; published online July 8, 2014; doi:10.1074/jbc.M114.571620 <b>Contact:</b> Laurie K. McCauley, University of Michigan School of Dentistry, Ann Arbor, Mich. e-mail: <a href="mailto:mccauley@umich.edu">mccauley@umich.edu</a>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Endocrine/metabolic disease</b>				
Cachexia	Adrenergic receptor $\beta_3$ (ADRB3)	<i>In vitro</i> and mouse studies suggest ADRB3 antagonists or NSAIDs could help treat cancer-associated cachexia. In multiple mouse models of cancer-induced cachexia, browning of white adipose tissue (WAT) began before signs of fat or muscle atrophy and increased as cachexia progressed. In a mouse model of skin cancer with cachexia, an ADRB3 antagonist or the generic cyclooxygenase-2 (COX-2) inhibitor sulindac prevented WAT browning and decreased cachexia severity compared with vehicle. In seven of eight patients with cancer-associated cachexia, markers of WAT browning were seen. Next steps include identifying new therapeutics that can inhibit WAT browning in cachexia.	Findings unpatented; available for partnering	Petruzzelli, M. <i>et al. Cell Metab.</i> ; published online July 17, 2014; doi:10.1016/j.cmet.2014.06.011 <b>Contact:</b> Erwin F. Wagner, Spanish National Cancer Research Center (CNIO), Madrid, Spain e-mail: <a href="mailto:ewagner@cnio.es">ewagner@cnio.es</a>
<b>SciBX 7(31); doi:10.1038/scibx.2014.920</b> <b>Published online Aug. 14, 2014</b>				
Cachexia	Parathyroid hormone- like hormone (PTH1H; PTH1RP)	<i>In vitro</i> and mouse studies suggest neutralizing PTH1RP could help treat cancer-associated cachexia. In a mouse model of Lewis lung carcinoma (LLC) with cachexia, knockout of <i>PR domain containing 16 (Prdm16)</i> , which is required for the browning of adipose tissue, prevented cachexia. A screen for proteins produced by LLC cells found that PTH1RP induced the browning of primary adipocytes. In the mouse model of LLC, an anti-PTH1RP antibody decreased cachexia symptoms compared with a control antibody. Next steps include developing a humanized PTH1RP antibody.	Patent application filed; available for licensing	Kir, S. <i>et al. Nature</i> ; published online July 13, 2014; doi:10.1038/nature13528 <b>Contact:</b> Bruce M. Spiegelman, Harvard Medical School, Boston, Mass. e-mail: <a href="mailto:bruce_spiegelman@dfci.harvard.edu">bruce_spiegelman@dfci.harvard.edu</a>
<b>SciBX 7(31); doi:10.1038/scibx.2014.921</b> <b>Published online Aug. 14, 2014</b>				
Diabetes	Fibroblast growth factor 1 (FGF1)	Mouse studies suggest recombinant FGF1 could help treat type 2 diabetes. In mouse models of genetic or diet-induced obesity, a single subcutaneous dose of recombinant mouse Fgf1 decreased glucose levels compared with saline without causing hypoglycemia. In these mouse models, chronic treatment decreased blood glucose levels and increased insulin sensitivity compared with saline and did not cause side effects associated with insulin-sensitizing therapeutics such as weight gain and bone loss. Next steps include testing recombinant FGF1 in large animal models of diabetes.	Patent applications filed; available for licensing	Suh, J.M. <i>et al. Nature</i> ; published online July 16, 2014; doi:10.1038/nature13540 <b>Contact:</b> Ronald M. Evans, Salk Institute for Biological Studies, La Jolla, Calif. e-mail: <a href="mailto:evans@salk.edu">evans@salk.edu</a>
<b>SciBX 7(31); doi:10.1038/scibx.2014.922</b> <b>Published online Aug. 14, 2014</b>				
Diabetes	G protein- coupled receptor 120 (GPR120; O3FAR1)	Cell culture and mouse studies have identified a GPR120 agonist that could be used to treat type 2 diabetes. In cell culture studies, a compound was identified that had selectivity for mouse Gpr120 over free fatty acid receptor 1 (Ffar1; Gpr40) and that activated downstream signaling in human and mouse GPR120 <sup>+</sup> cells. In mice fed a high-fat diet for 15 weeks, the compound improved glucose tolerance and decreased tissue macrophage infiltration and proinflammatory gene expression in adipocytes compared with no treatment. Researchers did not disclose next steps, which could include optimization of the compound.	Patent and licensing status undisclosed	Oh, D.Y. <i>et al. Nat. Med.</i> ; published online July 6, 2014; doi:10.1038/nm.3614 <b>Contact:</b> Jerrold M. Olefsky, University of California, San Diego, La Jolla, Calif. e-mail: <a href="mailto:jolefsky@ucsd.edu">jolefsky@ucsd.edu</a> <b>Contact:</b> Da Young Oh, same affiliation as above email: <a href="mailto:dayoungoh@ucsd.edu">dayoungoh@ucsd.edu</a>
<b>SciBX 7(31); doi:10.1038/scibx.2014.923</b> <b>Published online Aug. 14, 2014</b>				

