

**THIS WEEK**

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A Boston-based team and a group led by Roche's Genentech unit have each identified new kinase regulators of WNT signaling—YES1 and RIPK4, respectively—that provide two new, druggable targets. Each team will now look for the cancer subtypes most likely to respond to inhibitors of these kinases.

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By *Chris Cain, Senior Writer*

Two European teams have provided the strongest evidence to date that circular RNAs are widely expressed in human cells and have clear regulatory functions.<sup>1,2</sup> The biomedical relevance of circular RNAs remains largely unexplored, but the recent explosion of studies linking noncoding RNAs to disease may portend a similar trajectory for this emerging class of nucleic acids.

The refinement of high throughput sequencing methods over the past decade has led to the discovery of thousands of noncoding RNAs, including numerous microRNAs and long noncoding RNAs. Although initial studies were primarily catalogs of RNA transcripts,<sup>3</sup> subsequent functional analyses demonstrated that these molecules have widespread regulatory roles in human diseases.<sup>4</sup>

Numerous companies are now developing therapeutics or diagnostics that use or target miRNAs or lncRNAs in indications ranging from cardiovascular disease to cancer.

Although a handful of studies had suggested some individual RNA transcripts might exist in a circular form, until last year there were no reports of widespread RNA circles. That changed in 2012, when separate groups from **Stanford University** and **The University of North Carolina at Chapel Hill School of Medicine** published analyses of RNA sequencing data from human cells, suggesting thousands of transcripts may exist in a circular form.<sup>5,6</sup>

Norman Sharpless, who led one of the studies and is professor of medicine and genetics at the UNC School of Medicine, told *SciBX* that the discovery of abundant RNA circles was unexpected.

"At the time we started our study, there were maybe a handful known in mammals, and people thought of them as rare, low-copy artifacts that could be due to the occasional RNA splicing malfunction. But we found thousands of them—they are in some cases expressed at levels higher than the linear form of the transcript, and they are conserved in mouse and humans," he said.

Despite the striking results, neither study provided evidence of a specific molecular function for circular RNAs.

Now, independent teams at the **Max Delbrück Center for Molecular Medicine** and **Aarhus University** have shown that circular RNAs have clear functional significance.

Both teams focused on the same circular RNA, *cerebellar degeneration-related protein 1 antisense (ciRS-7; CDR1as)*, because computational analysis predicted more than 70 miRNA-7 (miR-7) binding sites within the transcript. They speculated that *ciRS-7* could

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act as a stable RNA sponge that could sequester miR-7 and prevent it from acting on its downstream targets.

To test this, the teams used immunoprecipitation experiments to show that miR-7 directly bound *ciRS-7*. Subsequent functional experiments showed that knockdown of *ciRS-7* increased expression of miR-7 target genes including *epidermal growth factor receptor (EGFR)* and *α-synuclein (SNCA)* compared with no knockdown.

Neither team could detect a linear form of *ciRS-7* in cells, whereas the circular form was abundant and highly stable.

In mice, the teams used immunohistochemistry to show that *ciRS-7* and miR-7 are coexpressed in brain tissue. The Max Delbruck team further showed that in zebrafish, injecting *ciRS-7* or knocking down miR-7 caused similar defects in brain development.

Finally, to expand the relevance of the results beyond *ciRS-7*, the Max Delbruck team used a computational approach to identify about

2,000 additional circular RNAs in a human cell line. The group chose a subset of transcripts to experimentally validate and confirmed 19 of 23 (83%). The Aarhus team did not take a systematic approach but instead showed that another circular RNA, *sex-determining region Y (SRY)* locus, contained binding sites for miR-138 and had a similar miRNA sequestration function.

Both studies were published in *Nature*.

**Circular functions**

More extensive profiling of circular RNAs is needed before the extent of their biomedical relevance becomes clear. Nevertheless, there are parallels between the discovery of circular RNAs and other noncoding RNAs that recently have become appreciated as drug targets.

Nikolaus Rajewsky, professor of systems biology and leader of the research team at Max Delbruck, told *SciBX* that RNA circles are just now being identified because of prior conceptual and technical limitations.

“Throughout the RNA world, one lesson has been that whenever you look for something that would not have been seen for technical reasons, you end up finding something new,” he said. “When people found small RNAs, it was thought to be degradation for a long time, but then it suddenly turned out it was tremendously important. Now we have found RNAs that are covalently closed and are functionally important.”

Julia Salzman, a postdoc at Stanford University who published the first catalog of widespread RNA circle expression early last year,<sup>5</sup> agreed that researchers’ mindsets have been a limiting factor in identifying circular RNA. “One difficulty with their identification has been that most people ignore sequencing reads that aren’t consistent with the current models of how splicing takes place,” she said.

She added that a technical difficulty with identifying circular RNA has been that most sequencing protocols use methods to select for polyadenylated (polyA) transcripts. Those methods would miss circular

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**—Nikolaus Rajewsky,  
Max Delbruck Center for  
Molecular Medicine**

RNAs, which lack a polyA tail.

“I think the vast majority of available data is based on polyA-selected samples, and that makes a comprehensive study of the phenomenon more difficult,” she said.

She added that the progress made in identifying circular RNAs over the last year has opened up an entire field of new molecules for functional exploration. “These papers are promising and exciting. RNA circles are so abundant and so diverse that it will lead to fruitful research efforts for many groups for many years,” she said.

Salzman said it was important to note that the papers focused primarily on a noncoding RNA found only in a circular form. Many RNAs exist in both circular and linear forms, and thus their functions will be much harder to tease apart, she said.

Salzman will continue her circular RNA studies in her own lab as an assistant professor at **Harvard Medical School** in the fall.

Arthur Krieg, president, cofounder and CEO of **RaNA Therapeutics Inc.**, agreed that the results will spur intense follow-up. “The way the RNA field has been going, this will generate significant interest, and people will be jumping on these results in the coming months,” he said. “I think from the therapeutic perspective, this could be yet another category of targets for us to pursue, and we now have the benefit of 20 years of advances in developing oligonucleotide therapeutics to guide us.”

RaNA is developing oligonucleotides that block the interaction between lncRNAs and polycomb repressive complex 2 (PRC2) to activate the expression of specific genes.

Sharpless cited lncRNAs as an example of how rapidly new classes of RNA have been linked to disease. First identified in abundance in 2005, lncRNAs are now associated with many human diseases, and in the last six months, new lncRNAs have been characterized with roles in inherited human diseases and in regulating the immune response.<sup>7,8</sup>

“This is an emerging field, and while I am not sure what the clinical and commercial implications of RNA circles are, I am sure these will turn out to be really important in some way that is not readily apparent,” he said.

Sharpless thinks circular RNA acting as a miRNA sponge may be only one example of how it can function. Sharpless is continuing to study the regulation of the *cyclin dependent kinase inhibitor 2A* (*CDKN2A*; *INK4a*; *ARF*; *p16INK4a*) and *CDKN2B* (*INK4B*; *MTS2*) locus by the lncRNA *CDKN2B antisense RNA 1* (*CDKN2B-AS1*; *ANRIL*) and its recently identified circular isoform, *cANRIL*.

Rajewsky also thinks the functions of circular RNAs likely extend beyond miRNA binding. “There is no reason to think that miRNAs are the only molecule they interact with, and we are systematically fishing for other molecules that sit on circular RNAs,” he said.

Pier Paolo Pandolfi, professor of medicine and pathology at Harvard Medical School and director of research at the Cancer Center at **Beth Israel Deaconess Medical Center**, agreed that circular RNAs as well as other noncoding RNAs may have diverse functions, including their ability to act as competitive endogenous RNAs (ceRNAs) for miRNAs. He said the identification of circular RNAs as miRNA sponges provides

an additional piece of evidence that competition for miRNA binding plays a key regulatory role within cells and in disease pathogenesis.

Recently, his group has been one of the leading proponents of an emerging hypothesis that competition between transcripts for miRNA binding has functional consequences, and he has demonstrated a regulatory role for ceRNAs in controlling the tumor suppressor PTEN (*MMAC1*; *TEP1*).<sup>9-11</sup>

### Circling drug development

Although the jury is still out on the extent of circular RNA's role in disease, **MiReven Pty. Ltd.** thinks the specific circular RNA identified by these studies could have direct implications for its oncology program.

MiReven was founded in 2010 to develop derivatives of miR-7 to treat cancer. Work published by its academic founders showed that miR-7 directly represses the expression of known oncogenes including *EGFR*. The program is in preclinical development.

