

**THIS WEEK****ANALYSIS****COVER STORY****1 Anti-CD20 therapy for heart attack**

A multinational team has used anti-CD20 mAbs to treat heart attacks by depleting inflammation-causing CD20<sup>+</sup> B cells at the infarct site. The researchers are planning a Phase IIa trial of Rituxan in MI, and at least one biotech with an anti-CD20 antibody is discussing the findings with its pharma partner.

**TARGETS & MECHANISMS****4 Two respiratory viruses, one antibody**

Humabs and the Institute for Research in Biomedicine have identified an antibody that could be used to prevent as well as treat RSV, thus providing an advantage over the prophylactic Synagis. The mAb also could be effective against metapneumovirus, another common respiratory virus.

**6 Hedgehog battles Down syndrome**

Researchers at Johns Hopkins have shown that a hedgehog pathway activator could help improve brain development, learning and memory in patients with Down syndrome. The team is trying to narrow the therapeutic window to maximize neuronal response to boosted hedgehog signaling.

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The Research Center for Molecular Medicine of the Austrian Academy of Sciences and Haplogen have generated a library of haploid knockout human cells that allows for the systematic investigation of gene function *in vitro*. Haplogen is using the library for its drug discovery programs.

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By Michael J. Haas, Senior Writer

A multinational team has taken a new approach to treating heart attacks: depleting the host of B cells that recruit monocytes to the infarct site, where they further inflame and damage tissue.<sup>1</sup> The mouse findings hand a new indication to companies that market or are developing antibodies against CD20 on B cells to treat cancer and autoimmune diseases.

The team is planning a Phase IIa trial of the anti-CD20 mAb Rituxan/MabThera rituximab in patients with myocardial infarction (MI) at several hospitals in Cambridge, U.K., and Paris and is discussing partnering options for the trial with one or more of the companies that market the mAb.

Meanwhile, at least one biotech that has an anti-CD20 antibody is discussing the new findings with its pharma partner.

The ischemic damage caused by MI reduces cardiac function and can lead to death or recurrence of MI. Multiple studies have shown that MI activates components of the innate immune system that contribute to cardiac inflammation and damage, including complement factors, neutrophils and monocytes.<sup>2-7</sup>

B cells, however, have been absent from that list because the cells' role in innate immune responses to post-ischemic and other types of acute injury is poorly understood.

Ziad Mallat and his team have now studied whether B cells play a role in cardiac inflammation and damage after MI and whether the cells or their downstream effectors could be targeted to treat the indication.

Mallat is professor of cardiovascular medicine at **Addenbrooke's Hospital** and team leader of the immunity, inflammation and atherosclerosis group at the **Institut National de la Santé et de la Recherche Médicale (INSERM)**.

The team examined cardiac tissue from mouse models of MI and found greater infiltration of mature B cells at the infarct site than that seen in cardiac tissue from healthy controls. The number of infiltrating B cells peaked at day five postinfarction and waned thereafter.

Circulating and cardiac levels of chemokine CC motif ligand 7 (Ccl7; Mcp3; Scya6)—a protein that can trigger mobilization of monocytes from bone marrow to injured tissue—were higher in the MI models than in healthy controls. Additional experiments in the models showed that after infarction, B cells in the heart and circulation secreted Ccl7, triggering the recruitment of proinflammatory monocytes to the infarction site.

Next, the team treated the mouse models at one hour and one day postinfarction with a murine anti-Cd20 mAb. The treatment decreased circulating levels of Ccl7 and consequent monocyte recruitment to the

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infarct site compared with vehicle, thereby reducing infarct size and increasing cardiac function.

Also in the mouse models of MI, the team found that deficiency in BLYS (Baff) receptor—which is necessary for maintaining mature B cells—decreased levels of circulating Ccl7 and increased cardiac function compared with what was seen in wild-type controls. Although the BLYS receptor deficiency did not affect infarct size, this did not necessarily mean BLYS receptor inhibition would be less effective than CD20 inhibition at treating MI. “The BLYS receptor was absent throughout development in the mice, which would not be the case in a short-term therapeutic strategy in adults,” Mallat told *SciBX*.

Lastly, the team showed that levels of CCL7 and BLYS ligand in the serum of patients with MI were associated with an increased risk of death and recurrent MI.

“Our findings suggest that a single dose of an anti-CD20 antibody delivered shortly after MI could reduce the risk of death or recurrence,” Mallat told *SciBX*.

The team included researchers from the **University Paris Descartes, Paris Diderot University, the Pierre and Marie Curie University, Lariboisière Hospital, Saint Antoine Hospital, Georges Pompidou European Hospital, the Medical University of Vienna, the Austrian Academy of Sciences, the Gladstone Institute of Cardiovascular Disease and Duke University Medical Center.**

Data were reported in *Nature Medicine*.

**Biogen Idec Inc., Roche** and its **Genentech Inc.** unit market Rituxan, a chimeric mAb against CD20, to treat rheumatoid arthritis (RA), multiple sclerosis (MS), inflammatory disease, lymphoma, non-Hodgkin’s lymphoma (NHL) and chronic lymphocytic leukemia (CLL). The partners also have the mAb in Phase III testing to treat mantle cell lymphoma (MCL).

**Repurposeful thinking**

Multiple companies market or are developing antibodies against CD20 for cancer, autoimmune diseases and inflammatory indications that could be repurposed to treat MI (see **Table 1**, “CD20: new angle of attack”).

Although the team’s findings in mouse models did not allow a direct comparison of therapeutic strategies, Mallat said that anti-CD20 antibodies would probably be more effective than inhibitors of BLYS–BLYS receptor signaling because the former deplete B cells rapidly after a single dose, whereas the latter take longer to deplete B cells and alter their functions.

Additionally, the BLYS receptor may be expressed on cells other than B cells and thus could lead to side effects, he said.

“The role of B cells in ischemic injury has long been neglected,” said Paul Parren, SVP and scientific director at **Genmab A/S**. “This new study certainly makes a strong case for investigating the impact of B cell depletion with anti-CD20 therapy after acute myocardial infarction.”

Genmab is focused on cancer, but Parren said that the possibility of repurposing its Arzerra ofatumumab “is certainly something we would want to discuss” with partner **GlaxoSmithKline plc**.

**“Our findings suggest that a single dose of an anti-CD20 antibody delivered shortly after MI could reduce the risk of death or recurrence.”**  
 —Ziad Mallat,  
*Institut National de la Santé et de la Recherche Médicale*

**Table 1. CD20: new angle of attack.** A study by a multinational team suggests that depleting B cells with anti-CD20 therapy shortly after myocardial infarction (MI) could reduce infarct size and improve cardiac function, thereby reducing the risk of death or recurrent MI. The findings offer a repurposing opportunity to companies that market or are developing anti-CD20 antibodies to treat cancer, autoimmune diseases and inflammatory indications. Additionally, at least eight other companies market or are developing biosimilars of the anti-CD20 antibody rituximab to treat cancer and autoimmune indications.

Source: *BCIQ: BioCentury Online Intelligence*

Company	Anti-CD20 antibody <sup>A</sup>	Antibody type	Status
<b>Biogen Idec Inc.</b> (NASDAQ:BIIB)/ <b>Roche</b> (SIX:ROG; OTCQX:RHHBY)/ <b>Genentech Inc.</b>	Rituxan/MabThera rituximab	Chimeric mAb	Marketed for chronic lymphocytic leukemia (CLL), lymphoma, non-Hodgkin's lymphoma (NHL), inflammatory disease, multiple sclerosis (MS) and rheumatoid arthritis (RA); Phase III to treat mantle cell lymphoma (MCL)
<b>Genmab A/S</b> (CSE:GEN;OTCBB:GMXAY)/ <b>GlaxoSmithKline plc</b> (LSE:GSK; NYSE:GSK)	Arzerra ofatumumab	Human mAb	Marketed for CLL; Phase III for B cell lymphoma, NHL, pemphigus vulgaris (PV) and RA; Phase II for MS
Roche/Genentech/ <b>Chugai Pharmaceutical Co. Ltd.</b> (Tokyo:4519)/ <b>Nippon Shinyaku Co. Ltd.</b> (Tokyo:4516; Osaka:4516)	Obinutuzumab (GA101; RG7159; RO5072759)	Glycoengineered, humanized mAb	In registration for CLL; Phase III for B cell lymphoma and NHL
Roche/Chugai Pharmaceutical/Genentech/ <b>Halozyne Therapeutics Inc.</b> (NASDAQ:HALO)	Subcutaneous rituximab	Chimeric mAb	In registration for NHL
Biogen Idec/Roche/Genentech	Ocrelizumab (R1594; RG1594)	Humanized mAb	Phase III for MS
<b>Immunomedics Inc.</b> (NASDAQ:IMMU)/ <b>Takeda Pharmaceutical Co. Ltd.</b> (Tokyo:4502)	Veltuzumab (hA20; IMMU-106)	Humanized mAb	Phase II for lupus; Phase I/II for CLL, NHL, hematological malignancies and idiopathic thrombocytopenic purpura (ITP); preclinical for pancreatic cancer
<b>LFB S.A./Ildong Pharmaceutical Co. Ltd.</b> (KSE:000230)/ <b>TG Therapeutics Inc.</b> (NASDAQ:TGTX)	Ublituximab (LFB-R603; TG-1101; TGTX-1101)	Chimeric mAb	Phase I/II for B cell lymphoma, CLL and NHL
<b>Biocon Ltd.</b> (NSE:BIOCON; BSE:BIOCON)/ <b>Vaccinex Inc.</b>	BVX-20	Humanized mAb	Phase I for NHL

<sup>A</sup>Does not include anti-CD20 antibodies that are radiolabeled, bispecific or multivalent.

