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Australian academics have used N-Gene's BGP-15, a small molecule inducer of Hsp72, to increase muscle strength and survival in mice with muscular dystrophy. The biotech, which is testing the compound in Phase IIb for diabetes, now hopes to find a partner for the new indication.

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Researchers from **The University of Texas Southwestern Medical Center** have discovered that knocking down microRNA-208a in the heart leads to systemic benefits in obesity and metabolic disease, in addition to the already known effects on preventing cardiac hypertrophy and fibrosis.<sup>1</sup> The findings could expand the potential indications for **miRagen Therapeutics Inc.**'s lead candidate, anti-miR-208, which is partnered with **Servier** and is in preclinical development for cardiac hypertrophy.

Team leader Eric Olson, chairman of molecular biology at UT Southwestern and a cofounder and chief scientific advisor to miRagen, said his group initially set out to study miR-208a's function in the heart but ended up uncovering a mechanism by which the heart regulates systemic metabolism.

"We didn't go into this anticipating that the heart regulated metabolism—it wasn't what we were looking for," said Olson.

Now, miRagen thinks targeting cardiac miR-208a could help treat metabolic disease in patients with heart disease and mitigate cardiovascular risk in patients with metabolic disease. The company is expanding its preclinical testing of anti-miR-208 into mouse obesity models.

**Heart miR miR**

Olson's team previously found that miR-208a was expressed in the heart, in which it negatively regulates the expression of a range of genes.<sup>2</sup> As a follow-up to that work, the team used anti-miR-208, a locked nucleic acid (LNA) oligomer, to study the effect of knocking down miR-208a.

Mice receiving a subcutaneous injection of anti-miR-208 were leaner than animals given injection of an untargeted control anti-miR. The slimming effect of miR-208a knockdown was even more pronounced when the mice were fed a high-fat diet. In overfed animals, anti-miR-208 decreased weight gain, white adipose tissue hypertrophy and insulin resistance compared with a control anti-miR.

Olson's team suspected that the effects of knocking down miR-208a stemmed from a key miR-208a-regulated gene called *MED13* (*mediator complex subunit 13*). Previously, the team had found that miR-208a knockdown led to increased levels of Med13 compared with normal miR-208a expression.

"Because *MED13* was one of the strongest targets of miR-208a, we wanted to determine the effect of loss- and gain-of-function of *MED13*," said Olson.

Indeed, overfed mice engineered to overexpress Med13 resembled overfed mice treated with anti-miR-208, suggesting the effects of knocking down miR-208a were likely due to increased levels of Med13.

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PO Box 1246  
San Carlos, CA 94070-1246  
T: +1 650 595 5333Chadds Ford  
223 Wilmington-West Chester Pike  
Chadds Ford, PA 19317  
T: +1 610 558 1873Chicago  
20 N. Wacker Drive, Suite 1465  
Chicago, IL 60606-2902  
T: +1 312 755 0798Oxford  
287 Banbury Road  
Oxford OX4 7JA  
United Kingdom  
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Washington, DC 20009  
T: +1 202 462 9582**Nature Publishing Group**New York  
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United Kingdom  
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Chiyoda Building 6F  
2-37 Ichigayatamachi  
Shinjuku-ku, Tokyo 162-0843  
Japan  
T: +81 3 3267 8751

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Olson's team also found that *Med13* knockout specifically in the heart led to greater weight gain, fat deposits and insulin insensitivity than normal *Med13* expression. Altogether, the findings implicate MED13 as a heart-specific regulator of systemic metabolism and point to miR-208a as a key controller of *MED13* expression.

Results were published in *Cell*. The findings are patented and licensed to miRagen.

**Obesity opportunity**

The most pressing question raised by Olson's work is how MED13's activity within the heart can strongly influence systemic metabolism. Olson thinks cardiac tissue likely sends an endocrine signal that affects energy utilization by other tissues, but the identity of such a signaling molecule remains unknown.

Although the mechanism remains murky, "perhaps it's not so surprising that the heart is communicating with the energy stores of the body," said Olson. "The heart has a tremendous appetite for energy but doesn't store energy on its own. It makes sense that there would be a system for signaling between the heart and fat deposits."

Olson now is trying to identify the signaling molecules that bridge the heart and metabolic system and hopes to uncover whether MED13 regulates metabolism in other tissues besides the heart. He noted that although miR-208a is found exclusively in the heart, a very similar miRNA called miR-208b is expressed in other tissues, along with *MED13*. Because miR-208a and miR-208b are so similar, it is possible that knocking down miR-208a could have effects on the periphery as well as the heart.

"We don't know what the signal is from the heart to the other tissues," said Olson. "We know that the effects of MED13 emanate from the heart, but this doesn't rule out that MED13 doesn't have roles in other tissues."

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Olson noted that the effects of miR-208a on cardiac hypertrophy and fibrosis are likely distinct from its effects on metabolic disease, as MED13 does not appear to be necessary for antimiR-208's effect on cardiac hypertrophy.

**“We didn't go into this anticipating that the heart regulated metabolism—it wasn't what we were looking for.”**

—Eric Olson,  
The University of Texas  
Southwestern Medical Center

This observation, said Olson, indicates there are likely additional miR-208a target genes involved in pathological cardiac remodeling, but the identity of those genes is not yet known.

miRagen CEO,  
president and cofounder

William Marshall said the company had already been looking at antimiR-208 to treat cardiac hypertrophy with preserved ejection volume, a form of heart disease that is commonly caused by metabolic syndrome and obesity.

The new findings open the possibility of pursuing a metabolic disease label.

Marshall said that antimiR-208 has a favorable preclinical safety profile in two animal models of cardiac hypertrophy and that the compound's effect on heart strength should, if anything, reduce cardiovascular event risk in obese or diabetic patients.

“Our data show a direct benefit to heart health with this compound, suggesting that liability to cardiovascular problems is not going to be

an issue,” said Marshall.

He added that Olson's findings “imply that antimiR-208 could be used for patients with obesity and metabolic syndrome but who don't necessarily yet have cardiac hypertrophy.” This hypothesis could be tested by stratifying patients based on both their weight and the state of their hearts.

Last year, miRagen partnered with Servier to co-develop antimiR-208 and two other therapeutic candidates for cardiovascular indications outside the U.S. and Japan. miRagen's LNA antisense technology is licensed from **Santaris Pharma A/S**.

In April, miRagen closed a \$20 million series B round.

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#### REFERENCES

1. Grueter, C.E. *et al. Cell*; published online April 27, 2012; doi:10.1016/j.cell.2012.03.029  
**Contact:** Eric N. Olson, The University of Texas Southwestern Medical Center, Dallas, Texas  
e-mail: [eric.olson@utsouthwestern.edu](mailto:eric.olson@utsouthwestern.edu)
2. van Rooij, E. *et al. Science* **316**, 575–579 (2007)

#### COMPANIES AND INSTITUTIONS MENTIONED

**miRagen Therapeutics Inc.**, Boulder, Colo.  
**Santaris Pharma A/S**, Horsholm, Denmark  
**Servier**, Neuilly-sur-Seine, France  
**The University of Texas Southwestern Medical Center**, Dallas, Texas

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# Building bridges

By Tracey Baas, Senior Editor

Johnson & Johnson has joined the ranks of funders supporting the California Institute for Quantitative Biosciences Bridging-the-Gap Awards by providing two grants. The company is the first pharma to put money behind the awards.

The Bridging-the-Gap Awards were established in 2007 by the California Institute for Quantitative Biosciences (QB3) and the Rogers Family Foundation, an Oakland-based philanthropic organization. The awards provide up to \$125,000 for proof-of-concept research and are renewable for a second year, with another allotment of \$125,000.

Each award includes membership in the QB3 Startup-in-a-Box program, which allows grantees to form a company, a prerequisite when applying for government-sponsored Small Business Innovation Research (SBIR) funds.

QB3 offers these startups small rental laboratory spaces in University of California incubators, dubbed Garages—a nod to old-school Silicon Valley startups like Apple or Hewlett-Packard.

Through 2011, the Rogers Family Foundation has been the primary funder of the Bridging-the-Gap Awards. It has supported 12 projects. Of those, 5 have resulted in startup companies that have raised a total of \$9 million and 4 have resulted in partnerships with established companies (see Table 1, “Trajectories of recipients of the California Institute for Quantitative Biosciences’ (QB3) Bridging-the-Gap Awards”).

