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THIS WEEK

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Translating autism

By Kai-Jye Lou, Staff Writer

Researchers at **McGill University** have mouse data showing a causal link between eIF4E-mediated translational dysregulation and autism-related deficits. The group also corrected the dysregulation—and the associated autistic phenotype—with a small molecule.[1]

The McGill group, led by Nahum Sonenberg, has been studying the role of eukaryotic translation initiation factor 4E (eIF4E) in protein synthesis for over three decades and has primarily focused on the factor's relevance in cancer. eIF4E binds to the cap structure on mRNA and helps to initiate the translation of the mRNA. Sonenberg is a professor in the Department of Biochemistry and at the Rosalind and Morris Goodman Cancer Research Centre at McGill.

The team previously reported that eIF4E-mediated protein translation is modulated by the phosphoinositide 3-kinase (PI3K), protein kinase B (PKB; PKBA; AKT; AKT1) and mammalian target of rapamycin (mTOR; FRAP; RAFT1) pathway, which is commonly disrupted in cancer.[2]

He said the initial connection to autism came after other research groups showed that autistic children carry mutations in genes upstream of *mTOR*. These genes included *PTEN* (*MMAC1*; *TEP1*) and *tuberous sclerosis complex tumor suppressor 1* (*TSC1*).[3–5]

Separately, a 2009 study from a research group in the U.K. showed an association between mutations that increased eIF4E promoter activity and autism.[6]

With multiple studies pointing to eIF4E-dependent processes in autism, the McGill group sought to determine whether dysregulation of eIF4E activity itself could cause an autistic phenotype. Indeed, past studies suggested that dysregulated translation of mRNA could be an underlying cause of autism[7] but never showed a causal relationship.

In a new study published in *Nature*, the McGill researchers showed that increasing eif4e activity in mice—by knocking out the gene encoding an eif4e repressor called eif4e binding protein 2 (eif4ebp2)—led to autism-associated electrophysiological abnormalities and behaviors.

In these mice, as well as mice that overexpressed eif4e, translation of neuroligin proteins was greater than that seen in wild-type controls. Alterations in neuroligin signaling occur in autism.[8,9]

In the mouse models, a small molecule inhibitor of eIF4E signaling called 4EGI-1 reversed the electrophysiological abnormalities and decreased autistic behaviors compared with vehicle. Knockdown of neuroligin 1 (Nlgn1) had similar effects.

Importantly, inhibition of eif4e and Nlgn1 activity did not affect electrophysiological and behavioral parameters in wild-type mice.

"The study is of particular interest for me because it provides strong

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evidence directly supporting the 'troubled translation' hypothesis that Mark Bear and I proposed in 2008, where we suggested that dysregulation of translation may be a core pathophysiological mechanism in autism," said Raymond Kelleher, an assistant professor of neurology at **Harvard Medical School** and a principal investigator at the Center for Human Genetic Research at **Massachusetts General Hospital**.

> **"It will be important to determine whether the mechanisms defined in this study apply to known genetic causes of autism—that is, whether known genetic causes of autism lead to dysregulation of cap-dependent translation and/or neuroligin expression."**
> ***—Raymond Kelleher, Harvard Medical School***

Kelleher said the new data also draw a direct link between translational dysregulation and the regulation of the balance of excitatory and inhibitory synaptic transmission by neuroligins, which is another candidate pathophysiological mechanism in autism.

Eric Klann, a professor in the Center for Neural Science at **New York University**, said the results are consistent with observations from ongoing work from his lab, which is investigating excessive eIF4E translation as a molecular mechanism underlying autism. He added that his group has been working with similar mouse autism models and with 4EGI-1.

Klann noted that his group has a complementary paper in the press that further solidifies the causal relationship between eIF4E-mediated translational dysregulation and autism.

"Our work and the Sonenberg data show that exaggerated eIF4E-dependent translation will cause synaptic and behavioral abnormalities consistent with autism," he told *SciBX*.

Validation needed

The findings now need to be validated in mice carrying mutations in genes known to cause autism and with more drug-like inhibitors of eIF4E-mediated protein translation than 4EGI-1.

A group at Harvard Medical School first identified 4EGI-1 in 2007 as a small molecule that inhibits translation of mRNA by disrupting the association between eIF4E and eIF4γ (EIF4G).[10] However, the researchers noted in their study that the compound does not have the potency necessary for development as a drug candidate.

Moreover, it is still unclear which subset of patients with autism should be targeted. Klann said fragile X–associated autism could be the place to start, as dysregulated mRNA translation also is seen in mouse models of fragile X syndrome.

About 15%–30% of patients with fragile X syndrome also have autism.[7]

Klann added that there already are multiple companies trying to target the eIF4E-regulated translational axis and related axes in cancer. "Some of the compounds these companies are developing could potentially cross the blood brain barrier and could thus be suitable for use in patients with autism," he told *SciBX*.

At least two eIF4E inhibitors are in development. **Isis Pharmaceuticals Inc.**'s ISIS-EIF4ERx, a second-generation antisense compound targeting eIF4E, is in Phase II testing to treat non–small cell lung cancer (NSCLC) and prostate cancer. **Translational Therapeutics Inc.**'s TRX-201, a Lipid Vector Technology (LVT) derivative of ribavirin, is in preclinical development to treat thyroid cancer.

The generic antiviral ribavirin also inhibits oncogenic eIF4E activity and has been tested in an investigator-led Phase II trial in patients with acute myelogenous leukemia (AML).[11,12] The researchers reported 5 responses and 4 cases of stable disease among 11 evaluable patients.

Kelleher wanted to see the McGill team's findings validated in other mouse autism models.

"It will be important to determine whether the mechanisms defined in this study apply to known genetic causes of autism—that is, whether known genetic causes of autism lead to dysregulation of cap-dependent translation and/or neuroligin expression," he told *SciBX*. "Similarly, it will be important to test whether partial inhibition of cap-dependent translation or knockdown of specific neuroligins can reverse synaptic and behavioral deficits in mouse models of known genetic causes of autism."

Sonenberg said his group is developing mice with eif4ebp2 knocked out in specific brain regions. His team also is trying to develop conditional knockout mice to determine whether loss of eif4ebp2 at different time points in early life would lead to the autistic phenotype.

Klann's group is now trying to determine whether targeting eif4e in fragile X mouse models would be able to correct the associated autistic behaviors. The team also is trying to develop a method to measure the translation of various proteins in the mouse autism models, which will help to identify common dysregulated proteins across the multiple models.

Finally, Klann said his group has been contacted by companies interested in testing compounds that inhibit the eIF4E translational regulatory pathway in the mouse autism models being used by his group.

The findings reported in *Nature* are unpatented. The mouse models are available for licensing.