Genmab and GSK market Arzerra, a human mAb against CD20, to treat CLL. Arzerra has breakthrough therapy designation for first-line treatment of CLL in the U.S.

The partners also have the mAb in Phase III testing to treat B cell lymphoma, NHL, RA and pemphigus vulgaris (PV) and in Phase II testing to treat MS.

Before deciding whether anti-CD20 therapy is feasible in patients with MI, “we would like to see investigations on timing and dosing in the mouse model,” Parren said. “In cardiac ischemic injury, the timing of treatment is of the essence. So it would be important to find out how much time there is—after cardiac injury—for the anti-CD20 therapy to be helpful.”

Additionally, he said, “titrating the dose of the anti-CD20 therapy in mice should indicate the magnitude of B cell depletion required to achieve the therapeutic effect, and repeat dosing should indicate whether prolonged therapy improves the results.”

Mallat said that his team already has run the type of timing and dosing studies suggested by Parren but declined to disclose details. He noted that the team also has unpublished data showing that the window of time during which monocyte recruitment to the infarct site can be blocked by depleting B cells is similar in the mouse models and in patients with MI.

INSERM and the **University of Cambridge** have filed for a patent covering the findings, and the IP is available for licensing, Mallat said.

He declined to disclose with which of the companies that market Rituxan—Biogen Idec, Roche or Genentech—his team is discussing a partnering deal for the Phase IIa trial.

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## COMPANIES AND INSTITUTIONS MENTIONED

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**Georges Pompidou European Hospital**, Paris, France  
**Gladstone Institute of Cardiovascular Disease**, San Francisco, Calif.  
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**Lariboisière Hospital**, Paris, France  
**Medical University of Vienna**, Vienna, Austria  
**Paris Diderot University**, Paris, France  
**Pierre and Marie Curie University**, Paris, France  
**Roche** (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland  
**Saint Antoine Hospital**, Paris, France  
**University of Cambridge**, Cambridge, U.K.  
**University Paris Descartes**, Paris, France

# Two respiratory viruses, one antibody

By Tracey Baas, Senior Editor

Humabs BioMed S.A. and the Institute for Research in Biomedicine at the University of Lugano have identified an antibody that could offer multiple advantages over the blockbuster respiratory syncytial virus prophylactic Synagis palivizumab. The group expects that their product, MPE8, could be used to both treat and prevent respiratory syncytial virus. It also could be effective against metapneumovirus, another common respiratory virus.<sup>1</sup>

Respiratory syncytial virus (RSV) and metapneumovirus (MPV) both can cause severe disease in premature newborns, hospitalized children and immune-compromised adults.<sup>2-5</sup>

Synagis from AstraZeneca plc's MedImmune LLC unit is marketed to prevent RSV infection in high-risk infants. The mAb posted sales of \$1.04 billion in 2012 but is not indicated as a therapeutic<sup>6</sup> and has been shown *in vivo* to lead to the generation of viral escape mutants resistant to the drug.<sup>7</sup>

There is no targeted therapeutic for MPV infection. Treatment includes routine symptomatic care and respiratory support. Ribavirin, which has broad antiviral activity, is the only approved therapy for RSV and is sometimes used as a last-ditch treatment in children with severe infections by RSV or MPV.

Both viruses are members of the paramyxovirus family and share 33% amino acid identity in the F protein, which is the primary target of neutralizing antibodies.<sup>8,9</sup>

A Humabs-led team hypothesized that rare cross-neutralizing antibodies—those able to inhibit both RSV and MPV—might exist in the sera of individuals who have been repeatedly exposed to both viruses.

The group screened a cohort of 200 blood donors and selected 7 individuals who showed high levels of serum neutralizing antibodies against both viruses. The researchers then immortalized memory B cells isolated from the donors and determined if any antibodies produced by the B cells could neutralize both RSV and MPV.

The team identified 30 antibodies against RSV, and of those, 2 also had activity against MPV.

*In vitro*, one of the cross-reactive antibodies, dubbed MPE8, neutralized a panel of RSV and MPV strains as well as two related animal paramyxoviruses. The antibody was about eightfold more potent than Synagis at neutralizing RSV. It also prevented RSV from spreading from cell to cell, suggesting MPE8 has potential as a therapeutic in patients in which infection already has taken hold.

In a mouse model of RSV infection, MPE8 given four hours before RSV nasal challenge decreased pulmonary infection 5- to 10-fold more than Synagis. In a mouse model of MPV infection, prophylactic use of MPE8 four hours before MPV nasal challenge decreased pulmonary infection compared with prophylactic use of vehicle.

The RSV mouse model is limited because it shows only modest viral replication, so the team next used a mouse model of infection with pneumonia virus of mice (PVM), which is lethal in mice and recapitulates the symptoms and pathology of human severe RSV infection. In the PVM mouse model, MPE8 given four hours before PVM nasal challenge protected the animals from lethality when given at doses as low as 0.12 mg/Kg. Furthermore, MPE8 also protected the mice when given up to three days after PVM nasal challenge, whereas ribavirin was ineffective.

The authors did not report virus titer data and instead showed percent reductions in viral mRNA, which they quantified using RT-PCR. Showing log reductions of virus titers would have required plaque assays, which measure actual virus.

Results were published in *Nature*.

## Going viral

Humabs is in discussions with companies to license MPE8 as well as other potent RSV-specific antibodies described in the study.

**“MPE8 represents a next-generation palivizumab with higher potency on RSV and higher breadth, being able to neutralize MPV as well. This considerably extends the target population and the therapeutic indications.”**

—Alcide Barberis,  
Humabs BioMed S.A.

“MPE8 represents a next-generation palivizumab with higher potency on RSV and higher breadth, being able to neutralize MPV as well. This considerably extends the target population and the therapeutic indications,” Humabs president and CEO Alcide Barberis told *SciBX*.

“We believe that MPE8 could represent a strong candidate for therapy of severe RSV/MPV infections,” said Antonio Lanzavecchia, director of the Institute for Research in Biomedicine at the University of Lugano and a Humabs cofounder. “Proof of concept in

humans could be obtained with a small trial in transplanted patients with documented RSV or MPV upper respiratory tract infection to block spread from upper to lower respiratory tract.”

Julian Symons, senior director of product development at infectious disease company **Alios BioPharma Inc.**, thought that tests of MPE8 in more traditional RSV and MPV animal models, which include the cotton rat and nonhuman primates, would be appropriate.

“Both viruses replicate more robustly in cotton rats than they do in mice,” said Symons.

He added, “It would be interesting to assess how broadly neutralizing MPE8 is against the members of the paramyxovirus family. The paper describes neutralizing activity versus RSV, MPV, BRSV [bovine RSV] and PMV [paramyxovirus], which are all members of the *Pneumovirinae* subfamily. Does MPE8 neutralize other paramyxoviruses such as the *Paramyxovirinae* subfamily members mumps, measles, hendra virus or parainfluenza viruses?”

Vu Truong, founder and CSO of **Aridis Pharmaceuticals LLC**, wanted to see a more detailed analysis comparing Synagis with MPE8 against RSV in potency and strain coverage. “The team presents their viral clearance data in terms of percent reduction of viral mRNA. However, more compelling data would be viral clearance presented in terms of log reduction of virus titers,” Truong said. “To be considered more effective, you would want to see at least a log or more decrease in viral replication and possibly reactivity against Synagis-resistant strains.”

**“It would be interesting to assess how broadly neutralizing MPE8 is against the members of the paramyxovirus family. The paper describes neutralizing activity versus RSV, MPV, BRSV [bovine RSV] and PMV [paramyxovirus], which are all members of the *Pneumovirinae* subfamily. Does MPE8 neutralize other paramyxoviruses such as the *Paramyxovirinae* subfamily members mumps, measles, hendra virus or parainfluenza viruses?”**

—Julian Symons,  
Alios BioPharma Inc.

Richard Hegele, chair of laboratory medicine and pathobiology at the University of Toronto, said that the team should run *in vivo* studies in different species that investigate escape virus mutants or the possibility of using two or more RSV antibodies that target different F protein epitopes.