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Obesity	Notch 1 (NOTCH1); $\gamma$ -secretase	<p>Mouse studies suggest inhibiting NOTCH1 or <math>\gamma</math>-secretase could help treat obesity. In mice, adipose-specific knockout of <i>Notch1</i> increased the number of thermogenic beige adipocytes and decreased the number of white adipocytes compared with no alteration. Adipose-specific <i>Notch1</i> knockout mice showed improved glucose tolerance and increased resistance to high-fat diet-induced obesity compared with wild-type controls. In a mouse model of obesity, a <math>\gamma</math>-secretase inhibitor that also blocks Notch signaling improved glucose tolerance and decreased weight gain compared with vehicle. Next steps include determining whether NOTCH1 signaling is involved in the formation of beige adipose tissue in humans and testing the effects of new <math>\gamma</math>-secretase or NOTCH1 inhibitors in mouse models of obesity.</p> <p><b>SciBX 7(31); doi:10.1038/scibx.2014.924</b> Published online Aug. 14, 2014</p>	Patent application filed covering NOTCH1 inhibitors to promote conversion of white fat to beige fat; available for licensing from the Purdue Research Foundation	<p>Bi, P. <i>et al. Nat. Med.</i>; published online July 20, 2014; doi:10.1038/nm.3615 <b>Contact:</b> Shihuan Kuang, Purdue University, West Lafayette, Ind. e-mail: <a href="mailto:skuang@purdue.edu">skuang@purdue.edu</a></p>
<b>Infectious disease</b>				
<i>Aspergillus</i>	C-type lectin domain family 7 member A (CLEC7A); DECTIN1); laminarin	<p><i>In vitro</i> and mouse studies suggest DECTIN1 chimeric antigen receptor (CAR)-expressing T cells could be used to treat opportunistic fungal infections by targeting fungal laminarin. In cocultures of <i>Aspergillus</i> and CAR T cells, DECTIN1 CAR-expressing T cells decreased viability and hyphae lengths of germinating <i>Aspergillus</i> spores compared with no treatment or treatment with CD19 CAR T cells. In immunosuppressed mice with invasive <i>Aspergillus</i> infection, Dectin1 CAR T cells decreased pulmonary <i>Aspergillus</i> load and led to smaller cutaneous fungal lesions compared with control T cells. Next steps include designing CAR T cells that target other carbohydrates produced by pathogens and tumor cells.</p> <p><b>SciBX 7(31); doi:10.1038/scibx.2014.925</b> Published online Aug. 14, 2014</p>	Patent and licensing status undisclosed	<p>Kumaresan, P.R. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online July 7, 2014; doi:10.1073/pnas.1312789111 <b>Contact:</b> Laurence J.N. Cooper, The University of Texas MD Anderson Cancer Center, Houston, Texas e-mail: <a href="mailto:ljncooper@mdanderson.org">ljncooper@mdanderson.org</a></p>
<i>Pseudomonas</i>	LecA	<p><i>In vitro</i> studies identified a ligand of the <i>Pseudomonas</i> virulence factor lecA that could help treat infection. An <i>in vitro</i> screen of a galactoside-conjugate array containing 625 monovalent and divalent glycans identified a divalent lecA ligand with a <math>K_D</math> of ~82 nM. In a human lung epithelial cell culture assay, the ligand inhibited <i>Pseudomonas</i> internalization by 90% at 5 <math>\mu</math>M. Next steps include testing the ligand in animal models of <i>Pseudomonas</i> infection.</p> <p><b>SciBX 7(31); doi:10.1038/scibx.2014.926</b> Published online Aug. 14, 2014</p>	Unpatented; screening technology available for licensing	<p>Novoa, A. <i>et al. Angew. Chem. Int. Ed.</i>; published online July 7, 2014; doi:10.1002/anie.201402831 <b>Contact:</b> Nicolas Winssinger, University of Geneva, Geneva, Switzerland e-mail: <a href="mailto:nicolas.winssinger@unige.ch">nicolas.winssinger@unige.ch</a> <b>Contact:</b> Winfried Römer, Albert Ludwigs University of Freiburg, Freiburg, Germany e-mail: <a href="mailto:winfried.roemer@bioss.uni-freiburg.de">winfried.roemer@bioss.uni-freiburg.de</a> <b>Contact:</b> Anne Imberty, University of Grenoble-Alpes and Centre National de la Recherche Scientifique (CNRS), Grenoble, France e-mail: <a href="mailto:imberty@cermav.cnrs.fr">imberty@cermav.cnrs.fr</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Inflammation</b>				
