

## THIS WEEK

## ANALYSIS

## COVER STORY

**1 A mind for precompetitive collaboration**

Although pharmas are cutting back on internal neuroscience R&D programs, the number of precompetitive consortia backed by industry continues to rise. Most initiatives are focused on developing better disease models and discovering new biomarkers. The challenge going forward will be to push the boundaries of the precompetitive space to advance the discovery of new disease-modifying targets and mechanisms.

## TARGETS &amp; MECHANISMS

**6 Mitochondrial gene therapy**

A University of Miami team has used mitochondrion-targeted gene therapy to restore functional ND4 levels in Leber's hereditary optical neuropathy. Next steps include optimizing the approach to cover several variants of the disease and determining the therapy's potential advantages over pharmacological strategies in development.

**8 PPAR's new course**

California researchers have shown that agonizing PPAR $\delta$  could help stave off fibrosis in a variety of chronic liver diseases. The findings could open new therapeutic real estate for the handful of biotechs working on PPAR $\delta$  modulators.

## TOOLS

**10 Dendrimers get cerebral**

U.S. researchers have developed a dendrimer-based therapy that reduced brain inflammation and improved the motor function of newborn rabbits with cerebral palsy. The team now needs to determine the therapy's treatment window and its efficacy in the multiple types of cerebral palsy.

## THE DISTILLERY

**12 This week in therapeutics**

Targeting miR-301a in MS; treating type 1 diabetes with IL-10- and proinsulin-secreting *Lactococcus lactis*; repairing bone with PPAR $\gamma$  inhibitor-treated human mesenchymal stem cells; and more...

**16 This week in techniques**

A *Shank2*-deficient mouse model of autism spectrum disorder; acyclic cucurbit[*n*]urils as molecular containers to improve drug solubility; epigenomic enhancer variants as biomarkers for colorectal cancer; and more...

## INDEXES

**19 Company and institution index****19 Target and compound index**

## A mind for precompetitive collaboration

By *Chris Cain, Senior Writer*

Although some pharmas are cutting back on internal neuroscience R&D programs, the number of precompetitive consortia backed by industry has continued to rise, with the latest two launching within the last two months. Most initiatives are focused on developing better disease models and discovering new biomarkers—the challenge going forward will be to push the boundaries of the precompetitive space to advance the discovery of new disease-modifying targets and mechanisms.

At least three pharmaceutical companies have publicly disclosed major cuts or reorganizations of their neuroscience R&D programs in the last two years. In February 2010, **GlaxoSmithKline plc** announced plans to eliminate discovery research in pain and depression. In March 2010, **AstraZeneca plc** ceased research in schizophrenia, bipolar disorder, depression and anxiety.<sup>1</sup>

Last December, **Novartis AG** said it would close its Basel CNS R&D facility, disband its Neuroscience Disease Area and shift to new directions based on the genetics of neurological diseases. This February, AstraZeneca said it is shrinking its 2,000 member neuroscience R&D group to 40–50 people focused exclusively on outside opportunities.<sup>2</sup>

In contrast to reductions within individual companies, there are at least eight new or ongoing precompetitive neuroscience collaborations with substantial industry participation (*see Table 1, "Selected ongoing precompetitive neuroscience industry collaborations"*).

According to Paul Chapman, general manager of **Takeda Pharmaceutical Co. Ltd.**'s Pharmaceutical Research Division, "Competitive advantage in industry comes mostly from making better judgments based on all available biological data and using it to create better molecules. Everything else can and should be shared."

Last month, Takeda joined two precompetitive initiatives—the **Structural Genomics Consortium** and the newly formed **CommonMind Consortium**.

Precompetitive initiatives have aims that vary widely—from developing better mouse models of disease to obtaining regulators' approval of enrollment criteria for clinical trials. Pharmaceutical partners and consortium leaders told *SciBX* that, ultimately, these programs all share the common goal of reducing the high failure rate and cost of drug development in neuroscience.

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PO Box 1246  
San Carlos, CA 94070-1246  
T: +1 650 595 5333Chadds Ford  
223 Wilmington-West Chester Pike  
Chadds Ford, PA 19317  
T: +1 610 558 1873Chicago  
20 N. Wacker Drive, Suite 1465  
Chicago, IL 60606-2902  
T: +1 312 755 0798Oxford  
287 Banbury Road  
Oxford OX4 7JA  
United Kingdom  
T: +44 (0)18 6551 2184Washington, DC  
2008 Q Street, NW, Suite 100  
Washington, DC 20009  
T: +1 202 462 9582**Nature Publishing Group**New York  
75 Varick Street, 9th Floor  
New York, NY 10013-1917  
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The Macmillan Building  
4 Crinan Street  
London N1 9XW  
United Kingdom  
T: +44 (0)20 7833 4000Tokyo  
Chiyoda Building 6F  
2-37 Ichigayatamachi  
Shinjuku-ku, Tokyo 162-0843  
Japan  
T: +81 3 3267 8751

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They also said the biggest obstacles to expanding the scope of precompetitive research include concerns over IP and demonstrating that collaborations can provide a worthwhile return on investment.

“It is a zero-sum game. Everyone is short on resources, and you have to feel confident that precompetitive investments are worth it,” said Hussein Manji, global therapeutic area head of neuroscience at Janssen R&D.

Janssen is a unit of **Johnson & Johnson**.

Last December, Janssen committed \$3 million to **One Mind for Research**, a program sponsored by the **International Mental Health Research Organization** that fosters precompetitive neuroscience research, education and awareness-building programs.

**Diagnosing the problem**

Companies involved in precompetitive neuroscience initiatives told SciBX the space is an area particularly in need of precompetitive collaboration.

Peter Andersen, SVP of external scientific relations and patents at **H. Lundbeck A/S**, said some companies have shied away from neuroscience R&D in part because fundamental aspects of the biology of neurological diseases are not understood.

“The underlying problem in brain research is that the biology is not sufficiently mature. CNS diseases are defined based on symptoms relative to normal behavior, whereas you normally would develop drugs based on a specific molecular target you want to interact with. This leads to a large risk of failure when you ultimately test compounds in patients,” he said.

Chapman agreed. “Neuroscience is particularly fruitful because the system is so complicated; the diseases are so poorly understood. In spite of some great science and some genuine progress in the field, compared

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to diabetes, cardiovascular disease, even oncology, neuroscience is, frankly, way behind.”

Manji emphasized it is not only the lack of understanding but also the need for new drugs that is driving precompetitive collaboration in the area. “Disorders like Alzheimer’s disease are going to bankrupt the healthcare system, and many companies are pulling away because it’s just too complex,” he said.

“Neuroscience is still an area with a very large unmet need, and there is a lot of opportunity for industry,” said Elisabetta Vaudano, principal scientific manager at the EU’s **Innovative Medicines Initiative** (IMI). “However, there has been a lot of failure—the success rate in neuroscience is among the lowest of therapeutic areas. There are bottlenecks which industry has not been able to tackle, and thus it is an area very ripe for public-private partnerships like the IMI.”

Indeed, IMI has been a leader in organizing precompetitive collaborations in the neuroscience space. Since 2009, IMI has put together 4 consortia focused on the topic, each with more than 20 members. Combined, the consortia have committed funding of €90 million (\$117 million).

### Observing the patient

Whereas newer initiatives led by IMI are beginning to broaden the definition of precompetitive collaboration to include preclinical discovery and tool building, the most tangible results over the last decade came from pooled efforts by companies to share data obtained from observational clinical trials, particularly in neurodegenerative diseases.

In 2004, after about three years of discussion with the pharmaceutical industry, the Alzheimer’s Disease Neuroimaging Initiative (ADNI) was established to monitor disease progression in 800 normal older individuals, people with mild cognitive impairment and patients with mild Alzheimer’s disease (AD) over 5 years. It has since expanded to enroll more than 1,000 patients.

ADNI has \$130 million committed thus far through a combination of support from the **National Institute on Aging** (NIA) and 28 current partners coordinated by the **Foundation for the National Institute of Health** (FNIH), including 25 from industry.

Neil Buckholtz, chief of the dementias of aging branch of the Division of Neuroscience at the NIA, told *SciBX*, “Even more critical than the funding has been the interaction of industry scientists with academic scientists, through the private partner scientific board as well as through participation in individual cores. ADNI is managed through a series of cores—biomarker discovery, MRI, PET, etc. People from industry sit in on the discussion from the cores, and they don’t manage the study, but the interaction is critical for success.”

Data from ADNI are made publicly available through a database accessible to researchers who register, and Buckholtz said that from the beginning it was clear this would be an IP-free initiative. “Some of the companies we spoke to in 2002–2003 were thinking of mounting this kind of study, but none could do it on their own, to this scale,” he said.

Among the first direct outcomes from the ADNI is the optimization of the use of cerebrospinal fluid  $\beta$ -amyloid ( $A\beta$ ) levels as a selection criterion for enrolling patients at risk for developing AD.

**The Biomarkers Consortium**, another precompetitive collaboration sponsored by the FNIH, also is using samples obtained from ADNI

to perform proteomics studies to identify biomarkers linked to AD progression.

Following the ADNI model, in 2010 **The Michael J. Fox Foundation for Parkinson’s Research** launched its Parkinson’s Progression Markers Initiative, a multicenter observational trial of 400 newly diagnosed patients with Parkinson’s disease (PD) and 200 healthy controls. The initiative is funded by the foundation and at least 10 industry partners.