“The failure to select MPE8 escape mutants *in vitro* gives us confidence that escape mutants are either extremely rare or may not exist,” said Lanzavecchia. “On this ground we suggest that a single antibody may be sufficient.”

On the safety side, Truong said, “It would be useful to initially test MPE8 against a panel of

human tissues to ensure the lack of cross-reactivity.”

Lanzavecchia agreed. “This is a standard procedure in the clinical development of antibodies. Our preliminary data indicate that there is no evident cross-reactivity.”

Humabs has filed for a patent covering MPE8 and the RSV-specific antibodies described in the study. The IP is available for licensing.

MedImmune declined requests for an interview.

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#### COMPANIES AND INSTITUTIONS MENTIONED

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# Hedgehog battles Down syndrome

By Lev Osherovich, Senior Writer

Researchers at **The Johns Hopkins University School of Medicine** have proposed that mental retardation caused by Down syndrome could be prevented or mitigated after birth with a small molecule activator of the sonic hedgehog homolog pathway.<sup>1</sup> The group's mouse data show improvements in brain development, learning and memory. However, the narrow therapeutic window and the long gap in time between treatment and evaluation of cognitive endpoints in patients will pose significant translational challenges.

Down syndrome arises from an extra copy of chromosome 21, leading to multiple craniofacial and neurological abnormalities. Compared with brains from healthy controls, the brains of patients with Down syndrome have smaller cerebellums and hippocampuses—regions that control motor activity and memory, respectively.

The likely cause of this small brain size is deficient signaling by the sonic hedgehog homolog (SHH) pathway, which controls the duration of stem and progenitor cell proliferation throughout development.

In 2006, a team led by Roger Reeves found that in a mouse model of Down syndrome, the neonatal brain did not respond properly to hedgehog signaling and had fewer mature neurons than controls.<sup>2</sup>

“People with Down syndrome have a smaller cerebellum [than healthy controls], and we found that the mice do as well,” said Reeves, who is a professor of physiology at the Institute of Genetic Medicine at Johns Hopkins. “The trisomic mice had a layer of precursor neurons that had the same number as in control mice, but they don't divide as much” in response to hedgehog signaling.

In the new study, Reeves' team reported that the neuronal deficiency in the brains of young mice with Down syndrome could be corrected by transient treatment with a small molecule activator of smoothed (SMO), a GPCR that is a downstream effector of hedgehog signaling.

Drawing on earlier evidence from a **University of California, San Francisco** study that suggested pharmacological activation of hedgehog pathway signaling promoted the proliferation of cerebellar neural precursors,<sup>3</sup> Reeves hypothesized that a hedgehog agonist could correct the shortage of cerebellar neurons in Down syndrome mice.

Reeves' team tested this hypothesis by injecting newborn Down syndrome mice with a small molecule SMO agonist and observed larger, more cellularized cerebellums than those in vehicle-treated controls. Indeed, the cerebellums of the treated mice resembled those of wild-type animals.

The team next examined the effect of the SMO agonist on hippocampal function. Mice receiving the compound had improved learning and memory and performed better in a widely used maze navigation test than untreated controls. In a brain slice assay of hippocampal function, tissue from treated mice was more responsive

to stimulation than that of untreated controls.

Reeves' team did not report whether the SMO agonist affected hippocampal morphology.

Results were published in *Science Translational Medicine* and are not patented.

## Stimulating development

Reeves' findings are surprising because the hedgehog pathway was not previously thought to affect development of the hippocampus during the postnatal period. What remains unclear is whether the hedgehog pathway directly acts in the hippocampus.

Because the cerebellum was previously believed to be the principal site of hedgehog signaling, one possibility is that having a bigger cerebellum could lead to improvements in other areas of the brain, including the hippocampus.

“The cerebellum is involved in motor function but is not thought to affect learning and memory,” said Reeves. “Perhaps we have fixed something in the cerebellum and this has effects elsewhere in the brain.”

In support of this idea, David Rowitch, a **Howard Hughes Medical Institute** investigator and a professor of pediatrics and neurosurgery at UCSE, said that the new findings are in line with recent evidence that the cerebellum can influence development of other brain tissues.

In 2011, Rowitch's team reported that a SMO agonist could prevent damage to the cerebellum in neonatal mice exposed to glucocorticoids, which are used to treat respiratory problems in premature infants.<sup>3</sup>

“There's a lot of attention now to the cerebellum as being of primary importance in development of other brain areas,” said Rowitch. “Further research is required to determine whether the effects of the hedgehog pathway on the cerebellum and hippocampus are related or distinct.”

To resolve this question, Rowitch recommended genetic experiments to selectively activate hedgehog signaling in various brain regions.

Reeves favors the idea that hedgehog signaling might act directly on the hippocampus independently of its effects on the cerebellum.

Evidence to support this view comes from a second study in which Reeves collaborated with the laboratory of Chris De Zeeuw, a professor at the **Netherlands Institute for Neuroscience**, to test the effect of a SMO agonist on cerebellar function.

In that study, published this week in *The Journal of Neuroscience*, the team showed that a SMO agonist increased the size of the cerebellum. However, the molecule did not improve two specific functions of that tissue—motor learning and light adaption—that are compromised in Down syndrome mice.<sup>4</sup>

Thus, Reeves suspects that the greater size of the cerebellum in mice treated with a SMO agonist may be a red herring, and the truly important site of hedgehog signaling may be the hippocampus itself.

“This study makes me excited to pursue the effects of a smoothed agonist on the hippocampus,” said Reeves.

## Clinical challenge

Regardless of where hedgehog signaling acts in the brain, the functional

“This study makes me excited to pursue the effects of a smoothed agonist on the hippocampus.”

—Roger Reeves,  
The Johns Hopkins University  
School of Medicine

benefits on learning and memory seen in mice make SMO activation an attractive therapeutic strategy for Down syndrome.

Reeves thinks that a therapy able to address even a subset of the neurological aspects of Down syndrome would help improve quality of life.

“I think this pathway certainly has therapeutic application for people born with Down syndrome,” he said.

The biggest obstacles for the hedgehog activation strategy are concerns about the safety of turning on a developmental pathway that is involved in a range of cancers, including a common pediatric brain tumor—medulloblastoma.

Indeed, drug development around the hedgehog pathway has focused exclusively on inhibiting overactive SMO in cancer. The most advanced SMO antagonist is Erivedge vismodegib, marketed by **Roche’s Genentech Inc.** unit to treat advanced basal cell carcinoma (BCC). It is in Phase II testing for medulloblastoma and other solid tumors. **Curis Inc.** co-developed Erivedge with Genentech.

“One has to be extremely careful about the potential toxicities and off-target effects” of activating hedgehog signaling, said Rowitch.

Nevertheless, Reeves and Rowitch noted that tumor growth likely requires chronic activation of the hedgehog pathway such as through gain-of-function mutations in *SMO*.

“The chances of transformation into a tumor are just theoretical because animal studies have not borne out a tumorigenic potential for a short course of treatment,” said Rowitch. “The kinds of situations that lead to tumors are oncogenic mutations where the cells can never escape from elevated hedgehog signaling.”

Reeves hopes to use clinical pathology data to narrow down the therapeutic window during which cerebellar and hippocampal neurons are most likely to respond to boosted hedgehog signaling.

He said that the ideal scenario would be that a brief course of a SMO agonist could be given over a relatively short period immediately after birth, when neurons are developing rapidly. However, it is not yet known how much stimulation would be needed for what length of time to elicit benefits without incurring cancer risk.

“It’s clear this neurodevelopmental process in people starts at least at birth and goes on for several years,” said Reeves. “Some studies suggest that this developmental process starts at or near birth, while other studies suggest a wave of proliferation occurs later in childhood.”

Previous clinical trials in patients with Down syndrome have focused

on improving cognitive functioning with neuromodulatory agents used for symptomatic treatment of age-related cognitive decline, which develops more rapidly in patients with Down syndrome than in healthy controls.

For example, Roche’s RG1662, a negative allosteric modulator of GABA<sub>A</sub> receptor  $\alpha_5$  (GABRA5), is in Phase I testing in adult patients with Down syndrome.

A neonatal prevention trial of the kind suggested by Reeves’ work has never been attempted and thus faces technical, regulatory and possibly ethical challenges.

For example, because the cognitive effects of Down syndrome involve a combination of motor, speech and learning deficits that are difficult to distinguish until later in childhood, it is not clear how long a trial should be, when it should begin and what endpoints would be most appropriate.

Rowitch thinks the predictable and severe nature of Down syndrome makes a potentially disease-modifying interventional trial in infants an appealing idea, but he said companies might steer clear of the space.