Christopher Wright, technology advisor and manager for MiReven, told *SciBX* that he wanted to see more details about where *ciRS-7* is expressed. “Our aim is to increase expression and activity of miR-7 in tumors, so clearly the reported observations that destruction of *ciRS-7* released increased levels of functional miR-7 into the cell is relevant. The tissue distribution of these RNAs is important, and it would appear that the coexpression of

miR-7 and *ciRS-7* in the brain makes this particularly interesting in the treatment of CNS tumors,” he said.

He added that in situations in which it might be desirable to knock down miRNA expression, circular RNAs could be engineered as an alternative to current antagomir approaches.

Indeed, Jørgen Kjems, professor of molecular biology at Aarhus University and corresponding author of one of the papers, said his team now plans to knock down *ciRS-7* and develop circular RNAs as potential therapeutics.

“Although we have only proven it for miR-7, a circular RNA should work on any other microRNA if the sequence is redesigned, and this is in fact something we are currently investigating,” Kjems said.

In addition, the Aarhus team showed that another miRNA, miR-671, cleaves *ciRS-7*, and now the team is considering testing miR-671 in models for cancer and Parkinson's disease (PD).

Rajewsky's next steps include analyzing the expression of circular RNAs in patient samples.

“We are running a project on looking at circular RNA expression in disease. Because they are stable and we have shown they are tissue specific, they could be good biomarkers. A good biomarker is of course difficult—there have been lots of promises and not too much success, but this is a completely novel class of molecules to look for, and we plan to screen, for example, blood, urine and saliva for circular RNAs,” he said.

Both teams intend to continue functional studies to develop a better molecular understanding of the specific factors required for RNA circularization.

Results from Kjems are patented and available for licensing from

**“I think from the therapeutic perspective, this could be yet another category of targets for us to pursue, and we now have the benefit of 20 years of advances in developing oligonucleotide therapeutics to guide us.”**

**—Arthur Krieg,  
RaNA Therapeutics Inc.**

Aarhus University. The patent and licensing status of the findings from the Max Delbruck team is undisclosed.

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#### REFERENCES

1. Memczak, S. *et al. Nature*; published online Feb. 27, 2013; doi:10.1038/nature11928  
**Contact:** Nikolaus Rajewsky, Max Delbruck Center for Molecular Medicine, Berlin, Germany  
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3. Kapranov, P. *et al. Science* **316**, 1484–1488 (2007)
4. Esteller, M. *Nat. Rev. Genet.* **12**, 861–874 (2011)
5. Salzman, J. *et al. PLoS ONE* **7**, e30733; published online Feb. 1, 2012; doi:10.1371/journal.pone.0030733
6. Jeck, W.R. *et al. RNA* **19**, 141–157 (2013)
7. Troy, A. & Sharpless, N.E. *J. Clin. Invest.* **122**, 3837–3840 (2012)
8. Gomez, J.A. *et al. Cell* **152**, 743–754 (2013)
9. Salmena, L. *et al. Cell* **146**, 353–358 (2011)
10. Tay, Y. *et al. Cell* **147**, 344–357 (2011)
11. Karreth, F.A. *et al. Cell* **147**, 382–395 (2011)

#### COMPANIES AND INSTITUTIONS MENTIONED

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**Harvard Medical School**, Boston, Mass.  
**Max Delbruck Center for Molecular Medicine**, Berlin, Germany  
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**RaNA Therapeutics Inc.**, Cambridge, Mass.  
**Stanford University**, Stanford, Calif.  
**The University of North Carolina at Chapel Hill School of Medicine**, Chapel Hill, N.C.

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# GSK goes deep with DPAC

By Lev Osherovich, Senior Writer

GlaxoSmithKline plc's Discovery Partnerships with Academia program has struck new deals with laboratories at the **Vanderbilt University School of Medicine** and **The Hospital For Sick Children** to identify compounds for severe obesity and cystic fibrosis, respectively. The partnerships aim to re-examine previously known targets in light of new structural and functional insights.

Meanwhile, GSK has cast a broad net to draw in new academic partners through a call for proposals in which academics vie for an opportunity to conduct screens of their most promising targets with GSK's compounds at the pharma's screening facilities.

Launched in 2010, Discovery Partnerships with Academia (DPAC) is an independent unit of GSK tasked with finding discovery opportunities deemed too early stage to qualify for conventional in-licensing.

Pearl Huang, VP and global head of DPAC, said her unit complements internal discovery efforts by searching the academic space for new druggable targets or unconventional strategies to address familiar targets.

"We're disease- and geography-agnostic," said Huang. "My team is fairly senior, with people with good contacts in the academic world and favorite areas that we like to mine."

The program has partnered with nine academic laboratories in the U.K., Europe, the U.S. and Canada to identify small molecules to treat a range of rare diseases (see **Table 1**, "GSK's Discovery Partnerships with Academia (DPAC deals)").

**"We're disease- and geography-agnostic. My team is fairly senior, with people with good contacts in the academic world and favorite areas that we like to mine."**  
— Pearl Huang, GlaxoSmithKline plc

## Courting melanocortin

The bulk of DPAC's nine partnerships are in the U.K. and Europe, but the two deals signed so far this year have been with North American researchers.

DPAC's deals are between GSK and individual academic researchers rather than through the researcher's academic institution or department. Projects typically involve two years or more of funding for discovery and preclinical work with an option to extend the collaboration through clinical development.

Huang did not disclose how much money a typical DPAC deal involves, but she said the pharma makes "significant in-kind contributions to advance these programs into the clinic."

She said the approach results in focused, milestone-driven research with prespecified payouts for achieving research goals. Because each DPAC involves different goals and technologies, Huang's team matches academics with appropriate in-house scientists and facilities and coordinates a collaborative work plan.

"At the core is a work plan for getting these compounds all the way into humans," said Huang. The most advanced DPAC programs are now in preclinical development.

These include an agreement with Roger Cone, professor of molecular physiology and biophysics at Vanderbilt, to identify positive allosteric modulators of melanocortin 4 receptor (MC4R).

MC4R is a GPCR involved in regulation of appetite. Loss-of-function mutations in even a single copy of *MC4R* cause hereditary severe obesity.

Cone said previous MC4R agonists, such as AZD2820 from **AstraZeneca plc** and **Palatin Technologies Inc.** and Palatin's bremelanotide, encountered safety problems in the clinic because of the receptor's other roles in controlling blood pressure. The compounds were discontinued in Phase I and Phase III trials, respectively.

**Table 1. GSK's Discovery Partnerships with Academia (DPAC) deals.** Since launching the DPAC program in 2010, GlaxoSmithKline plc has partnered with nine academic teams to discover therapeutics for a wide range of indications.

Institution	Lead researcher	Indication	Description
Fred Hutchinson Cancer Research Center	Stephen Tapscott	Musculoskeletal disease	Prevention of double homeobox 4 (DUX4)-mediated muscle atrophy in facioscapulohumeral muscular dystrophy (see Martz, L., <i>SciBX</i> 6(1); doi:10.1038/scibx.2013.2)
The Hospital for Sick Children	Christine Bear	Pulmonary disease	Potentiators/correctors of $\Delta F508$ -mutant cystic fibrosis transmembrane conductance regulator (CFTR) to treat cystic fibrosis (CF)
University of Cambridge	David Lomas	Endocrine/metabolic disease	Treatment of $\alpha_1$ -antitrypsin (AAT; A <sub>1</sub> AT; SERPINA1) deficiency using small molecule stabilizers
University College London	Mark Pepys	Endocrine/metabolic disease	Treatment of transthyretin (TTR) amyloidosis using TTR stabilizers
University of Dundee	Irwin McLean	Dermatology	Treatments for recessive dystrophic epidermolysis bullosa (see Haas, M.J., <i>SciBX</i> 4(25); doi:10.1038/scibx.2011.700)
University of Dundee	Susann Schweiger	Neurology	Development of a disease-modifying approach to treat Huntington's disease (HD)
The University of Edinburgh	Damian Mole	Gastrointestinal disease	Prevention of multiple organ failure in severe acute pancreatitis
University of Paris Descartes	Alain Hovnanian	Dermatology	Topical therapy for Netherton syndrome, rosacea and atopic dermatitis
Vanderbilt University School of Medicine	Roger Cone	Endocrine/metabolic disease	Positive allosteric modulators (PAMs) of the melanocortin 4 receptor (MC4R) to treat severe obesity

Instead of activating MC4R outright, Cone wants to find compounds that enhance the receptor's activity only in places where it encounters its natural ligand, the hormone  $\alpha$ -melanocyte stimulating hormone ( $\alpha$ -MSH).