Separate from these initiatives, the **Critical Path Institute’s** Coalition Against Major Diseases (CAMD) is analyzing clinical trial observations with an eye toward regulatory validation of biomarkers and disease models.

Diane Stephenson, associate director of the CAMD, told *SciBX* that CAMD aligns with other public-private partnerships such as ADNI and other discovery initiatives yet is distinct because its aim is to work closely with the **FDA** and the **EMA** to achieve qualification of new regulatory tools that can be used to speed drug development.

CAMD was launched in 2008 and currently has partnerships with about 20 not-for-profit and industry partners to accelerate the development of therapies for AD and PD.

One of CAMD’s signature achievements thus far is the creation of a unified clinical trial database. The database contains results from 6,000 AD patients, comprising placebo arms from 22 clinical trials contributed by 9 companies.

“The database is available to qualified researchers around the world and was originally set up to build a quantitative disease drug trial model for AD, a project aimed at informing clinical trial designs and optimizing the chances of success in the future clinical trials by learning from the past,” said Stephenson.

The Biomarkers Consortium has a similar ongoing project to examine industry clinical trial placebo data focused on pre-AD patients with mild cognitive impairment.

Stephenson said CAMD is now trying to get companies to share data about clinical biomarkers.

“I would say in all honesty the biggest challenge is that some companies define the precompetitive landscape differently than others,” she said. “Many companies will fund studies on biomarker performance, but because these studies may pose risks in a competitive landscape, they may be reluctant to share the data. We are hopeful that, in the future, companies will provide more than just placebo data, but it’s a fine line we are continuing to expand.”

She added: “Attitudes are changing quickly. Working together across diverse stakeholders to advance our understanding of AD is significantly easier than it has been in the past.”

### Group therapy

The next step in precompetitive neuroscience research will be to share in the creation of tools and knowledge that will enable the discovery of new therapies.

Janssen’s Manji and Lundbeck’s Andersen said industry’s involvement in precompetitive collaboration is now expanding to include the development of biomarkers, disease models and even discovery research.

However, they said that IP is one of the biggest concerns as collaborations move into the grey area between the competitive and precompetitive space.

“There is room for both IP and IP-free precompetitive collaboration; both are important,” said Manji.

An example of a completely IP-free effort is the CommonMind Consortium, announced last month by Takeda and Sage Bionetworks. The partners and collaborating academic institutions plan to obtain genomic information from neuropsychiatric patients and share it in an open-access database.

“The academic partners who founded this consortium saw the need to generate and analyze large-scale genomic data from human subjects with neuropsychiatric disease, which is exactly the type of effort that is best served by precompetitive collaboration especially as the data must, and will, be made broadly available to the public,” said Takeda’s Chapman.

Andersen cautioned that when IP is brought into the picture, it must be clearly negotiated up front. He told *SciBX* that Lundbeck had previously encountered problems with IP when participating in a collaboration with a biotech and two academic teams that was organized by **Top Institute Pharma**, a not-for-profit that manages academic-industry partnerships.

“We very quickly realized the drawback to this setup, which ultimately necessitated we buy out the other company involved in the collaboration after a year and a half because the rules around how to share IP were too complicated,” he said.

In addition to his role at Lundbeck, Andersen is chair of the research directors group of the **European Federation of Pharmaceutical Industries and Associations**, which coordinates the solicitation of IMI research proposals. He favors the IMI approach to IP. “Everything you bring into the collaboration you own; everything you invent together you share; everything you do afterwards is your own,” he said.

He said any problems with IP were eliminated after IMI made a dedicated IP lawyer available for consultation to adapt these rules to the needs of individual participants.

IMI is putting this flexible approach to the test with its four consortia focused on neuroscience, in which a broad range of potential projects are captured within each initiative.

For example, **NEWMEDS**, led by Lundbeck, has nine separately organized “work packages” that each have a distinct focus. While one work package is pooling clinical trial data to identify genetic factors underlying schizophrenia, another is developing animal models of cognitive dysfunction that relate to clinical endpoints.

**PharmaCog**, led by GSK, is seeking to develop better preclinical and clinical models of cognitive function. Jill Richardson, who leads the effort and is director of external alliance and development at GSK,

**“Competitive advantage in industry comes mostly from making better judgments based on all available biological data and using it to create better molecules. Everything else can and should be shared.”**

**—Paul Chapman,  
Takeda Pharmaceutical Co. Ltd.**

**Table 1. Selected ongoing precompetitive neuroscience industry collaborations.**

Initiative	Research goals	Industry partners	Nonindustry partners	Funding or organizing body	Committed funding <sup>A</sup>	Launched
CommonMind Consortium	Generate and analyze large-scale genomic data from patients with neuropsychiatric diseases	2	3	Sage Bionetworks	Undisclosed	2012
EU-AIMS: European Autism Interventions—A Multicenter Study for Developing New Medications	Develop autism research tools and diagnostics, and help select clinical endpoints for future trials	9	16	Innovative Medicines Initiative (IMI)	€35.9 million (\$48.1 million)	2012
Parkinson’s Progression Markers Initiative	A multisite observational clinical trial to determine the characteristics of Parkinson’s disease (PD) progression	11	Not applicable	The Michael J. Fox Foundation for Parkinson’s Research	\$45 million	2010
PharmaCog: Prediction of Cognitive Properties of New Drug Candidates for Neurodegenerative Diseases in Early Clinical Development	Develop and validate new tools to test Alzheimer’s disease (AD) drugs	16	13	IMI	€27.7 million (\$37.1 million)	2010
NEWMEDS: Novel Methods leading to New Medications in Depression and Schizophrenia	Develop new animal models and clinical trial tools for schizophrenia and depression	13	7	IMI	€24 million (\$34.6 million)	2009
EUROPAIN: Understanding Chronic Pain and Improving its Treatment	Identify mechanisms that contribute to pain, using new experimental models, human volunteers and clinical data of pain patients	8	12	IMI	€18.2 million (\$26.2 million)	2009
Coalition Against Major Diseases	Advance innovative tools and technologies through a regulatory path that accelerate the development of medical products for neurodegenerative diseases	16	Undisclosed	Critical Path Institute	Undisclosed	2008
Alzheimer’s Disease Neuroimaging Initiative	A multisite observational clinical trial to determine the characteristics of AD progression	25	3	Foundation for the National Institutes of Health and the National Institute on Aging	\$130 million	2004

<sup>A</sup>Innovative Medicines Initiative projects include value of in-kind contributions.

told *SciBX*, “GSK is involved in several precompetitive neuroscience initiatives, but, to date, the one we have invested in most is the IMI PharmaCog project.”

She added: “Joining up with external companies and organizations is as much about developing robust, harmonized methods, models and tools, networking, and sharing ideas as it is about intellectual property or access to drugs. So we don’t view IP as a barrier to participation.”

The other two IMI projects are EUROPAIN, which is focused on understanding new mechanisms involved in chronic pain, and EU-AIMS, announced in March, which is building new models for autism spectrum disorder (ASD).<sup>3</sup>

In addition to these government-backed efforts, disease foundations are beginning to consider ways to encourage precompetitive collaborations. For example, the **Myelin Repair Foundation** has been funding academic collaborations over the last 7–8 years and is now soliciting interest from industry to form a precompetitive consortium modeled on that effort.

Jay Tung, VP of drug discovery at the Myelin Repair Foundation, told *SciBX* the foundation has had discussions with at least four industry organizations about setting up a precompetitive consortium to identify biomarkers and imaging tools for myelin repair. They hope to launch an initiative within a year.

“We are an organization that represents patients and can serve as a neutral convener, and our interest is in identifying the tools necessary to run a clinical trial for myelin repair,” said Tung. “We are in the process of surveying pharma and biotech to ask what they would want addressed in this type of consortium, and at this point we have gone back to them two or three times and are continuing to hold discussions. We don’t want partners who just want to attend and listen; we want actively participating partners.”

Manji told *SciBX* he would eventually like to see precompetitive collaborations extend to target validation. “Many companies are investigating the same targets, and if we’re doing it anyway, we should

do it together. We’d have to share the spoils, but we could do more things together, and a quarter of the pie is better than no pie at all.”

But he added, “We are trying to be pragmatic, and that type of collaboration is going to be much more complicated.”