**Table 1. Trajectories of recipients of the California Institute for Quantitative Biosciences’ (QB3) Bridging-the-Gap Awards.**

| Principal investigator         | QB3 campus                              | Award year        | Project   | Status  |
|--------------------------------|---|-------------------|---|---|
| Tejal Desai                    | University of California, San Francisco | 2007              | Microengineered particles for oral delivery of chemotherapeutics  | Partnered and licensed technology to Zcube s.r.l., a unit of Zambon Co. S.p.A.  |
| Michael Marletta               | University of California, Berkeley      | 2007              | Engineer H-NOX (heme nitric oxide/oxygen binding)-family proteins for therapeutic delivery of oxygen and nitric oxide                                     | Founded Omniox Inc. in QB3 Garage and raised more than \$4 million in Small Business Innovation Research (SBIR) funding |
| Amy Herr                       | UCBerkeley                              | 2008              | Rapid autoantibody profiling for systemic lupus erythematosus (SLE) using micro- and nanotechnology   | Partnered and licensed technology to an undisclosed, international life sciences company                                |
| Brian Shoichet                 | UCSF                                    | 2009              | Chemoinformatic and statistical methods to uncover links between drugs and the biological targets responsible for disease                                 | Founded SeaChange Pharmaceuticals Inc. in QB3 Garage  |
| Jim Wells                      | UCSF                                    | 2009              | Apoptotic biomarkers for hematologic cancers  | Unpartnered   |
| Tejal Desai                    | UCSF                                    | 2009              | Titania nonporous membranes for constant-rate interferon- $\gamma$ (IFNA; IFN- $\gamma$ ) delivery to treat HCV   | Founded Nano Precision Medical Inc. in QB3 Garage; now at QB3 East Bay Innovation Center                                |
| Charles Chiu                   | UCSF                                    | 2010              | Pan-viral clinical diagnostic for respiratory and diarrheal illness   | Partnered with Akonni Biosystems Inc.   |
| Shuvo Roy                      | UCSF                                    | 2010              | Wearable hemofiltration device for renal replacement  | Forming startup   |
| Holger Schmidt                 | University of California, Santa Cruz    | 2010              | Portable, amplification-free virus detector using optofluidic chips   | Founded LiquiLume Diagnostics Inc. at the San Jose BioCenter  |
| Charles Craik                  | UCSF                                    | 2011              | Noninvasive imaging of cancer by targeting active proteases and their receptors   | Two industry partnerships under negotiation   |
| Tejal Desai                    | UCSF                                    | 2011              | Nanostructural biopolymer films for retinal drug delivery   | Forming startup   |
| John Kuriyan; Art Weiss        | UCBerkeley; UCSF                        | 2011              | Discover inhibitors of the catalytic activity of the T cell receptor (TCR) tyrosine kinase ZAP70 ( $\zeta$ -chain (TCR) associated protein kinase 70 kDa) | Unpartnered   |
| Adam Abate                     | UCSF                                    | 2012              | Microfluidic device to analyze rare circulating tumor cells   | Founded Torrent Bio Inc. in Redwood Shores, Calif.  |
| Roger Linington; Fitnat Yildiz | UCSC                                    | 2012              | Biofilm inhibitors as therapeutics for surface-associated bacterial infection   | Unpartnered   |
| Trever Bivona                  | UCSF                                    | 2012              | Systematic discovery of rational, molecularly targeted cancer polytherapies   | Unpartnered; clinical trials starting   |
| Matthew Jacobson; Scott Lokey  | UCSF; UCSC                              | 2012 <sup>A</sup> | Discovery platform for orally bioavailable inhibitors of therapeutically relevant protein-protein interactions  | Unpartnered   |
| Shuvo Roy                      | UCSF                                    | 2012 <sup>A</sup> | Intravascular capsule of pancreatic b islet cells to treat type 1 diabetes  | Unpartnered   |

<sup>A</sup>First set of projects funded by the Johnson & Johnson Corporate Office of Science & Technology (COSAT).

This year, the foundation has funded three proposals.

Johnson & Johnson, through its Corporate Office of Science & Technology (COSAT), has funded two projects. One award went to Shuvo Roy, associate professor of bioengineering and therapeutic sciences at the **University of California, San Francisco**, for research on an artificial pancreas. The other went to Scott Lokey and Matthew Jacobson to design and synthesize orally bioavailable macrocycles that target protein-protein interactions. Lokey is an associate professor of chemistry at the **University of California, Santa Cruz**, and Jacobson is vice chair and professor of pharmaceutical chemistry at UCSF.

In all cases, proposals are selected by a QB3 scientific committee that includes representatives of all three QB3 campuses—**University of California, Berkeley**, UCSF and UCSC—plus representatives from Rogers, COSAT and VCs.

According to Jeff Calcagno, senior director of emerging technologies at COSAT, “J&J COSAT’s funding of QB3’s Bridging-the-Gap program is structured as a gift, which is consistent with COSAT’s mission of catalyzing early stage external innovation through collaborations that are innovator friendly.”

Neena Kadaba, QB3’s director of industry alliances, sees COSAT’s investment as “a new model for industry, with researchers receiving precommercial support to address potential scientific risks in their technology before launching a startup and with established companies building early relationships with startups as they form.”

“If we’re working in a collaborative way with these external innovators starting at the early stages of research, then we will potentially become a partner-of-choice for these innovators as creative solutions mature,” Calcagno told *SciBX*.

J&J did not disclose how many more awards it plans to fund.

### On the COSAT wave

Roy is no newcomer to the QB3 award program. His team won a Bridging-the-Gap award in 2010 to develop a prototype of an artificial kidney, and his team has formed a startup to further develop the work toward a product.

His hope is that the team’s prior experience with silicon filtration membrane technology will transition from the kidney to the pancreas.

“The Bridging-the-Gap award will allow our team to do key proof-of-concept experiments to make the idea more attractive to investors,” Roy told *SciBX*. “Even though my laboratory has a strong foundation in silicon filtration membrane technology, moving from creating a bioreactor using kidney epithelial cells to pancreatic  $\beta$  islet cells is not trivial.”

He added: “Being a part of QB3 at UCSF is an advantage because I

can interact with a strong and broad group of specialists with skills such as islet cell biology, imaging techniques and transplant surgery that are outside my own realm of expertise. I can actually walk down the hallway and find some of these individuals to have a chat. It’s all very collegial and inspiring.”

According to Jacobson, the COSAT-backed Bridging-the-Gap award will give him and Lokey an opportunity “to provide the proof-of-concept experiments that will show companies that macrocyclic compounds are a viable therapeutic strategy to treat diseases that have protein-protein interactions to be targeted. Our first experiments will target protein-protein interactions mediated by  $\alpha$ -helices, of which there are many.”

Although Jacobson and Lokey are newcomers to the Bridging-the-Gap Awards, they have previously collaborated with **Pfizer Inc.** under the auspices of QB3, working

together to identify key principles to predict pharmacokinetic compound properties, such as oral bioavailability, and to use the principles to design macrocyclic compounds with better membrane permeability and oral bioavailability.<sup>1</sup>

“We are continuing our very productive collaboration with Pfizer to build on our published work with them, while we simultaneously explore other potential applications to other target classes, using the support from the J&J award,” Jacobson told *SciBX*.

Whereas J&J is the first pharma to participate in the Bridging-the-Gap Awards, it is not the first to work with QB3. In 2008, QB3 partnered with Pfizer’s External R&D Innovation (ERDI) center to foster collaborative projects and programs for sponsored research agreements, material transfers and scientist exchanges.

In March, the parties extended the deal by three years, through 2014. The agreement includes a program to fund postdoctoral research that has a direct impact on Pfizer’s R&D. Pfizer may also provide seed funding for startup companies spun out of QB3.

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### REFERENCES

- White, T.R. *et al. Nat. Chem. Biol.* 7, 810–817 (2011)

### COMPANIES AND INSTITUTIONS MENTIONED

**California Institute for Quantitative Biosciences**, San Francisco, Calif.

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

**Pfizer Inc.** (NYSE:PFE), New York, N.Y.

**Rogers Family Foundation**, Oakland, Calif.

**University of California**, Oakland, Calif.

**University of California, Berkeley**, Calif.

**University of California, San Francisco**, Calif.

**University of California, Santa Cruz**, Calif.

**“J&J COSAT’s funding of QB3’s Bridging-the-Gap program is structured as a gift, which is consistent with COSAT’s mission of catalyzing early stage external innovation through collaborations that are innovator friendly.”**

—Jeff Calcagno,  
Johnson & Johnson

# Heat shock hits muscular dystrophy

By Tim Fulmer, Senior Writer

Australian academics have used N-Gene Research Laboratories Inc.'s BGP-15, a small molecule inducer of heat shock 70 kDa protein 1A in Phase IIB testing for diabetes, to increase muscle strength and survival in two mouse models of muscular dystrophy.<sup>1</sup> The biotech now hopes to find a partner to help repurpose the compound for muscular dystrophy.

