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HER2's new mutations

By **Tim Fulmer**, Senior Writer

Washington University in St. Louis School of Medicine researchers have used next-generation sequencing to identify mutations in *HER2* that are missed by standard screening tests that identify only amplifications.¹ Based on the findings, the researchers are now recruiting patients with breast cancer expressing the mutations for a Phase II trial of **Puma Biotechnology Inc.**'s *HER2*-targeting compound, neratinib.

Amplification of the gene encoding *HER2* (EGFR2; ErbB2; neu) is a driver of aggressive forms of breast cancer and occurs about 23% of the time.² Based on 2012 epidemiological data from the **American Cancer Society**, that frequency translates to about 52,000 U.S. patients who might be eligible for drugs targeting amplified *HER2*.

If the neratinib trial is successful, about 4,000 additional patients with breast cancer in the U.S. could be eligible for treatment with *HER2* inhibitors.

Three breast cancer drugs target amplified *HER2*: the mAbs Herceptin trastuzumab and Perjeta pertuzumab from **Roche's Genentech Inc.** unit and the small

molecule Tykerb lapatinib from **GlaxoSmithKline plc**. Neratinib, also a small molecule, is in Phase I/II testing to treat metastatic breast cancer. That trial is distinct from the new trial.

Using next-generation genome sequencing methods, researchers have recently begun identifying *HER2* somatic mutations in patients with breast cancer who test negative for *HER2* amplification.³⁻⁵ Those findings have raised the question of whether *HER2* somatic mutations are also drivers of the disease and, if so, whether they would respond to any of the therapies on the market or in development.

HER2 somatic mutations are not detectable by standard methods used to identify *HER2* amplification, which rely on fluorescence *in situ* hybridization and immunohistochemistry.

The Washington University team, led by professors of medicine Ron Bose and Matthew Ellis, first analyzed data from 8 breast cancer genome sequencing projects in more than 1,500 patients. They identified 25 patients who had *HER2* somatic mutations but lacked *HER2* amplification.

“Based on the findings, we are now launching a Phase II trial to test neratinib in breast cancer patients who are negative for *HER2* amplification but positive for *HER2* somatic mutations.”

—**Ron Bose,**
Washington University in St. Louis School of Medicine

**EDITORIAL****Editor-in-Chief:** Karen Bernstein, Ph.D.**Managing Editor:** Gaspar Taroncher-Oldenburg, Ph.D.**Executive Editor:** Steve Edelson**Senior Editors:** Tracey Baas, Ph.D.; Joanne Kotz, Ph.D.**Writers:** Chris Cain, Ph.D.; Michael Flanagan; Tim Fulmer, Ph.D.;

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Research Director: Walter Yang**Research Manager:** Kevin Lehnbeuter**Production Editors:** Brandy Cafarella; Carol Evangelista; Ivelisse Robles**Copy Editor:** Nicole DeGennaro**Editorial Assistant:** Mark Zipkin**Design:** Claudia Bentley; Miles DaviesFor inquiries, contact editorial@scibx.com**PUBLISHING****Publisher:** Peter Collins, Ph.D.**Associate Publishers:** Gaspar Taroncher-Oldenburg, Ph.D.; Eric Pierce**Marketing:** Sara Girard; Rosy Rogers**Technology:** Anthony Barrera; Julia Kulikova**Sales:** Ron Rabinowitz; Dean Sanderson; Tim Tulloch**OFFICES****BioCentury Publications, Inc.**San Francisco
PO Box 1246
San Carlos, CA 94070-1246
T: +1 650 595 5333Chadds Ford
223 Wilmington-West Chester Pike
Chadds Ford, PA 19317
T: +1 610 558 1873Chicago
20 N. Wacker Drive, Suite 1465
Chicago, IL 60606-2902
T: +1 312 755 0798Oxford
287 Banbury Road
Oxford OX4 7JA
United Kingdom
T: +44 (0)18 6551 2184Washington, DC
2008 Q Street, NW, Suite 100
Washington, DC 20009
T: +1 202 462 9582**Nature Publishing Group**New York
75 Varick Street, 9th Floor
New York, NY 10013-1917
T: +1 212 726 9200London
The Macmillan Building
4 Crinan Street
London N1 9XW
United Kingdom
T: +44 (0)20 7833 4000Tokyo
Chiyoda Building 6F
2-37 Ichigayatamachi
Shinjuku-ku, Tokyo 162-0843
Japan
T: +81 3 3267 8751

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That result gave a mutational frequency of about 1.6%, which translates to about 4,000 patients per year in the U.S. who might carry at least one *HER2* somatic mutation. A total of 16 different *HER2* somatic mutations were identified in the study, some of which were shared by multiple patients.

In cell culture, 7 of the 16 *HER2* somatic mutations tested led to increased epidermal growth factor receptor (EGFR) signaling compared with wild-type *HER2*, confirming that they were activating mutations. In mouse xenografts, transplanted breast cancer cells bearing some of those activating mutations formed tumors more rapidly than transplanted cells expressing wild-type *HER2*.

To see if the mutations responded to current therapies, the researchers showed that neratinib inhibited growth of a panel of cell lines individually expressing the 7 activating mutations with IC₅₀ values of <2 nM. However, in the same cell lines, lapatinib was less potent, with some lines even showing resistance to the compound.

The findings were published in *Cancer Discovery*.

“Based on the findings, we are now launching a Phase II trial to test neratinib in breast cancer patients who are negative for *HER2* amplification but positive for *HER2* somatic mutations,” corresponding author Bose told *SciBX*.