Cain, C. *SciBX* 5(19); doi:10.1038/scibx.2012.483

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## COMPANIES AND INSTITUTIONS MENTIONED

**AstraZeneca plc** (LSE:AZN; NYSE:AZN), London, U.K.

**The Biomarkers Consortium**, Bethesda, Md.

**CommonMind Consortium**, Seattle, Wash.

**Critical Path Institute**, Tucson, Ariz.

**European Federation of Pharmaceutical Industries and Associations**, Brussels, Belgium

**European Medicines Agency**, London, U.K.

**Food and Drug Administration**, Silver Spring, Md.

**Foundation for the National Institutes of Health**, Bethesda, Md.

**GlaxoSmithKline plc** (LSE:GSK; NYSE:GSK), London, U.K.

**H. Lundbeck A/S** (CSE:LUN), Copenhagen, Denmark

**Innovative Medicines Initiative**, Brussels, Belgium

**International Mental Health Research Organization**, Rutherford, Calif.

**Johnson & Johnson** (NYSE:JNJ), New Brunswick, N.J.

**The Michael J. Fox Foundation for Parkinson’s Research**, New York, N.Y.

**Myelin Repair Foundation**, Saratoga, Calif.

**National Institute on Aging**, Bethesda, Md.

**Novartis AG** (NYSE:NVS; SIX:NOVN), Basel, Switzerland

**One Mind for Research**, Rutherford, Calif.

**Sage Bionetworks**, Seattle, Wash.

**Structural Genomics Consortium**, Oxford, U.K.

**Takeda Pharmaceutical Co. Ltd.** (Tokyo:4502), Osaka, Japan

**Top Institute Pharma**, Leiden, the Netherlands

# Mitochondrial gene therapy

By Lev Osherovich, Senior Writer

A **University of Miami** team has used mitochondrion-targeted gene therapy to restore functional NADH dehydrogenase subunit 4 levels in Leber's hereditary optical neuropathy.<sup>1</sup> Next steps include optimizing the approach to cover several variants of the disease and determining the therapy's potential advantages over pharmacological strategies in development.

Leber's hereditary optical neuropathy (LHON) affects about 1 in 30,000–50,000 people and manifests as sudden vision loss in early adulthood. Unlike in most hereditary diseases, the defective genes behind LHON are encoded by DNA in the mitochondria, not in the nucleus. The mitochondria, cellular subcompartments that generate energy for the cell, retain a small circular genome encoding a set of key proteins that cannot be correctly manufactured elsewhere in the cell.

The most common mutations underlying LHON are in a gene encoding NADH dehydrogenase subunit 4 (ND4). As a result of ND4 defects, mitochondria in retinal ganglion cells are unable to make energy and instead undergo apoptosis. Because retinal ganglion cells relay information from the retina's photoreceptors to the brain, their degeneration leads to rapid-onset blindness.

Now, a team led by John Guy, professor of ophthalmology at the Bascom Palmer Eye Institute at the **University of Miami Miller School of Medicine**, has devised an adeno-associated virus (AAV) vector that delivers a wild-type ND4 gene directly into the mitochondria.

Using this vector, Guy's team restored mitochondrial function and prevented disease progression in cell culture and mouse models of LHON.

"The advance was getting DNA into mitochondria and doing it efficiently. Nobody has been able to do that in the animals" until now, said Guy.

## Mitochondrial insertion

Guy told *SciBX* that getting transgenic DNA or proteins into mitochondria has been a major challenge for gene therapy for LHON. He said a number of research teams, including his own, have tried various strategies over the years, including formulations of DNA and protein designed to enter the cytoplasm and then penetrate the mitochondrion's double membrane layer.

"People have tried to use peptide nucleic acids or chaperone proteins to get DNA into mitochondria, but there were toxicity and efficacy problems with those techniques," said Guy.

While testing various AAV vectors, Guy's team devised a new delivery strategy. The group modified the exterior of the AAV capsid to incorporate a short peptide sequence that acts as a mitochondrial localization signal.

In a cell culture model of LHON, a fluorescently tagged version of the engineered AAV with a human ND4 gene localized to the mitochondria and increased ATP synthesis compared with no treatment. Guy said with the new construct, his team "saw a 25% increase in mitochondrial

efficiency compared to an older technology" involving nuclear delivery of the transgene.

Guy's team then injected the AAV vector into the vitreous body of the eyes of mice with a mutant allele of *Nd4* that causes degeneration and vision loss. The AAV vector led to slower degeneration of retinal ganglion cells than an AAV vector without the mitochondrial localization sequence.

Results were reported in the *Proceedings of the National Academy of Sciences*.

"They are targeting the entire virus into the mitochondria by putting the mitochondrial targeting sequence into the capsid of the virus, which by itself is quite astonishing," said William Beltran, assistant professor of ophthalmology at the **University of Pennsylvania**.

Beltran was part of a team that recently reported a gene therapy strategy for a form of retinitis pigmentosa, another hereditary vision loss disorder that affects a different part of the retina than LHON.<sup>2</sup>

He noted that the mutations behind hereditary vision disorders affect a variety of genes and manifest in different parts of the retina, so the specific details of an AAV-mediated gene delivery strategy will differ with each indication.

Guy's success with mitochondrial targeting "illustrates how the field of AAV vector-mediated gene therapy is going—the key point is tropism, tropism, tropism," said Beltran. "People are now making all kinds of modifications to allow cell- and even organelle-specific targeting."

## Universal vector

Although delivering a transgene to the mitochondria is a major step toward correcting the genetic lesions behind LHON, translation of the approach to the clinic is likely to require years of preclinical optimization.

One challenge is the heterogeneity of genetic etiologies behind LHON. Alfredo Sadun, professor of ophthalmology and neurological surgery at the **University of Southern California**, noted that Guy's strategy addresses only one of the three genetic lesions that cause LHON.

"In LHON, there are three possible mutated genes, all in different parts of the mitochondrial genome," said Sadun. "For a successful gene therapy, you'd have to fix the specific component" that is defective in each patient.

To that end, Guy said his next step is to make an optimized AAV vector construct that would be useful in any patient with LHON.

"I can fit all three LHON genes into one virus," said Guy. "Rather than making separate constructs [for each form of LHON], you would want to make a virus with a promoter that drives the expression of all three genes."

But Douglas Wallace, director of the Center for Mitochondrial and Epigenomic Medicine at **The Children's Hospital of Philadelphia**, thinks it will be challenging to make a universal vector that corrects mutations in all three LHON genes. He said mitochondrial protein levels are finely balanced, and overexpression of all three genes may throw off this balance.

Combining the multiple genes into one virus "is a good idea, but one of the concerns is that the mitochondrial energy complex is made of 54 polypeptides" that must be kept in proportion, said Wallace.

Wallace discovered the genetic basis for LHON in the 1980s and has since studied the global distribution of the disease and identified biomarkers for at-risk populations.<sup>3</sup>

Another concern is whether the mouse model used by Guy's team truly recapitulates the mitochondrial defects in LHON. The group used transgenic mice expressing a dominant-negative form of *ND4* rather

**“In LHON, there are three possible mutated genes, all in different parts of the mitochondrial genome. For a successful gene therapy, you'd have to fix the specific component.”**

—Alfredo Sadun,  
University of Southern California

than the loss-of-function mutations that lead to disease in humans.

“We need a preclinical model that accurately models this disease,” said Wallace, who noted that his own lab has been working on making such a model.

For now, Wallace and Beltran agreed that

further characterization of the effect of transgenic *ND4* expression and activity in mice is needed.

### Drugs vs. genes

Another open question is whether gene therapy will be more effective than the two pharmacological strategies for LHON that are in clinical testing.

Thomas Meier, CEO of **Santhera Pharmaceuticals Holding AG**, said that Guy's study establishes a proof of principle for the genetic correction of a specific LHON mutation but that the translational path for the approach will require overcoming many manufacturing, safety and efficacy hurdles.

“There is still a very long way before this can be considered an emerging therapy for humans,” said Meier.

Santhera's Catena idebenone (SNT-MC17), a co-enzyme Q10

derivative, is in registration for LHON in Europe and is marketed for Friedrich's ataxia in Canada.

Meier noted that Catena, which is thought to restore mitochondrial energy flow and reduce apoptosis in retinal ganglion cells, works irrespective of the specific mutations that underpin LHON in any particular patient.

Meanwhile, Sadun is enrolling patients in a Phase I/II LHON trial of EPI-743, a co-enzyme Q10 derivative from **Edison Pharmaceuticals Inc.** Sadun said EPI-743 is “about 500-fold more potent” than Catena.

Guy said he is trying to adapt his AAV vector for use in other mitochondrial diseases outside of the eye, including Leigh's disease, a rare neurological disorder.

The technology described in the *PNAS* paper is patented and available for licensing.

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### COMPANIES AND INSTITUTIONS MENTIONED

**The Children's Hospital of Philadelphia**, Philadelphia, Pa.  
**Edison Pharmaceuticals Inc.**, San Jose, Calif.  
**Santhera Pharmaceuticals Holding AG** (SIX:SANN), Liestal, Switzerland  
**University of Miami**, Miami, Fla.  
**University of Miami Miller School of Medicine**, Miami, Fla.  
**University of Pennsylvania**, Philadelphia, Pa.  
**University of Southern California**, Pasadena, Calif.

# PPAR's new course

By Steve Edelson, Executive Editor

California researchers have shown that agonizing PPAR $\delta$  could help stave off fibrosis in a variety of chronic liver diseases.<sup>1</sup> The findings could open new therapeutic areas for biotechs working on PPAR $\delta$  modulators, who thus far have focused on cardiovascular disease, liver disease associated with diabetes and diabetes itself.

Peroxisome proliferation-activated receptor- $\delta$  (PPAR $\delta$ ; PPAR $\delta$ ) agonists have many beneficial properties, such as mimicking the effects of exercise, improving homeostasis of glucose and lipids, and reducing inflammation.<sup>2,3</sup> At least seven PPAR $\delta$  agonists are in clinical and preclinical development for diabetes, atherosclerosis, dyslipidemia and nonalcoholic steatohepatitis (NASH).