"Our approach is different in that we're going after allosteric modulators that would only work in the presence of the endogenous agonists," said Cone. "We started this as an NIH-funded project to treat MC4R haploinsufficiency-associated morbid obesity, which causes 5% of syndromic obesity in children. These individuals have one good copy of the receptor. We wanted to bump up the activity twofold."

Cone said GSK's initial interest is in treating syndromic obesity caused by MCR4 mutations, but the bigger prize is to modulate the activity of wild-type MC4R in a broader population of patients with obesity.

"GSK thought that this target might be relevant to more common forms of obesity," he noted.

Before GSK entered the picture, Cone's team already had identified lead compounds at the Vanderbilt Center for Neuroscience Drug Discovery.

"GSK will work with us on our hits, providing the medicinal chemistry to make these more drug-like," said Cone. "We will be doing the pharmacology and the animal testing."

### Structure correction

DPAc's cystic fibrosis (CF) partnership is with Christine Bear, senior scientist in molecular structure and function at The Hospital for Sick Children and professor of physiology at the **University of Toronto**.

CF results from loss-of-function mutations in cystic fibrosis transmembrane conductance regulator (CFTR), an ion channel that transports chloride to epithelial cell surfaces. The most common form of CF is caused by the  $\Delta$ F508 mutation, which leads to a structurally defective protein that becomes trapped in the endoplasmic reticulum in a misfolded state and is unable to reach the cell surface.

Bear thinks the best way to treat  $\Delta$ F508-variant CF is to correct the normal structure of the protein with small molecules that directly bind the misfolded protein.

"We've been working on reconstituting full-length and mutant CFTR *in vitro* to understand the consequences of the CF-associated mutations and to understand what the molecules being developed for CF are doing to the protein's activity," said Bear. "I believe that small molecules for CF need to target the protein itself."

Bear has developed an assay of CFTR structure and function with purified recombinant CFTR inserted into reconstituted phospholipid micelles, which are membranous bubbles that mimic the cell surface.

Bear showed GSK preliminary assay results that suggested compounds that correct the structure of CFTR can also improve the protein's *in vitro* activity.

**"GSK will work with us on our hits, providing the medicinal chemistry to make these more drug-like. We will be doing the pharmacology and the animal testing."**

— Roger Cone,  
Vanderbilt University School of Medicine

"I presented results using proof-of-concept small molecules available to the academic community that could bind directly and correct the fold and function of CFTR," said Bear. "GSK has the capability to develop a screening platform for millions of compounds, something I don't otherwise have access to. They were interested in identification of leads and lead optimization."

Bear's *in vitro* screening approach contrasts with the cell-based phenotypic screening used by **Vertex Pharmaceuticals Inc.** Bear said

Vertex's approach is likely to hit other targets involved in CFTR folding and function besides CFTR itself.

Earlier this month, Vertex's lumacaftor (VX-809) entered Phase III testing for  $\Delta$ F508 CF in combination with Kalydeco ivacaftor, a potentiator that enhances CFTR's ion transport activity.

Under the DPAC deal, Bear said GSK will fund postdocs and technicians based in her academic lab who will help pharma counterparts to run the *in vitro* assay at GSK's screening facilities.

### Come one, come all

Huang's next step in growing DPAC is a call for proposals for academics who want to access the pharma's screening resources for their therapeutically relevant targets.

The contest, termed **Discovery Fast Track**, will start accepting entries in May. Huang said it will initially be open to U.S. and Canadian researchers.

"The first step is to send us a one-page, nonconfidential description of the proposed research," said Huang. "We will pick some finalists and ask them to submit a more detailed proposal with some confidentiality. If the investigator is bringing reagents to the table, we will arrange a material transfer agreement, and then we will run a pilot screen in house."

Huang hopes to select up to 10 such mini-projects a year for rapid preliminary screening and said some of these will go on to become full-fledged DPAC deals. She said DPAC has funds to sustain up to 13 concurrent full-scale collaborations.

Although all current DPAC projects involve small molecules, Huang said DPAC is open to targets that are better approached with biologics.

"What interests us is the strength of the hypothesis," she said.

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### COMPANIES AND INSTITUTIONS MENTIONED

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

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

**The Hospital for Sick Children**, Toronto, Ontario, Canada

**Palatin Technologies Inc.** (NYSE-M:PTN), Cranbury, N.J.

**University of Toronto**, Toronto, Ontario, Canada

**Vanderbilt University School of Medicine**, Nashville, Tenn.

**Vertex Pharmaceuticals Inc.** (NASDAQ:VRTX), Cambridge, Mass.

# Placing kinases in the WNT pathway

By Joanne Kotz, Senior Editor

Despite the well-established role of WNT signaling in many cancers, the pathway has proven difficult to modulate therapeutically because it is largely composed of hard-to-target protein-protein interactions. Now, a Boston-based team and a group led by Roche's Genentech Inc. unit have each identified a new kinase regulator of WNT signaling—YES1 and RIPK4, respectively—that provide two new druggable targets in the pathway.<sup>1,2</sup>

Each team will now look for the cancer subtypes most likely to respond to inhibitors of these kinases.

The wingless-type MMTV integration site (WNT) pathway plays a critical role during development and in maintaining adult tissues. In the pathway, WNT ligands bind to frizzled receptors, triggering a signaling cascade that leads to  $\beta$ -catenin (CTNNB1) accumulating in the cytoplasm and then translocating to the nucleus, where it acts in transcriptional complexes to regulate gene expression (see Figure 1, “WNT signaling in cancer”).

WNT pathway activation is likely a frequent driver of cancer. In colon cancer, somatic mutations that increase WNT signaling have been identified in multiple components of the pathway. In other cancer subtypes, WNT signaling is clearly elevated, but specific oncogenic alterations in the pathway have not been identified.

“The role of the WNT pathway has been very well established in colorectal cancer. Its relevance in other cancer types remains unclear,” said Christoph Lengauer, CSO at cancer company Blueprint Medicines. “Irrespectively, in spite of many efforts by numerous companies and academic centers, drugging this pathway has been challenging. This is due to the complexity of WNT signaling and the lack of targets in this pathway that are accessible to drug discovery.”

Few companies have taken WNT pathway modulators into the clinic in cancer. The most advanced program is OncoMed Pharmaceuticals Inc.'s vantictumab (OMP-18R5), an antibody that binds multiple frizzled receptors. The molecule, which is partnered with Bayer AG, started Phase I testing in solid tumors in 2011.

“Connecting kinases like YES1 and RIPK4 to the WNT pathway is exciting because kinases are druggable,” Lengauer added.

## YES gets a nod

A team led by William Hahn set out to identify new targets in  $\beta$ -catenin-driven cancers.<sup>1</sup> Hahn is deputy CSO and chief of the Division of Molecular and Cellular Oncology at the Dana-Farber Cancer Institute and a senior associate member of the Broad Institute of MIT and Harvard.

First, the team looked at small hairpin RNA screening data to identify genes essential for proliferation or survival in a panel of cancer

cell lines with increased levels of  $\beta$ -catenin activity. The screening data previously were generated through a joint effort by Dana-Farber and the Broad Institute called Project Achilles that included silencing more than 11,000 genes across about 100 genetically characterized cancer cell lines.

Surprisingly, transcription factor 4 (TCF4), which typically interacts with  $\beta$ -catenin to regulate gene expression, did not come up as essential.

This led the team to search for whether  $\beta$ -catenin could be forming a transcriptional complex that did not include TCF4 in these cancer cell lines.

In fact, many essential genes in the WNT-activated cancer cell lines were regulated instead by the transcriptional regulator yes-associated protein 1 (YAP1). Indeed, the team looked at colon cancer cell lines with activated WNT signaling and found that  $\beta$ -catenin formed a complex with YAP1, not TCF4, and this complex induced expression of antiapoptotic genes.

Because YAP1 originally was identified as a protein that interacts with v-yes-1 Yamaguchi sarcoma viral oncogene homolog 1 (YES1; Yes), the team next looked to see if YES1 could be regulating the activity of this transcriptional complex.

In a WNT-driven colon cancer cell line, YES1 interacted directly with YAP1, and knocking down YES1 decreased tumor formation in mice.

Finally, a panel of cancer cell lines with increased WNT activation was more sensitive to Sprycel dasatinib, an inhibitor of multiple

kinases including YES1, than cancer cell lines without WNT pathway activation.

Sprycel is marketed by Bristol-Myers Squibb Co. to treat acute lymphoblastic leukemia (ALL) and chronic myelogenous leukemia (CML).

Results were published in *Cell*.