The single-arm, open-label trial is expected to last about 2 years, with the goal of treating about 30 patients, said Bose. Besides Washington University, three other institutions will participate in the trial: the **Dana-Farber Cancer Institute**, the **Memorial Sloan-Kettering Cancer Center** and **The University of North Carolina at Chapel Hill**.

“We will use the same neratinib doses as are used in the other ongoing breast cancer trials and, during the course of the trial, we will use CAT scan to measure tumor size in response to treatment,” said Bose.

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Puma Biotechnology is sponsoring the trial, said Alan Auerbach, president, CEO and founder. “We anticipate expanding the trial to include additional centers beyond the original four,” he said. “In addition, we are interested in partnering to develop a companion diagnostic that identifies *HER2* somatic mutations and guides the use of neratinib in cancer patients expressing those mutations.”

Auerbach said *HER2* somatic mutations also occur in lung, colon and gastric cancers. “We would thus eventually be interested in running trials of neratinib in those indications as well,” he said.

Puma exclusively licensed neratinib from **Pfizer Inc.** in 2011. According to Auerbach, the compound is in six ongoing Phase I and Phase II trials, as both a single agent and in various combinations, to treat breast and lung cancers.

Unlike the *HER2*-targeting mAbs, which bind the extracellular portion of *HER2*, neratinib targets the intracellular tyrosine kinase activity of the receptor, said Auerbach. “We believe that difference gives neratinib a potential advantage in the treatment refractory setting, where the extracellular portion of *HER2* is often truncated, making it more difficult to target the receptor with an antibody alone,” he added.

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Contact: Ron Bose, Washington University in St. Louis School of Medicine, St. Louis, Mo.
e-mail: rbose@dom.wustl.edu
Contact: Matthew J. Ellis, same affiliation as above
e-mail: mellis@dom.wustl.edu
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COMPANIES AND INSTITUTIONS MENTIONED

American Cancer Society, Atlanta, Ga.
Dana-Farber Cancer Institute, Boston, Mass.
Genentech Inc., South San Francisco, Calif.
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Memorial Sloan-Kettering Cancer Center, New York, N.Y.
Pfizer Inc. (NYSE:PFE), New York, N.Y.
Puma Biotechnology Inc. (NYSE:PBYY), Los Angeles, Calif.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
The University of North Carolina at Chapel Hill, Chapel Hill, N.C.
Washington University in St. Louis School of Medicine, St. Louis, Mo.

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Overcoming amantadine resistance

By Lauren Martz, Staff Writer

A group of U.S. researchers has developed inhibitors of the influenza A virus matrix protein 2 mutant that is responsible for resistance to amantadine.¹ The first-generation inhibitor was widely used for years to treat flu, but in 2006 the **Centers for Disease Control and Prevention** recommended against its use due to resistance. **InfluMedix Inc.** has licensed the compounds and hopes to bring a new influenza antiviral to the market within five years.

Most mutations of the influenza A virus matrix protein 2 (M2) channel render the virus less transmissible than wild-type M2. As a result, only a handful of mutations are found in circulating influenza A viruses.

For example, virtually every amantadine-resistant transmissible influenza virus expresses the same M2 mutation—S31N—and more than 95% of circulating influenza A viruses express that mutation.

The problem is that the S31N mutation has a drug-binding site that is more difficult to target than the wild-type protein because the site in mutant M2 is smaller and more polar. To date, there have been no effective inhibitors of S31N M2.

Influenza virus instead is treated with neuraminidase (NEU1; SIAL1) inhibitors such as oral Tamiflu oseltamivir from **Roche** and **Gilead Sciences Inc.** or inhaled Relenza zanamivir from **GlaxoSmithKline plc** and **Biota Pharmaceuticals Inc.** The drugs are effective against influenza A viruses with the S31N mutation, but resistance to neuraminidase inhibitors is growing.

William DeGrado and colleagues therefore set out to find new therapeutic strategies to treat influenza A viruses with acquired resistance to amantadine and other drugs.

In 2008, DeGrado and colleagues first determined the high-resolution crystal structure of the wild-type M2 channel.² However, the mutant channel was harder to crystallize because its structure is more dynamic.

DeGrado is professor of pharmaceutical chemistry at the **University of California, San Francisco** and investigator at the university's Cardiovascular Research Institute. The team also included researchers from **Northwestern University**, **Temple University** and **InfluMedix**.

The group used *Xenopus laevis* oocytes to test inhibitors of the mutant channel and showed that analogs of amantadine with a CH₂-heteroaryl group conjugated to the drug's amine group blocked S31N M2 proton transport.

The group further modified the compounds to isoxazole-, isoxazoline- and oxadiazole-containing derivatives, some of which had IC₅₀ values <16 μM against S31N. This suggests the new inhibitors could be more potent against mutant M2 than amantadine is against the wild-type protein.

In an assay using influenza A virus expressing the S31N mutant, some of the most potent compounds completely inhibited the ability of the virus to infect and form colonies on a layer of host cells at 10 μM.

A similar dose of amantadine showed almost no efficacy.

Finally, the team found that the new inhibitors locked the proton channel's conformation. This allowed the group to capture a high-resolution structure of S31N in complex with an inhibitor, which could aid the design of inhibitors with improved potency.

Antiviral demand

InfluMedix has licensed the compounds and IP related to the proton channel structure. CEO Lidia Cristian said that next steps include evaluating the compounds in animal models of influenza infection to establish safety and efficacy.