The anti-inflammatory effects of PPAR $\delta$  agonists were of particular interest to researchers at the **Salk Institute for Biological Studies** and the **University of California, San Diego** who had been looking for ways to treat the fibrosis that accompanies chronic liver injury. The team, led by **University of California, San Diego School of Medicine** assistant professor of gastroenterology Bernd Schnabl, suspected PPAR $\delta$  agonists could be a good fit because of their known therapeutic effects in diabetes and associated liver damage.

Indeed, there were earlier hints that PPAR $\delta$  agonists could be a viable choice for treating chronic liver injury. For example, researchers at **Pennsylvania State University** showed in 2008 that the PPAR $\delta$  ligand GW0742 could reduce liver toxicity in mice.<sup>4</sup>

However, no mechanism of action had been described before the current study.

Thus, the California researchers set out to shed some light on how PPAR $\delta$  agonists might be acting in liver disease. The team opted to use two PPAR $\delta$  agonists—KD3010 and GW501516—as well as an undisclosed PPAR $\gamma$  (PPAR $\gamma$ ) agonist.

KD3010 is being developed by **Kalypsys Inc.** to treat diabetes and NASH. A few years ago, **GlaxoSmithKline plc** discontinued development of GW501516, a first-generation PPAR $\delta$  agonist, after finding that the molecule induced tumors in rodents. The compound, which had completed a Phase II trial in dyslipidemia, is available as a research reagent.

In mice with liver injury induced by carbon tetrachloride, KD3010 showed better antifibrotic effects than GW501516. The team saw similar results in a mouse model of cholestasis-induced liver injury.

Data were published in the *Proceedings of the National Academy of Sciences*.

Schnabl told *SciBX* that KD3010 also showed better results than the PPAR $\gamma$  agonist and that those data will be reported in a forthcoming publication.

“KD3010 did the best out of all three groups. GW501516 actually didn't do anything, which was a bit surprising” because the two molecules hit the same target, said Schnabl.

The paper's authors attributed the divergent results for KD3010

and GW501516 to multiple factors, “including different specificities for other PPAR isoforms, potencies of different synthetic compounds, and *in vivo* pharmacological properties of the compounds including differential tissue distribution, degradation, and clearance.”

*In vitro* studies shed further light on the differential pathways through which the two molecules exerted their effects. *In vitro*, KD3010 protected hepatocytes by stimulating Cyp enzymes, which are involved in oxidation and detoxification. In contrast, GW501516 had no such effects and instead was shown to induce a profibrogenetic cytokine called connective tissue growth factor (CTGF).

“The nice thing is we showed hepatoprotection *in vitro*,” said Schnabl. “It's clearly a PPAR $\delta$ -dependent process.”

## Delivering the liver

Schnabl told *SciBX* he wants to run a Phase II trial of KD3010 in HCV nonresponders—those who do not respond to standard care.

“The trial would enroll HCV patients who have ongoing liver injury and fibrosis. We'd get an invasive biopsy before starting treatment and upon completion of treatment and do gene expression analysis to assess the biopsies” for improvements in fibrosis, he said.

Schnabl acknowledged that patient recruitment could be difficult. He said IRBs usually approve studies that have liver biopsies, “but patients don't like to have needles stuck in

their liver—twice.”

Launching the study also could be problematic, as it is unclear whether Kalypsys is still operational. The company did not respond to interview requests, and its one-page website lists KD3010 as an asset available for partnering.

“The paper wasn't a huge surprise for us and really goes in the same direction of providing support for PPAR $\delta$  agonism in NASH,” said Rémy Hanf, VP of product development at **Genfit S.A.**

Genfit's GFT505 is a dual agonist of PPAR $\alpha$  (PPAR $\alpha$ ) and PPAR $\delta$ . The company is planning a Phase IIb trial of the compound to treat nonalcoholic fatty liver disease (NAFLD) and/or NASH. The study will measure histological regression of NASH and histological and biochemical markers.

Based on the paper, “we're considering new indications for GFT505 as we go forward. We'll consider things like primary biliary fibrosis, drug-induced fibrosis and alcohol-induced fibrosis,” said CSO Dean Hum. “NASH remains the priority.”

**Cerenis Therapeutics S.A.** is taking a slightly different tack with its PPAR $\delta$  agonist, CER-002. President and CEO Jean-Louis Dasseux said Cerenis “thought about developing CER-002 for NASH. But even though PPAR $\delta$  agonists can elevate HDL [high-density lipoprotein] and lower triglycerides, the clinical and regulatory paths are not easy. The development challenge is that it takes a while before patients develop NASH symptoms. And when it is established, it's a question of whether it's too late.”

For CER-002, Dasseux said the company has “interesting results in another disease that has nothing to do with lipid metabolism. We aren't disclosing it, but the disease is in a high-risk population with no good available treatments.”

“The nice thing is we showed hepatoprotection *in vitro*. It's clearly a PPAR $\delta$ -dependent process.”

—Bernd Schnabl,  
University of California,  
San Diego

The patent and licensing information for the findings described in *PNAS* is undisclosed.

Edelson, S. *SciBX* 5(19); doi:10.1038/scibx.2012.485  
Published online May 10, 2012

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**Contact:** Bernd Schnabl, University of California, San Diego School of Medicine, La Jolla, Calif.  
e-mail: [beschnabl@ucsd.edu](mailto:beschnabl@ucsd.edu)  
**Contact:** Ronald M. Evans, Salk Institute for Biological Studies, La Jolla, Calif.  
e-mail: [evans@salk.edu](mailto:evans@salk.edu)

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**Cerenis Therapeutics S.A.**, Labege, France  
**Genfit S.A.** (Euronext:ALGFT), Lille, France  
**GlaxoSmithKline plc** (LSE:GSK; NYSE:GSK), London, U.K.  
**Kalypsys Inc.**, San Diego, Calif.  
**Pennsylvania State University**, University Park, Pa.  
**Salk Institute for Biological Studies**, La Jolla, Calif.  
**University of California, San Diego**, La Jolla, Calif.  
**University of California, San Diego School of Medicine**, La Jolla, Calif.

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# Dendrimers get cerebral

By Tim Fulmer, Senior Writer

U.S. researchers have developed a dendrimer-based therapy that reduced brain inflammation and improved the motor function of newborn rabbits with cerebral palsy.<sup>1</sup> The team now needs to determine the therapy's treatment window and its efficacy in the multiple types of cerebral palsy.

Cerebral palsy encompasses a group of disorders characterized by motor impairments that result from damage to the fetal or infant brain. The most common causes of the disease are intrauterine infection, prenatal hypoxia, trauma during delivery and premature birth.

Compared with the other causes, intrauterine infection is often associated with an exaggerated inflammatory response in which activation of microglia and astrocytes in the neonatal brain leads to very high levels of proinflammatory cytokines that cause brain injury before and after birth.<sup>2,3</sup>

The challenge is figuring out how to design an anti-inflammatory therapy that crosses the blood brain barrier (BBB) in sufficient quantities and localizes in activated microglia and astrocytes.

To tackle the task, the team turned to dendrimers, which are highly branched polymers that can be linked to small molecules and used as drug delivery vehicles. In prior work, the team showed that direct injection of dendrimers into the neonatal rabbit brain led to accumulation in activated microglia and astrocytes.<sup>4</sup>

The researchers wanted a systemic therapy, and thus they decided to link the dendrimer to a therapeutic and shuttle it across the BBB to treat disease following an i.v. injection.

The linker was a disulfide molecule, which is rapidly cleaved by glutathione in microglia and astrocytes. For the therapeutic, the researchers chose N-acetylcysteine (NAC), a generic anti-inflammatory marketed to treat acetaminophen-induced liver injury.

Intraperitoneal delivery of NAC has shown anti-inflammatory and neuroprotective effects in rodent models of perinatal brain injury, suggesting the compound can cross the BBB by itself.<sup>5,6</sup>

The open question was whether attaching NAC to a dendrimer would result in significantly higher efficacy compared with unconjugated NAC in the brain of a mammal with cerebral palsy.

Indeed, in a rabbit model of prenatal endotoxin-induced cerebral palsy,<sup>7,8</sup> i.v. delivery of the dendrimer-NAC (D-NAC) conjugate within six hours of birth significantly increased motor function ( $p < 0.001$ ) and hind limb muscle tone ( $p < 0.001$ ) compared with injection of NAC or vehicle control.

In the brains of those rabbits, D-NAC significantly decreased the levels of molecular markers of oxidative injury ( $p < 0.01$ ), the activity of proinflammatory microglia ( $p < 0.01$ ) and neuronal cell loss ( $p < 0.01$ ) and increased myelination levels ( $p < 0.05$ ) compared with NAC or vehicle control.

In five-day-old brain sections stained for the proinflammatory marker complement receptor 3 (Cr3; Cd11b), D-NAC significantly lowered total microglia activation compared with NAC or vehicle ( $p < 0.01$ ).

The study was led by Rangaramanujam Kannan, professor of ophthalmology at **The Johns Hopkins University School of Medicine**, and Roberto Romero, chief of the Perinatology Research Branch and program director for Perinatal Research and Obstetrics at the **National Institute of Child Health & Human Development**.

Results were published in *Science Translational Medicine*.

"The effectiveness of the D-NAC treatment, administered in the postnatal period for a prenatal insult, suggests a new window of opportunity for the treatment of CP [cerebral palsy] after birth in humans," the authors wrote.