## RIP-ping into WNT

A team led by Vishva Dixit, VP of physiological chemistry at Genentech, arrived at its new WNT target by a very different route.<sup>2</sup>

The group started from the observation that humans with mutations in the kinase receptor-interacting serine-threonine kinase 4 (RIPK4; RIP4) develop Bartsocas-Papas syndrome, a rare genetic disease characterized by severe developmental defects.

To look at the pathway regulated by RIPK4, the team overexpressed the target in human cells and saw changes in gene expression that were similar to those seen when treating the cells with a WNT ligand.

As a result, the team decided to probe whether the kinase might be regulating WNT signaling. To do so, the researchers first identified proteins that interacted directly with RIPK4, which led them to dishevelled dsh homolog 2 (DVL2), a component of the WNT receptor signaling complex. In cells, RIPK4 directly phosphorylated DVL2 in response to WNT pathway activation.

Because of the frequent role of WNT pathway activation in cancer, the team next asked if RIPK4 might be altered in the disease. Indeed, microarray data from human ovarian tumor tissue showed that RIPK4

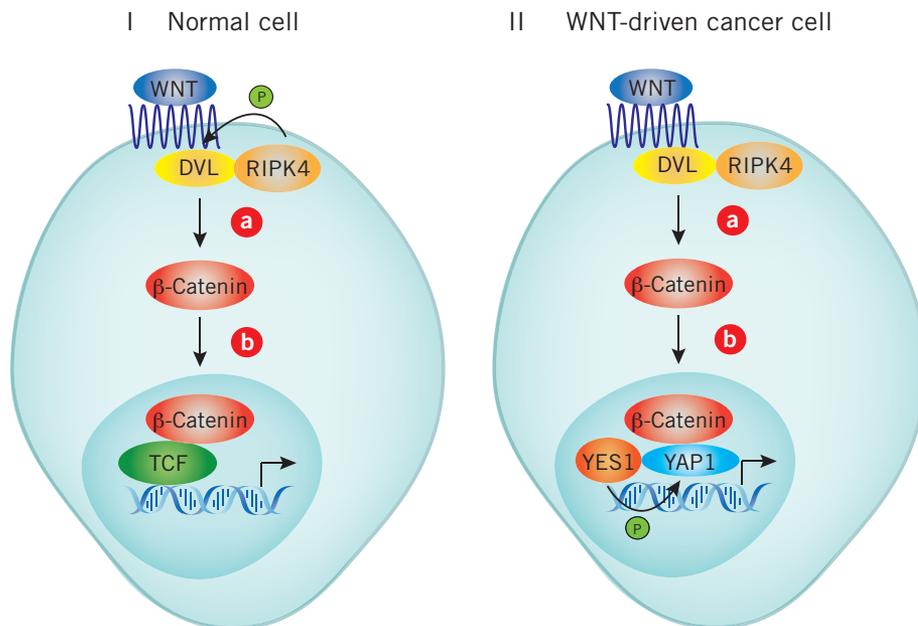
**“If the YAP1-YES1- $\beta$ -catenin axis could be further substantiated, this would be truly exciting because YES1 is a kinase and potentially druggable.”**

—Christoph Lengauer,  
Blueprint Medicines

**Figure 1. WNT signaling in cancer.** A Boston-based team and a **Genentech Inc.**-led team have each identified a new kinase—v-yes-1 Yamaguchi sarcoma viral oncogene homolog 1 (YES1; Yes) and receptor-interacting serine-threonine kinase 4 (RIPK4; RIP4), respectively—that acts in wingless-type MMTV integration site (WNT)-driven cancers.

The Genentech team found that RIPK4 acts at the WNT receptor complex to phosphorylate dishevelled dsh homolog 2 (DVL2). This induces  $\beta$ -catenin (CTNNB1) accumulation in the cytoplasm (II[a]) and translocation to the nucleus to regulate gene expression via the TCF family of transcription factors (II[b]). RIPK4 also appears to play a role in cancer cells (II[a]), as the kinase is overexpressed in ovarian cancers, and knocking down RIPK4 in a cancer cell line decreased tumor growth in mice.

The Boston team found that in cancer cell lines with increased  $\beta$ -catenin activity,  $\beta$ -catenin forms a transcriptional complex with yes-associated protein 1 (YAP1) and YES1 that regulates the increased expression of antiapoptotic genes (II[b]). Knocking down YES1 decreased the formation of WNT-driven colon tumors in mice.



was overexpressed compared with data from noncancerous ovarian tissue ( $p=8.9 \times 10^{-25}$ ).

Finally, the team looked to see if blocking RIPK4 might have a therapeutic effect. In a mouse xenograft model for a tumor driven by increased WNT receptor signaling, shRNA knockdown of *RIPK4* almost completely suppressed tumor growth.

Results were published in *Science*.

### Picking patients

A key next step will be determining the specific cancer patient subpopulations most likely to benefit from inhibiting RIPK4 or YES1.

"It is too early to predict which patient population will most benefit from RIPK4 inhibitors, but the data on RIPK4 overexpression in a large number of ovarian cancers together with its role regulating  $\beta$ -catenin levels makes a compelling case for targeting this protein," said Stefan Knapp, principal investigator at the **Structural Genomics Consortium** and director of chemical biology at the Target Discovery Institute in the Nuffield Department of Clinical Medicine at the **University of Oxford**.

"The recent data on YES1 are thought provoking and exciting because they suggest a molecular connection between YAP1 and  $\beta$ -catenin. If the YAP1-YES1- $\beta$ -catenin axis could be further substantiated, this would be truly exciting because YES1 is a kinase and potentially druggable," added Lengauer.

Knapp and Lengauer both said a logical next step would be developing selective kinase inhibitors that can be used in cancer cell lines and mouse models to further explore the potential of these kinases as therapeutic targets and identify potential biomarkers that predict response.

Lengauer said it is too early to tell how broad a role these kinases may play in WNT-driven cancers. "More tumors need to be studied because the role of  $\beta$ -catenin in cancer—though well established—is very complicated. Of course, it is unlikely that a single mechanism is important in all cancers of a particular subtype."

Indeed, both teams are now planning to look more closely at the role of these kinases in different cancer subpopulations.

Hahn told *SciBX* that the Boston team is setting up screens to look for YES1 or YAP1 inhibitors. With inhibitors in hand, the researchers plan to test whether specific inhibition of these targets recapitulates the genetic findings.

The Genentech team is now "carefully evaluating the potential of RIPK4 as a cancer target," said XiaoDong Andy Huang, a scientist in the Department of Molecular Diagnostics and Cancer Cell Biology at Genentech and the first author on the paper.

Huang cautioned that because RIPK4 sits far upstream in the WNT pathway, it is unlikely to have a therapeutic effect in many cancers with activated WNT signaling. He noted that most  $\beta$ -catenin-activated tumors are due to mutations of *adenomatous polyposis coli*

**"It is too early to predict which patient population will most benefit from RIPK4 inhibitors, but the data on RIPK4 overexpression in a large number of ovarian cancers together with its role regulating  $\beta$ -catenin levels makes a compelling case for targeting this protein."**

**—Stefan Knapp,  
Structural Genomics Consortium**

(APC) (about 85%) or  $\beta$ -catenin itself (about 10%). APC is a negative regulator of  $\beta$ -catenin stability in the cytoplasm.

"Therefore, a RIPK4 inhibitor is unlikely to have efficacy against those tumors since RIPK4 functions at an upstream level," said Huang. "Most likely, RIPK4 inhibitors will have an effect on tumors with abnormally high WNT pathway activity caused by players at or upstream of RIPK4, for example, WNT ligand overexpression or chromosome translocations of *R-Spondin* family members."

In 2012, a Genentech team reported in *Nature* that about 10% of tumors from patients with colon cancer contain gene fusions of R-Spondin family members *R-Spondin 2* (*RSPO2*) or *RSPO3*. Those genes code for secreted proteins known to potentiate WNT signaling, and the genetic alteration led to aberrant activation of the WNT pathway.<sup>3</sup>

A patent application has been filed by Dana-Farber and the Broad Institute covering the work reported in *Cell*. The IP is available for licensing.

Genentech did not disclose the patent or licensing status of its work.