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Harvard Medical School, Boston, Mass.
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Massachusetts General Hospital, Boston, Mass.
McGill University, Montreal, Quebec, Canada
New York University, New York, N.Y.
Translational Therapeutics Inc., Arlington, Mass.

Quebec's research resurrection

By Lev Osherovich, Senior Writer

AstraZeneca plc and **Pfizer Inc.** have partnered with the Quebec government to form the not-for-profit **Neomed Institute**. The drug development institute will resume work on pain compounds discontinued by AstraZeneca earlier this year and plans to build a new pipeline through collaborations with regional academic laboratories and biotech startups.

The public-private partnership extends a lifeline to a team of AstraZeneca researchers who previously were developing preclinical pain therapeutics at the Montreal site. The pharma is winding down the bulk of its internal neurology R&D as part of a restructuring announced earlier this year.[1]

The institute is located in a former AstraZeneca R&D center in Technoparc Montreal. Neomed has retained former AstraZeneca R&D staff but has hired new management led by President and CEO Max Fehlmann. Fehlmann was formerly president and CEO of the **Quebec Consortium for Drug Discovery**, another regional translational science public-private partnership.

Neomed has secured C$8 million ($8.1 million) in upfront cash from the government of Quebec, along with a five-year, non–interest-bearing loan of C$20 million ($20.4 million). Pfizer is contributing C$3.5 million ($3.6 million). AstraZeneca is contributing C$5 million ($5.1 million), as well as land and the facility, laboratory equipment and IP for three pain molecules.

Didier Jean-François, Neomed's VP of business development and marketing, said the startup money will be supplemented by additional fundraising and will give the institute at least five years of runway to build a pipeline that goes beyond the institute's core area of pain.

Jean-François previously was director of business development at Crucell N.V., which was acquired by **Johnson & Johnson** in 2011.

Neomed will retain about half a dozen former AstraZeneca employees to continue their work on the three pain compounds, said Jean-François. Those projects will be spearheaded by Neomed CSO Philippe Walker, formerly VP and head of AstraZeneca R&D in Montreal.

AstraZeneca said one of the donated compounds is a preclinical purinergic receptor P2X ligand-gated ion channel 3 (P2X3) antagonist in development for painful bladder syndrome and interstitial cystitis. Jean-François did not disclose the targets of the other two compounds.

"AstraZeneca's goal was to give the compounds to the people who had been developing them in-house," said Jean-François. "All of the IP for these pain compounds was given to Neomed, and if Neomed manages to develop these compounds to a commercial milestone," the institute's pharma partners Pfizer and AstraZeneca will both have the right of first negotiation to license these compounds.

Jean-François said that because the two pharma partners have different strategic goals it is unlikely that they both would want to compete for the same technology coming out of the institute. If the two pharmas do become interested in licensing the same technology, the right of first negotiation will likely go to the highest contributor to the institute's budget.

The two pharmas also will have rights of first negotiation for any additional technology emerging from the institute. AstraZeneca does not have clawback rights to its former compounds.

> **"The Neomed Institute is a translational research center with its own pipeline, but we're also an incubator."**
> ***—Didier Jean-François, Neomed Institute***

Jean-François added that he hopes to recruit at least two more pharmas into the partnership.

Meanwhile, Neomed is soliciting collaborative research proposals from academic researchers and startups. Jean-François said part of Neomed's operating expenses will be met by renting out floor space and laboratory facilities in its building.

Jean-François said Neomed has the capacity to in-license up to seven more preclinical projects and to advance them to the IND stage. He hopes to in-license early stage projects that are not far enough along toward translation to attract typical VC investors.

These programs do not necessarily have to come from Quebec-based researchers, but because the institute is funded in part by the Quebec regional government, one goal is to support the Quebec biotech industry.

"The Neomed Institute is a translational research center with its own pipeline, but we're also an incubator," said Jean-François. "We have a total of 15 staff, most of whom are working in discovery or development. We see ourselves as a development partner rather than as an exit for prior investors."

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Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Neomed Institute, Montreal, Quebec, Canada
Pfizer Inc. (NYSE:PFE), New York, N.Y.
Quebec Consortium for Drug Discovery, Nuns' Island, Quebec, Canada

Muscling up on Myozyme

By Tim Fulmer, Senior Writer

Oxyrane U.K. Ltd. and **BioMarin Pharmaceutical Inc.** have separately reported on their next-generation enzyme replacement therapies for Pompe's disease. Both molecules cleared glycogen from mouse muscle better than the marketed drug Myozyme from **Sanofi**.[1,2] BioMarin has moved its therapy into a Phase I/II trial, whereas Oxyrane is carrying out IND-enabling animal toxicology studies.

Pompe's disease is an inherited disorder of glycogen metabolism caused by an absence of or deficiency in the lysosomal enzyme acid α-glucosidase (GAA). The resulting accumulation of glycogen in cardiac and skeletal muscle leads to severe and progressive muscle weakness, cardiomyopathy and respiratory failure.

Sanofi's **Genzyme Corp.** unit markets the enzyme replacement therapy Myozyme and Lumizyme to treat the disease.

The problem is that skeletal muscle cells are less accessible to systemic enzyme replacement therapy than cells targeted in other lysosomal storage diseases. Indeed, the drugs are typically delivered at doses 20–30 times higher than other enzyme replacement therapies.[3] These high doses can lead to long infusion times and adverse reactions, including fever, tachycardia, cyanosis and hypotension.[4]

Thus, Oxyrane and BioMarin have been modifying GAA to improve its uptake into skeletal muscle and make possible the use of lower doses.

Both companies focused on modifying GAA to increase its affinity for the insulin-like growth factor 2 receptor (IGF2R; M6PR), which mediates uptake of GAA and other lysosomal enzymes into the muscle cell. The Oxyrane group used carbohydrate modifications, whereas the BioMarin researchers used a peptide modification (*see* **Figure 1, "Next-generation Myozyme"**).

The Oxyrane group hypothesized that enhancing levels of the carbohydrate mannose-6-phosphate (M-6-P) on the surface of GAA would increase its uptake by muscle cells. The binding of M-6-P to IGF2R is known to mediate delivery of proteins to the lysosome.[5–7]

Oxyrane used the yeasts *Yarrowia lipolytica* and *Pichia pastoris* to produce modified GAA. In prior work, Oxyrane researchers and colleagues had engineered those yeast to yield much higher levels of carbohydrate modifications than the mammalian cell lines used to produce Myozyme and Lumizyme.[8,9]

In the new paper, the group showed that the resulting carbohydrate-enriched GAA was purified from the yeast and treated with two processing enzymes to generate the final M-6-P-modified GAA, which had more than 15-fold higher M-6-P content than unmodified GAA.