## Looking long term

"Longer-term studies with significantly greater numbers of animals will be needed to work out the safety of D-NAC in the developing brain and over the lifetime of the animal," said Dorothea Jenkins.

Jenkins, an associate professor of pediatrics at the **Medical University of South Carolina**, told *SciBX* she has just completed a Phase I trial of unconjugated NAC to reduce brain injury in infants exposed to chorioamnionitis (intrauterine inflammation).

In that trial, i.v. NAC was delivered before birth to pregnant women diagnosed with chorioamnionitis and to their infants after birth. NAC "readily crosses the placenta and gets into the fetal bloodstream," Jenkins noted.

There, the molecule can protect the fetus from "even mild hypoxia-ischemia associated with fairly normal labor, which could otherwise be a second hit to the fetal brain following chorioamnionitis," she said.

Initial safety data from the trial were presented last month at the **American Pediatric Society and Society for Pediatric Research** meeting in Boston. Unconjugated NAC was safe and well tolerated in 25 mothers and their infants, said Jenkins.

A potential advantage of linking NAC to a dendrimer is that it "may make NAC more effective at lower doses," said Jenkins. "Though it may also be an expensive modification. So a cost-benefit analysis will be important."

Kannan said the dendrimer-based approach "may also work for other causes of cerebral palsy such as hypoxia-ischemia, where inflammation may have a secondary role in perpetuating the injury."

He also noted that dendrimers could be used to deliver many compounds besides NAC. "We will explore other drugs and combination therapies that could help treat cerebral palsy on multiple fronts," he said.

Kannan said it will be "very important to see if the improvement in motor function can be sustained up to adulthood in the animal studies."

The findings are covered by pending patents and are available for licensing.

Fulmer, T. *SciBX* 5(19); doi:10.1038/scibx.2012.486  
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**"Longer-term studies with significantly greater numbers of animals will be needed to work out the safety of D-NAC in the developing brain and over the lifetime of the animal."**

—Dorothea Jenkins,  
Medical University of South Carolina

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e-mail: [krangar1@jhmi.edu](mailto:krangar1@jhmi.edu)  
**Contact:** Roberto Romero, National Institute of Child Health & Human Development, Bethesda, Md.  
e-mail: [romeror@mail.nih.gov](mailto:romeror@mail.nih.gov)
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## COMPANIES AND INSTITUTIONS MENTIONED

**American Pediatric Society and Society for Pediatric Research**,  
The Woodlands, Texas  
**The Johns Hopkins University School of Medicine**,  
Baltimore, Md.  
**Medical University of South Carolina**, Charleston, S.C.  
**National Institute of Child Health & Human Development**,  
Bethesda, Md.



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## This week in therapeutics

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

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

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Autoimmune disease</b>				
Autoimmune disease	Dedicator of cytokinesis 2 (DOCK2)	<i>In vitro</i> and mouse studies identified a small molecule DOCK2 inhibitor that could help treat autoimmune disease. Deletion of <i>Dock2</i> has previously been shown to prevent the development of autoimmune diseases in mice. <i>In vitro</i> screening identified a compound that blocked DOCK2-mediated activation of a downstream GTPase. In mice, intraperitoneal injection of the compound decreased lymphocyte homing to the spleen compared with injection of vehicle. Next steps include developing more potent DOCK2 inhibitors.	Patent application filed; available for licensing	Nishikimi, A. <i>et al. Chem. Biol.</i> ; published online April 20, 2012; doi:10.1016/j.chembiol.2012.03.008 <b>Contact:</b> Yoshinori Fukui, Kyushu University, Fukuoka, Japan e-mail: <a href="mailto:fukui@bioreg.kyushu-u.ac.jp">fukui@bioreg.kyushu-u.ac.jp</a>
<b>SciBX 5(19); doi:10.1038/scibx.2012.487 Published online May 10, 2012</b>				
Multiple sclerosis (MS)	MicroRNA-301a (miR-301a)	A study in mice suggests antagonizing miR-301a could help treat MS. In an experimental autoimmune encephalomyelitis (EAE) mouse model of MS, miR-301a expression was upregulated during acute disease and downregulated during remission. In the EAE mice, engraftment of Cd4 <sup>+</sup> T cells transfected with an antagomir against miR-301a led to decreased disease symptoms compared with engraftment of the same cells transfected with a scrambled oligonucleotide control. Next steps include testing an miR-301a antagonist in animal models of MS.	Patent and licensing status undisclosed	Mycko, M.P. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online April 18, 2012; doi:10.1073/pnas.1114325109 <b>Contact:</b> Krzysztof W. Selmaj, Medical University of Lodz, Lodz, Poland e-mail: <a href="mailto:kselmaj@afazja.am.lodz.pl">kselmaj@afazja.am.lodz.pl</a>
<b>SciBX 5(19); doi:10.1038/scibx.2012.488 Published online May 10, 2012</b>				
<b>Cancer</b>				
Brain cancer	Hedgehog pathway; P glycoprotein (MDR1; ABCB1; P-gp; CD243)	Mouse studies suggest P-gp inhibitors could help reverse resistance to saridegib in medulloblastoma. In a mouse model of aggressive medulloblastoma, the hedgehog pathway inhibitor saridegib decreased tumor size and increased survival compared with vehicle. In the model, hedgehog pathway signaling rebounded and levels of P-gp, a transporter for which saridegib is a known substrate, increased after six weeks of treatment. In the same model, saridegib plus the P-gp inhibitor verapamil reversed the drug resistance seen at six weeks. Next steps could include testing a P-gp inhibitor plus saridegib in clinical trials for medulloblastoma. Infinity Pharmaceuticals Inc.'s saridegib is in Phase II trials to treat bone cancer and myeloproliferative disorder and is in preclinical development for non-small cell lung cancer (NSCLC). Verapamil is a generic calcium channel blocker approved for multiple cardiovascular indications.	Unpatented; licensing status not applicable	Lee, M.J. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online May 1, 2012; doi:10.1073/pnas.1114718109 <b>Contact:</b> James M. Olson, Fred Hutchinson Cancer Research Center, Seattle, Wash. e-mail: <a href="mailto:jolson@fhcrc.org">jolson@fhcrc.org</a>
<b>SciBX 5(19); doi:10.1038/scibx.2012.489 Published online May 10, 2012</b>				

## This week in therapeutics

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cancer	Autophagy	<i>In vitro</i> and mouse studies suggest dimeric chloroquine analogs could help treat cancer more effectively than hydroxychloroquine. In human glioblastoma, colon cancer and melanoma cell lines, a dimeric analog of chloroquine inhibited autophagy at low micromolar IC <sub>50</sub> values and induced greater cell death than hydroxychloroquine. In mouse xenograft models of melanoma and colon cancer, the dimeric analog inhibited tumor growth better than hydroxychloroquine. Ongoing work includes <i>in vivo</i> testing of the dimeric analog in combination with undisclosed cancer therapeutics. Hydroxychloroquine, a generic analog of chloroquine, is approved to treat or prevent malaria and to treat rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).  <b>SciBX 5(19); doi:10.1038/scibx.2012.490</b> <b>Published online May 10, 2012</b>	Patented; available for licensing or partnering	McAfee, Q. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online May 7, 2012; doi:10.1073/pnas.1118193109 <b>Contact:</b> Ravi K. Amaravadi, University of Pennsylvania, Philadelphia, Pa. e-mail: <a href="mailto:ravi.amaravadi@uphs.upenn.edu">ravi.amaravadi@uphs.upenn.edu</a> <b>Contact:</b> Jeffrey D. Winkler, same affiliation as above e-mail: <a href="mailto:winkler@sas.upenn.edu">winkler@sas.upenn.edu</a>
Solid tumors	Glucose-6-phosphate dehydrogenase (G6PD)	An SAR study identified G6PD inhibitors that could be useful for treating solid tumors. Previous studies suggested G6PD is critical for tumor growth. <i>In vitro</i> SAR experiments identified derivatives of dehydroepiandrosterone (DHEA), a weak inhibitor of G6PD, with up to 10-fold greater potency than the parent compound. Next steps include further lead optimization and <i>in vivo</i> testing in tumor xenograft models.  <b>SciBX 5(19); doi:10.1038/scibx.2012.491</b> <b>Published online May 10, 2012</b>	Unpatented; licensing status not applicable	Hamilton, N.M. <i>et al. J. Med. Chem.</i> ; published online April 16, 2012; doi:10.1021/jm300317k <b>Contact:</b> Niall M. Hamilton, The University of Manchester, Manchester, U.K. e-mail: <a href="mailto:nhamilton@picr.man.ac.uk">nhamilton@picr.man.ac.uk</a>
Solid tumors	Tumor necrosis factor- $\alpha$ (TNF- $\alpha$ )	Mouse studies suggest low-dose, recombinant TNF- $\alpha$ could be useful as an adjuvant for cancer immunotherapy. In mice with pancreatic neuroendocrine tumors, Tnf- $\alpha$ modified to target tumor vasculature increased survival compared with control. In the mice, low-dose, recombinant Tnf- $\alpha$ plus a cancer vaccine increased survival compared with either component alone. Next steps include testing recombinant TNF- $\alpha$ in combination with approved cancer vaccines.  <b>SciBX 5(19); doi:10.1038/scibx.2012.492</b> <b>Published online May 10, 2012</b>	Use of TNF- $\alpha$ in combination with chemotherapy has been patented; unavailable for licensing	Johansson, A. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online April 30, 2012; doi:10.1073/pnas.1118296109 <b>Contact:</b> Ruth Ganss, The University of Western Australia, Perth, Western Australia, Australia e-mail: <a href="mailto:ganss@waimr.uwa.edu.au">ganss@waimr.uwa.edu.au</a>
<b>Endocrine/metabolic disease</b>				
Diabetes	CD3; insulin (INS; proinsulin); IL-10	Studies in mice suggest <i>Lactococcus lactis</i> engineered to secrete both IL-10 and proinsulin could help treat type 1 diabetes. In diabetic mice, oral dosing of IL-10- and proinsulin-secreting <i>L. lactis</i> plus a low-dose systemic anti-CD3 mAb reversed autoimmune diabetes in 59% of the animals, whereas it was only reversed in 25% of mice given the antibody alone. Mice receiving the combination therapy also had lower insulinitis and better preservation of functional $\beta$ cell mass than animals given anti-CD3 mAb alone. Next steps include toxicology studies. ActoGeniX N.V.'s AG013, an oral rinsing solution containing <i>L. lactis</i> engineered to secrete trefoil factor 1 (TFF1), is in Phase I testing to prevent oral mucositis.  <b>SciBX 5(19); doi:10.1038/scibx.2012.493</b> <b>Published online May 10, 2012</b>	Patented by ActoGeniX; available for licensing	Takiishi, T. <i>et al. J. Clin. Invest.</i> ; published online April 9, 2012; doi:10.1172/JCI60530 <b>Contact:</b> Chantal Mathieu, Catholic University Leuven, Leuven, Belgium e-mail: <a href="mailto:chantal.mathieu@uzleuven.be">chantal.mathieu@uzleuven.be</a>