Kotz, J. *SciBX* 6(10); doi:10.1038/scibx.2013.231  
Published online March 14, 2013

#### REFERENCES

1. Rosenbluh, J. *et al. Cell*; published online Dec. 13, 2012; doi:10.1016/j.cell.2012.11.026  
**Contact:** William C. Hahn, Dana-Farber Cancer Institute, Boston, Mass.  
e-mail: [william\\_hahn@dfci.harvard.edu](mailto:william_hahn@dfci.harvard.edu)
2. Huang, X. *et al. Science*; published online Jan. 31, 2013; doi:10.1126/science.1232253  
**Contact:** Vishva M. Dixit, Genentech Inc., South San Francisco, Calif.  
e-mail: [dixit@gene.com](mailto:dixit@gene.com)
3. Seshagiri, S. *et al. Nature* **488**, 660–664 (2012)

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**Blueprint Medicines**, Cambridge, Mass.  
**Bristol-Myers Squibb Co.** (NYSE:BMJ), New York, N.Y.  
**Broad Institute of MIT and Harvard**, Boston, Mass.  
**Dana-Farber Cancer Institute**, Boston, Mass.  
**Genentech Inc.**, South San Francisco, Calif.  
**OncoMed Pharmaceuticals Inc.**, Redwood City, Calif.  
**Roche** (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland  
**Structural Genomics Consortium**, Oxford, U.K.  
**University of Oxford**, Oxford, U.K.

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# VentriGel goes into pigs

By Kai-Jye Lou, Staff Writer

Researchers at the **University of California, San Diego** and **Ventrix Inc.** have developed a catheter-compatible hydrogel that restored cardiac function in a pig model with myocardial infarction.<sup>1</sup> Ventrix is now scaling up manufacture of the hydrogel, called VentriGel, and hopes to take it into clinical trials by year end.

In prior work, UCSD and Ventrix developed a hydrogel scaffold derived from porcine cardiac extracellular matrix (ECM) and showed that injecting it into rat hearts improved cardiac repair and function.<sup>2,3</sup> The hydrogel was designed to mimic the mammalian heart's native ECM, which is important for proper cardiac function but is lost in the infarct region after a heart attack.

Now, the researchers have evaluated the same scaffold in a pig model of myocardial infarction (MI), which more accurately reflects human cardiac physiology.

In pigs, catheter-mediated delivery of VentriGel at two weeks post-MI increased cardiac function and decreased pathological left ventricular remodeling compared with delivery of saline control or no injection. Histology studies showed that VentriGel also increased cardiac muscle tissue and decreased fibrosis in the infarct region compared with controls.

A series of safety and biocompatibility studies showed that catheter-delivered VentriGel did not adversely affect peripheral tissues or cause arrhythmias in the pigs, nor did the hydrogel scaffold induce an immune rejection response or spontaneous formation of thromboemboli in rats. Finally, in human blood samples, the hydrogel did not affect coagulation.

Results were published in *Science Translational Medicine*. Ventrix cofounder Karen Christman, the corresponding author and an assistant professor of bioengineering at UCSD, led the research team.

"The current study is significant because it increases our confidence that our technology is working the way we think it is," said Ventrix CMO Paul Chamberlin. "The hydrogel scaffold improved wall motion in the heart, attenuated remodeling and didn't cause arrhythmias in the pig model. This work gives additional preclinical validation of our hypothesis that VentriGel, given post-MI, will help improve cardiac function."

Chamberlin added that VentriGel could be delivered to the heart using a minimally invasive catheter system, whereas most other injectable biomaterials being developed for cardiac repair need to be delivered via needle syringe, which would require an invasive surgical procedure.

"In many cases, other off-the-shelf injectable biomaterials are not capable of being delivered to the heart with a cardiac catheter," added Ventrix CEO and cofounder Adam Kinsey, a coauthor on the paper.

## Progressing into patients

Ventrix's initial clinical plans are to develop the hydrogel scaffold in the EU. The company is scaling up GMP manufacturing of clinical-grade VentriGel and expects to start a trial by year end.

Chamberlin said the company initially plans to evaluate catheter-mediated delivery of VentriGel in patients with a recent MI event but thinks the product also could be applied to patients who are further removed from the MI event.

"Our early clinical plans will be to develop our product to treat patients in the acute MI scenario. Generally speaking, we want to initially target patients who have Class I or II heart failure, but we think the use of our product could eventually be expanded to the broader heart failure population as well," he said.

According to New York Heart Association guidelines, patients with Class I heart failure have cardiac disease but show no limitations in physical activity, whereas those with Class II heart failure show slight limitations such as fatigue, palpitations, dyspnea or angina resulting from normal physical activity.

Another possible scenario for VentriGel is in patients already undergoing surgery to restore cardiac function, said Harald Ott, a fellow in cardiothoracic surgery at the **Massachusetts General Hospital** and instructor in surgery at **Harvard Medical School**. "Patients undergoing a ventricular restoration procedure may achieve additional benefit from an injection of this hydrogel scaffold."

Moving forward, "it will be important to know how the ECM hydrogel treatment and revascularization either by percutaneous coronary intervention or bypass grafting could be used in conjunction with one another," said Jun Liao, assistant professor of biomedical engineering at **Mississippi State University**. "It would also be interesting to know how treatment with this ECM hydrogel would affect standard pharmacological therapies such as  $\beta$ -blockers and ACE [angiotensin-converting enzyme] inhibitors."

Ott suggested that the researchers may want to look into how other implantable, porcine-derived products were developed, as this could provide insights on how to further assess the biocompatibility and potential immunogenicity of the hydrogel scaffold.

Examples of such pig-derived products include the acellular porcine collagen tissue matrices CollaMend, Permacol, Strattice and XenMatrix, which are marketed for hernia and abdominal wall repair. The Davol Inc. unit of **C.R. Bard Inc.** markets CollaMend and XenMatrix. **Covidien plc** markets Permacol, and the LifeCell Corp. unit of **Kinetic Concepts Inc.** markets Strattice.

UCSD has filed for patents covering the technology described in *Science Translational Medicine*. The IP is licensed to Ventrix, and the company's VentriGel program is available for partnering.

Lou, K.-J. *SciBX* 6(10); doi:10.1038/scibx.2013.232  
Published online March 14, 2013

## REFERENCES

- Seif-Naraghi, S.B. *et al. Sci. Transl. Med.*; published online Feb. 20, 2013; doi:10.1126/scitranslmed.3005503  
**Contact:** Karen L. Christman, University of California, San Diego, La Jolla, Calif.  
e-mail: [christman@eng.ucsd.edu](mailto:christman@eng.ucsd.edu)
- Singelyn, J.M. *et al. Biomaterials* 30, 5409–5416 (2009)
- Singelyn, J.M. *et al. J. Am. Coll. Cardiol.* 59, 751–763 (2012)

## COMPANIES AND INSTITUTIONS MENTIONED

**Covidien plc** (NYSE:COV), Dublin, Ireland  
**C.R. Bard Inc.** (NYSE:BCR), Murray Hill, N.J.  
**Harvard Medical School**, Boston, Mass.  
**Kinetic Concepts Inc.** (NYSE:KCI), San Antonio, Texas  
**Massachusetts General Hospital**, Boston, Mass.  
**Mississippi State University**, Mississippi State, Miss.  
**University of California, San Diego**, La Jolla, Calif.  
**Ventrix Inc.**, San Diego, Calif.