The lack of a functioning dystrophin (DMD) protein is the underlying cause of muscular dystrophy, but chronic muscle inflammation and loss of intracellular calcium homeostasis are what actually drive disease progression. Multiple proinflammatory signaling molecules, including tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), NF- $\kappa$ B and c-jun N-terminal kinase (JNK), are upregulated in the muscle tissue of animal models of muscular dystrophy.<sup>2-4</sup>

Because there are so many inflammatory factors at work in the disease, the challenge has been identifying a single target that inhibits the activity of multiple pathways in muscle.

The Australian researchers hypothesized that upregulating the heat shock response could accomplish the task. The team focused on heat shock 70 kDa protein 1A (Hsp72; HspA1), which inhibits NF- $\kappa$ B and JNK signaling and preserves the function of the calcium pumps ATPase Ca<sup>++</sup> transporting cardiac muscle fast twitch 1 (ATP2A1; SERCA1) and ATPase Ca<sup>++</sup> transporting cardiac muscle slow twitch 2 (ATP2A2; SERCA2A).<sup>5-8</sup>

The team crossed muscle-specific Hsp72-overexpressing mice with *mdx* mice, which lack the *dystrophin* gene and are the standard muscular dystrophy mouse model.

The resulting mice had significantly decreased whole-body muscle breakdown ( $p < 0.05$ ), increased strength and endurance ( $p = 0.002$ ) and better diaphragm histology ( $p < 0.05$ ) compared with *mdx* controls not overexpressing Hsp72.

In quadriceps muscles from the crossbred mice, the function of all SERCA pumps was increased compared with that in *mdx* mice ( $p < 0.008$ ), suggesting that Hsp72 overexpression protected SERCA from inactivation and helped preserve calcium homeostasis in muscle cells.

The researchers next asked whether they would see a similar result delivering an Hsp72-inducing small molecule to the *mdx* mice. They turned to N-Gene's BGP-15, which is in a Phase IIB trial to treat type 2 diabetes.

In that disease, the induction of Hsp72 blocks activation of JNK-associated proinflammatory pathways that contribute to insulin resistance. In its Phase I and Phase II diabetes trials, BGP-15 was safe and well tolerated.<sup>9,10</sup>

In the *mdx* mice, BGP-15 decreased both whole-body muscle breakdown ( $p < 0.01$ ) and diaphragm fibrosis ( $p < 0.05$ ) and increased

both diaphragm strength ( $p < 0.01$ ) and SERCA activity in diaphragm muscle ( $p < 0.05$ ) compared with vehicle.

Finally, the researchers delivered BGP-15 to dystrophic *dko* mice, which have double knockout of the *utrophin* and *dystrophin* genes and a much more severe disease phenotype than *mdx* mice. In the *dko* animals, BGP-15 decreased spinal curvature ( $p < 0.05$ ) and increased both muscle function ( $p < 0.01$ ) and lifespan ( $p < 0.05$ ) compared with vehicle.

Results were published in *Nature*. The team was led by Gordon Lynch, head of the Department of Physiology at The University of Melbourne, and Mark Febbraio, senior principal research fellow and head of the Cellular and Molecular Metabolism Laboratory at the Baker IDI Heart & Diabetes Institute.

Based on the *dko* mouse data, "it is likely that BGP-15 will work at least as well if not better than the other pharmacological approaches currently used in DMD [Duchenne muscular dystrophy] patients," such as corticosteroids, said Kay Davies, professor of physiology, anatomy and genetics at the University of Oxford.

Davies provided the *dko* mice used in the *Nature* study.

Activating Hsp72 in muscular dystrophy "has the potential to delay when patients will lose the ability to walk, delay when they'll need machines to help them breathe and potentially allow them to live longer with a better quality of life," Lynch told *SciBX*.

## Right patients, more indications

Eventually, Lynch, Febbraio and N-Gene plan to combine resources to run a trial of BGP-15 in muscular dystrophy. They also hope to find a partner to help them with the clinical development. They declined to provide a more detailed timeline.

Lynch said that prior to any clinical trials of BGP-15, additional work in the dystrophic mice should help determine the profiles of patients

who might benefit most from BGP-15. In particular, the researchers want to know whether treatment must start before a certain stage of disease to be effective and whether there is a specific treatment window to produce beneficial effects on muscle structure and function.

The findings showed that BGP-15 slowed disease progression when the animals were treated from as early an age as possible, said Lynch, "which is similar to a scenario where boys with DMD are placed on corticosteroids as soon as possible after diagnosis to have the best effect at slowing progression."

"We now want to establish in the mice whether starting treatment at a later time point will provide a benefit, especially if there is a significant infiltration of fibrosis and other noncontractile material," he continued.

"At this time we are not in a position to develop BGP-15 for diabetes and muscular dystrophy in parallel," N-Gene CEO Gabor Kalman told *SciBX*. "But at some point in the future, depending on the outcome of the ongoing diabetes trial, we would very much like to pursue this compound in muscular dystrophy, and we want to find a partner to help us move forward."

Hsp72 inducers like BGP-15 may have therapeutic effects in a broad range of diseases associated with stress-induced molecular damage

**"At this time we are not in a position to develop BGP-15 for diabetes and muscular dystrophy in parallel. But at some point in the future, depending on the outcome of the ongoing diabetes trial, we would very much like to pursue this compound in muscular dystrophy, and we want to find a partner to help us move forward."**

—Gabor Kalman,  
N-Gene Research Laboratories Inc.

and protein unfolding. “When activated by cellular stress, Hsp72 is a chaperone protein that prevents a misfolded protein response in the cell,” thus preserving the function of key proteins and helping to better maintain cellular homeostasis, said Febbraio. “BGP-15 could be useful in other diseases where a misfolded protein response is prevalent,” such as Alzheimer’s disease (AD).

BGP-15 “also may be efficacious for the treatment and management of numerous muscle diseases as well as nonmuscle diseases that present with skeletal muscle weakness and dysfunction,” said Russell Tupling. The reason, he said, is the compound “maintains normal SERCA pump function, allowing the damaged muscle cells to better deal with calcium influx, minimizing calcium overload and associated muscle damage and degeneration.”

Tupling is professor of kinesiology at the **University of Waterloo**. Tupling and colleagues previously showed that Hsp72 protects SERCA, thus preventing oxidative damage and cellular dysfunction.<sup>8,11</sup>

N-Gene has a series of small molecule heat shock protein inducers in preclinical development behind BGP-15. Early in the development of BGP-15 and its amidoxime analogs, N-Gene researchers and colleagues showed that the compound class had cytoprotective effects in diabetic wound healing, cardiac ischemia and cardiac reperfusion injury.<sup>12,13</sup>

N-Gene, Lynch and Febbraio have applied for a patent covering the use of BGP-15 to treat muscular dystrophy and other muscle disorders, Kalman said. Febbraio is a scientific consultant for N-Gene.

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#### REFERENCES

- Gehrig, S.M. *et al. Nature*; published online April 4, 2012; doi:10.1038/nature10980  
**Contact:** Gordon S. Lynch, The University of Melbourne, Melbourne, Victoria, Australia  
e-mail: [gsl@unimelb.edu.au](mailto:gsl@unimelb.edu.au)
- Porter, J.D. *et al. Hum. Mol. Genet.* **11**, 263–272 (2002)
- Acharyya, S. *et al. J. Clin. Invest.* **117**, 889–901 (2007)
- Kolodziejczyk, S.M. *et al. Curr. Biol.* **11**, 1278–1282 (2001)
- Senf, S.M. *et al. FASEB J.* **22**, 3836–3845 (2008)
- Park, H.-S. *et al. EMBO J.* **20**, 446–456 (2001)
- Chung, J. *et al. Proc. Natl. Acad. Sci. USA* **105**, 1739–1744 (2008)
- Tupling, A.R. *et al. J. Biol. Chem.* **279**, 52382–52389 (2004)
- Literáti-Nagy, B. *et al. Horm. Metab. Res.* **41**, 374–380 (2009)
- Literáti-Nagy, B. *et al. Brain Res. Bull.* **83**, 340–344 (2010)
- Fu, M.H. & Tupling, A.R. *Am. J. Physiol. Heart Circ. Physiol.* **296**, H1175–H1183 (2009)
- Szabados, E. *et al. Biochem. Pharmacol.* **59**, 937–945 (2000)
- Vígh, L. *et al. Nat. Med.* **3**, 1150–1154 (1997)

#### COMPANIES AND INSTITUTIONS MENTIONED

**Baker IDI Heart & Diabetes Institute**, Melbourne, Victoria, Australia  
**N-Gene Research Laboratories Inc.**, New York, N.Y.  
**The University of Melbourne**, Melbourne, Victoria, Australia  
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# Evolution not revolution

By Lev Osherovich, Senior Writer

An international team has engineered enzymes capable of replicating nucleic acid polymers that are made of non-natural nucleotides.<sup>1</sup> Despite general media reports that the findings are a breakthrough on the way to artificial life, the practical utility of the technology is in generating new types of aptamers.