"Currently there are only four antiviral drugs approved for use against influenza infections in humans: two targeting the M2 proton channel and two targeting neuraminidase. The emergence of drug resistance to both classes of flu drugs poses a major problem," she said. "Tamiflu resistance is on the rise, and there are concerning reports of the emergence of flu strains with dual resistance to both M2 and neuraminidase classes of drugs."

Rimantadine, the other first-generation M2 inhibitor, is a related derivative of amantadine with similar problems of drug resistance.

Makoto Yamashita, senior chief researcher at **Daiichi Sankyo Co. Ltd.**, noted that "we practically only clinically use neuraminidase inhibitors, and there does exist a necessity for agents that have a different mode of action."

Daiichi's Inavir laninamivir is a second-generation neuraminidase inhibitor approved in Japan to treat influenza A and B. The company has Japanese rights to the compound from Biota.

"These S31N variants are fully susceptible to the neuraminidase inhibitors, but the opportunity to potentially resurrect the older amantadine class of drug is a worthy goal," said Simon Tucker, VP of research at Biota.

According to the CDC reports for the 2012–2013 influenza season, about 78% of flu patients in the U.S. are infected with the A strain and 22% are infected with the B strain. The new S31N M2 inhibitors have the potential to treat most influenza A subtypes because almost all of the circulating strains carry the mutation, but the influenza B virus strains would not be amenable to treatment because they do not express M2.

Anil Diwan, president and chairman of **NanoViricides Inc.**, said any approach that goes directly after viral targets will likely be hampered by resistance issues.

"A major disadvantage of small chemical antiviral strategies is that mutant, resistant viruses can be generated rapidly. Viruses are intelligent nanomachines that reprogram themselves," said Diwan.

NanoViricides's FluCide is a nanoviricide designed to mimic influenza-targeted cells, bind the virus and encapsulate it. The company has both i.v. and oral FluCide candidates in preclinical development.

"A major disadvantage of small chemical antiviral strategies is that mutant, resistant viruses can be generated rapidly. Viruses are intelligent nanomachines that reprogram themselves."
—Anil Diwan, NanoViricides Inc.

(Continues on p. 5)

What to do with PKM2

By Tracey Baas, Senior Editor

Novartis AG researchers have shown that the absence of pyruvate kinase M2 isozyme has no effect on cancer cell proliferation in mice and suggest that inhibiting the enzyme alone might not be an effective strategy to stop tumor growth.¹ The finding is surprising, given that knocking down the target is known to impair proliferation of cultured cancer cells. Biotechs working on modulators of the enzyme think it is too early to write off the target.

Pyruvate kinase occurs as two main isoforms—pyruvate kinase M1 isozyme (PKM1) is expressed in most normal cells as a constitutively active tetramer, whereas PKM2 is expressed in cancer cells either as a high-activity tetramer or a low-activity dimer. PKM2's oligomerization and activity is allosterically regulated by glycolysis intermediates.

The PKM1 tetramer and each form of PKM2 can catalyze the transfer of phosphate from phosphoenolpyruvate (PEP) to ADP, producing ATP and pyruvate. The PKM2 dimer does so at a much slower rate than either tetramer, leading to a bottleneck in the metabolic pathway.

This slowdown effectively redirects the use of glucose from energy production to biomass synthesis, allowing tumor cells to rapidly proliferate.

There are two opposing schools of thought on controlling PKM2 activity: inhibition or activation (see Figure 1, “Metabolic pathways regulated by pyruvate kinase”).

Both strategies have yielded positive results. Research from groups working with PKM2 inhibitors have shown that the kinase was required

(Continued from “Overcoming amantadine resistance,” p. 4)

Cristian noted that “the potential caveat, as with any newly developed antiviral, is the emergence of resistance. However, M2 is a remarkably conserved viral protein that tolerates very few mutations that are present within transmissible viruses and are of clinical relevance.”

She said that the first class of M2 inhibitors was used for more than 30 years before resistance became widespread and that InfluxMedix does not expect resistance to the new M2 inhibitors to develop quickly.

The University of Pennsylvania, where DeGrado conducted earlier work on this project prior to moving to UCSF, and InfluxMedix have filed a patent application covering the compounds. InfluxMedix has licensed the IP, and licensing opportunities are available through the company.

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for initial growth and for establishing tumors in mice.^{2,3} In contrast, a Massachusetts Institute of Technology team working with a PKM2 activator showed that the high-activity enzyme increased the tumor latency period and decreased tumor size compared with vehicle during initial tumor growth.⁴

Novartis asked a slightly different question: whether PKM2 is required for the maintenance and growth of established tumors.

In cultured colon carcinoma or adenocarcinoma cells, small hairpin RNA-mediated knockdown of both PKM1 and PKM2 increased levels of PEP and decreased pyruvate kinase activity and cellular proliferation compared with no knockdown. Knocking down either PKM1 or PKM2 alone had little effect.

Metabolic labeling studies showed that knockdown of PKM2 reduced the conversion of glucose to pyruvate and diminished, but did not block, lactate production. However, biosynthesis of serine and glycine was ramped up, suggesting that alternative pathways were being turned on to feed cancer cells' need for biomass to proliferate.

In mice with established colon carcinoma or adenocarcinoma, inhibiting Pkm1 and Pkm2—either separately or in combination—increased PEP levels and decreased pyruvate kinase activity but did not decrease tumor growth.

Together, the results suggest that inhibiting pyruvate kinase activity is not enough to stop the growth of established tumors and instead may cause cancer cells to meet their need for energy and biomass by turning to alternative metabolic pathways.