“In neonates with Down syndrome, you have a very high likelihood of severe mental

deficit, so parents can be desperate to do something,” said Rowitch. “On the other hand, it’s very risky to work in a population where adverse consequences of treatment could incur liabilities. Not many companies are willing to venture in neonatal therapeutics.”

Osherovich, L. *SciBX* 6(37); doi:10.1038/scibx.2013.1017  
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#### COMPANIES AND INSTITUTIONS MENTIONED

**Curis Inc.** (NASDAQ:CRIS), Lexington, Mass.  
**Genentech Inc.**, South San Francisco, Calif.  
**Howard Hughes Medical Institute**, Chevy Chase, Md.  
**The Johns Hopkins University School of Medicine**, Baltimore, Md.  
**Netherlands Institute for Neuroscience**, Amsterdam, the Netherlands  
**Roche** (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland  
**University of California, San Francisco**, Calif.

**“There’s a lot of attention now to the cerebellum as being of primary importance in development of other brain areas. Further research is required to determine whether the effects of the hedgehog pathway on the cerebellum and hippocampus are related or distinct.”**

—David Rowitch,  
Howard Hughes Medical Institute

# Trapping human genes

By Amy Donner, Senior Editor

The Research Center for Molecular Medicine of the Austrian Academy of Sciences and Haplogen GmbH have generated a library of haploid knockout human cells that, for the first time, allows for the systematic interrogation of gene function *in vitro*.<sup>1</sup> The partners are completing the library, although the collection already is available to the scientific community and is being used for Haplogen's internal drug discovery efforts.

In model organisms, gene inactivation has been a powerful approach to elucidate protein function. In particular, libraries of haploid yeast cells—with one gene inactivated per cell—have been invaluable to helping understand basic cellular processes, gene-gene interactions and gene-drug interactions.

“For scientists working with human cells, however, there are no single knockout libraries available. We use RNAi or genome engineering strategies, but there is no equivalent to yeast libraries for mammalian cells,” noted Sebastian Nijman, a principal investigator at the Research Center for Molecular Medicine (CeMM) and cofounder of Haplogen.

A group led by Nijman, Thijn Brummelkamp and Giulio Superti-Furga set out to generate the first library of human cells comparable to what is available to the yeast community. Brummelkamp is group leader at The Netherlands Cancer Institute, adjunct principal investigator at CeMM and cofounder and head of research at Haplogen. Superti-Furga is CEO, scientific director and a principal investigator at CeMM and cofounder of Haplogen.

The biggest hurdle was the difference in genome copy number between yeast and humans. Unlike mammalian cells, haploid yeast occur naturally, which makes it easier to generate gene-specific knockouts. The human genome is diploid—cells contain two copies of every chromosome—which complicates the generation of gene-specific knockouts in cells.

Prior studies by Brummelkamp had provided proof of concept for using a gene-trap retrovirus to inactivate single human genes in a natural, stable, near-haploid human cell line called KBM7. The cell line was subcloned from a patient with *BCR-ABL*<sup>+</sup> chronic myelogenous leukemia (CML).<sup>2</sup>

Although the approach worked, it was both labor intensive and time consuming. Moreover, it did not allow for the creation of a library for the systematic analysis of gene function across the entire genome.

Brummelkamp performed that research when he was at the Whitehead Institute for Biomedical Research.

To generate an actual library that would allow researchers to investigate specific genes on demand, the team engineered the gene-trap construct to contain barcodes of unique DNA sequences to facilitate identification and isolation of individual knockout clones. Following

random integration of the construct into thousands of cells, analysis of the resulting clones indicated that gene trapping resulted in near-complete gene inactivation.

In the majority of cells in the library, gene inactivation was reversible. According to Nijman, reversible expression is helpful because it allows a scientist “to rule out passenger mutations as the cause of an interesting phenotype that emerges from a screen” and thus is a simple way to establish a functional connection between the trapped gene and the observed phenotype.

With the right gene-trap insertion, essential genes could also be targeted without killing the cells—a feature that improves the utility of the platform in research.

To validate the utility of the collection, the scientists showed that cells with mutations in genes downstream of multiple cytokines were no longer responsive to the proteins. The cytokine genes included *tumor necrosis factor- $\alpha$*  (*TNF- $\alpha$* ) and *interferon- $\gamma$*  (*IFNG*; *IFN- $\gamma$* ), the ligand *TNF-related apoptosis-inducing ligand* (*TRAIL*) and the growth factor *transforming growth factor- $\beta$*  (*TGF $\beta$* ).

Results were published in *Nature Methods*.

“Having knockout lines for all human genes available as reagents that are delivered within days will fundamentally change the way we perform and plan experiments.”

—Georg Casari, Haplogen GmbH

## Going for full coverage

The library reported in the paper so far covers about a third of all protein-coding genes. Work

to complete the collection is ongoing, and the library should double in size within 12 months. New clones will be added to the collection as they become available.

According to Nijman, “The main objective is to generate a collection to cover the entire genome.”

Haplogen CEO and cofounder Georg Casari added that “our goal is to provide a library that has a knockout clone for each human gene that can be removed. Having knockout lines for all human genes available as reagents that are delivered within days will fundamentally change the way we perform and plan experiments. Many experiments will now be limited only by having the right question or idea rather than by overcoming technical obstacles associated with genetic experiments in human cells.”

Nijman's lab is now using the library to evaluate the mechanism of action for drugs and to elucidate gene-drug interactions.

Haplogen will use the library internally for drug discovery and development. “We will be able to perform novel screens for drug targets, mostly in the area of infectious diseases. Those programs can fuel our drug development pipeline, which already contains several targets identified using haploid genetics,” noted Casari.

The Human Gene Trap Mutant Collection was generated as a public-private partnership between CeMM and Haplogen and is available to the scientific community at <http://clones.haplogen.org/>.

“The collection is available pretty much without limits for academic research via a material transfer agreement,” said Nijman. The library is also available to companies through a licensing agreement or partnership with Haplogen.

Nijman and Casari expect the completed library will soon be followed by related libraries from their team and others. New genome editing methodologies, including clustered, regularly interspaced short palindromic repeats (CRISPR) and transcription activator-like effector

nucleases (TALENs),<sup>3</sup> could also be used to generate gene-specific knockouts, and libraries generated with these alternative technologies will likely provide access to complementary capabilities. But Nijman pointed out that useful features of the current library such as reversibility and DNA barcoding might be difficult to recreate with these other technologies.

Haplogen is seeking licensing and partnership opportunities and already has undisclosed partnerships in a variety of areas, including cancer and metabolic disease.

The library is not patented. The gene-trapping technology is patented by the Whitehead Institute.

Donner, A. *SciBX* 6(37); doi:10.1038/scibx.2013.1018  
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**Haplogen GmbH**, Vienna, Austria  
**The Netherlands Cancer Institute**, Amsterdam, the Netherlands  
**Research Center for Molecular Medicine of the Austrian Academy of Sciences**, Vienna, Austria  
**Whitehead Institute for Biomedical Research**, Cambridge, Mass.