Aptamers are small nucleic acid oligomers selected for high-affinity binding to specific protein or nucleic acid targets. To find an aptamer that hits a given target, researchers perform a recursive *in vitro* selection procedure called systematic evolution of ligands by exponential enrichment (SELEX). In SELEX, aptamers that bind their targets are purified and replicated by polymerases, and then the cycle is repeated. After many such cycles, only the highest-affinity aptamers remain.

Although SELEX has been very good at generating potent aptamers, the molecules are seldom stable *in vivo* because they are recognized by host antiviral defenses and are rapidly degraded.

To improve the biological stability of aptamers, researchers have previously made aptamers with non-natural sugar backbones that are resistant to degradation. However, the polymerases used in the SELEX procedure do not readily recognize these non-natural nucleotides. As a result, manipulating and refining non-natural aptamers has been difficult.

Now, a team led by Philipp Holliger, group leader in the Laboratory for Molecular Biology at the **Medical Research Council (MRC)**, has bridged the gap between SELEX and degradation-proof aptamers. The group engineered a set of DNA polymerases and reverse transcriptases that can copy short oligonucleotides made from non-natural nucleotides.

Because aptamers made with these new polymerases are non-natural and thus less likely to be recognized by the body's host defenses, they could have high *in vivo* stability.

"Natural nucleic acids don't have much stability, so you can find aptamers with some utility *in vitro* but you can rarely use them for medicine," said Vitor Pinheiro, investigator scientist at MRC and the lead author of a report in *Science* describing the new enzymes. "You can now synthesize and replicate synthetic nucleic acids" that might be more suitable as therapeutics.

Further refinement of the enzymes also could yield high-potency aptamers with new structural features resulting from their non-natural sugar backbones.

## Dispensing with DNA

The MRC team began by conducting an *in vitro* evolution procedure to identify mutant DNA polymerases capable of copying DNA into an RNA-like polymer containing either of two non-natural nucleotides. The team performed a similar procedure to obtain a mutant reverse

transcriptase capable of copying this non-natural RNA-like molecule back into DNA.

The researchers used these two mutant enzymes as starting points for further *in vitro* evolution experiments, yielding a toolkit of engineered polymerases and reverse transcriptases that could copy and reverse transcribe aptamers made from any of six non-natural nucleotides.

As a proof of principle, the group conducted a SELEX-like procedure with the new enzymes to identify non-natural nucleic acid aptamers that bound to the HIV transactivation response (TAR) element and to hen egg lysozyme, a model protein.

Pinheiro said other groups have made aptamers with non-natural nucleotides,<sup>2</sup> but his team's engineered enzymes improve on those methods by eliminating the need for a DNA template.

"There have been previous synthetic aptamer systems where it was possible to copy genetic information, but this required the continuing attachment of the DNA," said Pinheiro.

Getting rid of the DNA template streamlines the aptamer selection procedure and makes it possible to identify conformationally new aptamers that are not confined by the helical structure of DNA, he noted.

The MRC team's findings are patented and available for licensing.

## Toward better aptamers

The popular press characterized the *Science* report as the creation of artificial life, but in fact the findings are the latest incremental advance in a long line of research on non-natural nucleic acid polymers.

Although the technology could in principle be used to create artificial genes, the utility of non-natural genetic polymers is hobbled by the poor efficiency of the engineered polymerases and the lack of compatible cellular machinery to support survival of the artificial genes outside of a test tube.

Instead, Pinheiro and companies in the nucleic acid space agree that the technology is best suited for making new types of aptamers.

Arthur Levin, EVP of R&D at **miRagen Therapeutics Inc.**, said Pinheiro and Holliger's enzymes "have obvious utility for SELEX-derived therapeutics. Using these modified nucleotides could greatly expand what kinds of molecules one could pull out" of aptamer screens.

miRagen is developing locked nucleic acid (LNA) antisense therapeutics against microRNAs involved in cardiovascular disease.

Levin cautioned that the mutations that allow the MRC team's engineered polymerases to use non-natural nucleotides appear to cripple the enzymes, leading to a high error rate and to premature termination of replication. As a result, aptamers made by the new enzymes tend to be short and heterogeneous, potentially limiting their therapeutic utility.

Pinheiro agreed that using the enzymes for therapeutic aptamer discovery will require improving their accuracy and staying power.

Larry Gold, chairman, CEO and founder of aptamer diagnostics company **SomaLogic Inc.**, said the potency of the non-natural aptamers needs to be improved.

"They showed that they can do SELEX with non-natural molecules with not very good affinity" for their targets, said Gold. "They are a long way away from good aptamers."

**"Natural nucleic acids don't have much stability, so you can find aptamers with some utility *in vitro* but you can rarely use them for medicine."**

— Vitor Pinheiro,  
Medical Research Council

Gold co-invented SELEX in 1990 (ref. 3) and founded NeXagen Inc. in 1991 to commercialize the procedure. In 1995, NeXagen and Vestar Inc. merged to become NeXstar Inc., which **Gilead Sciences Inc.** acquired in 1999. Gilead exclusively licensed SELEX to SomaLogic for diagnostic use in 1999 and to **Archemix Corp.** for therapeutic use in 2001.

Archemix is being liquidated.

Gold thinks a better way to create new aptamers is to chemically modify the bases of nucleotides rather than the sugars. He cited a 2010 study from his own team at SomaLogic that used aptamers with normal sugars but modified pyrimidine bases to find protein biomarkers of chronic kidney disease.<sup>4</sup>

“Futzung with pyrimidines is naturally acceptable to many polymerases, more so than adapting them to modified sugars,” said Gold.

Pinheiro thinks the biggest draw of non-natural aptamers will likely be increased bioavailability compared with conventional aptamers. He noted that several of the non-natural nucleotides used by his team “have been reported to be quite stable *in vivo*.”

Testing non-natural aptamers in cell culture and animal models of disease is thus a logical next step. Indeed, Pinheiro plans to screen for non-natural aptamers to treat hematological malignancies.

Osherovich, L. *SciBX* **5(18)**; doi:10.1038/scibx.2012.458  
Published online May 3, 2012

#### REFERENCES

1. Pinheiro, V.B. *et al. Science*; published online April 20, 2012; doi:10.1126/science.1217622  
**Contact:** Philipp Holliger, Medical Research Council, Cambridge, U.K.  
e-mail: [ph1@mrc-lmb.cam.ac.uk](mailto:ph1@mrc-lmb.cam.ac.uk)
2. Yu, H. *et al. Nat. Chem. Biol.* **4**, 183–187 (2012)
3. Tuerk, C. & Gold, L. *Science* **249**, 505–510 (1990)
4. Gold, L. *et al. PLoS ONE* **5**, e15004; published online Dec. 7, 2010; doi:10.1371/journal.pone.0015004

#### COMPANIES AND INSTITUTIONS MENTIONED

**Archemix Corp.**, Cambridge, Mass.  
**Gilead Sciences Inc.** (NASDAQ:GILD), Foster City, Calif.  
**Medical Research Council**, Cambridge, U.K.  
**miRagen Therapeutics Inc.**, Boulder, Colo.  
**SomaLogic Inc.**, Boulder, Colo.