Data were published in the *Proceedings of the National Academy of Sciences*. Novartis declined requests for an interview.

PKM2 ups and downs

Biotechs contacted by *SciBX* said it is too early to give up on targeting PKM2 because there is so much metabolic variation from tumor to tumor. (Continues on p. 6)

“If a PKM2 therapeutic causes the tumor to rewire its metabolism, then the next step is to understand that shift and find a complementary control point and companion drug to block tumor metabolism and proliferation.”

—Neil Thompson,
Astex Pharmaceuticals Inc.

Contact: William F. DeGrado, University of California, San Francisco, Calif.

e-mail: william.degrado@ucsf.edu

Contact: Yibing Wu, same affiliation as above

e-mail: yibing.wu@ucsf.edu

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COMPANIES AND INSTITUTIONS MENTIONED

Biota Pharmaceuticals Inc. (NASDAQ:BOTA), Rockville, Md.

Centers for Disease Control and Prevention, Atlanta, Ga.

Daiichi Sankyo Co. Ltd. (Tokyo:4568; Osaka:4568),

Tokyo, Japan

Gilead Sciences Inc. (NASDAQ:GILD), Foster City, Calif.

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

InfluxMedix Inc., Radnor, Pa.

NanoViricides Inc. (OTCBB:NNVC), West Haven, Conn.

Northwestern University, Evanston, Ill.

Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland

Temple University, Philadelphia, Pa.

University of California, San Francisco, Calif.

University of Pennsylvania, Philadelphia, Pa.

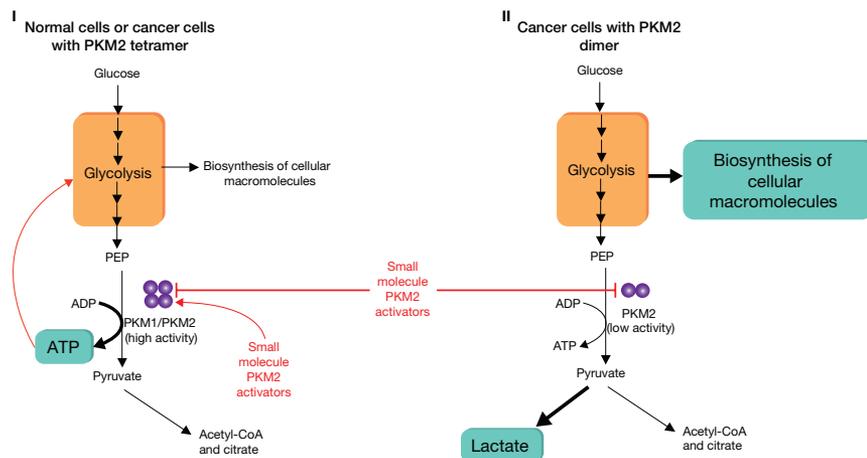
Figure 1. Metabolic pathways regulated by pyruvate kinase.

To block the cancer metabolism pathway driven by the pyruvate kinase M2 isozyme (PKM2) dimer, researchers are working to develop small molecules that either inhibit the enzyme or keep the enzyme in its high-activity tetramer state. However, results from Cortés-Cros *et al.* suggest that blocking PKM2 may not be enough to prevent tumor proliferation.

PKM1 is expressed in most normal cells as a constitutively active tetramer, whereas PKM2 is expressed in cancer cells either as a high-activity tetramer or a low-activity dimer.

(I) In normal cells with the PKM1 tetramer or cancer cells with the PKM2 tetramer, the kinase catalyzes the transfer of phosphate from phosphoenolpyruvate (PEP) to ADP, generating ATP and pyruvate. Pyruvate then is shuttled into the tricarboxylic acid cycle to produce acetyl-CoA and citrate. The process is balanced to allow the production of both ATP and the biosynthesis of cellular macromolecules to sustain growing cells.

(II) In cancer cells with the PKM2 dimer, the low-activity kinase also catalyzes the transfer of phosphate from PEP to ADP, generating ATP and pyruvate. The PKM2 dimer does so at a much slower rate than the PKM2 tetramer or PKM1 tetramer, leading to a bottleneck in the metabolic pathway. The buildup of intermediate metabolites of glycolysis feed other biosynthetic pathways to produce large quantities of cellular macromolecules. In addition, the decreased generation of pyruvate leads to lactate production.



“Targeting metabolic pathways to treat cancer is a difficult business,” said Neil Thompson, SVP of biology at **Astex Pharmaceuticals Inc.** “Astex is taking a very unbiased approach to screening molecules that target PKM2 and has identified both activators and inhibitors, some that bind to novel sites on PKM2.”

He continued: “We’re going to have to take the time to find specific features of a tumor that make it more sensitive to metabolic pathway disruptions—perhaps an abnormality that would make the tumor more dependent on ATP. You need to find the right patients with specific tumor biomarkers that will respond to your targeted small molecule. If a PKM2 therapeutic causes the tumor to rewire its metabolism, then the next step is to understand that shift and find a complementary control point and companion drug to block tumor metabolism and proliferation.”

At least three companies—Astex, **Dynamix Pharmaceuticals Ltd.** and **Tolero Pharmaceuticals Inc.**—are trying to block tumor growth by turning the low-activity dimeric form of PKM2 into the high-activity tetramer form.

“We have demonstrated that Dynamix’s PKM2 activators indeed inhibit tumor growth *in vitro*, and we have also demonstrated robust, statistically significant inhibition of tumor growth *in vivo*,” said Oren Becker, president and CEO of Dynamix. “The inherent selectivity of these activators, which are allosteric in nature and affect only PKM2 and not PKM1, suggest that they will have favorable safety as well.”