## This week in therapeutics

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Hepatic disease</b>				
Liver fibrosis	Peroxisome proliferation-activated receptor- $\delta$ (PPAR $\delta$ ; PPAR $\delta$ )	<p>Cell culture and mouse studies suggest PPAR<math>\delta</math> agonists could help treat liver fibrosis. In mouse models of chemical-induced liver fibrosis and cholestasis-induced liver fibrosis, the PPAR<math>\delta</math> agonist KD3010 decreased levels of liver fibrosis compared with the PPAR<math>\delta</math> agonist GW501516 or vehicle. Next steps could include a Phase II trial of KD3010 to treat liver fibrosis in HCV nonresponders.</p> <p>KD3010 from Kalypsys Inc. has completed Phase I testing in endocrine/metabolic and hepatic indications. GlaxoSmithKline plc discontinued GW501516 after a Phase II trial in dyslipidemia due to safety concerns.</p> <p>At least three other companies have PPAR<math>\delta</math> agonists in Phase I or Phase II trials for endocrine/metabolic or cardiovascular indications (<i>see PPAR's new course, page 8</i>).</p> <p><b>SciBX 5(19); doi:10.1038/scibx.2012.494</b> Published online May 10, 2012</p>	Patent and licensing status undisclosed	<p>Iwaisako, K. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online April 25, 2012; doi:10.1073/pnas.1202464109</p> <p><b>Contact:</b> Bernd Schnabl, University of California, San Diego School of Medicine, La Jolla, Calif. e-mail: <a href="mailto:beschnabl@ucsd.edu">beschnabl@ucsd.edu</a></p> <p><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></p>
<b>Inflammation</b>				
Inflammation	High mobility group box 1 (HMGB1); IL-1 $\beta$ ; tumor necrosis factor- $\alpha$ (TNF- $\alpha$ )	<p>Rat and cell culture studies identified gold complexes of 6-substituted purine derivatives that could help treat inflammation. In a human immune cell line, three of the identified gold complexes decreased signaling of the proinflammatory cytokines TNF-<math>\alpha</math>, IL-1<math>\beta</math> and HMGB1 compared with vehicle. In a rat model of hind paw edema, the complexes lowered inflammation compared with vehicle. Next steps include determining the dose, therapeutic index and bioactivity of the lead complexes.</p> <p><b>SciBX 5(19); doi:10.1038/scibx.2012.495</b> Published online May 10, 2012</p>	Patent application filed; available for licensing	<p>Travnicek, Z. <i>et al. J. Med. Chem.</i>; published online April 30, 2012; doi:10.1021/jm201416p</p> <p><b>Contact:</b> Zdenek Travnicek, Palacký University, Olomouc, Czech Republic e-mail: <a href="mailto:zdenek.travnicek@upol.cz">zdenek.travnicek@upol.cz</a></p>
<b>Musculoskeletal disease</b>				
Bone repair	Peroxisome proliferation-activated receptor- $\gamma$ (PPAR $\gamma$ ; PPAR $\gamma$ )	<p>Mouse studies suggest PPAR<math>\gamma</math> inhibitor-treated human mesenchymal stem cells (MSCs) and MSC-derived extracellular matrix (ECM) could help repair bone. In a mouse model of cranial bone injury, human MSCs pretreated with a PPAR<math>\gamma</math> inhibitor repaired 60% of bone damage, whereas nonpretreated MSCs repaired only 30%. In the models, PPAR<math>\gamma</math> inhibitor-pretreated MSCs and a human MSC-derived ECM scaffold repaired 80%–100% of bone damage, whereas ECM scaffold alone repaired only 10%–15%. Results for the use of the pretreated MSCs and ECM scaffold to repair femur damage in rodents will be reported in a future publication. Blast Therapeutics Inc., the licensee of the findings, is developing biomaterials that accelerate bone repair and regeneration.</p> <p><b>SciBX 5(19); doi:10.1038/scibx.2012.496</b> Published online May 10, 2012</p>	Patented by Texas A&M University; licensed to Blast Therapeutics	<p>Zeitouni, S. <i>et al. Sci. Transl. Med.</i>; published online May 2, 2012; doi:10.1126/scitranslmed.3003396</p> <p><b>Contact:</b> Carl A. Gregory, Texas A&amp;M Health Science Center, Temple, Texas e-mail: <a href="mailto:cgregory@medicine.tamhsc.edu">cgregory@medicine.tamhsc.edu</a></p>
Muscular dystrophy	<i>D4Z4 binding element transcript (DBE-T)</i>	<p>Cell culture studies suggest inhibiting <i>DBE-T</i> could help treat facioscapulohumeral dystrophy (FSHD), which is a common autosomal-dominant type of muscular dystrophy. Earlier studies have shown that patients with FSHD have reductions in the copy number of the <i>D4Z4</i> repeats, which leads to reduced repression of disease-associated genes. In cultured muscle cells from FSHD patients, a long noncoding RNA called <i>DBE-Transcript</i> was expressed and associated with <i>D4Z4</i>, whereas <i>DBE-T</i> was not expressed in muscle cells from healthy controls. In cells expressing <i>DBE-T</i>, small hairpin RNA against <i>DBE-T</i> decreased FSHD-associated gene expression compared with control shRNA. Next steps include testing knockdown of <i>DBE-T</i> in animal models.</p> <p><b>SciBX 5(19); doi:10.1038/scibx.2012.497</b> Published online May 10, 2012</p>	Unpatented; available for collaboration	<p>Cabianca, D.S. <i>et al. Cell</i>; published online April 26, 2012; doi:10.1016/j.cell.2012.03.035</p> <p><b>Contact:</b> Davide Gabellini, San Raffaele Scientific Institute, Milan, Italy e-mail: <a href="mailto:gabellini.davide@hsr.it">gabellini.davide@hsr.it</a></p>