## This week in therapeutics

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

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

| Indication  | Target/marker/pathway  | Summary  | Licensing status                                  | Publication and contact information   |
|---|--|--|---|---|
| <b>Autoimmune disease</b>   |  |  |   |   |
| Osteoarthritis  | Filamin A (FLNA); core-binding factor $\beta$ -subunit (CBF $\beta$ ); CBF $\beta$ ) | <i>In vitro</i> and mouse studies suggest the small molecule kartogenin could help treat osteoarthritis. Image-based high throughput screening of a small molecule library found that kartogenin promotes human chondrocyte differentiation. SAR studies showed that kartogenin increased chondrocyte formation by binding FLNA and disrupting the FLNA-CBF $\beta$ interaction. In two mouse models of osteoarthritis, kartogenin increased cartilage repair or decreased osteoarthritis symptoms compared with vehicle. Next steps could include optimizing the potency of kartogenin. Novartis AG declined to comment on the status of this program.  | Patent and licensing status unavailable           | Johnson, K. <i>et al. Science</i> ; published online April 5, 2012; doi:10.1126/science.1215157<br><b>Contact:</b> Peter G. Schultz, The Scripps Research Institute, La Jolla, Calif.<br>e-mail: <a href="mailto:schultz@scripps.edu">schultz@scripps.edu</a><br><b>Contact:</b> Kristen Johnson, Genomics Institute of the Novartis Research Foundation, San Diego, Calif.<br>e-mail: <a href="mailto:kjohnson@gnf.org">kjohnson@gnf.org</a> |
| <b>SciBX 5(18); doi:10.1038/scibx.2012.459<br/>Published online May 3, 2012</b> |  |  |   |   |
| <b>Cancer</b>   |  |  |   |   |
| Acute myelogenous leukemia (AML)  | FMS-like tyrosine kinase 3 (FLT3; CD135)   | Patient sample studies identified resistance-causing mutations in FLT3 that could be targeted to treat AML. FLT3 inhibitors can lead to disease relapse in patients with AML. In a screen of AML samples from relapsed patients, mutations in residues of the FLT3 kinase domain were identified that were associated with treatment resistance. Next steps include identifying small molecules or biologics that interact with the resistant mutants. Ambit Biosciences Corp. and Astellas Pharma Inc. are developing quizartinib, a FLT3 inhibitor in Phase II testing to treat AML. At least nine other companies have FLT3 inhibitors in clinical and preclinical testing to treat cancer. | Patent application filed; available for licensing | Smith, C.C. <i>et al. Nature</i> ; published online April 15, 2012; doi:10.1038/nature11016<br><b>Contact:</b> Neil P. Shah, University of California, San Francisco, Calif.<br>e-mail: <a href="mailto:nshah@medicine.ucsf.edu">nshah@medicine.ucsf.edu</a>  |
| <b>SciBX 5(18); doi:10.1038/scibx.2012.460<br/>Published online May 3, 2012</b> |  |  |   |   |
| Breast cancer   | Mitochondria; glycolysis   | Studies in cell culture suggest combining mitochondrial antioxidants and glycolysis inhibitors could help treat breast cancer. In cultured breast cancer cell lines, a combination of the glycolysis inhibitor 2-deoxyglucose (2-DG) and the mitochondria-targeted antioxidant compounds MitoQ or MitoCP decreased intracellular ATP levels, colony formation and cell survival compared with either treatment alone. Next steps include preclinical pharmacokinetic and safety studies. Antipodean Pharmaceuticals Inc.'s MitoQ is in Phase II testing for HCV. In 2011, Threshold Pharmaceuticals Inc. discontinued development of 2-DG, which was in Phase I testing for solid tumors.      | Patented; available for licensing                 | Cheng, G. <i>et al. Cancer Res.</i> ; published online March 19, 2012; doi:10.1158/0008-5472.CAN-11-3928<br><b>Contact:</b> Balaraman Kalyanaraman, Medical College of Wisconsin, Milwaukee, Wis.<br>e-mail: <a href="mailto:balarama@mcw.edu">balarama@mcw.edu</a>   |
| <b>SciBX 5(18); doi:10.1038/scibx.2012.461<br/>Published online May 3, 2012</b> |  |  |   |   |

## This week in therapeutics (continued)

| Indication | Target/marker/pathway  | Summary  | Licensing status                            | Publication and contact information  |
|------------|--|--|---|--|
| Cancer     | Phosphoinositide 3-kinase- $\gamma$ (PI3K $\gamma$ ); PTEN (MMAC1; TEP1) | Cell culture and mouse studies suggest targeting PI3K $\gamma$ could help treat patients with PTEN-null tumors. In a panel of 422 human cancer cell lines, cells with mutations in <i>PTEN</i> were more likely to be sensitive to the newly identified PI3K $\gamma$ -selective inhibitor KIN-193 than cells with wild-type <i>PTEN</i> . In mice with PTEN-null tumors, KIN-193 decreased tumor growth compared with vehicle, whereas the drug did not reduce tumor growth in mice that had wild-type PTEN tumors. Next steps include additional testing of KIN-193 in preclinical cancer models.<br><br><b>SciBX 5(18); doi:10.1038/scibx.2012.462</b><br><b>Published online May 3, 2012</b>   | Unpatented; licensing status not applicable | Ni, J. <i>et al. Cancer Discov.</i> ; published online April 12, 2012; doi:10.1158/2159-8290.CD-12-0003<br><b>Contact:</b> Jean Zhao, Dana-Farber Cancer Institute, Boston, Mass.<br>e-mail: <a href="mailto:jean_zhao@dfci.harvard.edu">jean_zhao@dfci.harvard.edu</a><br><b>Contact:</b> Nathanael Gray, same affiliation as above<br>e-mail: <a href="mailto:nathanael_gray@dfci.harvard.edu">nathanael_gray@dfci.harvard.edu</a> |
| Cancer     | Phosphoserine aminotransferase 1 (PSAT1)                                 | Studies in cell culture suggest inhibiting PSAT1 could help treat cancer. In human colon and lung cancer cells grown in serine starvation conditions, RNAi knockdown of <i>PSAT1</i> , a tumor-associated enzyme in the serine synthesis pathway, led to lower cancer cell proliferation than normal expression of <i>PSAT1</i> . Next steps could include testing PSAT1 inhibition in animal models.<br><br><b>SciBX 5(18); doi:10.1038/scibx.2012.463</b><br><b>Published online May 3, 2012</b>   | Patent and licensing status unavailable     | Ye, J. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online April 16, 2012; doi:10.1073/pnas.1204176109<br><b>Contact:</b> Craig B. Thompson, Memorial Sloan-Kettering Cancer Center, New York, N.Y.<br>e-mail: <a href="mailto:thompsonc@mskcc.org">thompsonc@mskcc.org</a>  |
| Cancer     | Purinergic receptor P2X ligand-gated ion channel 7 (P2RX7; P2X7)         | Mouse studies suggest inhibiting P2X7 could help treat cancer. In mice, injection of mouse carcinoma cells that had high levels of P2x7 expression led to tumor formation faster than injection of carcinoma cells with low levels of P2x7 expression. In mice injected with mouse melanoma or human neuroblastoma cells, a P2X7 antagonist or small hairpin RNA knockdown of <i>P2X7</i> decreased tumor growth compared with no treatment. Next steps include animal studies with P2X7 antagonists that have been used in clinical trials in other indications.<br>GlaxoSmithKline plc's GSK1482160, a purinergic ATP receptor antagonist that targets P2X7, is in Phase I testing to treat pain.<br>Evotec AG's EVT 401, an oral small molecule P2X7 receptor antagonist, is in Phase I testing to treat rheumatoid arthritis (RA) and preclinical development to treat inflammatory bowel disease (IBD).<br>Affectis Pharmaceuticals AG's AFC-5128, a P2X7 antagonist, is in preclinical development to treat pain and multiple sclerosis (MS).<br><br><b>SciBX 5(18); doi:10.1038/scibx.2012.464</b><br><b>Published online May 3, 2012</b> | Unpatented; available for licensing         | Adinolfi, E. <i>et al. Cancer Res.</i> ; published online April 13, 2012; doi:10.1158/0008-5472.CAN-11-1947<br><b>Contact:</b> Francesco Di Virgilio, University of Ferrara, Ferrara, Italy<br>e-mail: <a href="mailto:fdv@unife.it">fdv@unife.it</a>  |
| Cancer     | Receptor for advanced glycation endproducts (RAGE)                       | <i>In vitro</i> and mouse studies suggest antibodies against RAGE could help prevent cancer metastasis to the lungs. In mice injected with lung cancer or melanoma cell lines, pretreatment with an anti-RAGE antibody decreased tumor formation in the lungs compared with a control antibody pretreatment. Next steps include developing antibodies against the specific RAGE domains involved in mediating metastasis.<br>Dynamis Therapeutics Inc.'s RAGE inhibitor, DYN-15, is in preclinical testing to treat diabetic retinopathy.<br><br><b>SciBX 5(18); doi:10.1038/scibx.2012.465</b><br><b>Published online May 3, 2012</b>   | Unpatented; unavailable for licensing       | Mizumoto, S. <i>et al. J. Biol. Chem.</i> ; published online April 9, 2012; doi:10.1074/jbc.M111.313437<br><b>Contact:</b> Kazuyuki Sugahara, Hokkaido University, Hokkaido, Japan<br>e-mail: <a href="mailto:k-sugar@sci.hokudai.ac.jp">k-sugar@sci.hokudai.ac.jp</a>   |