The company’s DNX-03047 PKM2 activator is in preclinical development to treat cancer.

Tolero’s PKM2 activator, TP-1454, is in preclinical development to treat cancer. The company licensed the molecule from Astex.

A fourth company, **Agios Pharmaceuticals Inc.**, has PKM2 modulators in preclinical development to treat cancer. Agios declined to discuss its program.

The patent and licensing status of Novartis’ findings are undisclosed.

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e-mail: marta.cortes-cros@novartis.com
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COMPANIES AND INSTITUTIONS MENTIONED

Agios Pharmaceuticals Inc., Cambridge, Mass.
Astex Pharmaceuticals Inc. (NASDAQ:ASTX), Dublin, Calif.
Dynamix Pharmaceuticals Ltd., Rehovot, Israel
Massachusetts Institute of Technology, Cambridge, Mass.
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Tolero Pharmaceuticals Inc., Salt Lake City, Utah

γ -Secretase lost and sound

By Lev Osherovich, Senior Writer

Researchers in Boston and Japan have devised a pharmacological method to transform inner ear epithelial cells into working hair cells and have used the method to restore hearing in deaf mice.¹ The finding provides proof of concept for treating hearing loss by manipulating developmental pathways in the adult ear, but figuring out the precise pathway to hit in humans will require further work.

Hair cells in the inner ear transmit sound waves into electromechanical signals sensed by the nervous system. The cells can be damaged by chronic exposure to loud noise and die off in aging adults, leading to age-related hearing loss that affects up to 50 million Americans.

The inner ears of adults with the condition are thought to be functional aside from the dead hair cells. Regenerating those cells has

been a goal for the hearing field. Most strategies have focused on restoring hair cells through transplantation or reactivation of latent stem cells.

Now, a Boston-Japan team has proposed an alternative strategy—transdifferentiation of existing epithelial tissue.

In mice, the researchers blocked the activity of notch 1 (Notch1), a developmental factor that influences the differentiation of embryonic stem cells into specialized structures of the cochlea.

“Notch signaling works in the embryo to influence hair cell development,” said team leader Albert Edge, associate professor of otology and laryngology at **Harvard Medical School** and investigator at the **Massachusetts Eye and Ear Infirmary**. “Embryologists had previously found that development of the cochlear structure uses Notch signaling to turn a layer of undifferentiated epithelial cells into the organ of Corti, which consists of alternating layers of hair cells and supporting cells.”

Edge said there was prior evidence suggesting “that after the first few weeks of life, this signaling pathway was turned down, so it was previously thought that this pathway wasn’t active in adults and thus this wouldn’t be relevant to hearing loss.”

His team turned off the activity of Notch1 using a small molecule inhibitor of γ -secretase, a proteolytic complex that activates Notch1. In cell culture and in mice, inhibition of γ -secretase led to the growth of new hair cells out of a population of supporting epithelial cells.

“We tested this in adult mice and to our surprise found that a γ -secretase inhibitor was effectively making new hair cells,” said Edge.

Edge’s team screened cultured murine inner ear stem cells with a panel of γ -secretase inhibitors and found at least one compound that

caused the cells to express markers associated with hair cell identity.

The next step was to test whether such treatment could yield hair cells in adult ears. Indeed, in cultured organ of Corti explants from mice engineered to lose their hair cells, the γ -secretase inhibitor increased the number of hair cells and decreased the number of supporting epithelial cells compared with vehicle-treated controls.

The team then surgically introduced the molecule into the inner ear of experimentally deafened mice and observed greater numbers of new hair cells growing out of the epithelial cell layer of the organ of Corti than those seen in vehicle-treated controls. Electrophysiological experiments revealed that these new hair cells restored some degree of hearing in deafened mice.

Results were reported in *Neuron*, and the team included researchers at **Keio University School of Medicine**.

Edge’s study shows “for the first time that modulation of the Notch signaling system provides a measurable degree of auditory recovery,” said John Brigande, associate professor of otolaryngology at **Oregon Health & Science University**.

Brigande noted that hair cell loss also underlies vestibular system disorders for regulating the sense of balance. Thus, he thinks Edge’s technique could be useful for a number of conditions besides acute hearing loss.

“If you’re thinking about treatments for hearing loss and even vestibular disorders, this is a pharmacological system that could be used to regenerate hair cells and preserve their functions in the inner ear,” said Brigande.

Edge said the findings imply that Notch signaling is active in the ears of recently deafened adult animals, which was not previously thought to be the case.

Hear here

Despite the positive findings, questions remain about the relevance of the model used in the study to common forms of hearing loss, as well as the suitability of γ -secretase as a clinical target.

For example, the *in vivo* hearing loss model used by Edge involved acute damage by extremely loud noise rather than the chronic exposure to moderately loud noise that is thought to underlie most cases of deafness.

It thus is possible that Notch signaling is reactivated as an immediate result of noise-induced damage. If so, it remains unclear how long the pathway would remain targetable in patients with long-term hearing loss.

To answer this question, Edge plans to examine whether blocking Notch signaling can cause hair cell regeneration long after the initial loss of hearing.

Another concern is whether hitting Notch signaling will be safe in humans. γ -Secretase inhibitors such as **Eli Lilly and Co.**’s semagacestat have encountered safety and tolerability problems in clinical trials in Alzheimer’s disease (AD), which is caused by abnormal processing of amyloid precursor protein (APP), a Notch-like protein.