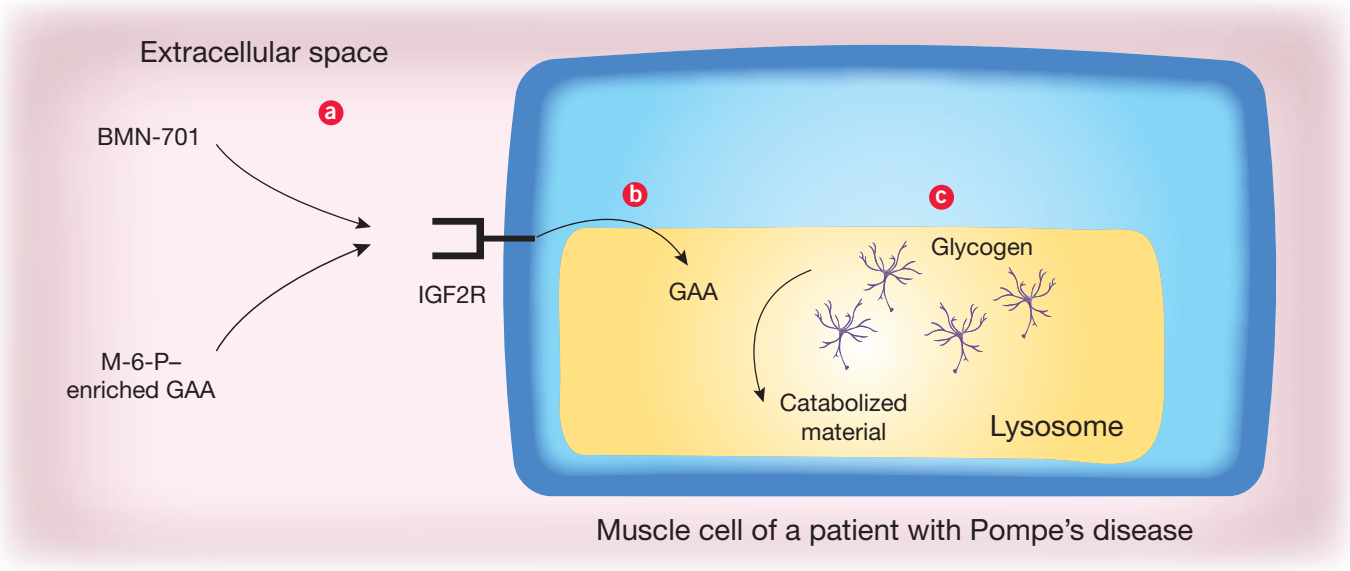

Figure 1. Next-generation Myozyme. Researchers from **Oxyrane U.K. Ltd.** and **BioMarin Pharmaceutical Inc.** have separately published two new strategies for delivering Pompe's disease enzyme replacement therapy.

Pompe's disease results from a lack of or deficiency in the enzyme acid α-glucosidase (GAA), which leads to pathological buildup of glycogen in the lysosomes of muscle cells. The only drugs approved for the disease are Myozyme and Lumizyme, enzyme replacement therapies marketed by **Sanofi**'s **Genzyme Corp.** unit.

The new strategies each modify GAA to enhance its affinity for its receptor on muscle cells, potentially allowing for the use of lower doses than those for Myozyme. BioMarin attached the peptide insulin-like growth factor-2 (IGF-2) to GAA, creating a compound dubbed BMN-701 (IGF-2-GAA), whereas Oxyrane enriched the surface of GAA with the carbohydrate mannose-6-phosophate (M-6-P).

The modified forms of GAA bound their receptor, insulin-like growth factor 2 receptor (IGF2R; M6PR), on the surface of muscle cells [**a**] and were internalized by receptor-mediated endocytosis [**b**]. In mice, GAA broke down glycogen deposits in the lysosome [**c**] and decreased muscle tissue pathology better than unmodified GAA or Myozyme.

Importantly, those higher M-6-P levels led to greater uptake of GAA by cultured fibroblasts from patients with Pompe's disease than uptake of unmodified GAA.

Finally, in a mouse model of Pompe's disease, the M-6-P-enhanced GAA cleared more glycogen from heart and thigh muscle than unmodified GAA.

The BioMarin group expected that linking a high-affinity endogenous ligand of IGF2R to GAA would increase uptake of the enzyme into muscle cells. Thus, they tagged GAA with a portion of insulin-like growth factor-2 (IGF-2), a ligand previously shown by some of the same BioMarin researchers to promote uptake of the lysosomal enzyme β-glucuronidase into fibroblasts.[10]

The tagged GAA, dubbed BMN-701 (IGF-2-GAA) was produced in mammalian cells, purified and shown to have the same enzymatic activity as untagged GAA. Moreover, BMN-701 showed greater uptake by rodent fibroblasts than Myozyme.

In mice with Pompe's disease, BMN-701 increased clearance of glycogen from the heart, diaphragm and multiple skeletal muscles compared with Myozyme.

The Oxyrane and BioMarin findings were published in *Nature Biotechnology* and *The Journal of Biological Chemistry*, respectively.

Pompe and circumstance

BMN-701 is in an ongoing Phase I/II trial, with top-line data expected in 1Q13, corresponding author and BioMarin staff scientist Jonathan LeBowitz told *SciBX*.

"We think it is possible that BMN-701 could achieve the same clinical benefit in patients as Myozyme but at lower doses. However, there is also the possibility, which is our current hope, that BMN-701 will show greater clinical benefit than the marketed drug at comparable higher doses," he said.

"The IGF-2 tagging approach doesn't rely on post-translational carbohydrate modifications, which can be difficult to control in large-scale bioreactors and could lead to regulatory challenges."
—Jonathan LeBowitz, BioMarin Pharmaceuticals Inc.

A potential advantage of BMN-701 over carbohydrate-modified GAA, said LeBowitz, is that "the IGF-2 tagging approach doesn't rely on post-translational carbohydrate modifications, which can be difficult to control in large-scale bioreactors and could lead to regulatory challenges."

Indeed, differences in carbohydrate modifications of Myozyme produced in a 4,000-liter bioreactor versus enzyme produced in the original 160-liter bioreactor led the FDA to require a separate approval for the drug at the higher scale. The resulting product is marketed as Lumizyme.[11]

Oxyrane's M-6-P-enriched GAA "is currently in the midst of six-month chronic animal toxicology studies, having successfully completed a four-week pilot toxicology study," corresponding author and Oxyrane CTO Wouter Vervecken told *SciBX*.

The company intends "to submit an IND next year with a view to advancing the product into Pompe's disease trials," he said. He declined to provide additional details on the timeline.

He added that Oxyrane's manufacturing process "is robust and scalable, and the company is already producing material based on fermentation at the 35-cubic-meter scale."

BioMarin and Oxyrane have patents covering their respective findings and therapies.