## This week in therapeutics (continued)

| Indication                         | Target/marker/<br>pathway           | Summary  | Licensing status                                 | Publication and contact<br>information   |
|------------------------------------|-------------------------------------|--|--|--|
| Melanoma                           | VEGF; BRAF                          | <p>Studies in mice suggest combined use of metformin and VEGF inhibitors could help treat melanoma. In a xenograft mouse model of <i>BRAF</i>-mutant melanoma, metformin increased VEGF expression, blood vessel density and tumor volume compared with vehicle control, whereas it did not increase VEGF expression or tumor growth in mice with <i>neuroblastoma Ras viral oncogene (NRAS)</i>-mutant melanoma. In mice with <i>BRAF</i>-mutant melanoma, treatment with Avastin bevacizumab plus metformin lowered tumor volume compared with vehicle or Avastin alone. Next steps include starting a clinical trial of metformin plus a VEGF inhibitor in patients with <i>BRAF</i>-mutation-positive melanoma.</p> <p>Metformin is a generic approved to treat diabetes and is in clinical testing to treat various cancers. Roche's Genentech Inc. unit and Chugai Pharmaceutical Co. Ltd. market Avastin to treat various cancers.</p> <p><b>SciBX 5(18); doi:10.1038/scibx.2012.466</b><br/>Published online May 3, 2012</p> | Unpatented; licensing status not applicable      | <p>Martin, M.J. <i>et al. Cancer Discov.</i>; published online March 31, 2012; doi:10.1158/2159-8290.CD-11-0280</p> <p><b>Contact:</b> Richard Marais, The University of Manchester, Manchester, U.K.<br/>e-mail: <a href="mailto:rmarais@picr.man.ac.uk">rmarais@picr.man.ac.uk</a></p>   |
| <b>Endocrine/metabolic disease</b> |                                     |  |  |  |
| Metabolic syndrome                 | AMP-activated protein kinase (AMPK) | <p><i>In vitro</i> and mouse studies suggest the aspirin metabolite salicylate activates AMPK to improve serum lipid levels and treat metabolic disease. <i>In vitro</i>, salicylate directly activated AMPK at low mM concentrations. In mice, injection of salicylate increased AMPK activation and decreased serum fatty acids compared with vehicle injection. Next steps include identifying which effects of salicylate are mediated by AMPK and which are mediated by cyclooxygenase (COX).</p> <p><b>SciBX 5(18); doi:10.1038/scibx.2012.467</b><br/>Published online May 3, 2012</p>  | Unpatented; licensing status not applicable      | <p>Hawley, S.A. <i>et al. Science</i>; published online April 19, 2012; doi:10.1126/science.1215327</p> <p><b>Contact:</b> D. Grahame Hardie, University of Dundee, Dundee, U.K.<br/>e-mail: <a href="mailto:d.g.hardie@dundee.ac.uk">d.g.hardie@dundee.ac.uk</a></p>  |
| Metabolic syndrome                 | Not applicable                      | <p>Studies in mice suggest depleting invariant NK T (iNKT) cells could help treat metabolic disorders. In mouse models of obesity, mice engineered to lack iNKT cells had similar body weight and triglyceride levels but decreased insulin resistance and lipid accumulation in the liver compared with wild-type mice. Next steps include investigating iNKT cell function in obese patients.</p> <p><b>SciBX 5(18); doi:10.1038/scibx.2012.468</b><br/>Published online May 3, 2012</p>   | Unpatented; licensing status unavailable         | <p>Wu, L. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online April 9, 2012; doi:10.1073/pnas.1200498109</p> <p><b>Contact:</b> Luc Van Kaer, Vanderbilt University School of Medicine, Nashville, Tenn.<br/>e-mail: <a href="mailto:luc.van.kaer@vanderbilt.edu">luc.van.kaer@vanderbilt.edu</a></p> <p><b>Contact:</b> Lan Wu, same affiliation as above<br/>e-mail: <a href="mailto:lan.wu@vanderbilt.edu">lan.wu@vanderbilt.edu</a></p> |
| Metabolic syndrome; obesity        | MicroRNA-208a (miR-208a)            | <p>Studies in mice suggest antagonizing miR-208a could help treat metabolic syndrome and obesity. In a mouse model of diet-induced obesity, an oligonucleotide antagonist of miR-208a increased glucose tolerance and decreased visceral fat and weight gain compared with an untargeted oligonucleotide control. Next steps include preclinical development of the miR-208a antagonist in preparation for metabolic disease trials. miRagen Therapeutics Inc. and Servier have partnered to develop antimir-208, the preclinical compound used in this study, for cardiovascular and metabolic indications (<i>see Heart beats fat</i>, page 1).</p> <p><b>SciBX 5(18); doi:10.1038/scibx.2012.469</b><br/>Published online May 3, 2012</p>   | Patent pending; licensed to miRagen Therapeutics | <p>Grueter, C.E. <i>et al. Cell</i>; published online April 27, 2012; doi:10.1016/j.cell.2012.03.029</p> <p><b>Contact:</b> Eric N. Olson, The University of Texas Southwestern Medical Center, Dallas, Texas<br/>e-mail: <a href="mailto:eric.olson@utsouthwestern.edu">eric.olson@utsouthwestern.edu</a></p>   |

## This week in therapeutics (continued)

| Indication               | Target/marker/<br>pathway  | Summary  | Licensing status   | Publication and contact<br>information   |
|--------------------------|--|--|--|--|
| <b>Hematology</b>        |  |  |  |  |
| Thalassemia              | Hepcidin antimicrobial peptide (HAMP); transmembrane protease serine 6 (TMPRSS6; matriptase-2) | <p>Mouse studies suggest inhibiting TMPRSS6 could help treat <math>\alpha</math>-thalassemia. In a mouse model of <math>\alpha</math>-thalassemia, <i>Tmprss6</i> knockout increased mRNA levels of the iron metabolism and storage regulator <i>Hamp</i> and decreased anemia compared with wild-type <i>Tmprss6</i> expression. Next steps could include screening for compounds that inhibit TMPRSS6.</p> <p>Alnylam Pharmaceuticals Inc.'s ALN-TMP, an RNAi targeting TMPRSS6, is in preclinical development to treat hemoglobinopathies, including <math>\alpha</math>-thalassemia and sickle cell anemia.</p> <p><b>SciBX 5(18); doi:10.1038/scibx.2012.470</b><br/>Published online May 3, 2012</p>   | Patent and licensing status unavailable                  | <p>Nai, A. <i>et al. Blood</i>; published online April 6, 2012;<br/>doi:10.1182/blood-2012-01-401885<br/><b>Contact:</b> Clara Camaschella, Vita-Salute San Raffaele University, Milan, Italy<br/>e-mail:<br/><a href="mailto:camaschella.clara@hsr.it">camaschella.clara@hsr.it</a></p>   |
| <b>Neurology</b>         |  |  |  |  |
| Alzheimer's disease (AD) | $\beta$ -Site APP-cleaving enzyme 1 (BACE1); cytochrome P450 3A4 (CYP3A4)                      | <p>Two separate studies identified BACE1 inhibitors that could help treat AD. <i>In vitro</i>, a series of hydroxyethylamine derivatives were identified that had greater potency against BACE1, metabolic stability in human and mouse liver microsomes and oral bioavailability in rats than the parent compound. In rats, the compounds had increased penetration into the CNS. The best compound lowered toxic <math>\beta</math>-amyloid (A<math>\beta</math>) levels in the plasma, cerebrospinal fluid and brain compared with vehicle control.</p> <p>In the second study, hydroxyethylamine derivatives incorporating alkyl groups or N-heterocycle groups resulted in dual inhibition of BACE1 and CYP3A4 and improved CNS penetration. <i>In vitro</i> and in rats, the derivatives had greater metabolic stability and decreased <math>\beta</math>-amyloid levels compared with the parent compound. The derivatives also were able to penetrate the BBB and showed potency against BACE1 and CYP3A4. In dogs, i.v. administration of the dual inhibitors showed greater cardiovascular safety than administration of the parent compound.</p> <p>Next steps for both studies could include additional pharmacodynamic and toxicity studies.</p> <p>At least five companies have BACE1 inhibitors in clinical and preclinical testing to treat AD.</p> <p><b>SciBX 5(18); doi:10.1038/scibx.2012.471</b><br/>Published online May 3, 2012</p> | Patent and licensing status unavailable for both studies | <p>Weiss, M.M. <i>et al. J. Med. Chem.</i>; published online April 2, 2012;<br/>doi:10.1021/jm300119p<br/><b>Contact:</b> Matthew M. Weiss, Amgen Inc., Cambridge, Mass.<br/>e-mail:<br/><a href="mailto:mmweiss@amgen.com">mmweiss@amgen.com</a></p> <p>Dineen, T.A. <i>et al. J. Med. Chem.</i>; published online April 2, 2012;<br/>doi:10.1021/jm300118s<br/><b>Contact:</b> Thomas A. Dineen, Amgen Inc., Cambridge, Mass.<br/>e-mail:<br/><a href="mailto:tdineen@amgen.com">tdineen@amgen.com</a></p> |