## This week in therapeutics

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

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

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Autoimmune disease</b>				
Psoriasis	IL-17 receptor (IL17R; IL17RA); IL-17A	<i>In vitro</i> and mouse studies identified variants of IL17RA that could help treat plaque psoriasis. In cell-based assays, soluble, mutated versions of IL17RA bound IL-17A and decreased IL-17A-induced secretion of inflammatory cytokines from human fibroblast cells compared with the soluble, wild-type receptor. In a mouse model for plaque psoriasis, subcutaneous injection of an IL17RA variant improved skin recovery with potency comparable to that of dexamethasone, a generic anti-inflammatory steroid. Next steps include preclinical testing of the compounds in additional autoimmune indications.  Amgen Inc. and AstraZeneca plc have brodalumab, a humanized mAb against IL17RA, in Phase III testing to treat psoriasis.  At least two other companies have inhibitors or antibodies targeting IL17RA in Phase II testing or earlier to treat psoriasis.	Patent application filed; available for licensing	Zaretsky, M. <i>et al. Chem. Biol.</i> ; published online Feb. 21, 2013; doi:10.1016/j.chembiol.2012.11.012 <b>Contact:</b> Amir Aharoni, Ben-Gurion University of the Negev, Be'er Sheva, Israel e-mail: <a href="mailto:aaaharoni@bgu.ac.il">aaaharoni@bgu.ac.il</a>
<b>SciBX 6(10); doi:10.1038/scibx.2013.233</b> <b>Published online March 14, 2013</b>				
<b>Cancer</b>				
Brain cancer	Placental growth factor (PGF; PIGF); neuropilin 1 (NRP1)	<i>In vitro</i> and mouse studies suggest inhibiting PIGF or NRP1 could help treat medulloblastoma. In medulloblastoma samples of different subtypes, expression of PIGF and its NRP1 receptor was greater than that in cerebellum samples from healthy controls. In genetic and xenograft mouse models for medulloblastoma, an antibody against human and mouse PIGF inhibited primary tumor growth and spinal metastasis and increased survival compared with a control antibody. Next steps include clinical trials. ThromboGenics N.V. and BioInvent International AB have TB-403, a mAb targeting PIGF, in Phase I/II testing to treat brain cancer.	Patented; licensed to ThromboGenics; unavailable for licensing	Snuderl, M. <i>et al. Cell</i> ; published online Feb. 28, 2013; doi:10.1016/j.cell.2013.01.036 <b>Contact:</b> Rakesh K. Jain, Massachusetts General Hospital, Boston, Mass. e-mail: <a href="mailto:jain@steele.mgh.harvard.edu">jain@steele.mgh.harvard.edu</a>
<b>SciBX 6(10); doi:10.1038/scibx.2013.234</b> <b>Published online March 14, 2013</b>				
Cancer	Eukaryotic translation initiation factor 2 $\alpha$ kinase 3 (EIF2AK3; PERK); eukaryotic translation initiation factor 2A (EIF2A)	Mouse studies suggest inhibiting PERK and EIF2A signaling could help treat radiotherapy-resistant cancers. In mouse xenograft models for human colorectal cancer and glioma, greater PERK and EIF2A signaling was associated with increased tolerance to hypoxia and tumor resistance to radiotherapy compared with normal PERK and EIF2A signaling. In a mouse xenograft model for colorectal cancer with increased PERK and EIF2A signaling, inhibition of EIF2A signaling decreased both hypoxia tolerance and radiotherapy resistance compared with no inhibition. Next steps include developing PERK inhibitors and testing them in preclinical models.	Unpatented; licensing status not applicable	Rouschop, K.M. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online March 7, 2013; doi:10.1073/pnas.1210633110 <b>Contact:</b> Bradly G. Wouters, University of Toronto, Toronto, Ontario, Canada e-mail: <a href="mailto:bwouters@uhnresearch.ca">bwouters@uhnresearch.ca</a> <b>Contact:</b> Kasper M. Rouschop, Maastricht University Medical Center, Maastricht, the Netherlands e-mail: <a href="mailto:kasper.rouschop@maastrichtuniversity.nl">kasper.rouschop@maastrichtuniversity.nl</a>
<b>SciBX 6(10); doi:10.1038/scibx.2013.235</b> <b>Published online March 14, 2013</b>				

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Cardiovascular disease</b>				
Hypertrophy	Endothelial cell nitric oxide synthase 3 (NOS3; eNOS); regulator of G-protein signaling 4 (RGS4)	<i>In vitro</i> and mouse studies suggest inhibiting eNOS or increasing RGS4 could help prevent cardiac hypertrophy. In a mouse model for angiogenesis-driven myocardial hypertrophy, Rgs4 expression was lower and eNos-produced NO was greater than that seen in normal mice. In the same mouse model, Rgs4 overexpression or eNos inhibition prevented hypertrophy. Next steps include studying the mechanism in pathological hypertrophy and myocardial ischemia.	Patent application filed; available for licensing	Jaba, I.M. <i>et al. J. Clin. Invest.</i> ; published online March 1, 2013; doi:10.1172/JCI65112 <b>Contact:</b> Daniela Tirziu, Yale School of Medicine, New Haven, Conn. e-mail: <a href="mailto:daniela.tirziu@yale.edu">daniela.tirziu@yale.edu</a>
<b>SciBX 6(10); doi:10.1038/scibx.2013.236 Published online March 14, 2013</b>				
Myocardial infarction (MI)	MicroRNA-34a (miR-34a); protein phosphatase 1 regulatory subunit 10 (PPP1R10)	Patient tissue and mouse studies suggest inhibiting miR-34a or increasing PPP1R10 levels could help improve post-MI recovery. In a mouse model for MI, an miR-34a-targeting antagomir increased Ppp1r10 levels in the heart, decreased cardiac cell death and fibrosis and led to better cardiac contractile function compared with a control antagomir. In the same model, vector-mediated expression of Ppp1r10 prevented cardiac contractile dysfunction and decreased cardiomyocyte apoptosis compared with what was seen using control vector. Next steps include testing the effects of inhibiting miR-34a in genetic mouse models and large animals models.	Patent application filed; unlicensed	Boon, R.A. <i>et al. Nature</i> ; published online Feb. 20, 2013; doi:10.1038/nature11919 <b>Contact:</b> Stefanie Dimmeler, Goethe University Frankfurt, Frankfurt, Germany e-mail: <a href="mailto:dimmeler@em.uni-frankfurt.de">dimmeler@em.uni-frankfurt.de</a>
<b>SciBX 6(10); doi:10.1038/scibx.2013.237 Published online March 14, 2013</b>				
<b>Dermatology</b>				
Dermatology	Heat shock protein 70 (Hsp70)	Studies in mice and in patient samples suggest a modified form of Hsp70 could help treat vitiligo, an autoimmune skin disease characterized by loss of pigmentation. Hsp70 activates dendritic cells (DCs) and was previously shown to be required for the development of vitiligo. In a mouse model for vitiligo, vaccination with a DNA vector expressing a mutant form of Hsp70 that does not activate DCs prevented the development of vitiligo. In human skin samples, the mutant form of Hsp70 reduced T cell activation, whereas wild-type Hsp70 induced T cell activation. Next steps include a clinical trial to test the safety of mutant Hsp70 in patients with vitiligo.	Patent application filed; available for licensing	Mosenson, J.A. <i>et al. Sci. Transl. Med.</i> ; published online Feb. 27, 2013; doi:10.1126/scitranslmed.3005127 <b>Contact:</b> I. Caroline Le Poole, Loyola University Chicago, Maywood, Ill. e-mail: <a href="mailto:ilepool@lumc.edu">ilepool@lumc.edu</a> <b>Contact:</b> Jose A. Guevara-Patino, same affiliation as above e-mail: <a href="mailto:jaguevara@lumc.edu">jaguevara@lumc.edu</a>
<b>SciBX 6(10); doi:10.1038/scibx.2013.238 Published online March 14, 2013</b>				
Wounds	Basic fibroblast growth factor (bFGF)	<i>In vitro</i> studies suggest a heparin mimetic could be used to stabilize bFGF for use in indications such as wound healing. In human dermal fibroblasts, bFGF conjugated to a heparin-mimicking polymer promoted cell proliferation and showed greater stability under various stressors than unconjugated bFGF or bFGF conjugated to a different polymer. Next steps include determining long-term stability of the conjugates in different storage conditions and testing in preclinical models for wound healing. Johnson & Johnson markets Fiblast trafermin, a human bFGF, to treat dermal ulcers.	Patent application filed; available for licensing	Nguyen, T.H. <i>et al. Nat. Chem.</i> ; published online Feb. 17, 2013; doi:10.1038/nchem.1573 <b>Contact:</b> Heather D. Maynard, University of California, Los Angeles, Calif. e-mail: <a href="mailto:maynard@chem.ucla.edu">maynard@chem.ucla.edu</a>
<b>SciBX 6(10); doi:10.1038/scibx.2013.239 Published online March 14, 2013</b>				