Allergy	Spleen tyrosine kinase (SYK)	<p>Mouse studies suggest inhibiting SYK could help prevent food allergy. In a mouse model of peanut allergy, mice exposed to subanaphylactic doses of peanut butter had increased IgE levels, mast cell activity and peanut-specific T helper 2 (Th2) cell responses and decreased peanut-specific, antiallergic T<sub>reg</sub> cell responses compared with unexposed mice. In the model, antibody-mediated neutralization of IgE or pharmacological inhibition of Syk, which functions downstream of IgE receptors in mast cells, reversed allergic sensitivity, decreased Th2 cell and increased T<sub>reg</sub> cell responses compared with vehicle or no treatment. Next steps include further evaluating the effects of SYK inhibition and using the model to further investigate allergen uptake and antigen-presenting cell functions in the gut and associated lymphoid tissues.</p> <p><b>SciBX 7(31); doi:10.1038/scibx.2014.927</b> Published online Aug. 14, 2014</p>	Patent and licensing status undisclosed	<p>Burton, O.T. <i>et al. Immunity</i>; published online July 10, 2014; doi:10.1016/j.immuni.2014.05.017 <b>Contact:</b> Hans C. Oettgen, Harvard Medical School, Boston, Mass. e-mail: <a href="mailto:hans.oettgen@childrens.harvard.edu">hans.oettgen@childrens.harvard.edu</a></p>
<b>Neurology</b>				
Alzheimer's disease (AD)	Transcription factor EB (TFEB); $\beta$ -amyloid (A $\beta$ )	<p>Mouse studies suggest increasing astrocyte levels of TFEB could help treat AD. In a mouse model of AD, hippocampal delivery of an astrocyte-specific adeno-associated viral (AAV) vector encoding <i>Tfeb</i> decreased interstitial fluid A<math>\beta</math> half-life and increased lysosomal biogenesis compared with delivery of a control AAV vector. In an aged mouse model of AD, an AAV vector encoding <i>Tfeb</i> decreased total A<math>\beta</math> levels and amyloid plaque load compared with control AAV. Next steps include determining the effect of TFEB activation on other cell types in the brain.</p> <p><b>SciBX 7(31); doi:10.1038/scibx.2014.928</b> Published online Aug. 14, 2014</p>	Patent and licensing status undisclosed	<p>Xiao, Q. <i>et al. J. Neurosci.</i>; published online July 16, 2014; doi:10.1523/JNEUROSCI.3788-13.2014 <b>Contact:</b> Jin-Moo Lee, Washington University in St. Louis School of Medicine, St. Louis, Mo. e-mail: <a href="mailto:leejm@wustl.edu">leejm@wustl.edu</a> <b>Contact:</b> Abhinav Diwan, same affiliation as above e-mail: <a href="mailto:adiwan@dom.wustl.edu">adiwan@dom.wustl.edu</a></p>
Itch	$\gamma$ -aminobutyric acid (GABA)	<p>Mouse studies suggest transplantation of GABAergic progenitor cells into the spinal cord could help treat chronic neuropathic itch. In a mouse model of chronic itch, transplantation of GABAergic progenitor cells into the spinal cord region that controls the itch-affected area decreased scratching, licking and biting compared with no transplantation. In the mice, the GABAergic progenitor cells decreased or eliminated lesions compared with vehicle. Next steps could include testing the therapeutic approach in additional animal models of itch.</p> <p><b>SciBX 7(31); doi:10.1038/scibx.2014.929</b> Published online Aug. 14, 2014</p>	Patent and licensing status unavailable	<p>Braz, J.M. <i>et al. J. Clin. Invest.</i>; published online July 8, 2014; doi:10.1172/JCI75214 <b>Contact:</b> Joao M. Braz, University of California, San Francisco, Calif. e-mail: <a href="mailto:bjoao@phy.ucsf.edu">bjoao@phy.ucsf.edu</a></p>