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COMPANIES AND INSTITUTIONS MENTIONED

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Genzyme Corp., Cambridge, Mass.
Oxyrane U.K. Ltd., Manchester, U.K.
Sanofi (Euronext:SAN; NYSE:SNY), Paris, France

Pulmonary edema on a chip

By Lauren Martz, Staff Writer

Researchers at the **Wyss Institute for Biologically Inspired Engineering at Harvard University** have described the first disease model to emerge from the institute's organ-on-a-chip microfluidic device technology.[1,2] The model of pulmonary edema could be better than culture models at predicting whether therapeutics will translate to humans.

The team already has used the lung-on-a-chip model in proof-of-concept studies to test potential pulmonary edema therapeutic candidates including **GlaxoSmithKline plc**'s GSK2193874, an inhibitor of transient receptor potential vanilloid 4 (TRPV4; VRL2),[3] and wants to expand the use of the chip to model multiple lung diseases.

GSK2193874 was also proven effective in a mouse model of pulmonary edema, validating the results that were found in the chip model (*see* **Box 1, "TRPV4 inhibition"**).

The microfluidics system on a chip is about 2 cm long and mimics the alveolar-capillary interface and mechanical effects of breathing. The device is composed of two channels—a layer of human alveolar epithelial cells exposed to air and pulmonary microvascular endothelial cells exposed to flowing culture medium.

The channels are separated by a porous polymer-coated extracellular matrix. The channel interface is bordered by two chambers that can deform the polymer membrane upon application of a vacuum to mimic the mechanical effects of breathing.

Notably, the ability to simulate the mechanics of breathing is absent in 3D culture models of the lung.

Previous studies by the Boston team showed that the model can replicate the key physiological features of lung function, but it was unknown whether the device could model pulmonary diseases.[2,4]

Now, Donald Ingber and colleagues have generated a model that captures features of edema, provides insights into disease mechanisms and can help assess therapeutic candidates.

Ingber is a professor of vascular biology at **Harvard Medical School** and **Boston Children's Hospital**, professor of bioengineering at **Harvard University** and director of the Wyss Institute.

Pulmonary edema involves the abnormal accumulation of intravascular fluid in the alveolar air spaces and interstitial tissues of the lung. Most often it is the result of elevated intravascular pressure caused by heart disease or is a toxic side effect of some drugs, such as IL-2.

Indeed, Ingber and colleagues used IL-2 to develop their disease model. The team delivered a clinically relevant dose of the cytokine through the fluid microchannel and monitored fluid leak across the endothelium and into the alveolar air space.

IL-2 induced a fluid leak that continued for four days and decreased air volume compared with no treatment. The administration of both IL-2 and human blood plasma proteins caused fluid leak and fibrin clot formation that occur during the disease.

The application of mechanical strains to mimic breathing further compromised the barrier between the endothelium and alveolar epithelium and enhanced the leakage caused by IL-2. In contrast, mechanical strain in the absence of IL-2 did not alter barrier integrity.

These findings suggest breathing may exacerbate pulmonary edema and that artificial ventilation may be counterproductive in patients with pulmonary edema.

Finally, the Wyss group used the model to test potential therapeutics. Application of GSK2193874 or angiopoietin 1 (ANG1; ANGPT1), an antagonist of the edema-inducing ANG2 (ANGPT2), inhibited IL-2-induced pulmonary edema.

Silence Therapeutics plc has Atu111, a small interfering RNA therapeutic targeting ANG2, in preclinical testing to treat acute lung injury.

The data were published in *Science Translational Medicine*. The authors included researchers from GSK and **Seoul National University**.

Breathing easy

The Boston team hopes to use the organ-on-a-chip technology to decrease the number of or replace many types of preclinical studies.

"Our next step is to explore what additional data might be required to convince pharmaceutical companies and the FDA that data produced by an on-chip model of human pulmonary edema could be used in place of results from an animal model of this condition to advance a drug toward testing in humans," Ingber told *SciBX*.

He said that unlike other *in vitro* models, the lung on a chip allows the study of organ-level functions. As for *in vivo* models, he said, "the chips should be faster and cheaper than animals."

Wolfgang Kübler, associate professor of surgery and physiology at the **University of Toronto**, was less bullish on the potential for taking animal studies out of the equation. "The model does not replicate animal experiments and the ability to study an entire organ or body," he said. "The litmus test still has to be *in vivo*, but this is certainly a good screening tool that may give a better indication of therapeutic success than simple cell cultures."

> **"The litmus test still has to be *in vivo*, but this is certainly a good screening tool that may give a better indication of therapeutic success than simple cell cultures."**
>
> ***—Wolfgang Kübler, University of Toronto***

Ingber said the model should be extendable to other lung conditions. For example, he said, the device could monitor the effects of aerosol-based toxins or aerosolized nanoparticles, aerosol-based drug delivery, smoke or chemical inhalation injury, radiation injury, fibrosis, pneumonias and metastasis.

His team is working on models of small airways on a chip to test drugs for diseases including asthma, chronic obstructive pulmonary disease (COPD) and cystic fibrosis (CF). The small airway model is designed to include multilayered ciliated epithelium from small lung bronchioles lined by endothelium—future plans include integrating immune cells and airway smooth muscle cells into the model. The team is also in discussions with pharmaceutical and biotech companies to test other therapeutics using the organ-on-a-chip models.

"One limitation is the throughput. The technology is currently not suitable for high throughput screening. However, we do not see this limiting their application in the drug discovery and development process because we expect this technology to be used to produce

Box 1. TRPV4 inhibition.

While the Boston team tested **GlaxoSmithKline plc**'s transient receptor potential vanilloid 4 (TRPV4; VRL2) inhibitor GSK2193874 in a lung-on-a chip model, the pharma reported on the discovery and subsequent animal studies of the edema therapeutic.

TRPV4 is known to mediate Ca^{2+} flux across the plasma membrane and promote vascular relaxation when activated by mechanical activities such as enhanced pressure.[5,6]

Previous studies, including work at the **University of South Alabama**, showed that knocking out Trpv4 in mice prevented increased vessel permeability and pressure-induced pulmonary edema.[7] Now, the group from South Alabama has teamed up with GSK to develop a TRPV4 inhibitor.

In a paper published in *Science Translational Medicine*,[3] Kevin Thorneloe and colleagues used small molecule screening and chemical optimization to develop GSK2193874. Thorneloe is a senior scientific investigator at GSK.

In isolated mouse and rat lungs, GSK2193874 reversed pulmonary edema. The therapeutic had no effect on the lungs at low pressure, suggesting it acts specifically against pressure-induced vessel leakage.

GSK2193874 also normalized pressure and decreased pulmonary edema compared with vehicle control in mouse models of chronic and acute venous pressure elevation. In the chronic model, GSK2193874 given one week after myocardial infarction–induced increases in pressure reversed pulmonary edema.