Some of the toxic effects of γ -secretase inhibitors are thought to result from the compounds’ interference with Notch signaling in the skin and intestine, which use that pathway for normal functions in adult tissue.

Indeed, Edge’s team used surgical delivery of a γ -secretase inhibitor to deafen mice after an oral formulation caused tolerability issues.

“If you’re thinking about treatments for hearing loss and even vestibular disorders, this is a pharmacological system that could be used to regenerate hair cells and preserve their functions in the inner ear.”

**—John Brigande,
Oregon Health &
Science University**

David Weber, president and CEO of ear drug delivery company **Otonomy Inc.**, thinks Edge's approach will require localized delivery technology. Weber suspects that repeated or long-term application of a γ -secretase inhibitor will be needed to regenerate hair cells because the compound is likely to have a short half-life inside the ear.

"This paper clearly illustrates that it's one thing to have a therapeutic agent but another thing to make it an effective therapy and bring it to the market," said Weber. "They tried to deliver it orally but encountered systemic toxicity issues and had to go to direct injection. However, the local delivery technique in this paper is not practical for clinical development in humans, as it would require surgery."

Instead, Weber advocated formulating γ -secretase inhibitors in a sustained-release gel for transtympanic injection, which is Otonomy's core technology.

The company's lead candidate is OTO-104, a formulation of dexamethasone for Meniere's disease. It will enter a pivotal Phase IIb trial this year. OTO-201, a formulation of ciprofloxacin, is in Phase I testing for otitis media.

Edge said his team used surgical injection because of the difficulty of transtympanic injection into mouse ears, which are very small.

Brigande and Edge both said other developmental pathways besides Notch signaling are likely to be at play in hair cell development, citing wingless-type MMTV integration site (WNT), sonic hedgehog homolog (SHH), transforming growth factor- β (TGFB; TGF- β) and fibroblast growth factors (FGFs) as other potential targets.

Edge now plans to use a combination of mouse genetic and pharmacological assays to figure out whether hitting any of these other pathways can improve on the safety and efficacy of inhibiting γ -secretase.

Edge is a cofounder of **Audion Therapeutics B.V.**, which is working with **Sanofi** to develop technology to stimulate regeneration of hair cells to treat hearing loss. Edge said Audion's work is related to prior discoveries from his laboratory and does not concern the findings in the *Neuron* study. The status of IP related to the *Neuron* paper is undisclosed.

Another company, **Inception 3 Inc.**, has licensed technology for hair cell protection and regeneration developed at **Stanford University**. **Roche** has rights to acquire Inception 3 at the time the biotech completes an IND package.

Massachusetts Eye and Ear Infirmary has filed patents based on the discoveries.

Osherovich, L. *SciBX* 6(2); doi:10.1038/scibx.2013.29
Published online Jan. 17, 2013

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Contact: Albert S.B. Edge, Harvard Medical School, Boston, Mass.
e-mail: albert_edge@meei.harvard.edu

COMPANIES AND INSTITUTIONS MENTIONED

Audion Therapeutics B.V., Amsterdam, the Netherlands
Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
Harvard Medical School, Boston, Mass.
Inception 3 Inc., San Diego, Calif.
Keio University School of Medicine, Tokyo, Japan
Massachusetts Eye and Ear Infirmary, Boston, Mass.
Oregon Health & Science University, Portland, Ore.
Otonomy Inc., San Diego, Calif.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
Sanofi (Euronext:SAN; NYSE:SNY), Paris, France
Stanford University, Stanford, Calif.