Parkinson's disease (PD)	$\alpha$ -synuclein (SNCA)	<p>Mouse and cell culture studies have identified antibodies against the SNCA C terminus that could help stabilize SNCA and treat PD. In a mouse model of PD with transgenic SNCA expression, antibodies against the SNCA C terminus decreased accumulation of SNCA aggregates, axonal pathology and behavioral deficits with similar efficacy to an antibody targeting full-length SNCA. In cell culture assays that measure interneuronal SNCA propagation, anti-SNCA C terminus antibodies prevented the transmission of SNCA from SNCA-expressing cells to nonexpressing cells. Next steps include further characterizing the antibodies' mechanism of action and developing single-chain versions with high affinity and high brain penetration.</p> <p><b>SciBX 7(31); doi:10.1038/scibx.2014.930</b> Published online Aug. 14, 2014</p>	Patent application filed; licensed to Prothena Corp. plc	<p>Games, D. <i>et al. J. Neurosci.</i>; published online July 9, 2014; doi:10.1523/JNEUROSCI.5314-13.2014 <b>Contact:</b> Eliezer Masliah, University of California, San Diego, La Jolla, Calif. e-mail: <a href="mailto:emasliah@ucsd.edu">emasliah@ucsd.edu</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Seizures	Abhydrolase domain containing 6 (ABHD6)	Mouse studies suggest inhibiting ABHD6 could help prevent seizures. In a mouse model of chemical-induced seizures, pretreatment with an ABHD6 inhibitor prevented seizure-related mortality and decreased seizure frequency and severity compared with vehicle pretreatment. In a mouse model of Huntington's disease (HD)-associated seizures, acute or chronic treatment with the ABHD6 inhibitor prevented spontaneous behavioral seizures without inducing drug tolerance. Next steps could include determining the types of seizures that are susceptible to ABHD6 blockade.  <i>SciBX</i> 7(31); doi:10.1038/scibx.2014.931 Published online Aug. 14, 2014	Patent and licensing status unavailable	Naydenov, A.V. <i>et al. Neuron</i> ; published online July 16, 2014; doi:10.1016/j.neuron.2014.06.030 <b>Contact:</b> Nephi Stella, University of Washington, Seattle, Wash. e-mail: <a href="mailto:nstella@uw.edu">nstella@uw.edu</a>
<b>Various</b>				
Diabetes; retinitis	Endoplasmic reticulum to nucleus signaling 1 (ERN1; IRE1)	<i>In vitro</i> and rodent studies suggest inhibition of IRE1 could help treat endoplasmic reticulum stress-related diseases such as retinitis pigmentosa and diabetes. In two rat models of retinitis pigmentosa, intravitreal injection of an IRE1 antagonist partially protected against photoreceptor degeneration. In a mouse model of diabetes with endoplasmic reticulum stress-induced $\beta$ cell apoptosis, i.p. injection of the antagonist increased glucose tolerance compared with vehicle injection. Next steps include testing the inhibitors in additional animal models of endoplasmic reticulum stress-induced cell degeneration.  <i>SciBX</i> 7(31); doi:10.1038/scibx.2014.932 Published online Aug. 14, 2014	Patent applications filed; licensing discussions in progress with undisclosed company; unavailable for licensing	Ghosh, R. <i>et al. Cell</i> ; published online July 10, 2014; doi:10.1016/j.cell.2014.07.002 <b>Contact:</b> Feroz R. Papa, University of California, San Francisco, Calif. e-mail: <a href="mailto:frpapa@medicine.ucsf.edu">frpapa@medicine.ucsf.edu</a> <b>Contact:</b> Scott A. Oakes, same affiliation as above e-mail: <a href="mailto:scott.oakes@ucsf.edu">scott.oakes@ucsf.edu</a>