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Endocrine/metabolic disease</b>				
Mitochondrial disease	Pyruvate dehydrogenase kinase (PDK)	<i>In vitro</i> and <i>in vivo</i> studies suggest phenylbutyrate could help treat mitochondrial pyruvate dehydrogenase complex (PDHC) deficiency, the most common genetic form of lactic acidosis. In enzymatic assays, phenylbutyrate bound PDK to prevent inactivation of PDHC. In 9 of 15 patient-derived, PDHC-deficient fibroblast cell lines, phenylbutyrate increased PDHC activity compared with no treatment. In zebrafish and mouse models for lactic acidosis, phenylbutyrate decreased lactate levels compared with no treatment. Next steps include designing a clinical trial for patients with PDHC deficiency. Valeant Pharmaceuticals International Inc. and Hyperion Therapeutics Inc. market Ravicti glycerol phenylbutyrate to treat urea cycle disorder. The compound is in Phase II testing to treat liver disease.  <b>SciBX 6(10); doi:10.1038/scibx.2013.240</b> <b>Published online March 14, 2013</b>	Unpatented; unlicensed	Ferriero, R. <i>et al. Sci. Transl. Med.</i> ; published online March 6, 2013; doi:10.1126/scitranslmed.3004986 <b>Contact:</b> Nicola Brunetti-Pierri, Telethon Institute of Genetics and Medicine, Naples, Italy e-mail: <a href="mailto:brunetti@tigem.it">brunetti@tigem.it</a>
<b>Infectious disease</b>				
Influenza virus	Influenza virus neuraminidase	<i>In vitro</i> , cell culture and mouse studies suggest covalent neuraminidase inhibitors could be useful for treating influenza infection. <i>In vitro</i> , a class of 2,3-difluorosialic acid derivatives showed longer-lasting inhibition of neuraminidase activity than the marketed neuraminidase inhibitors Relenza zanamivir and Tamiflu oseltamivir. In cell culture, the lead compound showed more potent inhibition of Relenza-resistant influenza A virus and influenza B virus than Relenza. In a mouse model for lethal influenza infection, the lead compound decreased viral load and increased survival with an effect comparable to that of Relenza. Next steps include out-licensing and preclinical development of the lead compound. Relenza is marketed by GlaxoSmithKline plc and Biota Pharmaceuticals Inc. to treat and prevent influenza A. Tamiflu is marketed by Roche and Gilead Sciences Inc. to treat and prevent influenza A. Two other neuraminidase inhibitors are marketed outside the U.S. to treat and prevent influenza infection: PeramiFlu peramivir from BioCryst Pharmaceuticals Inc., Green Cross Corp. and Shionogi & Co. Ltd., and Inavir laninamivir from Daiichi Sankyo Co. Ltd. and Biota.  <b>SciBX 6(10); doi:10.1038/scibx.2013.241</b> <b>Published online March 14, 2013</b>	Patent pending; available for licensing from CDRD Ventures Inc.	Kim, J.-H. <i>et al. Science</i> ; published online Feb. 21, 2013; doi:10.1126/science.1232552 <b>Contact:</b> Stephen G. Withers, The University of British Columbia, Vancouver, British Columbia, Canada e-mail: <a href="mailto:withers@chem.ubc.ca">withers@chem.ubc.ca</a>
<b>Inflammation</b>				
Asthma	Formyl peptide receptor-like 1 (FPRL1; FPR2)	Cell culture studies suggest agonizing FPR2 in innate immune cells could be useful for treating asthma. Patients with severe asthma showed higher levels of active innate immune cells in blood and lungs than healthy controls. In patient-derived innate immune cell cocultures, the FPR2 ligand lipoxin A4 (LXA4) increased NK cell-mediated apoptosis of eosinophils and decreased levels of the inflammatory cytokine IL-13 compared with vehicle. Next steps include clinical testing of LXA4 analogs in models of asthma.  <b>SciBX 6(10); doi:10.1038/scibx.2013.242</b> <b>Published online March 14, 2013</b>	Patents pending; available for licensing	Barnig, C. <i>et al. Sci. Transl. Med.</i> ; published online Feb. 27, 2013; doi:10.1126/scitranslmed.3004812 <b>Contact:</b> Bruce D. Levy, Brigham and Women's Hospital, Boston, Mass. e-mail: <a href="mailto:blevy@partners.org">blevy@partners.org</a>

## This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
<b>Neurology</b>				
Migraine; pain	Caspase-1 (CASP1); high mobility group box 1 (HMGB1); NF- κB; pannexin 1 (PNX1)	<p>Mouse studies suggest inhibiting PNX1 in neurons could help treat migraine aura and headache. In the mouse brain, a migraine-linked electrophysiological phenomenon called cortical spreading depression (CSD) opened neuronal Pnx1 channels and activated Casp1, which led to Hmgb1 release in neurons and Nf-kb activation in astrocytes. In the mouse brain, PNX1 channel blockers and small interfering RNA-mediated knockdown of <i>Pnx1</i> inhibited the CSD-induced signaling cascade, whereas vehicle and control siRNA did not. Next steps could include evaluating the behavioral effects of inhibiting PNX1 in animal models for migraine.</p> <p><b>SciBX 6(10); doi:10.1038/scibx.2013.243</b> Published online March 14, 2013</p>	Patent and licensing status unavailable	<p>Karatas, H. <i>et al. Science</i>; published online March 1, 2013; doi:10.1126/science.1231897 <b>Contact:</b> Turgay Dalkara, Hacettepe University, Ankara, Turkey e-mail: <a href="mailto:tdalkara@hacettepe.edu.tr">tdalkara@hacettepe.edu.tr</a></p>
<b>Pulmonary disease</b>				
Pulmonary fibrosis	Rho kinase; myocardin-related transcription factor A (MKL1; MAL; MRTF-1)	<p>Human tissue and mouse studies suggest inhibiting Rho kinase or MKL1 could help treat pulmonary fibrosis. Pulmonary myofibroblasts from patients with idiopathic pulmonary fibrosis (IPF) or a mouse model for lung fibrosis had greater activation of Rho kinase signaling than myofibroblasts from uninjured controls. In a mouse model for lung fibrosis, the Rho kinase inhibitor Eril fasudil or knockout of <i>Mkl1</i> decreased fibrosis compared with saline or no knockout. Next steps include finding a partner to start Phase II studies of Rho kinase inhibitors in patients with IPF.</p> <p>Eril is marketed by Asahi Kasei Pharma Corp. to treat aneurysm.</p> <p>At least four other companies have Rho kinase inhibitors in preclinical development to Phase III trials for ophthalmic, pulmonary and cardiovascular indications.</p> <p><b>SciBX 6(10); doi:10.1038/scibx.2013.244</b> Published online March 14, 2013</p>	Unpatented; licensing status not applicable	<p>Zhou, Y. <i>et al. J. Clin. Invest.</i>; published online Feb. 22, 2013; doi:10.1172/JCI66700 <b>Contact:</b> Victor J. Thannickal, The University of Alabama at Birmingham, Birmingham, Ala. e-mail: <a href="mailto:vjthan@uab.edu">vjthan@uab.edu</a> <b>Contact:</b> Yong Zhou, same affiliation as above e-mail: <a href="mailto:yzhou@uab.edu">yzhou@uab.edu</a></p>
<b>Various</b>				
Cancer; neurology	MicroRNA-7 (miR-7); cerebellar degeneration- related protein 1 antisense (ciRS-7; CDRIas)	<p><i>In silico</i> and cell culture studies suggest inhibiting the circular RNA ciRS-7 upregulates miR-7 expression, which could help treat cancer or neurological diseases. MiR-7 was previously proposed as a therapeutic for various diseases including cancer. A computational analysis of RNA sequencing data from a human cell line predicted the existence of about 2,000 circular RNA transcripts including ciRS-7, which contains multiple binding sites for miR-7. In cell culture, small interfering RNA against ciRS-7 increased the expression of miR-7 target genes compared with control siRNA. Next steps include screens and functional characterization of circular RNAs in disease.</p> <p>MiReven Pty. Ltd. has miR-7 derivatives in preclinical development to treat cancer (<i>see Squaring the RNA circle</i>, page 1).</p> <p><b>SciBX 6(10); doi:10.1038/scibx.2013.245</b> Published online March 14, 2013</p>	<p>Patent and licensing status undisclosed for findings in first study</p> <p>Patent application filed for findings in second study; available for licensing</p>	<p>Memczak, S. <i>et al. Nature</i>; published online Feb. 27, 2013; doi:10.1038/nature11928 <b>Contact:</b> Nikolaus Rajewsky, Max Delbrück Center for Molecular Medicine, Berlin, Germany e-mail: <a href="mailto:rajewsky@mdc-berlin.de">rajewsky@mdc-berlin.de</a></p> <p>Hansen, T.B. <i>et al. Nature</i>; published online Feb. 27, 2013; doi:10.1038/nature11993 <b>Contact:</b> Jørgen Kjems, Aarhus University, Aarhus, Denmark e-mail: <a href="mailto:jk@mb.au.dk">jk@mb.au.dk</a> <b>Contact:</b> Thomas B. Hansen, same affiliation as above e-mail: <a href="mailto:tbh@mb.au.dk">tbh@mb.au.dk</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>			
MicroRNA detection with hairpin-mediated quadratic enzymatic amplification (HQEA)	HQEA for miRNAs could enable sensitive detection of disease-associated miRNAs in clinical samples. The method involves hybridizing a molecular beacon probe with the targeted miRNA and then synthesizing an inactive DNA duplex of the probe that is activated by an endonuclease to emit the fluorescent signal. In a proof-of-concept study, a detection assay using HQEA detected miRNA-21 (miR-21) in a 15 microliter sample with a detection limit of 10 femtomolar at 37 °C and 1 attomolar at 4 °C. In cell lysates from patient breast cancer samples or human breast and prostate cancer cell lines, the assay detected miR-21 and miR-221. Next steps include developing gene chips that use HQEA for detecting disease-associated miRNAs.	Patented; unavailable for licensing	Duan, R. <i>et al. J. Am. Chem. Soc.</i> ; published online Feb. 27, 2013; doi:10.1021/ja311313b <b>Contact:</b> Fan Xia, Huazhong University of Science & Technology, Wuhan, China e-mail: <a href="mailto:xiafan@hust.edu.cn">xiafan@hust.edu.cn</a>
<b>SciBX 6(10); doi:10.1038/scibx.2013.246 Published online March 14, 2013</b>			
<b>Drug delivery</b>			
A peptide fragment based on CD47 to prolong circulation time and improve nanoparticle delivery	Mouse studies identified a CD47-derived peptide that could improve the bioavailability of nanoparticle drug delivery vehicles. In mice, nanobeads linked to human CD47 or a synthetic peptide that mimics the binding region of CD47 showed better circulation than a scrambled peptide or nanobeads alone. In mice with human lung cancer xenografts, nanobeads that were loaded with paclitaxel and expressed the minimal CD47 peptide showed greater accumulation in the tumor tissues than paclitaxel alone. Next steps include testing the peptide as an aid to delivering other therapeutics.	Patent application filed; unavailable for licensing	Rodriguez, P.L. <i>et al. Science</i> ; published online Feb. 22, 2013; doi:10.1126/science.1229568 <b>Contact:</b> Dennis E. Discher, University of Pennsylvania, Philadelphia, Pa. e-mail: <a href="mailto:discher@seas.upenn.edu">discher@seas.upenn.edu</a>
<b>SciBX 6(10); doi:10.1038/scibx.2013.247 Published online March 14, 2013</b>			
Mucosal delivery to improve cancer vaccine efficacy	Mouse studies suggest cancer vaccines formulated for mucosal delivery could have better efficacy against mucosal tumors than vaccines delivered via subcutaneous injection. In orthotopic mouse models for mucosal tissue head and neck cancers, an intranasal formulation of a Shiga toxin-based cancer vaccine decreased tumor growth and increased survival compared with an analogous cancer vaccine formulated for intramuscular delivery. In the mouse models, the intranasal vaccine formulation induced a stronger antigen-specific CD8 <sup>+</sup> T cell response in the mucosa than the intramuscular formulation. Next steps include developing an intranasal formulation of an existing vaccine for mucosal delivery and then evaluating it in a clinical trial against an analogous vaccine delivered via intramuscular injection.	Work unpatented; cancer vaccine tested in study patented; licensing details available from the Curie Institute's Technology Transfer Office	Sandoval, F. <i>et al. Sci. Transl. Med.</i> ; published online Feb. 13, 2013; doi:10.1126/scitranslmed.3004888 <b>Contact:</b> Eric Tartour, Institut National de la Santé et de la Recherche Médicale (INSERM), Paris, France e-mail: <a href="mailto:eric.tartour@egp.aphp.fr">eric.tartour@egp.aphp.fr</a> <b>Contact:</b> Federico Sandoval, same affiliation as above e-mail: <a href="mailto:fedemedcr@yahoo.com">fedemedcr@yahoo.com</a>
<b>SciBX 6(10); doi:10.1038/scibx.2013.248 Published online March 14, 2013</b>			