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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>Cancer</b>				
Brain cancer	K(lysine) acetyltransferase 2B (KAT2B; PCAF)	Cell culture and mouse studies suggest inhibiting PCAF could help treat brain cancer by reducing sonic hedgehog homolog (SHH) signaling. A small interfering RNA screen of histone acetyltransferases found that knockdown of PCAF impeded SHH pathway activation. In glioblastoma and medulloblastoma cell lines, knockdown of PCAF decreased growth compared with no knockdown. In mice, intracranial injection of neural stem cells with PCAF knockdown led to lower tumor growth than injection of cells with no knockdown. Next steps include seeking collaborators to develop PCAF inhibitors.  <b>SciBX 6(37); doi:10.1038/scibx.2013.1019</b> <b>Published online Sept. 26, 2013</b>	Unpatented; licensing status not applicable	Malatesta, M. <i>et al. Cancer Res.</i> ; published online Aug. 13, 2013; doi:10.1158/0008-5472.CAN-12-4660 <b>Contact:</b> Kristian Helin, University of Copenhagen, Copenhagen, Denmark e-mail: <a href="mailto:kristian.helin@bric.ku.dk">kristian.helin@bric.ku.dk</a>
Breast cancer	Dual specificity phosphatase 4 (DUSP4; MKP2); c-jun N-terminal kinase (JNK); MEK	<i>In vitro</i> and mouse studies suggest inhibiting MEK and JNK could help treat triple-negative breast cancer by targeting cancer stem cells. DUSP4 normally suppresses MEK and JNK pathways, but it is downregulated in basal-like breast cancer cells. In cultured, triple-negative, basal-like breast cancer cells, inhibition of MEK and JNK or overexpression of DUSP4 decreased expression of cancer stem cell markers compared with no treatment. Next steps could include testing MEK and JNK inhibition in animal models of the cancer. GlaxoSmithKline plc markets Mekinist trametinib (GSK1120212), a small molecule MEK inhibitor, to treat melanoma. At least 14 other companies have MEK inhibitors in Phase III testing or earlier to treat various cancers.  <b>SciBX 6(37); doi:10.1038/scibx.2013.1020</b> <b>Published online Sept. 26, 2013</b>	Patent and licensing status unavailable	Balko, J.M. <i>et al. Cancer Res.</i> ; published online Aug. 21, 2013; doi:10.1158/0008-5472.CAN-13-1385 <b>Contact:</b> Carlos L. Arteaga, Vanderbilt University, Nashville, Tenn. e-mail: <a href="mailto:carlos.artea@vanderbilt.edu">carlos.artea@vanderbilt.edu</a>
Cancer	Alkylglycerone phosphate synthase (AGPS)	Studies in patient samples and mice suggest inhibiting AGPS could help treat cancer. In tumor samples from patients with breast cancer, AGPS levels were higher than those in matched normal tissues. In human breast cancer and melanoma cell lines, small hairpin RNA against AGPS decreased motility, growth and invasiveness compared with control shRNA. In mouse xenograft models of breast cancer or melanoma, shRNA knockdown of AGPS decreased tumor growth compared with no knockdown. Next steps include conducting further studies to characterize the role of AGPS in cancer cell metabolism and developing small molecule inhibitors.  <b>SciBX 6(37); doi:10.1038/scibx.2013.1021</b> <b>Published online Sept. 26, 2013</b>	Unpatented; licensing status not applicable	Benjamin, D.I. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Aug. 26, 2013; doi:10.1073/pnas.1310894110 <b>Contact:</b> Daniel K. Nomura, University of California, Berkeley, Calif. e-mail: <a href="mailto:dnomura@berkeley.edu">dnomura@berkeley.edu</a>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Cancer	E1A binding protein p300 (EP300; p300)	<p>Studies in mice suggest inhibiting p300 could help treat cancer by promoting antitumor immunity. In an immunocompetent mouse model of cancer, animals with T<sub>reg</sub>-specific p300 knockout had lower tumor growth and tumor T<sub>reg</sub> infiltration and greater CD8<sup>+</sup> T cell infiltration than mice without p300 knockout. In two immunocompetent mouse models of cancer, a small molecule p300 inhibitor increased antitumor immune responses and decreased tumor growth compared with vehicle. Next steps include testing more potent inhibitors of p300 with better pharmacokinetics.</p> <p>Acylin Therapeutics Inc. has p300 inhibitors in preclinical development.</p> <p><b>SciBX 6(37); doi:10.1038/scibx.2013.1022</b> Published online Sept. 26, 2013</p>	Patent application filed; available for licensing	<p>Liu, Y. <i>et al. Nat. Med.</i>; published online Aug. 18, 2013; doi:10.1038/nm.3286</p> <p>Contact: Wayne W. Hancock, The Children's Hospital of Philadelphia and Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pa. e-mail: <a href="mailto:whancock@mail.med.upenn.edu">whancock@mail.med.upenn.edu</a></p>
Cancer	Enhancer of zeste homolog 2 (EZH2); embryonic ectoderm development (EED)	<p><i>In vitro</i> studies suggest inhibiting EZH2-EED interactions could help treat cancer. Chemical synthesis and <i>in vitro</i> testing of stapled peptide analogs of the EED-binding domain of EZH2 identified a lead peptide with nanomolar binding affinity for EED. In a murine leukemia cell line and human breast and prostate cancer cell lines, the peptide inhibited EZH2-EED interactions and decreased proliferation compared with a control peptide. In human lymphoma cell lines harboring <i>EZH2</i> mutations, the peptide and a small molecule inhibitor of the EZH2 catalytic site decreased proliferation compared with either agent alone. Ongoing work includes optimizing the lead peptide and testing it in a range of cancers.</p> <p>Epizyme Inc. and Eisai Co. Ltd. have EPZ6438 (E7438), a selective inhibitor of EZH2, in Phase I/II testing to treat lymphoma and non-Hodgkin's lymphoma (NHL).</p> <p>Constellation Pharmaceuticals Inc., Novartis AG and GlaxoSmithKline plc have EZH2 inhibitors in preclinical development to treat cancer.</p> <p><b>SciBX 6(37); doi:10.1038/scibx.2013.1023</b> Published online Sept. 26, 2013</p>	Patented by the Dana-Farber Cancer Institute; available for licensing or partnering	<p>Kim, W. <i>et al. Nat. Chem. Biol.</i>; published online Aug. 25, 2013; doi:10.1038/nchembio.1331</p> <p>Contact: Stuart H. Orkin, Boston Children's Hospital, Boston, Mass. e-mail: <a href="mailto:stuart_orkin@dfci.harvard.edu">stuart_orkin@dfci.harvard.edu</a></p> <p>Contact: Loren Walensky, same affiliation as above e-mail: <a href="mailto:loren_walensky@dfci.harvard.edu">loren_walensky@dfci.harvard.edu</a></p>
Cancer	Follistatin-like 1 (FSTL1)	<p>Mouse and cell culture studies suggest inhibiting FSTL1 could help prevent cancer metastasis to the bone. In mouse and human cancer cell lines, small interfering RNA knockdown of <i>FSTL1</i> decreased invasiveness and expression of bone metastasis-associated factors compared with no knockdown. In mouse xenograft models of melanoma, siRNA against <i>Fstl1</i> decreased tumor growth, metastasis to the bone and survival compared with control siRNA. Next steps include developing FSTL1 inhibitors and conducting studies in patient samples to determine whether there is a correlation between elevated FSTL1 levels and bone metastasis.</p> <p><b>SciBX 6(37); doi:10.1038/scibx.2013.1024</b> Published online Sept. 26, 2013</p>	Patent application filed; available for licensing from the Keio University School of Medicine Contact: Koji Nakamoto, Keio University School of Medicine, Tokyo, Japan e-mail: <a href="mailto:koji.nakamoto@adst.keio.ac.jp">koji.nakamoto@adst.keio.ac.jp</a>	<p>Kudo-Saito, C. <i>et al. Cancer Res.</i>; published online Aug. 21, 2013; doi:10.1158/0008-5472.CAN-13-1364</p> <p>Contact: Chie Kudo-Saito, Keio University School of Medicine, Tokyo, Japan e-mail: <a href="mailto:kudoc@a3.keio.jp">kudoc@a3.keio.jp</a></p>