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## This week in techniques

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

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

Approach	Summary	Licensing status	Publication and contact information
<b>Assays &amp; screens</b>			
EnPlex, a high throughput flow cytometry platform to assess potency and selectivity of small molecule enzyme inhibitors	The platform EnPlex could enable multiplexed, high throughput evaluation of the potency and selectivity of small molecule inhibitors of enzymes. In the assay, enzymes are coupled to differently colored polystyrene microspheres and competitive binding to small molecule inhibitors is assessed with a biotinylated activity-based probe. A two-laser flow cytometer identifies each enzyme by microsphere color, and a biotin-dependent colorimetric assay determines the degree of inhibition. In an analysis of 94 serine hydrolases, 55 known small molecule inhibitors yielded on-target $IC_{50}$ values consistent with published data but revealed previously unknown off-target interactions. Next steps could include adapting EnPlex for additional enzyme families.	Patent and licensing status unavailable	Bachovchin, D.A. <i>et al. Nat. Chem. Biol.</i> ; published online July 6, 2014; doi:10.1038/nchembio.1578 <b>Contact:</b> Todd R. Golub, the Broad Institute of MIT and Harvard, Cambridge, Mass. e-mail: <a href="mailto:golub@broadinstitute.org">golub@broadinstitute.org</a>
	<b>SciBX 7(31); doi:10.1038/scibx.2014.933</b> <b>Published online Aug. 14, 2014</b>		
One-bead, one-compound peptoid-encoded $\alpha$ -helix mimetic library to identify chaperones or inhibitors of protein-protein interactions	Cell culture studies suggest a one-bead, one-compound peptoid-encoded $\alpha$ -helix mimetic library could be used to identify chaperones or inhibitors of $\alpha$ -helix-mediated protein-protein interactions. Each bead displays one of 1,458 triazine-piperazine-triazine-based $\alpha$ -helix mimetics on the outside and a peptoid coding tag on the inside, enabling identification of the corresponding inhibitory mimetic. A screen of the one-bead, one-compound library against the myeloid leukemia cell differentiation protein (MCL1) identified two MCL1-binding compounds that also antagonized the interaction between MCL1 and the proapoptotic protein Bcl2 homology domain 3 (BH3). A screen of the library against recombinant $\alpha$ -synuclein (SNCA) protein also identified two SNCA-binding compounds that delayed the onset of SNCA aggregation. Ongoing work includes optimizing the identified compounds and preparing more diverse and larger libraries of $\alpha$ -helix mimetics to screen against different targets.	Patented; available for licensing	Oh, M. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online July 14, 2014; doi:10.1073/pnas.1320556111 <b>Contact:</b> Hyun-Suk Lim, Pohang University of Science and Technology, Pohang, South Korea e-mail: <a href="mailto:hslim@postech.ac.kr">hslim@postech.ac.kr</a> <b>Contact:</b> Quyen Q. Hoang, Indiana University School of Medicine, Indianapolis, Ind. e-mail: <a href="mailto:qqhoang@iu.edu">qqhoang@iu.edu</a>
	<b>SciBX 7(31); doi:10.1038/scibx.2014.934</b> <b>Published online Aug. 14, 2014</b>		
Screening for biological activity of alternative splicing protein products of aminoacyl tRNA synthetases (AARSs)	<i>In vitro</i> studies suggest proteins formed from alternative splicing of AARSs could be new therapeutics and therapeutic targets. PCR and deep sequencing studies of AARS gene transcripts identified splice variants for each AARS that lost normal catalytic function but gained new biologic activity. In a panel of primary human cell-based assays, new biological functions of the alternatively spliced proteins were identified, such as the ability to stimulate skeletal muscle fiber formation. Next steps could include identifying specific protein variants that have potential as drugs or drug targets. aTyr Pharma Inc. is developing therapeutics based on physiocrine biology to treat rare diseases. Resokine, a protein therapy based on noncanonical functions of secreted forms of AARSs, is in Phase I testing to treat rare diseases related to the immune system.	Patent applications filed by aTyr Pharma and collaborators; available for licensing	Lo, W.-S. <i>et al. Science</i> ; published online July 18, 2014; doi:10.1126/science.1252943 <b>Contact:</b> Paul Schimmel, Hong Kong University of Science and Technology, Hong Kong, China e-mail: <a href="mailto:schimmel@scripps.edu">schimmel@scripps.edu</a>
	<b>SciBX 7(31); doi:10.1038/scibx.2014.935</b> <b>Published online Aug. 14, 2014</b>		