## This week in therapeutics

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Tissue injury; muscular dystrophy	MicroRNA-206 (miR-206)	Mouse studies suggest agonizing miR-206 could be useful for treating muscle injury and Duchenne muscular dystrophy (DMD). In a mouse model of muscle injury, miR-206 deficiency delayed muscle regeneration. In a mouse model of DMD, miR-206 deficiency increased disease severity compared with that seen in nondeficient controls. Next steps include developing a way to increase endogenous miR-206 levels or deliver miR-206 mimics in mouse models of muscle injury and DMD.  <b>SciBX 5(19); doi:10.1038/scibx.2012.498</b> <b>Published online May 10, 2012</b>	Patent pending; licensed to miRagen Therapeutics Inc.	Liu, N. <i>et al. J. Clin. Invest.</i> ; published online May 1, 2012; doi:10.1172/JCI62656 <b>Contact:</b> Eric N. Olson, The University of Texas Southwestern Medical Center, Dallas, Texas e-mail: <a href="mailto:eric.olson@utsouthwestern.edu">eric.olson@utsouthwestern.edu</a>
<b>Transplantation</b>				
Graft-versus- host disease (GvHD)	Not applicable	Mouse studies suggest antibiotics could be useful for treating GvHD. In mice with both GvHD and elevated intestinal levels of pathogenic <i>Escherichia coli</i> , an oral antibiotic reduced both intestinal <i>E. coli</i> levels and GvHD severity compared with vehicle. Next steps include human validation studies.  <b>SciBX 5(19); doi:10.1038/scibx.2012.499</b> <b>Published online May 10, 2012</b>	Unpatented; unavailable for licensing	Eriguchi, Y. <i>et al. Blood</i> ; published online April 24, 2012; doi:10.1182/blood-2011-12-401166 <b>Contact:</b> Takanori Teshima, Kyushu University Graduate School of Medical Sciences, Fukuoka, Japan e-mail: <a href="mailto:tteshima@cancer.med.kyushu-u.ac.jp">tteshima@cancer.med.kyushu-u.ac.jp</a>
<b>Various</b>				
Cancer; inflammation	Bromodomain containing 4 (BRD4)	An <i>in vitro</i> study suggests the epigenetic target BRD4 also has kinase activity, which could be inhibited to treat cancer or inflammation. In <i>in vitro</i> and cellular assays, BRD4 catalyzed phosphorylation of serine 2 (SER2) on RNA polymerase II, a site that needs to be phosphorylated for active transcription to occur. In cells, a BRD4 inhibitor lowered levels of SER2 phosphorylation on RNA polymerase II compared with no treatment. Next steps include screening for molecules that inhibit BRD4 kinase activity with high selectivity. Tensha Therapeutics Inc. has inhibitors of BET bromodomain, a class that includes BRD4, in preclinical development for cancer. Constellation Pharmaceuticals Inc. has BET bromodomain inhibitors in preclinical development for cancer and immunological indications.  <b>SciBX 5(19); doi:10.1038/scibx.2012.500</b> <b>Published online May 10, 2012</b>	Unpatented; licensing status not applicable	Devaiah, B.N. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online April 16, 2012; doi:10.1073/pnas.1120422109 <b>Contact:</b> Dinah Singer, National Institutes of Health, Bethesda, Md. e-mail: <a href="mailto:dinah.singer@nih.gov">dinah.singer@nih.gov</a>

## 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>			
Aptamer-based assay against secreted proteins for the identification of new cancer biomarkers	An aptamer-based assay of secreted proteins may help identify new cancer biomarkers. The screen consisted of an RNA aptamer library that bound proteins secreted from a pancreatic cancer cell line but not proteins from a noncancerous pancreatic cell line. The screen identified an aptamer that bound serum cyclophilin B (CYPB; PPIB) and was able to distinguish patients with pancreatic cancer from healthy volunteers with 92% accuracy and a 4% false positive rate. Next steps include testing an optimized aptamer-based assay in patients with early stage pancreatic cancer or benign pancreatic disease and using the method to look for biomarkers in additional cancers.  <b>SciBX 5(19); doi:10.1038/scibx.2012.501</b> <b>Published online May 10, 2012</b>	Unpatented; licensing status not applicable	Ray, P. <i>et al. J. Clin. Invest.</i> ; published online April 9, 2012; doi:10.1172/JCI62385 <b>Contact:</b> Rebekah R. White, Duke University School of Medicine, Durham, N.C. e-mail: <a href="mailto:rebekah.white@duke.edu">rebekah.white@duke.edu</a> <b>Contact:</b> Partha Ray, same affiliation as above e-mail: <a href="mailto:partha.ray@duke.edu">partha.ray@duke.edu</a>
Paper-based assay for reporting blood type as text	A paper-based assay was used to identify and display blood type as text. The paper assays are designed with invisible A, B, O, and <sup>+</sup> or <sup>-</sup> text patterns that become visible to report blood type according to the ABO and Rhesus blood-typing systems, respectively. In the assays, correct blood type was displayed for all 99 tested samples. The assays were sensitive enough to identify A and B blood type antigens after blood dilution by a factor of four and the Rhesus D antigens after dilution by a factor of two. Next steps include production of the device.  <b>SciBX 5(19); doi:10.1038/scibx.2012.502</b> <b>Published online May 10, 2012</b>	Idea and prototype patented by Monash University; licensed to an undisclosed party	Li, M. <i>et al. Angew. Chem. Int. Ed.</i> ; published online April 18, 2012; doi:10.1002/anie.201201822 <b>Contact:</b> Wei Shen, Monash University, Clayton, Victoria, Australia e-mail: <a href="mailto:wei.shen@eng.monash.edu.au">wei.shen@eng.monash.edu.au</a>
<b>Computational models</b>			
Algorithm for creating charged antibodies to improve stability and preserve activity	<i>In silico</i> and <i>in vitro</i> studies identified a strategy to create positively charged antibodies that have better stability and lower aggregation than unmodified counterparts. A computational software package from Rosetta Genomics Ltd. was used to identify sites on an antibody in which substitution with charged amino acids would not disrupt binding function. As proof of principle, <i>in silico</i> results were used to design variants of the bacteriophage MS2 single-chain variable fragment antibody. <i>In vitro</i> , those variants showed greater stability in normal culture conditions than the wild-type antibody. When heated to 70 °C for one hour, the antibody variants showed decreased aggregation compared with the wild-type antibody and maintained 70% of their initial target-binding affinity. Next steps include validating the use of a server that applies the method to other antibodies.  <b>SciBX 5(19); doi:10.1038/scibx.2012.503</b> <b>Published online May 10, 2012</b>	Findings unpatented; Rosetta Genomics computational design package, protein design tools and homology modeling technology are open source; unavailable for licensing	Miklos, A.E. <i>et al. Chem. Biol.</i> ; published online April 20, 2012; doi:10.1016/j.chembiol.2012.01.018 <b>Contact:</b> Andrew D. Ellington, The University of Texas at Austin, Austin, Texas e-mail: <a href="mailto:ellingtonlab@gmail.com">ellingtonlab@gmail.com</a>
<b>Disease models</b>			
Dopamine D2 receptor expression as a measure of Huntington's disease (HD) pathology	Measuring dopamine D2 receptor expression in mouse models of HD could aid the study of therapeutics to treat the disease. Alterations in dopamine signaling have previously been linked to HD pathology. Four genetic mouse models of HD were engineered to express a fusion of a dopamine D2 receptor and a fluorescent protein to monitor dopamine signaling during disease progression. In the models, fluorescence levels decreased with age compared with those in healthy controls. In one of the models, small hairpin RNA against mutant <i>huntingtin</i> ( <i>HTT</i> ) led to greater fluorescence levels than control shRNA. Next steps could include using the models to screen for compounds that increase dopamine D2 receptor expression.  <b>SciBX 5(19); doi:10.1038/scibx.2012.504</b> <b>Published online May 10, 2012</b>	Patent and licensing status unavailable	Crook, Z.R. & Housman, D.E. <i>Proc. Natl. Acad. Sci. USA</i> ; published online April 23, 2012; doi:10.1073/pnas.1204542109 <b>Contact:</b> David E. Housman, Massachusetts Institute of Technology, Cambridge, Mass. e-mail: <a href="mailto:dhousman@mit.edu">dhousman@mit.edu</a>

## This week in techniques

Approach	Summary	Licensing status	Publication and contact information
Mice with working memory deficits as models of dementia-related delirium	Mice with short-term deficits in working memory could be useful models of dementia-related delirium and could aid the discovery of new treatments. In mice trained to perform a visuo-spatial memory task, systemic lipopolysaccharide (LPS) plus an immunotoxin induced basal forebrain cholinergic lesions and led to acute deficits in working memory. In these mice, an acetylcholinesterase (AChE) inhibitor decreased working memory deficits compared with vehicle. Upcoming studies will elucidate the roles of existing neurodegenerative and proinflammatory factors in the models.  <b>SciBX 5(19); doi:10.1038/scibx.2012.505</b> <b>Published online May 10, 2012</b>	Unpatented; available for partnering	Field, R.H. <i>et al. J. Neurosci.</i> ; published online May 2, 2012; doi:10.1523/JNEUROSCI.4673-11.2012 <b>Contact:</b> Colm Cunningham, Trinity College Dublin, Dublin, Ireland e-mail: <a href="mailto:colm.cunningham@tcd.ie">colm.cunningham@tcd.ie</a>
<i>SH3 and multiple ankyrin repeat domains 2</i> (SHANK2)-deficient mouse model of autism spectrum disorder (ASD)	Mice lacking <i>Shank2</i> could be used as models to study ASD and develop new treatments for the condition. Mutations in <i>SHANK2</i> have previously been associated with ASD in humans. Mice lacking <i>Shank2</i> developed symptoms of ASD including hyperactivity and impaired social interactions and had decreased glutamatergic synaptic transmission compared with wild-type mice. Next steps include using the model to evaluate drugs to treat ASD.  <b>SciBX 5(19); doi:10.1038/scibx.2012.506</b> <b>Published online May 10, 2012</b>	Unpatented; unavailable for licensing	Schmeisser, M.J. <i>et al. Nature</i> ; published online April 29, 2012; doi:10.1038/nature11015 <b>Contact:</b> Tobias M. Boeckers, University of Ulm, Ulm, Germany e-mail: <a href="mailto:tobias.boeckers@uni-ulm.de">tobias.boeckers@uni-ulm.de</a>
<b>Drug delivery</b>			
Acyclic cucurbit[ <i>n</i> ]urils as molecular containers to improve drug solubility	Acyclic cucurbit[ <i>n</i> ]uril compounds may be useful as molecular containers to increase the solubility of poorly soluble drugs. Solubility enhancement studies showed the containers increased the solubility of 10 drugs by 23–2,750-fold compared with drug alone. In cell-based assays, the generic chemotherapeutic paclitaxel complexed with the container increased cell death compared with the drug or container alone. The container was well tolerated in mice at doses up to 1,230 mg/kg. Next steps include developing additional container-drug conjugates and testing their bioactivity.  <b>SciBX 5(19); doi:10.1038/scibx.2012.507</b> <b>Published online May 10, 2012</b>	Patent applications filed; available for licensing or partnering	Ma, D. <i>et al. Nat. Chem.</i> ; published online April 15, 2012; doi:10.1038/nchem.1326 <b>Contact:</b> Lyle Isaacs, University of Maryland, College Park, Md. e-mail: <a href="mailto:lisaacs@umd.edu">lisaacs@umd.edu</a> <b>Contact:</b> Volker Briken, same affiliation as above e-mail: <a href="mailto:vbriken@umd.edu">vbriken@umd.edu</a>
<b>Drug platforms</b>			
Gene therapy for Leber's hereditary optical neuropathy (LHON)	Cell culture and mouse studies suggest a mitochondria-targeted transgene could be useful for treating LHON. The majority of patients with LHON have mutations in NADH dehydrogenase subunit 4 (ND4), a mitochondrial protein involved in energy production. In a cell culture model of LHON, transfection with an adeno-associated virus (AAV) vector bearing the <i>ND4</i> gene increased mitochondrial function compared with transfection using a nontransgenic control vector. In a mouse model of LHON, the <i>ND4</i> -bearing AAV vector increased mitochondrial function and decreased vision loss compared with a control vector. Next steps include optimizing the viral expression vector. Santhera Pharmaceuticals Holding AG's Catena idebenone (SNT-MC17) is under review in Europe to treat LHON ( <i>see Mitochondrial gene therapy</i> , page 6).  <b>SciBX 5(19); doi:10.1038/scibx.2012.508</b> <b>Published online May 10, 2012</b>	Patented; available for licensing	Yu, H. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online April 20, 2012; doi:10.1073/pnas.1119577109 <b>Contact:</b> John Guy, University of Miami Miller School of Medicine, Miami, Fla. e-mail: <a href="mailto:jguy@med.miami.edu">jguy@med.miami.edu</a>