## This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cancer	Lysine-specific demethylase 2 (KDM2); KDM7	<i>In vitro</i> and cell culture studies identified a hydroxamate-based inhibitor of KDM2 and KDM7 that could help treat cancer. <i>In vitro</i> and computational modeling studies identified a compound that inhibited KDM2 and KDM7 at low or submicromolar concentrations. In cancer cell lines, the compound decreased proliferation compared with no treatment. Next steps include testing the compound in xenograft mouse models of cancer.  <b>SciBX 6(37); doi:10.1038/scibx.2013.1025</b> <b>Published online Sept. 26, 2013</b>	Patent application filed; available for licensing	Suzuki, T. <i>et al. J. Med. Chem.</i> ; published online Aug. 21, 2013; doi:10.1021/jm400624b <b>Contact:</b> Naoki Miyata, Nagoya City University, Nagoya, Japan e-mail: <a href="mailto:miyata-n@phar.nagoya-cu.ac.jp">miyata-n@phar.nagoya-cu.ac.jp</a> <b>Contact:</b> Tamio Mizukami, Nagahama Institute of Bio-Science and Technology, Shiga, Japan e-mail: <a href="mailto:mizukami@nagahama-i-bio.ac.jp">mizukami@nagahama-i-bio.ac.jp</a> <b>Contact:</b> Takayoshi Suzuki, Kyoto Prefectural University of Medicine, Kyoto, Japan e-mail: <a href="mailto:suzukit@koto.kpu-m.ac.jp">suzukit@koto.kpu-m.ac.jp</a>
Colorectal cancer (CRC)	Fibroblast growth factor receptor 4 (FGFR4; CD334)	Cell culture and mouse studies suggest antagonizing FGFR4 could help treat colorectal cancer. In cell culture, human CRC cells cocultured with tumor-associated fibroblasts had higher levels of FGFR4 than control cultures without fibroblasts. In a mouse xenograft model of CRC, small hairpin RNA knockdown of <i>FGFR4</i> decreased tumor growth and metastasis and increased survival compared with no knockdown. Next steps include identifying and testing pharmacological inhibitors of FGFR4.  <b>SciBX 6(37); doi:10.1038/scibx.2013.1026</b> <b>Published online Sept. 26, 2013</b>	Unpatented; licensing status not applicable	Liu, R. <i>et al. Cancer Res.</i> ; published online Aug. 13, 2013; doi:10.1158/0008-5472.CAN-12-4718 <b>Contact:</b> Canhua Huang, Sichuan University, Chengdu, China e-mail: <a href="mailto:hcanhua@hotmail.com">hcanhua@hotmail.com</a>
Head and neck cancer	CXC chemokine receptor 7 (CXCR7)	Mouse studies suggest CXCR7-targeting nanobodies could help treat head and neck cancers. In a xenograft mouse model of CXCR7 <sup>+</sup> human head and neck squamous cell carcinoma, injection of a CXCR7-targeting nanobody decreased tumor growth compared with saline injection. Next steps could include evaluating the CXCR7-targeting nanobody in additional head and neck cancer models.  Ablynx N.V. collaborated on the study and has multiple nanobodies in clinical and preclinical development for various diseases. The company has not disclosed if there is a CXCR7-targeting nanobody in its pipeline.  ChemoCentryx Inc.'s CCX650, a small molecule CXCR7 antagonist, is in preclinical development to treat brain cancer.  <b>SciBX 6(37); doi:10.1038/scibx.2013.1027</b> <b>Published online Sept. 26, 2013</b>	Patent and licensing status unavailable	Maussang, D. <i>et al. J. Biol. Chem.</i> ; published online Aug. 26, 2013; doi:10.1074/jbc.M113.498436 <b>Contact:</b> Martine J. Smit, Free University Amsterdam, Amsterdam, the Netherlands e-mail: <a href="mailto:mj.smit@vu.nl">mj.smit@vu.nl</a>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Prostate cancer	Hydroxysteroid 3 $\beta$ dehydrogenase 1 (HSD3B1)	<i>In vitro</i> and mouse studies suggest inhibiting HSD3B1 could help treat castration-resistant prostate cancer. HSD3B1 is required for testosterone-independent synthesis of dihydrotestosterone (DHT), which contributes to prostate cancer growth. An acquired gain-of-function mutation in HSD3B1 that increased DHT levels was identified in 3 of 25 castration-resistant prostate tumors. In prostate cancer cells or a mouse xenograft model of prostate cancer, small hairpin RNA knockdown of HSD3B1 decreased DHT levels and cell or tumor proliferation compared with no knockdown. Next steps include identifying small molecule inhibitors of the target.	Two provisional patent applications filed; potentially available for licensing	Chang, K.-H. <i>et al. Cell</i> ; published online Aug. 29, 2013; doi:10.1016/j.cell.2013.07.029 Contact: Nima Sharifi, Cleveland Clinic, Cleveland, Ohio e-mail: <a href="mailto:sharifn@ccf.org">sharifn@ccf.org</a>
<b>Cardiovascular disease</b>				
Myocardial infarction (MI)	CD20; chemokine CC motif ligand 7 (CCL7; MCP3; SCYA6)	Human serum and mouse studies suggest antibodies against CD20 could help treat MI. In mouse models of MI, B cells and monocytes in cardiac tissue and levels of Ccl7 secreted by B cells in blood and cardiac tissue were higher than those in healthy controls. In these models, an anti-Cd20 mAb decreased Ccl7 levels and infarct size and increased cardiac function compared with vehicle. In serum from patients with MI, CCL7 levels were associated with risk of death and recurrent MI. Planned work includes testing anti-CD20 antibodies in patients following MI. Rituxan/MabThera rituximab, an antibody against CD20 from Biogen Idec Inc. and the Genentech Inc. unit of Roche, is marketed for a variety of autoimmune diseases and hematological cancers. Arzerra ofatumumab, a mAb against CD20 from Genmab A/S and GlaxoSmithKline plc, is marketed for chronic lymphocytic leukemia (CLL); see <i>Anti-CD20 therapy for heart attack</i> , page 1).	Patent application filed by the Institut National de la Santé et de la Recherche Médicale (INSERM) and University of Cambridge; available for licensing	Zouggari, Y. <i>et al. Nat. Med.</i> ; published online Sept. 15, 2013; doi:10.1038/nm.3284 Contact: Ziad Mallat, Institut National de la Santé et de la Recherche Médicale (INSERM), Paris, France e-mail: <a href="mailto:zm255@medschl.cam.ac.uk">zm255@medschl.cam.ac.uk</a>
<b>Endocrine/metabolic disease</b>				
Diabetes	v-Maf musculoaponeurotic fibrosarcoma oncogene homolog A (MAFA; RIPE3b1); microRNA-204 (miR-204)	Mouse and cell culture studies suggest inhibiting miR-204 could help treat diabetes. In a mouse model of type 2 diabetes, miR-204 expression in islets was greater than that in islets from lean control mice. In an islet $\beta$ cell line and in primary human islets, miR-204 overexpression decreased insulin expression and levels of the insulin regulator MAFA compared with wild-type expression. Next steps include developing and optimizing miR-204 inhibitors.	Patent application filed covering use in diabetes; available for licensing from the UAB Research Foundation	Xu, G. <i>et al. Nat. Med.</i> ; published online Aug. 25, 2013; doi:10.1038/nm.3287 Contact: Anath Shalev, The University of Alabama at Birmingham, Birmingham, Ala. e-mail: <a href="mailto:shalev@uab.edu">shalev@uab.edu</a>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Inflammation</b>				
Asthma	<i>Aspergillus fumigatus</i> asperamide B	<i>In vitro</i> and mouse studies suggest inhibiting asperamide B could help treat asthma triggered by <i>Aspergillus</i> . In mice, <i>A. fumigatus</i> activated pulmonary invariant NK T (iNKT) cells and induced airway hyperresponsiveness, which was prevented by Cd1d knockout. In cocultures of bone marrow-derived cells and iNKT cells, asperamide B purified from <i>A. fumigatus</i> directly activated iNKT cells. Next steps include additional studies to understand how <i>Aspergillus</i> causes severe asthma.  <b>SciBX 6(37); doi:10.1038/scibx.2013.1031</b> <b>Published online Sept. 26, 2013</b>	Provisional patent application filed; available for licensing	Albacker, L.A. <i>et al. Nat. Med.</i> ; published online Sept. 1, 2013; doi:10.1038/nm.3321 <b>Contact:</b> Dale T. Umetsu, Harvard Medical School, Boston, Mass. e-mail: <a href="mailto:dale.umetsu@childrens.harvard.edu">dale.umetsu@childrens.harvard.edu</a>
<b>Neurology</b>				
Alzheimer's disease (AD)	Ryanodine receptor 1 (RyR1); RyR2	Studies in mice suggest ryanodine receptor agonists could be useful for treating AD. In a mouse model of hereditary AD, ryanodine receptor-mediated calcium release and hippocampal RyR1 and RyR2 levels were lower than those in normal mice. In mouse brain slices, knockdown of RyR1 and RyR2 decreased activity-dependent calcium release and neuronal activity compared with no knockdown. Next steps could include testing the effects of moderate ryanodine receptor agonists on cognitive function in mouse models of AD.  <b>SciBX 6(37); doi:10.1038/scibx.2013.1032</b> <b>Published online Sept. 26, 2013</b>	Patent and licensing status undisclosed	Wu, B. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Aug. 5, 2013; doi:10.1073/pnas.1304171110 <b>Contact:</b> Jie Shen, Harvard Medical School, Boston, Mass. e-mail: <a href="mailto:jshen@rics.bwh.harvard.edu">jshen@rics.bwh.harvard.edu</a>
Cognitive dysfunction	Retinoblastoma binding protein 4 (RBBP4; RBAP48)	Studies in patient samples and mice suggest increasing RBAP48 levels could help treat age-associated memory impairment. Gene expression analysis in postmortem brain tissue samples showed that RBAP48 levels decreased with age. In young transgenic mice, inhibition of Rbap48 signaling in the dentate gyrus impaired performance on memory tasks. In aged mice, lentiviral expression of <i>Rbap48</i> in the dentate gyrus improved memory performance, whereas expression of a control gene did not. Next steps could include developing brain-permeable compounds that increase RBAP48 activity in the brain.  <b>SciBX 6(37); doi:10.1038/scibx.2013.1033</b> <b>Published online Sept. 26, 2013</b>	Patent and licensing status unavailable	Pavlopoulos, E. <i>et al. Sci. Transl. Med.</i> ; published online Aug. 28, 2013; doi:10.1126/scitranslmed.3006373 <b>Contact:</b> Eric R. Kandel, Columbia University, New York, N.Y. e-mail: <a href="mailto:erk5@columbia.edu">erk5@columbia.edu</a> <b>Contact:</b> Scott A. Small, same affiliation as above e-mail: <a href="mailto:sas68@columbia.edu">sas68@columbia.edu</a>
Depression	Calcium calmodulin-dependent protein kinase II $\beta$ (CAMK2B)	Rodent studies suggest decreasing CAMK2B activity in the lateral habenula region of the brain could help treat depression. In three rat models of depression, Camk2b levels were higher in this region than those in healthy controls. In a rat model of depression, both the generic antidepressant imipramine and <i>Camk2b</i> -targeting RNAi decreased Camk2b levels and depression symptoms compared with vehicle or control RNAi. Next steps include developing a method for targeted drug delivery to the lateral habenula.  <b>SciBX 6(37); doi:10.1038/scibx.2013.1034</b> <b>Published online Sept. 26, 2013</b>	Patent application filed; licensing status undisclosed	Li, K. <i>et al. Science</i> ; published online Aug. 30, 2013; doi:10.1126/science.1240729 <b>Contact:</b> Hailan Hu, Chinese Academy of Sciences, Shanghai, China e-mail: <a href="mailto:hailan@ion.ac.cn">hailan@ion.ac.cn</a>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Depression	Histone deacetylase 6 (HDAC6)	<i>In vitro</i> and mouse studies suggest inhibiting HDAC6 in the brain could help treat depression. <i>In vitro</i> , ACY-738 had an IC <sub>50</sub> of 1.7 nM against HDAC6 with 100-fold selectivity over other class I HDACs, whereas ACY-775 had an IC <sub>50</sub> of 7.5 nM but was 700-fold more selective for HDAC6 over HDAC1. In mouse models of depression, ACY-738 or ACY-775 were brain penetrant and decreased symptoms of depression compared with vehicle when administered via intraperitoneal injection, although ACY-775 had to be given in suspension because of limited solubility. Ongoing work in collaboration with Acetylon Pharmaceuticals Inc. includes identifying an orally available and selective HDAC6 inhibitor that has appropriate safety and pharmacokinetic properties.  <b>SciBX 6(37); doi:10.1038/scibx.2013.1035</b> <b>Published online Sept. 26, 2013</b>	Patent application filed; licensing status undisclosed	Jochems, J. <i>et al.</i> <i>Neuropsychopharmacology</i> ; published online Aug. 19, 2013; doi:10.1038/npp.2013.207 <b>Contact:</b> Oliver Berton, University of Pennsylvania, Philadelphia, Pa. e-mail: <a href="mailto:bertonol@mail.med.upenn.edu">bertonol@mail.med.upenn.edu</a>
Down syndrome	Smoothed (SMO)	Mouse studies suggest agonizing SMO could be useful for treating neurodevelopmental deficits in patients with Down syndrome. In a mouse model of Down syndrome, cerebellar and hippocampal development were compromised. Perinatal treatment with a Smo-agonizing compound improved cerebellar and hippocampal development and performance in motor and learning tasks. Next steps include mouse studies to identify the brain tissues most directly affected by SMO agonists and dose-ranging and teratogenicity studies ( <i>see Hedgehog battles Down syndrome, page 6</i> ).  <b>SciBX 6(37); doi:10.1038/scibx.2013.1036</b> <b>Published online Sept. 26, 2013</b>	Unpatented; licensing status not applicable	Das, I. <i>et al.</i> <i>Sci. Transl. Med.</i> ; published online Sept. 4, 2013; doi:10.1126/scitranslmed.3005983 <b>Contact:</b> Roger H. Reeves, The Johns Hopkins University School of Medicine, Baltimore, Md. e-mail: <a href="mailto:rreeves@jhmi.edu">rreeves@jhmi.edu</a>
Huntington's disease	Glutathione peroxidase 1 (GPX1); glutathione peroxidase 3 plasma (GPX3)	Yeast and fly studies suggest glutathione peroxidase mimics could be used to treat Huntington's disease. In a yeast-based, genome-wide screen, gpx1 and gpx3 were identified as suppressors of mutant huntingtin (htt) protein toxicity. In a <i>Drosophila</i> model of Huntington's disease, a glutathione peroxidase mimic decreased degeneration of photoreceptor neurons compared with no treatment and restored normal locomotor activity. Next steps include testing glutathione peroxidase mimics in mouse models of Huntington's disease.  <b>SciBX 6(37); doi:10.1038/scibx.2013.1037</b> <b>Published online Sept. 26, 2013</b>	Unpatented; licensing status not applicable	Mason, R.P. <i>et al.</i> <i>Nat. Genet.</i> ; published online Aug. 25, 2013; doi:10.1038/ng.2732 <b>Contact:</b> Flaviano Giorgini, University of Leicester, Leicester, U.K. e-mail: <a href="mailto:fg36@le.ac.uk">fg36@le.ac.uk</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>			
Highly specific, recombinant antibodies to detect histone H3 trimethylation	Antibodies highly specific for H3K4me3 and H3K9me3 could be used to aid epigenetic drug development. A problem with the analysis of histone modifications is that many antibodies lack lot-to-lot consistency and may be nonspecific. Phage display and <i>in vitro</i> mutagenesis were used to generate recombinant antibodies with greater specificity for H3K4me3 or H3K9me3 than commercially available antibodies. <i>In vitro</i> , the H3K9me3 antibody was used in a histone methyltransferase assay to generate a stronger detection signal than was seen when using a commercially available antibody. Next steps include establishing drug screening and diagnostic assays using the antibodies.	Patent application filed; available for licensing	Hattori, T. <i>et al. Nat. Methods</i> ; published online Aug. 18, 2013; doi:10.1038/nmeth.2605 <b>Contact:</b> Shohei Koide, The University of Chicago, Chicago, Ill. e-mail: <a href="mailto:skoide@uchicago.edu">skoide@uchicago.edu</a>
<b>Chemistry</b>			
Synthesis of simaomicin- $\alpha$ to enable derivatization	A method to synthesize the natural compound simaomicin- $\alpha$ could help the development of analogs for use in cancer. Simaomicin- $\alpha$ , a polycyclic xanthone, is derived from an actinomycete and was previously shown to synergize with the DNA-damaging agent bleomycin to kill cancer cells. <i>In vitro</i> , simaomicin- $\alpha$ was synthesized using palladium-mediated dehydrogenative coupling of two aryl rings to create the key biaryl linkage in the molecule. In multiple human cancer cell lines, the synthetic simaomicin- $\alpha$ inhibited growth with nanomolar IC <sub>50</sub> values comparable to those of natural simaomicin- $\alpha$ . Next steps include studies to understand the mechanism of simaomicin- $\alpha$ .	Unpatented; available for licensing	Wang, Y. <i>et al. Angew. Chem. Int. Ed.</i> ; published online Aug. 22, 2013; doi:10.1002/anie.201304812 <b>Contact:</b> Joseph M. Ready, The University of Texas Southwestern Medical Center, Dallas, Texas e-mail: <a href="mailto:joseph.ready@utsouthwestern.edu">joseph.ready@utsouthwestern.edu</a>
<b>Computational models</b>			
A computational model to reconstruct network effects of microRNAs and identify targets	A computational model that reconstructs dynamic network effects of miRNAs could help identify miRNA targets for drug discovery. MIRna Dynamic Regulator Events Miner (mirDREM) analyzes miRNA and mRNA expression data at multiple time points to predict the targets of miRNAs. In a mouse model of lung development, mirDREM identified miRNAs already known to be important for lung development and predicted six new miRNAs and their targets, which were validated in a mouse lung epithelial cell line. Using publically available data from patients with idiopathic pulmonary fibrosis, mirDREM predicted five miRNAs that were expressed at lower levels and one miRNA that was expressed at higher levels than those in healthy individuals. Next steps could include the application of mirDREM to discover potential miRNA targets in other diseases.	Patent and licensing status not applicable; mirDREM available at <a href="http://www.cs.cmu.edu/~maschulz/mirdrem/">http://www.cs.cmu.edu/~maschulz/mirdrem/</a>	Schulz, M.H. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Aug. 28, 2013; doi:10.1073/pnas.1303236110 <b>Contact:</b> Ziv Bar-Joseph, Carnegie Mellon University, Pittsburgh, Pa. e-mail: <a href="mailto:zivbj@cs.cmu.edu">zivbj@cs.cmu.edu</a>