## This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
<b>Computational models</b>			
Platypus, a reference genome-free algorithm that rapidly calls variants in clinical sequencing data	<i>In silico</i> studies with available sequence data suggest Platypus can be used for one-step, rapid processing of high throughput clinical sequencing data. The algorithm separates a sensitivity-optimizing candidate generation phase from a specificity-optimizing haplotype-based calling stage. In publicly available whole-genome and whole-exome clinical sequencing data, Platypus achieved 95% sensitivity for <i>de novo</i> mutations in sequence data with an average 35' coverage. Next steps include adapting the algorithm to detect somatic mutations in cancer tissue.	Unpatented; licensing status not applicable	Rimmer, A. <i>et al. Nat. Genet.</i> ; published online July 13, 2014; doi:10.1038/ng.3036 <b>Contact:</b> Gerton Lunter, University of Oxford, U.K. e-mail: <a href="mailto:gerton.lunter@well.ox.ac.uk">gerton.lunter@well.ox.ac.uk</a>
	<b>SciBX 7(31); doi:10.1038/scibx.2014.936</b> Published online Aug. 14, 2014		
<b>Drug platforms</b>			
Generation of hematopoietic cell grafts from human endothelial cells	Endothelial cells reprogrammed into hematopoietic cells could be useful for generating grafts to treat hematological disorders, leukemia, lymphoma and other diseases. Cocultures of a human cell monolayer that modeled the vascular microenvironment and human endothelial cells transduced with four key transcription factors induced outgrowth of multipotent progenitor (MPP) cells that expressed hematopoietic markers. In irradiated mice, transplanted MPP cells differentiated into multiple lineages of functional myeloid and lymphoid cells in peripheral blood, bone marrow and spleen. Next steps include reprogramming autologous endothelial cells from patients with sickle cell disease into hematopoietic cells that express wild-type hemoglobin- $\beta$ (HBB) and evaluating such cells as a potential gene therapy or cell-based therapy.	Patent application filed; available for licensing	Sandler, V.M. <i>et al. Nature</i> ; published online July 2, 2014; doi:10.1038/nature13547 <b>Contact:</b> Shahin Rafii, Weill Cornell Medical College, New York, N.Y. e-mail: <a href="mailto:srafi@med.cornell.edu">srafi@med.cornell.edu</a>
	<b>SciBX 7(31); doi:10.1038/scibx.2014.937</b> Published online Aug. 14, 2014		
<b>Markers</b>			
A two-gene signature distinguishes between psoriasis and eczema	Human sample studies suggest a two-gene classifier can be used to distinguish between psoriasis and eczema. In skin samples from a cohort of 24 patients with both psoriasis and eczema, differentially expressed genes in normal, eczema or psoriasis skin samples were identified. In a separate cohort, a two-gene signature classifier, based on upregulation of <i>chemokine CC motif ligand 27 (CCL27)</i> and downregulation of <i>inducible nitric oxide synthase 2 (NOS2; iNOS)</i> , distinguished between psoriasis and eczema. In a third cohort, the classifier-based diagnosis matched clinical and histological diagnosis in 33 of 34 cases. Next steps include validating the signature and establishing its effectiveness based on protein expression.	Patent filed; unavailable for licensing	Quaranta, M. <i>et al. Sci. Transl. Med.</i> ; published online July 9, 2014; doi:10.1126/scitranslmed.3008946 <b>Contact:</b> Kilian Eyerich, Technical University Munich, Munich, Germany e-mail: <a href="mailto:kilian.eyerich@lrz.tum.de">kilian.eyerich@lrz.tum.de</a> <b>Contact:</b> Stefanie Eyerich, same affiliation as above e-mail: <a href="mailto:stefanie.eyerich@lrz.tum.de">stefanie.eyerich@lrz.tum.de</a>
	<b>SciBX 7(31); doi:10.1038/scibx.2014.938</b> Published online Aug. 14, 2014		
Copy number alteration (CNA) burden to predict prostate cancer recurrence	Studies in patient samples suggest CNA burden could help predict prostate cancer recurrence and metastasis. In primary prostate tumor samples from 272 patients, high CNA burden, calculated as total CNA relative to total autosomal tumor genome, was associated with high recurrence risk and increased long-term risk of metastasis. Next steps could include developing an assay to quantify CNA burden using samples from thin needle biopsies.	Patent and licensing status unavailable	Hieronimus, H. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online July 14, 2014; doi:10.1073/pnas.1411446111 <b>Contact:</b> Charles L. Sawyers, Memorial Sloan-Kettering Cancer Center, New York, N.Y. e-mail: <a href="mailto:sawyersc@mskcc.org">sawyersc@mskcc.org</a>
	<b>SciBX 7(31); doi:10.1038/scibx.2014.939</b> Published online Aug. 14, 2014		