## This week in therapeutics (continued)

| Indication                | Target/marker/pathway                      | Summary   | Licensing status                                     | Publication and contact information  |
|---------------------------|--|---|--|--|
| Alzheimer's disease (AD)  | Glycogen synthase kinase 3 $\beta$ (GSK3B) | <p>Cell culture studies identified pyrazine-based inhibitors of GSK3B that could help treat neurodegenerative diseases such as AD. <i>In vitro</i>, a lead compound of the series inhibited GSK3B-mediated microtubule-associated protein-<math>\tau</math> (MAPT; TAU; FTDP-17) phosphorylation with nanomolar IC<sub>50</sub> values, showed properties associated with good brain penetration and had good target selectivity across a panel of 26 kinases. Researchers did not disclose next steps, which could include evaluating the lead inhibitor in animal models of AD.</p> <p>AstraZeneca plc's lead pyrazine analog GSK3B inhibitor is in preclinical development.</p> <p>Tideglusib, a GSK3 inhibitor from Noscira S.A., is in Phase II testing to treat AD.</p> <p>Neu-120, a selective uncompetitive NMDAR modulator and monoamine oxidase B (MAO-B) and GSK3B inhibitor from Neurim Pharmaceuticals Ltd., is in Phase II testing for Parkinson's disease (PD).</p> <p>DiaMedica Inc's DM-99, an undisclosed naturally occurring protein that inhibits GSK3B, is in preclinical development for AD.</p> <p><b>SciBX 5(18); doi:10.1038/scibx.2012.472</b><br/>Published online May 3, 2012</p> | Patent status undisclosed; unavailable for licensing | <p>Berg, S. <i>et al. J. Med. Chem.</i>; published online April 10, 2012; doi:10.1021/jm201724m</p> <p><b>Contact:</b> Stefan Berg, AstraZeneca R&amp;D, Soedertaelje, Sweden<br/>e-mail: <a href="mailto:stefan.berg@astrazeneca.com">stefan.berg@astrazeneca.com</a></p> |
| <b>Ophthalmic disease</b> |  |   |  |  |
| Blindness                 | Not applicable                             | <p>Mouse studies suggest transplantation of rod photoreceptor cells could restore vision after retinal degeneration. In mice that lack photoreceptor rod function and have night blindness, transplantation of rod precursor cells led to the formation of rod photoreceptors that established synaptic connections in the eye and were light sensitive. In two different visual function tests, mice receiving transplants had increased visual function compared with sham-operated controls, although visual function was still lower than that in wild-type controls with normal vision. Next steps include identifying a way to increase the number of active photoreceptors.</p> <p><b>SciBX 5(18); doi:10.1038/scibx.2012.473</b><br/>Published online May 3, 2012</p>   | Patent and licensing status unavailable              | <p>Pearson, R.A. <i>et al. Nature</i>; published online April 18, 2012; doi:10.1038/nature10997</p> <p><b>Contact:</b> Robin R. Ali, University College London, London, U.K.<br/>e-mail: <a href="mailto:r.ali@ucl.ac.uk">r.ali@ucl.ac.uk</a></p>                          |
| <b>Pulmonary disease</b>  |  |   |  |  |
| Acute lung injury         | Not applicable                             | <p>Mouse studies suggest bone marrow-derived stromal cells (BMSCs) may help treat acute lung injury by restoring alveolar bioenergetics. In mice with lipopolysaccharide (LPS)-induced acute lung injury, airway-delivered wild-type BMSCs released mitochondria into the alveolar epithelia, and increased alveolar ATP concentrations and decreased lung injury compared with airway-delivered BMSCs with dysfunctional mitochondria. Next steps include optimizing methods for using BMSCs as a cell therapy to treat acute lung injury.</p> <p><b>SciBX 5(18); doi:10.1038/scibx.2012.474</b><br/>Published online May 3, 2012</p>  | Unpatented; licensing status not applicable          | <p>Islam, M.N. <i>et al. Nat. Med.</i>; published online April 15, 2012; doi:10.1038/nm.2736</p> <p><b>Contact:</b> Jahar Bhattacharya, Columbia University, New York, N.Y.<br/>e-mail: <a href="mailto:jb39@columbia.edu">jb39@columbia.edu</a></p>                       |

## This week in techniques

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

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

| Approach  | Summary  | Licensing status   | Publication and contact information   |
|---|--|--|---|
| <b>Assays &amp; screens</b>   |  |  |   |
| Microarray of modified RNAs to identify therapeutic RNAs against folded RNA targets               | A microarray displaying a library of modified RNAs could help identify therapeutics against folded RNA targets. A microarray was constructed that displayed about 90,000 2'-O-methylated RNAs, including all possible sequences 4–8 nucleotides in length. Using the microarray, short, modified RNAs were identified that bound the folded RNA component of human telomerase in four distinct regions. Some of the identified modified RNAs inhibited telomerase activity in biochemical and cell-based assays. Ongoing work has identified modified RNAs that target the microRNA-17-92 (miR-17-92) cluster and HCV RNA.   | Patent applications filed; optioned exclusively to Ontorii Inc.  | Gude, L. <i>et al. J. Biol. Chem.</i> ; published online March 26, 2012; doi:10.1074/jbc.M111.316596<br><b>Contact:</b> Gregory L. Verdine, Harvard University, Cambridge, Mass.<br>e-mail: <a href="mailto:gregory_verdine@harvard.edu">gregory_verdine@harvard.edu</a>  |
| <b>SciBX 5(18); doi:10.1038/scibx.2012.475</b><br>Published online May 3, 2012                    |  |  |   |
| <b>Disease models</b>   |  |  |   |
| Mice with humanized ectopic bone engraftments to test leukemia therapeutics                       | Mice with humanized ectopic bone engraftments could help identify new leukemia therapeutics. In mice, subcutaneous injection of a combination of human endothelial colony-forming cells (ECFCs), mesenchymal stem cells (MSCs) and Matrigel generated well-vascularized, bone-like tissues in the flank. In the same mice, i.v. transplantation of human acute myelogenous leukemia (AML) cells led to human AML engraftment in mouse skeleton and humanized ectopic bone. Also in the model, mice with MSC-specific hypoxia-inducible factor 1 $\alpha$ (Hif1 $\alpha$ ; Hif1 $\alpha$ ) small hairpin RNA expression had a 50% decrease in AML engraftment in humanized ectopic bone compared with mice that had MSC-specific control shRNA expression. Next steps include reducing the time to bone marrow formation. | Patent application filed; available for licensing  | Chen, Y. <i>et al. Blood</i> ; published online April 5, 2012; doi:10.1182/blood-2011-11-389957<br><b>Contact:</b> Michael Andreeff, The University of Texas MD Anderson Cancer Center, Houston, Texas<br>e-mail: <a href="mailto:mandreef@mdanderson.org">mandreef@mdanderson.org</a>  |
| <b>SciBX 5(18); doi:10.1038/scibx.2012.476</b><br>Published online May 3, 2012                    |  |  |   |
| <b>Drug delivery</b>  |  |  |   |
| Targeted delivery of small interfering RNA using single-chain variable antibody fragments (scFvs) | Studies in mice suggest scFv-mediated delivery of siRNA could help treat cancer. In an orthotopic xenograft mouse model of HER2 <sup>+</sup> (EGFR2; ERBB2; neu) breast cancer, i.v. injection of a polo-like kinase 1 (PLK1; STPK13) siRNA complexed with an anti-HER2 scFv-protamine fusion protein decreased tumor growth compared with injection of PLK1 siRNA alone. In a xenograft mouse model of metastatic cancer, the complexed siRNA increased survival of animals with HER2 <sup>+</sup> cancer compared with siRNA or scFv alone. Next steps could include applying the platform to the delivery of additional siRNA therapeutics.   | Patent application filed; nonexclusively licensed to Alnylam Pharmaceuticals Inc.; available for licensing | Yao, Y.-d. <i>et al. Sci. Transl. Med.</i> ; published online April 18, 2012; doi:10.1126/scitranslmed.3003601<br><b>Contact:</b> Erwei Song, Sun Yat-Sen Memorial Hospital, Guangzhou, China<br>e-mail: <a href="mailto:songerwei02@yahoo.com.cn">songerwei02@yahoo.com.cn</a><br><b>Contact:</b> Jun Wang, University of Science and Technology of China, Hefei, China<br>e-mail: <a href="mailto:jwang699@ustc.edu.cn">jwang699@ustc.edu.cn</a><br><b>Contact:</b> Judy Lieberman, Children's Hospital Boston, Boston, Mass.<br>e-mail: <a href="mailto:lieberman@idi.harvard.edu">lieberman@idi.harvard.edu</a> |
| <b>SciBX 5(18); doi:10.1038/scibx.2012.477</b><br>Published online May 3, 2012                    |  |  |   |