## This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
<b>Disease models</b>			
A doxycycline-inducible serum amyloid A (SAA) transgenic mouse model of systemic amyloidosis	Mice expressing a doxycycline-inducible SAA transgene could help model systemic amyloidosis. Systemic amyloidosis is a complication of chronic inflammation that can lead to renal failure. In the mouse model, doxycycline-induced expression of SAA specifically in the liver led to reversible, systemic amyloid deposition. In the mice, re-induction of SAA overproduction at a later time point led to rapid amyloid deposition in the kidney and renal failure. Next steps could include using the model to discover factors that influence the sites of amyloid deposition or for the development of noninvasive, <i>in vivo</i> amyloid imaging methods.  <b>SciBX 6(37); doi:10.1038/scibx.2013.1041</b> <b>Published online Sept. 26, 2013</b>	Patent and licensing status unavailable	Simons, J.P. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Aug. 19, 2013; doi:10.1073/pnas.1306621110 <b>Contact:</b> Philip N. Hawkins, University College London, London, U.K. e-mail: <a href="mailto:p.hawkins@ucl.ac.uk">p.hawkins@ucl.ac.uk</a> <b>Contact:</b> J. Paul Simons, same affiliation as above e-mail: <a href="mailto:p.simons@ucl.ac.uk">p.simons@ucl.ac.uk</a>
Brain organoids to model microcephaly <i>in vitro</i>	Cell culture studies suggest induced pluripotent stem (iPS) cell-derived brain tissue could aid the discovery of therapeutics for neurodevelopmental disorders. In a 3D cell culture system, iPS cells treated with neural differentiation factors formed small organoids with distinct cell layers and gross morphology analogous to those of adult human brains. Brain organoids derived from iPS cells of patients with microcephaly were smaller and less complex than organoids derived from healthy individuals. Next steps include growing and characterizing brain organoids from iPS cells of patients with other neurological diseases.  <b>SciBX 6(37); doi:10.1038/scibx.2013.1042</b> <b>Published online Sept. 26, 2013</b>	Patent and licensing status undisclosed	Lancaster, M.A. <i>et al. Nature</i> ; published online Aug. 28, 2013; doi:10.1038/nature12517 <b>Contact:</b> Jürgen A. Knoblich, Institute of Molecular Biotechnology of the Austrian Academy of Sciences, Vienna, Austria e-mail: <a href="mailto:juergen.knoblich@imba.oeaw.ac.at">juergen.knoblich@imba.oeaw.ac.at</a>
Collection of haploid human isogenic cell lines with mutations in individual genes	A collection of haploid human isogenic cell lines with single mutations could be useful for creating new disease models and identifying therapeutic targets. The collection was generated by mutating and barcoding 3,396 genes in stable haploid human cells cloned from a chronic myelogenous leukemia cell line. The mutagenesis method induced reversible mutations in the haploid cells that cause near complete inactivation of the targeted gene. Next steps include increasing the number of knockout cell lines to cover additional genes and using the cell lines to support target and drug discovery efforts at Haplogen GmbH ( <i>see Trapping human genes</i> , page 8).  <b>SciBX 6(37); doi:10.1038/scibx.2013.1043</b> <b>Published online Sept. 26, 2013</b>	Patent status undisclosed; available for licensing and partnerships through Haplogen	Bürckstümmer, T. <i>et al. Nat. Methods</i> ; published online Aug. 25, 2013; doi:10.1038/nmeth.2609 <b>Contact:</b> Sebastian M.B. Nijman, Research Center for Molecular Medicine of the Austrian Academy of Sciences, Vienna, Austria e-mail: <a href="mailto:snijman@cemm.oeaw.ac.at">snijman@cemm.oeaw.ac.at</a>
Mice with epidermal-specific knockout of epidermal growth factor receptor (Egfr) to model skin toxicity associated with EGFR-targeted cancer therapy	Mice with epidermal-specific knockout of Egfr could help model skin rashes that develop in patients receiving EGFR inhibitors. In the mouse model, the number of inflammatory immune cells and the levels of proinflammatory cytokines in the skin were greater than those in <i>Egfr</i> -expressing animals, and defects in epidermal differentiation accumulated over time. In skin samples from patients undergoing EGFR-targeted therapy, comparable changes in inflammatory cell accumulation, levels of proinflammatory cytokines and skin barrier defects were observed. Next steps could include using the model to identify potential therapeutics that can target the inflammatory response in the skin.  <b>SciBX 6(37); doi:10.1038/scibx.2013.1044</b> <b>Published online Sept. 26, 2013</b>	Patent and licensing status unavailable	Lichtenberger, B.M. <i>et al. Sci. Transl. Med.</i> ; published online Aug. 21, 2013; doi:10.1126/scitranslmed.3005886 <b>Contact:</b> Maria Sibilja, Medical University of Vienna, Vienna, Austria e-mail: <a href="mailto:maria.sibilja@meduniwien.ac.at">maria.sibilja@meduniwien.ac.at</a> <b>Contact:</b> Bernhard Homey, Heinrich Heine University of Duesseldorf, Duesseldorf, Germany e-mail: <a href="mailto:bernhard.homey@uni-duesseldorf.de">bernhard.homey@uni-duesseldorf.de</a>