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This week in therapeutics

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

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

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cancer				
B cell lymphoma	Mucosa associated lymphoid tissue lymphoma translocation gene 1 (MALT1)	<i>In vitro</i> and mouse studies identified small molecule MALT1 inhibitors that could help treat patients with the activated B cell (ABC) subtype of diffuse large B cell lymphoma (DLBCL). In cultured ABC-DLBCL cells, phenothiazine derivatives, including the generic antipsychotic drug thioridazine, inhibited MALT1 and cell growth at 5–10 μ M concentrations. In cultured ABC-DLBCL cells, a second study showed that an unrelated compound, MI-2, inhibited MALT1 and cell growth at nanomolar concentrations. In mouse models of ABC-DLBCL, both compounds decreased tumor growth compared with vehicle. Next steps for both groups include additional preclinical characterization of MALT1 inhibitors, including comparative and combination studies with other therapeutics such as Bruton's tyrosine kinase (BTK) inhibitors. SciBX 6(2); doi:10.1038/scibx.2013.30 Published online Jan. 17, 2013	Patent and licensing status for findings in first study undisclosed Patent application filed for MALT1 inhibitors identified in second study; available for licensing from the Cornell Center for Technology Enterprise and Commercialization	Nagel, D. <i>et al. Cancer Cell</i> ; published online Dec. 11, 2012; doi:10.1016/j.ccr.2012.11.002 Contact: Daniel Krappmann, German Research Center for Environmental Health, Neuherberg, Germany e-mail: daniel.krappmann@helmholtz-muenchen.de Fontan, L. <i>et al. Cancer Cell</i> ; published online Dec. 11, 2012; doi:10.1016/j.ccr.2012.11.003 Contact: Ari Melnick, Weill Cornell Medical College, New York, N.Y. e-mail: amm2014@med.cornell.edu Contact: Hao Wu, Boston Children's Hospital, Boston, Mass. e-mail: hao.wu@childrens.harvard.edu
Brain cancer	Inhibitor of DNA binding 1 (ID1)	Patient sample, mouse and cell culture studies suggest inhibiting ID1 could help treat glioblastoma. In patient biopsy samples, increased ID1 expression correlated with increased tumor grade and invasiveness. In glioblastoma cell culture, small interfering RNA against ID1 decreased growth and invasiveness compared with control siRNA. In a mouse xenograft model of human glioblastoma, small hairpin RNA against ID1 decreased tumor invasiveness and increased survival compared with control shRNA. Next steps include evaluating ID1 inhibitors in additional mouse glioblastoma models and testing the molecules in combination with other glioblastoma therapeutics. SciBX 6(2); doi:10.1038/scibx.2013.31 Published online Jan. 17, 2013	Covered by issued, pending and filed patents; available for licensing	Soroceanu, L. <i>et al. Cancer Res.</i> ; published online Dec. 13, 2012; doi:10.1158/0008-5472.CAN-12-1943 Contact: Pierre-Yves Desprez, California Pacific Medical Center, San Francisco, Calif. e-mail: pydesprez@cpmcri.org
Breast cancer	Phosphoinositide 3-kinase (PI3K); mammalian target of rapamycin (mTOR; FRAP; RAFT1); Janus kinase-2 (JAK-2)	<i>In vitro</i> and mouse studies suggest JAK-2 inhibitors could help increase the efficacy of PI3K and mTOR inhibitors against triple-negative breast cancer. In cancer cell lines, a dual PI3K and mTOR inhibitor increased JAK-2 expression compared with vehicle. In a mouse xenograft model of human breast cancer, a PI3K and mTOR inhibitor plus a JAK-2 inhibitor synergistically decreased tumor growth and metastasis and increased overall survival compared with either compound alone. Next steps could include testing the combination in additional animal models. At least 28 companies have PI3K or mTOR inhibitors in development stages ranging from preclinical to marketed to treat cancers. At least 10 companies have JAK-2 inhibitors in clinical and preclinical testing for various indications. SciBX 6(2); doi:10.1038/scibx.2013.32 Published online Jan. 17, 2013	Patent and licensing status unavailable	Britschgi, A. <i>et al. Cancer Res.</i> ; published online Dec. 11, 2012; doi:10.1016/j.ccr.2012.10.023 Contact: Mohamed Bentires-Alj, Friedrich Miescher Institute for Biomedical Research, Basel, Switzerland e-mail: bentires@fmi.ch

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cancer	p53	Cell culture and mouse studies suggest reducing dietary serine could help treat p53-deficient cancers. In p53-deficient human colorectal cancer cells, compared with non-p53-deficient cells, serine depletion led to decreased proliferation. In a mouse xenograft model of p53-deficient human colorectal cancer, a serine-depleted diet decreased tumor volumes compared with that seen in non-p53-deficient tumors. Next steps could include evaluating serine depletion in additional models of p53-deficient cancers. SciBX 6(2); doi:10.1038/scibx.2013.33 Published online Jan. 17, 2013	Patent and licensing status unavailable	Maddocks, O.D.K. <i>et al. Nature</i> ; published online Dec. 16, 2012; doi:10.1038/nature11743 Contact: Karen H. Vousden, The Beatson Institute for Cancer Research, Glasgow, U.K. e-mail: k.vousden@beatson.gla.ac.uk
Non-small cell lung cancer (NSCLC)	Epidermal growth factor receptor (EGFR)	A high throughput screening study suggests the staurosporine-based research compound G66967 could aid the development of new treatments for NSCLCs with resistance mutations in EGFR. In human NSCLC lines, G66967 inhibited proliferation of cell lines with resistance mutations in EGFR, including the T790M mutation, at nanomolar IC ₅₀ values. In mice with NSCLC tumors that had a resistance mutation in EGFR, the structurally related compound midostaurin reversibly inhibited the mutant protein and decreased tumor growth compared with vehicle. Next steps include determining whether human pharmacokinetic data will support the use of midostaurin in patients with lung cancer that have resistance mutations in EGFR. Novartis AG's midostaurin, a protein kinase C (PKC) inhibitor, is in Phase III testing to treat acute myelogenous leukemia (AML). SciBX 6(2); doi:10.1038/scibx.2013.34 Published online Jan. 17, 2013	Patent and licensing status undisclosed	Lee, H.-J. <i>et al. Cancer Discov.</i> ; published online Dec. 10, 2012; doi:10.1158/2159-8290.CD-12-0357 Contact: Jeff Settleman, Genentech Inc., South San Francisco, Calif. e-mail: jeffrees@gene.com
Infectious disease				
Bacterial infection	Undecaprenyl diphosphate synthase (uppS)	<i>In vitro</i> and mouse studies identified inhibitors of uppS that could help treat bacterial infection. Crystallographic and <i>in vitro</i> studies identified a lead compound that inhibited uppS at 100 nM and inhibited <i>Staphylococcus aureus</i> growth at concentrations below 1 µg/mL. In mice infected with <i>S. aureus</i> , a 10 mg/kg injection of the lead compound increased survival compared with vehicle injection. Next steps include synthesizing analogs and solving additional crystal structures of the compounds. SciBX 6(2); doi:10.1038/scibx.2013.35 Published online Jan. 17, 2013	Patent applications filed; available for licensing	Zhu, W. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Dec. 17, 2012; doi:10.1073/pnas.1219899110 Contact: Eric Oldfield, University of Illinois at Urbana-Champaign, Urbana, Ill. e-mail: eo@chad.scs.uiuc.edu Contact: Yonghui Zhang, same affiliation as above e-mail: yhzhang@illinois.edu Contact: J. Andrew McCammon, University of California, San Diego, La Jolla, Calif. e-mail: jmccammon@ucsd.edu