## This week in techniques (continued)

| Approach   | Summary   | Licensing status  | Publication and contact information  |
|--|---|---|--|
| <b>Drug platforms</b>  |   |   |  |
| Enzyme toolkit for replication of unnatural nucleic acids  | <i>In vitro</i> studies suggest engineered polymerases could enable screening for new, unnatural nucleic acid aptamers. <i>In vitro</i> , engineered polymerases copied DNA and RNA templates into locked nucleic acid (LNA) aptamers with a variety of unnatural sugar backbones. The polymerases were able to make DNA and RNA copies from LNA templates. Next steps include improving the read length of the engineered polymerases and testing the therapeutic utility of LNA aptamers identified through <i>in vitro</i> selection (see <i>Evolution not revolution</i> , page 8).   | Patent pending; available for licensing   | Pinheiro, V.B. <i>et al. Science</i> ; published online April 20, 2012; doi:10.1126/science.1217622<br><b>Contact:</b> Philipp Holliger, Medical Research Council, Cambridge, U.K.<br>e-mail: <a href="mailto:ph1@mrc-lmb.cam.ac.uk">ph1@mrc-lmb.cam.ac.uk</a>   |
|  | <b>SciBX 5(18); doi:10.1038/scibx.2012.478</b><br>Published online May 3, 2012  |   |  |
| High throughput synthesis of transcription activator-like effector nucleases (TALENs)                        | A high throughput TALEN synthesis system could enable rapid, large-scale modification of regions of the genome. TALENs are a class of proteins engineered to bind almost any given DNA sequence depending on the composition of amino acid repeats within each TALEN's DNA-binding domain. DNA fragments encoding the TALEN repeats were conjugated to magnetic beads, allowing the automation of serial DNA cloning steps to produce many unique TALEN sequences using a robotic system. The system enabled the targeting and modification of about 88% of 96 test genes involved in cancer and epigenetic regulation. Next steps include improving the precision of TALENs generated using this method.   | Patent application filed; available for licensing from Massachusetts General Hospital<br><b>Contact:</b> Juliana Leung, Partners Research Ventures & Licensing, Boston, Mass.<br>e-mail: <a href="mailto:jl537@partners.org">jl537@partners.org</a> | Reyon, D. <i>et al. Nat. Biotechnol.</i> ; published online April 8, 2012; doi:10.1038/nbt.2170<br><b>Contact:</b> J. Keith Joung, Massachusetts General Hospital, Charlestown, Mass.<br>e-mail: <a href="mailto:jjoung@partners.org">jjoung@partners.org</a><br><b>Contact:</b> Jeffrey D. Sander, same affiliation as above<br>e-mail: <a href="mailto:jsander@partners.org">jsander@partners.org</a>  |
|  | <b>SciBX 5(18); doi:10.1038/scibx.2012.479</b><br>Published online May 3, 2012  |   |  |
| <i>In vivo</i> reprogramming of cardiac fibroblasts into cardiomyocytes                                      | <i>In vivo</i> conversion of cardiac fibroblasts into cardiomyocytes could help treat heart damage. Previous studies identified three transcription factors—GATA binding protein 4 (GATA4), myocyte enhancer factor 2C (MEF2C) and T-box 5 (TBX5)—capable of reprogramming cardiac fibroblasts into cardiomyocytes. In a mouse model of myocardial infarction, intramyocardial injection of a retroviral vector expressing the 3 factors 48 hours postinjury induced fibroblast conversion to cardiomyocytes and led to an increase in cardiac function compared with vector control injection. Also in the model, co-injection of the retroviral vector plus proangiogenic and fibroblast-activating peptide thymosin $\beta$ 4 further improved cardiac function. Next steps include testing the approach in pigs.<br>RegeneRx Biopharmaceuticals Inc.'s RGN-352, an injectable formulation of thymosin $\beta$ 4, is in Phase II testing to treat acute myocardial infarction. | Patent application filed; available for licensing   | Qian, L. <i>et al. Nature</i> ; published online April 18, 2012; doi:10.1038/nature11044<br><b>Contact:</b> Deepak Srivastava, The J. David Gladstone Institutes, San Francisco, Calif.<br>e-mail: <a href="mailto:dsrivastava@gladstone.ucsf.edu">dsrivastava@gladstone.ucsf.edu</a>  |
|  | <b>SciBX 5(18); doi:10.1038/scibx.2012.480</b><br>Published online May 3, 2012  |   |  |
| Structural and biochemical insights into human bromodomain-containing proteins for epigenetic drug discovery | Structural and biochemical insights into bromodomains may help guide the development of drugs that target the protein family. Bromodomain-containing proteins recognize epigenetic modifications and bind to acetylated histones to modulate gene transcription. X-ray crystal structures were solved for 29 of the 61 human bromodomain-containing proteins. <i>In vitro</i> binding assays determined the affinities of 33 bromodomain-containing proteins for peptides representing all possible acetylated histone sites. Next steps include developing selective inhibitors of bromodomain-containing proteins, including ATPase family AAA domain containing 2 (ATAD2), as tool compounds.  | Unpatented; licensing status not applicable   | Filippakopoulos, P. <i>et al. Cell</i> ; published online March 30, 2012; doi:10.1016/j.cell.2012.02.013<br><b>Contact:</b> Stefan Knapp, University of Oxford, Oxford, U.K.<br>e-mail: <a href="mailto:stefan.knapp@sgc.ox.ac.uk">stefan.knapp@sgc.ox.ac.uk</a><br><b>Contact:</b> Panagis Filippakopoulos, same affiliation as above<br>e-mail: <a href="mailto:panagis.filippakopoulos@sgc.ox.ac.uk">panagis.filippakopoulos@sgc.ox.ac.uk</a> |
|  | <b>SciBX 5(18); doi:10.1038/scibx.2012.481</b><br>Published online May 3, 2012  |   |  |

## This week in techniques (continued)

| Approach   | Summary   | Licensing status                        | Publication and contact information  |
|--|---|---|--|
| <b>Imaging</b>   |   |   |  |
| Radiolabeled anti-prostate-specific antigen (KLK3; PSA) antibody for prostate cancer diagnostics | <p>A radiolabeled anti-PSA antibody could help image bone metastases and determine response to prostate cancer therapy. To enable prostate tumor-specific imaging, an antibody targeting free PSA (fPSA), a form of PSA unbound by serum proteins, was radiolabeled with <sup>89</sup>Zr. In a PET study of prostate cancer xenograft mice, the antibody detected a decrease in fPSA levels in the xenograft after treatment with the anti-androgen receptor small molecule MDV3100 compared with after treatment using vehicle. In mice, the antibody detected xenograft prostate cancer lesions injected into bone but did not detect lesions caused by mechanical bone injury. Next steps include humanizing the antibody and conducting clinical testing in 2013.</p> <p>MDV3100, a triple-acting oral anti-androgen receptor from Medivation Inc. and Astellas Pharma Inc., is in Phase III testing to treat castration-resistant prostate cancer (CRPC). Corresponding author Charles Sawyers is a co-inventor of MDV3100.</p> <p><b>SciBX 5(18); doi:10.1038/scibx.2012.482</b><br/>Published online May 3, 2012</p> | Patent and licensing status undisclosed | <p>Ulmert, D. <i>et al. Cancer Discov.</i>; published online March 31, 2012; doi:10.1158/2159-8290.CD-11-0316</p> <p><b>Contact:</b> Charles L. Sawyers, Memorial Sloan-Kettering Cancer Center, New York, N.Y.<br/>e-mail: <a href="mailto:sawyersc@mskcc.org">sawyersc@mskcc.org</a></p> <p><b>Contact:</b> Jason S. Lewis, same affiliation as above<br/>e-mail: <a href="mailto:lewisj2@mskcc.org">lewisj2@mskcc.org</a></p> <p><b>Contact:</b> Hans Lilja, same affiliation as above<br/>e-mail: <a href="mailto:liljah@mskcc.org">liljah@mskcc.org</a></p> |

## CORRIGENDA AND ERRATA

## Corrigendum: Analysis: Targets &amp; Mechanisms

Haas, M.J. *SciBX* 5(15); doi:10.1038/scibx.2012.381  
Published online April 12, 2012

The Analysis item “DEL1: taking the bite out of periodontitis” misstated the name of the researcher who developed the DEL1 ELISA. Perumal Thiagarajan, professor of pathology and immunology at Baylor College of Medicine, developed the ELISA.

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