## This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
<b>Imaging</b>			
Monitoring response to preventive therapy in patients with Huntington's disease (HD) using <sup>18</sup> F-labeled fluorodeoxyglucose PET (FDG-PET) imaging	PET imaging of the brain could help monitor treatment responses in patients with presymptomatic and early symptomatic HD. In two independent cohorts of patients with HD, longitudinal <sup>18</sup> F-labeled FDG-PET imaging of multiple brain regions identified a pattern of region-specific increases and decreases in metabolic activity that were not seen in healthy individuals. The pattern intensified over time and correlated with years to onset, an empirical estimate of the time remaining until clinical symptoms of HD appear. Planned work includes validating the method in a two-year observational study of about 1,500 patients with presymptomatic HD.	Patent application filed by The Feinstein Institute for Medical Research; unlicensed	Tang, C.C. <i>et al. J. Clin. Invest.</i> ; published online Aug. 29, 2013; doi:10.1172/JCI69411 <b>Contact:</b> David Eidelberg, The Feinstein Institute for Medical Research, Manhasset, N.Y. e-mail: <a href="mailto:david1@nshs.edu">david1@nshs.edu</a>
<b>Markers</b>			
Genetic markers of statin-induced myopathy	Genetic studies identified SNPs that could help stratify patients based on their risk for statin-induced myopathy. Use of statin drugs such as simvastatin is associated with a small increase in risk of myopathy. In an analysis of gene expression in lymphoblastoid cell lines derived from 480 subjects in a clinical trial of simvastatin, six SNPs at the <i>glycine amidinotransferase</i> ( <i>GATM</i> ; <i>AGAT</i> ) gene locus were associated with decreased risk of statin-induced myopathy. Next steps include assessing the role of <i>GATM</i> in statin-mediated changes to cholesterol metabolism and muscle health.	Unpatented; licensing status unavailable	Mangravite, L.M. <i>et al. Nature</i> ; published online Aug. 28, 2013; doi:10.1038/nature12508 <b>Contact:</b> Lara M. Mangravite, Sage Bionetworks, Seattle, Wash. e-mail: <a href="mailto:lara.mangravite@sagebase.org">lara.mangravite@sagebase.org</a>
Measuring CD8 <sup>+</sup> T cell tumor infiltration to guide immunotherapy selection	Studies in mice and in patient samples suggest measuring CD8 <sup>+</sup> T cell infiltration of tumors could help identify patients who will respond to immunotherapies. In samples from patients with melanoma, CD8 <sup>+</sup> T cell infiltration correlated with elevated tumor levels of indoleamine 2,3-dioxygenase (INDO; IDO) and programmed cell death 1 ligand 1 (CD274 molecule; PD-L1; B7-H1). In xenograft mice, CD8 <sup>+</sup> T cell infiltration led to immunosuppressive T <sub>reg</sub> accumulation by driving T <sub>reg</sub> recruitment and proliferation in the tumor microenvironment. Next steps include integrating this information into immunotherapy trials and testing combinations of immunotherapies in preclinical models.	Patent and licensing status undisclosed	Spranger, S. <i>et al. Sci. Transl. Med.</i> ; published online Aug. 28, 2013; doi:10.1126/scitranslmed.3006504 <b>Contact:</b> Thomas F. Gajewski, The University of Chicago, Chicago, Ill. e-mail: <a href="mailto:tgajewsk@medicine.bsd.uchicago.edu">tgajewsk@medicine.bsd.uchicago.edu</a>
Single lipid vesicle assay to measure hydrolysis of disease-associated phospholipids	An assay using single vesicles to measure phospholipid hydrolysis could be used to identify and quantify disease-associated biomarkers. In the assay, single vesicles containing fluorescently labeled phospholipids were incubated with phospholipase A <sub>2</sub> (PLA <sub>2</sub> ) and enzyme activity was quantified by fluorescence microscopy. In cerebrospinal fluid samples from two patients with Alzheimer's disease (AD) and two healthy controls, PLA <sub>2</sub> concentrations varied by up to 56%, but PLA <sub>2</sub> activity varied by only 7%, suggesting that although enzyme levels may be higher in patients with AD, enzyme activity is not. Next steps include developing an advanced data analysis strategy that will help guide biomarker discovery.	Patent application filed covering a device to perform this analytical method; not yet available for licensing; additional information available from GU Holding AB <b>Contact:</b> Svante Hojer, GU Holding AB, Gothenburg, Sweden e-mail: <a href="mailto:svante.hojer@holding.gu.se">svante.hojer@holding.gu.se</a>	Tabaei, S.R. <i>et al. J. Am. Chem. Soc.</i> ; published online Aug. 19, 2013; doi:10.1021/ja4046313 <b>Contact:</b> Fredrik Höök, Chalmers University of Technology, Gothenburg, Sweden e-mail: <a href="mailto:fredrik.hook@chalmers.se">fredrik.hook@chalmers.se</a>

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