"GSK2193874 is still a discovery effort. Safety and toxicology studies are the next steps," said Thorneloe.

"TRPV4 is expressed in most cells in the body. This is a potential problem for inhibitors, and they may therefore be doing things that you don't want them to do, but the authors of the paper did a good job addressing some of the potential problems," said Wolfgang Kübler, associate professor of surgery and physiology at the **University of Toronto**. "For example, they showed that heart rate, blood pressure and kidney function were not affected by the inhibitors. They also showed that the effects of diuretics, which you would still want to give patients, were not altered."

He added, "This proves that if you block the TRPV4 channel, you can inhibit the further effects on fluid leakage. It also may support another pathological mechanism for TRPV4 that we have found. TRPV4 may also stimulate a cascade that inhibits the removal of fluid from the air spaces, so inhibiting the channel may both prevent leakage and increase fluid removal, but the team would need to confirm the relevance of this mechanism."

Thorneloe said GSK has filed for patents covering GSK2193874. *—LM*

high-quality, high-content predictive data. The data can be used to inform critical, high-value decisions such as selection or prioritization of a lead compound to move toward human testing," said Ingber.

Patent applications covering the chips, aerosol-based delivery, materials used in fabrication and different organ systems have been filed, and the IP is available for licensing.

Martz, L. *SciBX* 5(48); doi:10.1038/scibx.2012.1251
Published online Dec. 13, 2012

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   Contact: Donald E. Ingber, Harvard University, Boston, Mass.
   e-mail: don.ingber@wyss.harvard.edu
   Contact: Geraldine A. Hamilton, same affiliation as above
   e-mail: geraldine.hamilton@wyss.harvard.edu
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3. Thorneloe, K.S. *et al. Sci. Transl. Med.*; published online Nov. 7, 2012; doi:10.1126/scitranslmed.3004276
   Contact: Kevin S. Thorneloe, GlaxoSmithKline plc, King of Prussia, Pa.
   e-mail: kevin.s.thorneloe@gsk.com
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COMPANIES AND INSTITUTIONS MENTIONED

Boston Children's Hospital, Boston, Mass.
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Harvard Medical School, Boston, Mass.
Harvard University, Boston, Mass.
Seoul National University, Seoul, South Korea
Silence Therapeutics plc (LSE:SLN), London, U.K.
University of Toronto, Toronto, Ontario, Canada
University of South Alabama, Mobile, Ala.
Wyss Institute for Biologically Inspired Engineering at Harvard University, Cambridge, Mass.

This week in therapeutics

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

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

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Cancer				
Brain cancer	Natural cytotoxicity triggering receptor 1 (NCR1; NKP46; CD335); natural killer p30 receptor (NKp30; NCR3; CD337)	Mouse and cell culture studies suggest inhibiting NCR1 or NCR3 could enhance oncolytic viral therapies to treat glioblastoma. In mice with human glioblastoma cells injected with the oncolytic herpes virus rQNestin34.5, depletion of NK cells increased tumor levels of rQNestin34.5 and survival compared with no NK cell depletion. In human glioblastoma cells, rQNestin34.5 increased levels of the NK cell receptors NCR1 and NCR3 compared with mock treatment. In the glioblastoma xenograft mice treated with rQNestin34.5, those transplanted with Ncr1-deficient NK cells showed greater survival than those transplanted with wild-type NK cells. Next steps include identifying NCR1 and NCR3 ligands that are unregulated. *SciBX* 5(48); doi:10.1038/scibx.2012.1252 Published online Dec. 13, 2012	rQNestin34.5 patented by Massachusetts General Hospital; available for licensing	Alvarez-Breckenridge, C.A. *et al. Nat. Med.*; published online Nov. 25, 2012; doi:10.1038/nm.3013 **Contact:** E. Antonio Chiocca, Brigham and Women's Hospital, Dana-Farber Cancer Institute and Harvard Medical School, Boston, Mass. e-mail: eachiocca@partners.org **Contact:** Michael A. Caligiuri, The Ohio State University, Columbus, Ohio e-mail: michael.caligiuri@osumc.edu
Cancer	Epsin 1 (EPN1); EPN2	Mouse studies suggest inhibiting EPN1 and EPN2 could help treat cancer. In mouse models of cancer, conditional knockout of *Epn1* and *Epn2* in vascular endothelial cells increased survival and decreased tumor growth, incidence and size compared with no knockout. Next steps include screening and testing compounds for activity against epsins. *SciBX* 5(48); doi:10.1038/scibx.2012.1253 Published online Dec. 13, 2012	Patent application filed; available for licensing	Pasula, S. *et al. J. Clin. Invest.*; published online Nov. 26, 2012; doi:10.1172/JCI64537 **Contact:** Hong Chen, Oklahoma Medical Research Foundation, Oklahoma City, Okla. e-mail: hong-chen@omrf.org
Cancer	Retinoid X receptor-α (RXRA; RXRα); tumor necrosis factor-α (TNF-α)	Cell culture studies suggest a xanthone called CF31, isolated from the *Cratoxylum formosum* plant, could be useful for treating cancer. An *in vitro* screen identified CF31 as an inhibitor of truncated RXRα. In human cancer cell lines, CF31 induced apoptosis via a TNF-α-dependent pathway. Next steps could include studies to optimize CF31's anticancer effect and evaluate the compound in additional preclinical models. *SciBX* 5(48); doi:10.1038/scibx.2012.1254 Published online Dec. 13, 2012	Compound patented; available for licensing	Zhang, X.-k. *et al. Cancer Res.*; published online Nov. 14, 2012; doi:10.1158/0008-5472.CAN-12-2038 **Contact:** Xiao-kun Zhang, Sanford-Burnham Medical Research Institute, La Jolla, Calif. e-mail: xzhang@sanfordburnham.org
Lung cancer	Oncostatin M (OSM)	Mouse studies suggest the cytokine OSM could help treat lung cancer. OSM is produced by mesenchymal stem cells and promotes differentiation. In cultured human lung cancer cell lines, OSM inhibited migration and invasion. In mice, injection of OSM-pretreated lung cancer cells followed by intratumoral dosing with the cytokine decreased tumor growth and metastasis compared with vehicle injection. Next steps include evaluating the combination of OSM and chemotherapy. *SciBX* 5(48); doi:10.1038/scibx.2012.1255 Published online Dec. 13, 2012	Patent applications in progress; unavailable for licensing	Wang, M.-L. *et al. Cancer Res.*; published online Nov. 8, 2012; doi:10.1158/0008-5472.CAN-12-1568 **Contact:** Cheng-Wen Wu, National Yang-Ming University, Taipei, Taiwan e-mail: cwwu@ym.edu.tw