## This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
<b>Drug platforms</b>			
Clustered, regularly interspaced short palindromic repeats (CRISPR) interference system for gene regulation	The CRISPR interference platform for modulating gene expression could be used to modify DNA in diverse biological systems. CRISPR systems use a small guide RNA (sgRNA), which pairs with a target DNA sequence and the CRISPR-associated protein (Cas9) to excise target DNA. In <i>Escherichia coli</i> cells, expression of a modified Cas9 without endonuclease activity plus sgRNA against a target gene led to reversible gene knockout. The same system also knocked down genes in human embryonic kidney cells. Next steps include testing and optimizing the CRISPR interference platform in patient-derived cells.  <b>SciBX 6(10); doi:10.1038/scibx.2013.249</b> <b>Published online March 14, 2013</b>	Patent application filed; available for licensing	Qi, L.S. <i>et al. Cell</i> ; published online Feb. 28, 2013; doi:10.1016/j.cell.2013.02.022 <b>Contact:</b> Lei S. Qi, University of California, San Francisco, Calif. e-mail: <a href="mailto:stanley.qi@ucsf.edu">stanley.qi@ucsf.edu</a>
Injectable extracellular matrix (ECM) hydrogel for treating heart failure following myocardial infarction (MI)	An injectable, porcine-derived ECM hydrogel could be useful for treating MI. In a porcine model for MI, catheter-mediated delivery of the ECM hydrogel decreased pathological left ventricular remodeling and increased cardiac function compared with delivery of saline. In rats, the hydrogel was biodegradable and biocompatible. In human blood samples, the hydrogel was hemo-compatible and triggered minimal platelet activation. Next steps include scaled-up GMP manufacturing of the clinical-grade version of the hydrogel, called VentriGel. Ventrix Inc.'s VentriGel is in preclinical development to prevent left ventricular remodeling and reduce heart failure following MI ( <i>see VentriGel goes into pigs, page 10</i> ).  <b>SciBX 6(10); doi:10.1038/scibx.2013.250</b> <b>Published online March 14, 2013</b>	Patents pending; licensed to Ventrix; available for partnering from Ventrix	Seif-Naraghi, S.B. <i>et al. Sci. Transl. Med.</i> ; published online Feb. 20, 2013; doi:10.1126/scitranslmed.3005503 <b>Contact:</b> Karen L. Christman, University of California, San Diego, La Jolla, Calif. e-mail: <a href="mailto:christman@eng.ucsd.edu">christman@eng.ucsd.edu</a>
Predicting disease progression by measuring the evolution of mutational heterogeneity in cancer samples	Computational analysis of patient whole-exome sequencing data could be used to measure the evolution of tumor heterogeneity and help predict disease progression. Whole-exome sequencing and subsequent computational analysis of 149 samples from patients with chronic lymphocytic leukemia (CLL) identified more than 3,000 mutations in total and quantified the prevalence of mutations in each cancer sample. In 12 matched patient samples taken before and after chemotherapy, sequence analysis identified driver mutations that expanded in prevalence after treatment and predicted poor survival. Next steps include determining whether the presence of these driver mutations or the measurement of chemotherapy-induced tumor evolution can predict patient outcomes in prospective clinical trials.  <b>SciBX 6(10); doi:10.1038/scibx.2013.251</b> <b>Published online March 14, 2013</b>	Patent applications filed; available for licensing and freely available for academic and not-for-profit organizations	Landau, D.A. <i>et al. Cell</i> ; published online Feb. 14, 2013; doi:10.1016/j.cell.2013.01.019 <b>Contact:</b> Catherine J. Wu, Dana-Farber Cancer Institute, Boston, Mass. e-mail: <a href="mailto:cwu@partners.org">cwu@partners.org</a> <b>Contact:</b> Gad Getz, Broad Institute of MIT and Harvard, Cambridge, Mass. e-mail: <a href="mailto:gadgetz@broadinstitute.org">gadgetz@broadinstitute.org</a>
<b>Imaging</b>			
Chemiluminescence resonance energy transfer (CRET) for detection of myeloperoxidase (MPO)	An imaging method called CRET could help assess oxidative stress and inflammation <i>in vivo</i> . In resected lungs from mice challenged with proinflammatory lipopolysaccharide (LPS), CRET imaging yielded about 40-fold greater luminescence emission in response to MPO than a control non-CRET imaging method. In a mouse xenograft model for systemic breast cancer metastasis, CRET imaging detected all metastatic lesions via the associated MPO activity. Next steps include developing a clinical imaging system and clinical-grade imaging reagents.  <b>SciBX 6(10); doi:10.1038/scibx.2013.252</b> <b>Published online March 14, 2013</b>	Patent application filed; available for licensing from PerkinElmer Inc. <b>Contact:</b> Mark Roskey, PerkinElmer Inc., Waltham, Mass. e-mail: <a href="mailto:mark.roskey@perkinelmer.com">mark.roskey@perkinelmer.com</a>	Zhang, N. <i>et al. Nat. Med.</i> ; published online March 3, 2013; doi:10.1038/nm.3110 <b>Contact:</b> Ning Zhang, Pharmaron, Beijing, China e-mail: <a href="mailto:ning.zhang@pharmaron.com">ning.zhang@pharmaron.com</a>

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