**This week in techniques (continued)**

Approach	Summary	Licensing status	Publication and contact information
Mutations in <i>p53</i> and <i>SMAD</i> family member 4 ( <i>MADH4</i> ; <i>SMAD4</i> ; <i>DPC4</i> ) as risk factors for esophageal cancer	Genome sequencing studies suggest mutations in <i>p53</i> and <i>SMAD4</i> could help identify patients with Barrett's esophagus who have a high probability of developing esophageal adenocarcinoma. Individuals with Barrett's esophagus have an increased risk of developing esophageal adenocarcinoma but most do not progress to invasive disease. Genomic sequencing of patient samples showed that mutations in <i>p53</i> or <i>SMAD4</i> were associated with progression from Barrett's esophagus to high-grade dysplasia or esophageal adenocarcinoma. Next steps could include validating the study prospectively.  <b>SciBX 7(31); doi:10.1038/scibx.2014.940</b> <b>Published online Aug. 14, 2014</b>	Patent and licensing status unavailable	Weaver, J.M.J. <i>et al. Nat. Genet.</i> ; published online June 22, 2014; doi:10.1038/ng.3013 <b>Contact:</b> Rebecca C. Fitzgerald, University of Cambridge, Cambridge, U.K. e-mail: <a href="mailto:rcf29@mrc-cu.cam.ac.uk">rcf29@mrc-cu.cam.ac.uk</a>



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**Erratum: The Distillery: infectious disease: viral infection**

SciBX 7(29); doi:10.1038/scibx.2014.867

Published online July 31, 2014

A Therapeutics item on infectious disease, highlighting an article by Chung *et al.*, misstated the target. The target/marker/pathway column should read “Venezuelan equine encephalitis viral nsP2 protein (VEEV nsP2).” The study suggests that inhibitors of this target could help treat Venezuelan equine encephalitis viral infection.

**Erratum: Analysis: Tools**

Lou, K.-J. &amp; Oshrovich, L. SciBX 7(30); doi:10.1038/scibx.2014.885

Published online Aug. 7, 2014

The Analysis item “High throughput remyelination” misquoted Tassie Collins and misstated her title at Myelin Repair Foundation. Collins is VP of translational medicine, and her quote in the 13th paragraph should read: “This assay takes oligodendrocyte differentiation to the next step of asking whether the cell is undergoing the necessary shape changes. It allows them to determine whether the cell is doing the right sort of morphological rearrangement.” A paraphrase attributed to her in the 20th paragraph should read: “Collins said that the MRF is also working on a scalable coculture system with live axons and oligodendrocytes. She said that such a system is important to have because there is evidence suggesting that axons and oligodendrocytes have dynamic interactions that affect the process of myelination.” Additionally, the 11th paragraph in Box 1 was erroneously attributed to Collins.