This week in therapeutics

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Endocrine/metabolic disease				
Diabetes; obesity	Not applicable	A clinical study suggests gastric bypass and gastric banding lead to equivalent and weight loss–dependent improvements in insulin sensitivity and β cell function. Previous studies have suggested gastric bypass may cause weight loss–independent effects that normalize glucose homeostasis in patients with obesity. In 20 obese, nondiabetic patients who received either treatment, both groups showed comparable improvements in insulin sensitivity and β cell function that were directly correlated with weight loss. Next steps could include additional studies in patients with diabetes. *SciBX* 5(48); doi:10.1038/scibx.2012.1256 Published online Dec. 13, 2012	Patent and licensing status not applicable	Bradley, D. *et al. J. Clin. Invest.*; published online Nov. 26, 2012; doi:10.1172/JCI64895 **Contact:** Samuel Klein, Washington University in St. Louis School of Medicine, St. Louis, Mo. e-mail: sklein@dom.wustl.edu
Metabolic disease; obesity	Phosphoenolpyruvate carboxykinase 1 (PCK1)	A zebrafish screening study identified metabolic activators that could protect against obesity-related metabolic dysregulation. A high throughput screening study using transgenic reporter zebrafish identified two ligands that increased *Pck1* promoter activity compared with vehicle. In mice with diet-induced obesity, subcutaneous injection of the lead ligand decreased hepatosteatosis and glucose intolerance compared with vehicle. Next steps include further characterizing the effects of the lead screening hit and using the zebrafish screen to identify more compounds with similar effects on metabolism. *SciBX* 5(48); doi:10.1038/scibx.2012.1257 Published online Dec. 13, 2012	Unpatented; licensing status not applicable	Gut, P. *et al. Nat. Chem. Biol.*; published online Dec. 2, 2012; doi:10.1038/nchembio.1136 **Contact:** Didier Y.R. Stainier, University of California, San Francisco, Calif. e-mail: didier.stainier@mpi-bn.mpg.de **Contact:** Philipp Gut, same affiliation as above e-mail: philipp.gut@ucsf.edu
Musculoskeletal disease				
Muscular dystrophy	Wingless-type MMTV integration site family member 7A (WNT7A)	Mouse studies suggest increasing WNT7A signaling could help treat muscular dystrophy. In the *mdx* mouse model of muscular dystrophy, plasmids that mediated Wnt7a expression increased muscle weight and muscle strength compared with control plasmids. Next steps include optimizing and producing the protein for therapeutic use. Fate Therapeutics Inc.'s FT301, a WNT7A analog, is in preclinical development to treat muscular dystrophy. *SciBX* 5(48); doi:10.1038/scibx.2012.1258 Published online Dec. 13, 2012	Covered by pending patents; licensed to Fate Therapeutics	Von Maltzahn, J. *et al. Proc. Natl. Acad. Sci. USA*; published online Nov. 26, 2012; doi:10.1073/pnas.1215765109 **Contact:** Michael A. Rudnicki, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada e-mail: mrudnicki@ohri.ca
Myotonic dystrophy type 1 (DM1)	Glycogen synthase kinase 3β (GSK3B)	Mouse studies suggest inhibiting GSK3B could help treat DM1. In a mouse model of DM1, activated GSK3B was upregulated prior to the development of muscle weakness. In the mouse model, the nonspecific GSK3B inhibitor lithium increased muscle strength and decreased myotonia in skeletal muscles compared with no treatment. Next steps could include clinical testing of lithium or other GSK3B inhibitors in patients with DM1. Jeil Pharmaceutical Co. Ltd.'s GSK3B inhibitor, JGK-216/263, is in discovery to treat Alzheimer's disease (AD) and amyotrophic lateral sclerosis (ALS). *SciBX* 5(48); doi:10.1038/scibx.2012.1259 Published online Dec. 13, 2012	Findings unpatented; licensing status not applicable	Jones, K. *et al. J. Clin. Invest.*; published online Nov. 19, 2012; doi:10.1172/JCI64081 **Contact:** Lubov T. Timchenko, Baylor College of Medicine, Houston, Texas e-mail: lubovt@bcm.tmc.edu

This week in therapeutics

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Neurology				
Alzheimer's disease (AD)	Amyloid precursor protein (APP)	Studies in mice suggest preventing the accumulation of the C99 peptide fragment of APP could help prevent or treat AD. In brain tissue from a mouse model of AD, immunohistochemical staining revealed intracellular aggregates of C99, a partially cleaved form of APP that is the precursor of β-amyloid (Aβ). Next steps include testing for the presence of C99 in brain tissue from patients with AD and controls. *SciBX* 5(48); doi:10.1038/scibx.2012.1260 Published online Dec. 13, 2012	Unpatented; licensing status not applicable	Lauritzen, I. *et al. J. Neurosci.*; published online Nov. 14, 2012; doi:10.1523/JNEUROSCI.2775-12.2012 **Contact:** Frédéric Checler, University of Nice Sophia Antipolis, Nice, France e-mail: checler@ipmc.cnrs.fr
Alzheimer's disease (AD)	Arrestin β2 (ARRB2)	*In vitro* and mouse studies suggest antagonizing ARRB2 could help treat AD. *In vitro*, ARRB2 coimmunoprecipitated with γ-secretase, a proteolytic complex that generates β-amyloid (Aβ). In cell culture, overexpression of ARRB2 increased production of Aβ and small interfering RNA knockdown of ARRB2 decreased Aβ levels compared with what was seen using vector controls. In a mouse model of AD, Arrb2 knockout mice had lower levels of Aβ than wild-type controls. Next steps include identifying pharmacological modulators of G protein–coupled receptor 3 (GPR3), a receptor that appears to work upstream of ARRB2 and previously has been implicated in Aβ production. *SciBX* 5(48); doi:10.1038/scibx.2012.1261 Published online Dec. 13, 2012	Patent pending; unavailable for licensing	Thathiah, A. *et al. Nat Med.*; published online Dec. 2, 2012; doi:10.1038/nm.3023 **Contact:** Bart De Strooper, Catholic University Leuven, Leuven, Belgium e-mail: bart.destrooper@cme.vib-kuleuven.be **Contact:** Amantha Thathiah, same affiliation as above e-mail: amantha.thathiah@cme.vib.kuleuven.be
Alzheimer's disease (AD)	Glycogen dependent kinase 3 (GSK3)	Mouse studies suggest inhibiting GSK3 could help to treat AD. In a mouse model of aggressive AD, animals showed hyperactive GSK3 and developed massive cerebral β-amyloid (Aβ) loads, memory deficits and neuronal loss. Nasal delivery of the GSK3 inhibitor L803-mt decreased Aβ deposits and increased cognitive function compared with no treatment. Next steps include completing preclinical safety and toxicity studies. *SciBX* 5(48); doi:10.1038/scibx.2012.1262 Published online Dec. 13, 2012	Patented by Ramot at Tel Aviv University; available for licensing	Avrahami, L. *et al. J. Biol. Chem.*; published online Nov. 15, 2012; doi:10.1074/jbc.M112.409250 **Contact:** Hagit Eldar-Finkelman, Tel Aviv University, Tel Aviv, Israel e-mail: heldar@post.tau.ac.il **Contact:** Dan Frenkel, same affiliation as above e-mail: dannyf34@gmail.com
Alzheimer's disease (AD)	IL-12; IL-23	Patient sample and mouse studies suggest inhibiting IL-12 and IL-23 signaling could help treat AD. In a transgenic mouse model of AD, microglia production of p40, a subunit common to IL-12 and IL-23, was greater than that in healthy controls. In the same mouse model, intracerebroventricular delivery of an anti-p40 antibody decreased cognitive deficits and β-amyloid (Aβ) burden compared with delivery of an isotype control. In cerebrospinal fluid samples from patients with AD, p40 levels were higher than those in samples from healthy controls. Next steps include studying the downstream effects and mechanisms related to targeting p40. Bristol-Myers Squibb Co. and Johnson & Johnson market Stelara ustekinumab, a human mAb that inhibits IL-12 and IL-23, to treat psoriasis. Abbott Laboratories' briakinumab, a human mAb against IL-12 and IL-23, is under regulatory review for the same indication. At least four other companies have compounds targeting both IL-12 and IL-23 in Phase II testing or earlier to treat various autoimmune or inflammatory diseases. *SciBX* 5(48); doi:10.1038/scibx.2012.1263 Published online Dec. 13, 2012	Patent application filed; available for licensing from Unitectra via the University of Zurich	Vom Berg, J. *et al. Nat. Med.*; published online Nov. 25, 2012; doi:10.1038/nm.2965 **Contact:** Frank L. Heppner, Charité–University Hospital Berlin, Berlin, Germany e-mail: frank.heppner@charite.de **Contact:** Burkhard Becher, University of Zurich, Zurich, Switzerland e-mail: becher@immunology.uzh.ch