## This week in techniques

Approach	Summary	Licensing status	Publication and contact information
<b>Markers</b>			
Epigenomic enhancer variants as biomarkers for colorectal cancer	<i>In vitro</i> studies identified epigenomic markers that could be used as biomarkers for colorectal cancer. In colorectal samples, 197 epigenomic markers controlled by monomethylated histone H3 lysine 4 occurred in all 9 samples, whereas the markers did not occur in any of 9 healthy colon samples. The epigenomic markers were identified on cancer-related genes, suggesting they control cancer-associated gene expression. Next steps include identifying the transcription factors or chromatin regulators that form the epigenomic markers.	Findings unpatented; available for licensing	Akhtar-Zaidi, B. <i>et al. Science</i> ; published online April 12, 2012; doi:10.1126/science.1217277 <b>Contact:</b> Peter C. Scacheri, Case Western Reserve University, Cleveland, Ohio e-mail: <a href="mailto:pxs183@case.edu">pxs183@case.edu</a>
	<b>SciBX 5(19); doi:10.1038/scibx.2012.509</b> <b>Published online May 10, 2012</b>		
Genomic and expression analysis–derived breast cancer subgroups to predict response to therapy	Genomic and expression analysis–derived subgroups of breast cancer may help predict response to therapy. Copy number and gene expression analysis of about 1,000 breast tumor samples identified 10 biological subgroups. The subgroups were then validated in an independent set of 1,000 breast tumor samples and correlated with distinct clinical outcomes. Next steps include testing whether the different subgroups predict response to therapeutics.	Unpatented; licensing status not applicable	Curtis, C. <i>et al. Nature</i> ; published online April 18, 2012; doi:10.1038/nature10983 <b>Contact:</b> Samuel Apariciot, The University of British Columbia, Vancouver, British Columbia, Canada e-mail: <a href="mailto:saparicio@bccrc.ca">saparicio@bccrc.ca</a> <b>Contact:</b> Carlos Caldas, Cancer Research UK and University of Cambridge, Cambridge, U.K. e-mail: <a href="mailto:carlos.caldas@cancer.org.uk">carlos.caldas@cancer.org.uk</a>
	<b>SciBX 5(19); doi:10.1038/scibx.2012.510</b> <b>Published online May 10, 2012</b>		

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

ActoGeniX N.V. 13  
 American Pediatric Society and Society for Pediatric Research 10  
 AstraZeneca plc 1

**B**

Biomarkers Consortium 3  
 Blast Therapeutics Inc. 14

**C**

Cerenis Therapeutics S.A. 8  
 Children's Hospital of Philadelphia 6  
 CommonMind Consortium 1  
 Constellation Pharmaceuticals Inc. 15  
 Critical Path Institute 3

**E**

Edison Pharmaceuticals Inc. 7  
 European Federation of Pharmaceutical Industries and Associations 4  
 European Medicines Agency 3

**F**

Food and Drug Administration 3  
 Foundation for the National Institutes of Health 3

**G**

Genfit S.A. 8  
 GlaxoSmithKline plc 1,8,14

**H**

H. Lundbeck A/S 2

**I**

Infinity Pharmaceuticals Inc. 12  
 Innovative Medicines Initiative 3  
 International Mental Health Research Organization 2

**J**

Johns Hopkins University School of Medicine 10  
 Johnson & Johnson 2

**K**

Kalypsys Inc. 8,14

**M**

Medical University of South Carolina 10  
 Michael J. Fox Foundation for Parkinson's Research 3

miRagen Therapeutics Inc. 15  
 Monash University 16  
 Myelin Repair Foundation 5

**N**

National Institute of Child Health & Human Development 10  
 National Institute on Aging 3  
 Novartis AG 1

**O**

One Mind for Research 2

**P**

Pennsylvania State University 8

**R**

Rosetta Genomics Ltd. 16

**S**

Sage Bionetworks 4  
 Salk Institute for Biological Studies 8  
 Santhera Pharmaceuticals Holding AG 7,17  
 Structural Genomics Consortium 1

**T**

Takeda Pharmaceutical Co. Ltd. 1  
 Tensha Therapeutics Inc. 15  
 Texas A&M University 14  
 Top Institute Pharma 4

**U**

University of California, San Diego School of Medicine 8  
 University of Miami 6  
 University of Miami Miller School of Medicine 6  
 University of Pennsylvania 6  
 University of Southern California 6

.....

**Target and compound index****A**

A $\beta$  3  
 ABCB1 12  
 ABO 16  
 Acetaminophen 10  
 Acetylcholinesterase 17  
 AChE 17  
 Acyclic cucurbit[n]uril 17  
 AG013 13  
 Autophagy 13

**B**

$\beta$ -Amyloid 3  
 BRD4 15  
 Bromodomain containing 4 15

**C**

Calcium channel 12  
 Catena 7,17  
 CD3 13  
 Cd4 12  
 Cd11b 10  
 CD243 12  
 CER-002 8  
 Chloroquine 13  
 Co-enzyme Q10 7  
 Complement receptor 3 10  
 Connective tissue growth factor 8  
 Cr3 10  
 CTGF 8  
 Cyclophilin B 16  
 CYPB 16

**D**

*DAZ4 binding element transcript* 14  
*DBE-T* 14  
*DBE-Transcript* 14  
 Dedicator of cytokinesis 2 12  
 Dehydroepiandrosterone 13  
 DHEA 13  
 DOCK2 12  
*Dopamine D2 receptor* 16

**E**

EPI-743 7

**G**

G6PD 13  
 GFT505 8  
 Glucose-6-phosphate dehydrogenase 13  
 GTPase 12  
 GW0742 8  
 GW501516 8,14

**H**

Hedgehog pathway 12  
 High mobility group box 1 14  
 HMGB1 14  
 HTT 16  
 Huntingtin 16  
 Hydroxychloroquine 13

**I**

Idebenone 7,17  
 IL-10 13  
 IL-1 $\beta$  14

INS 13

Insulin 13

**K**

KD3010 8,14

**L**

Lipopolysaccharide 17  
 LPS 17

**M**

MDR1 12  
 MicroRNA-206 15  
 MicroRNA-301a 12  
 miR-206 15  
 miR-301a 12

**N**

NAC 10  
 N-Acetylcysteine 10  
 NADH dehydrogenase subunit 4 6,17  
 ND4 17

**P**

Paclitaxel 17  
 Peroxisome proliferation-activated receptor- $\delta$  8,14  
 Peroxisome proliferation-activated receptor- $\gamma$  14  
 P glycoprotein 12  
 P-gp 12  
 PPAR $\alpha$  8  
 PPARA 8  
 PPAR $\delta$  8,14  
 PPARD 8,14  
 PPAR $\gamma$  8,14  
 PPARG 8,14  
 PPIB 16  
 Proinsulin 13

**R**

Rhesus D 16  
 RNA polymerase II 15

**S**

Saridegib 12  
*SH3 and multiple ankyrin repeat domains 2* 17  
*SHANK2* 17  
 SNT-MC17 7,17

**T**

TFF1 13  
 TNF- $\alpha$  13,14  
 Trefoil factor 1 13  
 Tumor necrosis factor- $\alpha$  13,14

**V**

Verapamil 12