## INDEXES

**Company and institution index****A**

Agency for Science, Technology and Research 8  
Astellas Pharma Inc. 7  
AstraZeneca plc 8  
aTyr Pharma Inc. 16  
Autism Speaks 6

**B**

Bayer AG 8  
Beatson Institute for Cancer Research 7  
Biogen Idec Inc. 2  
Boehringer Ingelheim GmbH 5  
Boston Children’s Hospital 2

**C**

Cancer Research Technology Ltd. 7  
Cancer Research UK 7  
Circuit Therapeutics Inc. 5

**D**

Duke University 3

**E**

Epilepsy Foundation 8  
Evotec AG 8

**F**

Food and Drug Administration 6,9  
Fraunhofer Society 8

**G**

GlaxoSmithKline plc 7

**H**

Harvard Medical School 9  
Harvard University 2  
HD Biosciences Co. Ltd. 8

**I**

Icahn School of Medicine at Mount Sinai 3  
ImmunID S.A.S. 8  
Institute of Medicine 6  
Intellimedix Inc. 8

**J**

Johns Hopkins University School of Medicine 3  
Johnson & Johnson 8

**K**

Karolinska Institute 8

**L**

Liver Cell Therapies Inc. 9

**M**

Marshall University 8  
Massachusetts Institute of Technology 1  
Max Planck Institute of Molecular Physiology 8  
Mayo Clinic 9  
Medical Research Council 8

**N**

National Institutes of Health 5,7  
Novartis AG 11

**O**

Ono Pharmaceutical Co. Ltd. 8  
Organ Solutions LLC 9

Orion Bionetworks Inc. 2

**P**

Partikula LLC 11  
Partners HealthCare 10  
Pfizer Inc. 8  
Prothena Corp. plc 14  
PsychoGenics Inc. 2  
Purdue Research Foundation 13

**R**

Rutgers University 10

**S**

Salk Institute for Biological Studies 4

**T**

Takeda Pharmaceutical Co. Ltd. 8

**U**

UCB Group 8  
University Medical Center Utrecht 10  
University of Oxford 8,10  
University of Tokyo 8

**V**

Vital Therapies Inc. 10

.....

**Target and Compound index**

3-O-methyl-D-glucose 9

**A**

$\alpha$ -synuclein 14,16  
A $\beta$  14

ABHD6 15

Abhydrolase domain containing 6 15

ADRB3 12

Adrenergic receptor  $\beta_3$  12

AEB071 11

Atg5 7

ATG5 autophagy related 5

homolog 7

Atg7 7

ATP 9

**B**

$\beta$ -amyloid 14

Bcl2 homology domain 3 16

BH3 16

**C**

C-type lectin domain family 7 member A 13

CCL27 17

CD19 13

Chemokine CC motif

ligand 27 17

Cisplatin 11

CLEC7A 13

COX-2 12

Cyclooxygenase-2 12

**D**

DECTIN1 13

DPC4 18

**E**

Endoplasmic reticulum to nucleus signaling 1 15

ERN1 15

<b>F</b>		<i>Inducible nitric oxide synthase 2</i>	17	Notch 1	13	<b>S</b>	
Ffar1	12	<i>iNOS</i>	17	NOTCH1	13	Serine hydrolase	16
FGF1	12	Insulin-like growth factor-1	4	<b>O</b>		SH3 and multiple ankyrin repeat domains 3	3
Fibroblast growth factor 1	12	IRE1	15	O3FAR1	12	Shank3	3
Free fatty acid receptor 1	12	<b>L</b>		<b>P</b>		<i>SMAD family member 4</i>	18
<b>G</b>		L-dopa	1	<i>p53</i>	18	<i>SMAD4</i>	18
$\gamma$ -aminobutyric acid	14	Lactadherin	11	Parathyroid hormone-like hormone	12	SNCA	14,16
$\gamma$ -secretase	13	Laminarin	13	Platin-M	11	Sotrastaurin	11
G protein-coupled receptor 120	12	LecA	13	Polyethylene glycol	9	SPANK-2	3
GABA	14	<b>M</b>		<i>PR domain containing 16</i>	12	Spleen tyrosine kinase	14
GPR120	12	<i>MADH4</i>	18	<i>Prdm16</i>	12	Sulindac	12
Gpr40	12	MCL1	16	PRKCB	11	SYK	14
<b>H</b>		MECP2	4	PROSAP2	3	<b>T</b>	
HBB	17	Methyl CpG binding protein 2	4	Protein kinase C $\beta$	11	TFEB	14
Hemoglobin- $\beta$	17	MFGE8	11	PTHLH	12	Transcription factor EB	14
HMFG	11	Myeloid leukemia cell differentiation protein	16	PTHRP	12		
Hydroxychloroquine	7	<b>N</b>		<b>R</b>			
<b>I</b>		<i>NOS2</i>	17	Resokine	16		
IGF-1	4			RTT	4		

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