This week in therapeutics

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Alzheimer's disease (AD)	SRSF protein kinase 2 (SRPK2)	Human sample and mouse studies suggest inhibiting SRPK2 signaling could help treat AD. In brain tissue samples from patients with AD, levels of activated SRPK2 were higher in AD-associated pathological structures than surrounding tissue. In a mouse model of AD, small hairpin RNA against *Srpk2* in the dentate gyrus of the brain increased memory performance and decreased microtubule-associated protein-τ (Mapt; Tau; Ftdp-17) phosphorylation compared with control shRNA. Next steps could include screening for small molecules that could inhibit SRPK2 signaling. ***SciBX* 5(48); doi:10.1038/scibx.2012.1264** **Published online Dec. 13, 2012**	Unpatented; licensing status not applicable	Hong, Y. *et al. J. Neurosci.*; published online Nov. 28, 2012; doi:10.1523/JNEUROSCI.3300-12.2012 **Contact:** Keqiang Ye, Emory University School of Medicine, Atlanta, Ga. e-mail: kye@emory.edu **Contact:** Chi Bun Chan, same affiliation as above e-mail: cbchan@emory.edu
Excessive sleepiness	$GABA_A$ receptor	*In vitro* and clinical studies suggest $GABA_A$ receptor inhibitors could help treat hypersomnias (excessive sleepiness). Increased $GABA_A$ receptor signaling has been associated with increased drowsiness. In cell culture, cerebrospinal fluid (CSF) from patients with hypersomnias plus γ-aminobutyric acid (GABA) increased $GABA_A$ receptor activity compared with CSF from non-hypersomnolent individuals plus GABA. In the cells, treatment with the generic $GABA_A$ receptor antagonist flumazenil prevented the increased activity caused by the CSF from hypersomnolent individuals. In seven hypersomnolent patients, flumazenil increased psychomotor vigilance and alertness compared with saline control. Next steps include larger clinical studies. ***SciBX* 5(48); doi:10.1038/scibx.2012.1265** **Published online Dec. 13, 2012**	Patent and licensing status unavailable	Rye, D.B. *et al. Sci. Transl. Med.*; published online Nov. 21, 2012; doi:10.1126/scitranslmed.3004685 **Contact:** David B. Rye, Emory University School of Medicine, Atlanta, Ga. e-mail: drye@emory.edu
Neurology	Platelet derived growth factor A (PDGFA; PDGF1)	A study in mice suggests lithium could help treat neonatal hydrocephalus, an expansion of the cerebral ventricles. In a mouse model of Bardet-Biedl syndrome (BBS) in which the animals develop hydrocephalus, oligodendrocyte precursor cells from the diseased mice had a decreased response to PDGFA, a known survival signaling pathway in these cells, compared with the same cell population from wild-type mice. In BBS mice, lithium, which nonspecifically stimulates downstream effectors in the PDGFA pathway, decreased ventricle volume compared with control treatment. Next steps include testing the effects of lithium in additional hydrocephalus mouse models and the effects of combination therapy using lithium and antiapoptotic drugs. ***SciBX* 5(48); doi:10.1038/scibx.2012.1266** **Published online Dec. 13, 2012**	Unpatented; licensing status not applicable	Carter, C.S. *et al. Nat. Med.*; published online Nov. 18, 2012; doi:10.1038/nm.2996 **Contact:** Val C. Sheffield, University of Iowa Carver College of Medicine, Iowa City, Iowa e-mail: val-sheffield@uiowa.edu

This week in techniques

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

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

Approach	Summary	Licensing status	Publication and contact information
Assays & screens			
Antibiotic mode of action profile (BioMAP) screening to identify and classify antibiotics in natural product extracts	Comparing the inhibitory profiles of natural product extracts with those of known classes of antibiotics could help identify new antibiotic leads. MICs of 72 commercially available antibiotics with multiple mechanisms of action were determined against 15 bacterial strains. A computational analysis that compared the MIC profiles of these known drugs with the MIC profile of natural product extract fractions helped identify a structurally unique naphthoquinone antibiotic with a distinct inhibitory profile. *In vitro*, the antibiotic inhibited bacterial cell growth at 12.5–50 μM concentrations. Next steps include screening a 5,000-member marine natural product library to identify additional antibiotic scaffolds for development. *SciBX* 5(48); doi:10.1038/scibx.2012.1267 Published online Dec. 13, 2012	Unpatented; licensing status not applicable; compounds can be screened on a fee-for-service basis through the University of California, Santa Cruz Chemical Screening Center	Wong, R.W. *et al. Chem. Biol.*; published online Nov. 21, 2012; doi:10.1016/j.chembiol.2012.09.014 **Contact:** Roger G. Linington, University of California, Santa Cruz, Calif. e-mail: rlinington@ucsc.edu
Design of Genuine Structures (DOGS) software for *de novo* computer-assisted drug design	A computational software package called DOGS could be useful for discovering new therapeutic leads to treat cancer and other diseases. The software uses a library of 25,000 molecular building blocks and a set of 83 chemical reactions to design chemotypes with scaffolds that are distinct from a template molecule but still mimic its pharmacophore features. The software was used to design an inhibitor of the cancer-associated polo-like kinase 1 (PLK1; STPK13). In a human cervical cancer cell line, the designed compound inhibited proliferation with an EC_{50} value of 4 μM. Next steps include evaluating the DOGS software in ongoing drug discovery projects in collaboration with industry partners. *SciBX* 5(48); doi:10.1038/scibx.2012.1268 Published online Dec. 13, 2012	Patent and licensing status undisclosed	Spänkuch, B. *et al. Angew. Chem. Int. Ed.*; published online Nov. 20, 2012; doi:10.1002/anie.201206897 **Contact:** Gisbert Schneider, Swiss Federal Institute of Technology Zurich (ETHZ), Zurich, Switzerland e-mail: gisbert.schneider@pharma.ethz.ch
Disease models			
Mouse model for invasive lobular breast cancer metastasis	A mouse model for invasive lobular breast cancer metastasis could aid the understanding of metastasis and help test new therapeutic candidates. Wild-type mice were orthotopically implanted with invasive lobular carcinoma tumor fragments and then had a mastectomy after primary tumors were established. The majority of these mice died because of metastatic disease in the lymph nodes, lungs, liver and spleen. In the model, chemotherapy delayed the development of metastatic disease compared with saline. Next steps could include using the model to evaluate therapeutics that could prevent metastasis. *SciBX* 5(48); doi:10.1038/scibx.2012.1269 Published online Dec. 13, 2012	Unpatented; available for licensing	Doornebal, C.W. *et al. Cancer Res.*; published online Nov. 14, 2012; doi:10.1158/0008-5472.CAN-11-4208 **Contact:** Karin E. de Visser, The Netherlands Cancer Institute, Amsterdam, the Netherlands e-mail: k.d.visser@nki.nl
Drug platforms			
Boosting antitumor immune response by blocking glycolysis	A study in mice suggests blocking glycolysis with a small molecule could help enhance an antitumor immune response. In a mouse tumor model, a combination of the chemotherapeutic agent etoposide with a low dose of the glycolysis inhibitor 2-deoxy-D-glucose (2-DG) increased an antitumor T cell response and survival and decreased tumor size compared with either treatment alone. Next steps include testing 2-DG in combination with other chemotherapeutics. In 2011, Threshold Pharmaceuticals Inc. discontinued development of 2-DG, which was in Phase I testing for solid tumors. *SciBX* 5(48); doi:10.1038/scibx.2012.1270 Published online Dec. 13, 2012	Patent pending; available for licensing	Bénéteau, M. *et al. Proc. Natl. Acad. Sci. USA*; published online Nov. 19, 2012; doi:10.1073/pnas.1206360109 **Contact:** Jean-Ehrland Ricci, Institut National de la Santé et de la Recherche Médicale (INSERM), Nice, France e-mail: ricci@unice.fr

This week in techniques

Approach	Summary	Licensing status	Publication and contact information
Insulin-like growth factor-2 (IGF-2) peptide tag to improve enzyme replacement therapies to treat Pompe's disease	A lysosome-targeting peptide tag may be useful for producing Pompe's disease enzyme replacement therapies that have better tissue uptake than unmodified acid α-glucosidase (GAA). A fusion protein consisting of a portion of IGF-2 linked to recombinant human GAA was expressed in and purified from mammalian cells. *In vitro*, the resulting BMN-701 (IGF-2-GAA) showed better uptake by rodent myoblasts than unmodified GAA. In a mouse model of Pompe's disease, BMN-701 led to lower levels of glycogen in heart, diaphragm and skeletal muscle than unmodified GAA. BMN-701 is in Phase I/II testing to treat Pompe's disease, with topline data expected 1Q13. Myozyme and Lumizyme are human recombinant GAA enzyme replacement therapies marketed by Sanofi's Genzyme Corp. unit to treat Pompe's disease (*see* **Muscling up on Myozyme, page 5**). *SciBX* 5(48); doi:10.1038/scibx.2012.1271 Published online Dec. 13, 2012	Findings patented; licensing status undisclosed	Maga, J.A. *et al. J. Biol. Chem.*; published online Nov. 27, 2012; doi:10.1074/jbc.M112.438663 **Contact:** Jonathan H. LeBowitz, BioMarin Pharmaceuticals Inc., Novato, Calif. e-mail: jlebowitz@bmrn.com
Yeast cell lines for producing improved enzyme replacement therapies to treat Pompe's disease	Genetically modified strains of the yeasts *Yarrowia lipolytica* and *Pichia pastoris* may be useful for producing Pompe's disease enzyme replacement therapies that have better tissue uptake than unmodified acid α-glucosidase (GAA). The yeast strains were modified to express a highly glycosylated form of human recombinant GAA, the lysosomal enzyme that is absent or dysfunctional in Pompe's disease. GAA was then purified from the yeast and treated with two bacterial glycosidase enzymes to generate GAA highly enriched in mannose-6-phosphate (M-6-P), a carbohydrate that targets GAA to the lysosome. *In vitro*, the M-6-P-enriched GAA was taken up by Pompe's disease patient fibroblasts in larger quantities than unmodified GAA. In a mouse model of Pompe's disease, the M-6-P-enriched GAA cleared heart and thigh muscle of glycogen better than unmodified GAA. Next steps carried out by Oxyrane U.K. Ltd. include animal toxicology studies. Myozyme and Lumizyme are human recombinant GAA enzyme replacement therapies marketed by Sanofi's Genzyme Corp. unit to treat Pompe's disease (*see* **Muscling up on Myozyme, page 5**). *SciBX* 5(48); doi:10.1038/scibx.2012.1272 Published online Dec. 13, 2012	Findings patented; licensing status undisclosed	Tiels, P. *et al. Nat. Biotechnol.*; published online Nov. 18, 2012; doi:10.1038/nbt.2427 **Contact:** Wouter Vervecken, Oxyrane U.K. Ltd., Manchester, U.K. e-mail: wvervecken@oxyrane.com **Contact:** Nico Callewaert, Flanders Institute for Biotechnology (VIB), Ghent, Belgium e-mail: nico.callewaert@dmbr.vib-ugent.be **Contact:** Han Remaut, same affiliation as above e-mail: han.remaut@vib-vub.be

Company and institution index

Target and compound index