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Malaria	Platelet factor 4 (PF4; CXCL4)	<i>In vitro</i> and mouse studies suggest small molecule mimetics of PF4 could help treat malaria. <i>In vitro</i> , the host defense peptide PF4 induced lysis of the <i>Plasmodium falciparum</i> digestive vacuole at low micromolar concentrations. A screen of small molecule host defense peptide mimetics identified a compound that killed <i>P. falciparum</i> at low nanomolar concentrations. In a mouse model of malaria, i.v. injection of a lead mimetic decreased parasite load and increased survival compared with vehicle injection. Next steps include increasing the oral bioavailability of the compounds. The study was carried out in collaboration with PolyMedix Inc., which has antimalarial host defense peptide mimetics in preclinical development. SciBX 6(2); doi:10.1038/scibx.2013.36 Published online Jan. 17, 2013	Patent application filed; licensing status undisclosed	Love, M.S. <i>et al. Cell Host Microbe</i> ; published online Dec. 13, 2012; doi:10.1016/j.chom.2012.10.017 Contact: Doron C. Greenbaum, University of Pennsylvania, Philadelphia, Pa. e-mail: dorong@upenn.edu
Sepsis	Leukocyte cell-derived chemotaxin 2 (LECT2)	<i>In vitro</i> and mouse studies suggest LECT2 could help treat sepsis. In a mouse model of bacterial-induced sepsis, plasma levels of Lect2 were lower than those in healthy mice. In three different mouse models of sepsis, recombinant mouse Lect2 increased survival compared with saline when administered before or during sepsis. In mouse macrophages, Lect2 increased phagocytosis and bacterial clearance compared with saline control. Next steps include pharmacokinetic and toxicology testing. SciBX 6(2); doi:10.1038/scibx.2013.37 Published online Jan. 17, 2013	Patent application filed in China for use of LECT2 in sepsis; unavailable for licensing	Lu, X.-J. <i>et al. J. Exp. Med.</i> ; published online Dec. 17, 2012; doi:10.1084/jem.20121466 Contact: Jiong Chen, Ningbo University, Ningbo, China e-mail: jchen1975@163.com
Musculoskeletal disease				
Musculoskeletal disease	Peroxisome proliferation-activated receptor- γ coactivator 1 α isoform 4 (PPARGC1A4; PGC-1 α 4)	Mouse studies suggest upregulating PGC-1 α 4 could help increase muscle mass. In mice engineered to overexpress PGC-1 α 4 in skeletal muscle, muscle mass and strength were greater than those in wild-type controls. Next steps could include screening for small molecules designed to induce PGC-1 α 4 expression. SciBX 6(2); doi:10.1038/scibx.2013.38 Published online Jan. 17, 2013	Patent and licensing status undisclosed	Ruas, J.L. <i>et al. Cell</i> ; published online Dec. 7, 2012; doi:10.1016/j.cell.2012.10.050 Contact: Bruce M. Spiegelman, Dana-Farber Cancer Institute and Harvard Medical School, Boston, Mass. e-mail: bruce_spiegelman@dfci.harvard.edu Contact: Jorge L. Ruas, same affiliation as above e-mail: jorge.ruas@ki.se
Neurology				
Parkinson's disease (PD)	Dopamine D2 receptor	<i>In vitro</i> and mouse studies suggest dopamine D2 receptor agonists could help treat neuroinflammation in diseases such as PD. Mice with <i>dopamine D2 receptor</i> knockout showed greater astrocyte activation and expression of inflammatory factors, lower levels of neuroprotective crystallin α B (CRYAB; HSPB5) and more severe toxin-induced neuroinflammation than wild-type mice. In a mouse model of PD, the dopamine D2 receptor agonist quinpirole decreased neuroinflammation and loss of dopaminergic neurons compared with saline. Next steps include developing astrocyte-specific dopamine D2 receptor agonists. Quinpirole is a research compound. At least nine companies have dopamine receptor D2 agonists in development stages ranging from preclinical to marketed for neurological indications. SciBX 6(2); doi:10.1038/scibx.2013.39 Published online Jan. 17, 2013	Unpatented; licensing status not applicable	Shao, W. <i>et al. Nature</i> ; published online Dec. 16, 2012; doi:10.1038/nature11748 Contact: Jia-wei Zhou, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai, China e-mail: jwzhou@ion.ac.cn

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Other				
Hearing loss	γ -Secretase; notch 1 (NOTCH1)	<p>Studies in cell culture and in rodents suggest blocking NOTCH1 processing using γ-secretase inhibitors could help treat hearing loss. In cultured inner ear stem cells and inner ear tissue explants, small molecule inhibitors of γ-secretase induced growth of middle ear hair cells, which are damaged in noise-induced hearing loss. In mouse models of hereditary and noise-induced hearing loss, local or systemic delivery of a γ-secretase inhibitor caused the regrowth of hair cells and restored hearing. Next steps could include optimizing dosage and delivery to minimize toxicity of γ-secretase inhibitors. Audion Therapeutics B.V., cofounded by the study's leader, and Inception 3 Inc., have preclinical compounds to treat hearing loss (<i>see γ-Secretase lost and sound, page 7</i>).</p> <p><i>SciBX</i> 6(2); doi:10.1038/scibx.2013.40 Published online Jan. 17, 2013</p>	Patent pending; licensing status undisclosed	<p>Mitzutari, K. <i>et al</i> <i>Neuron</i>; published online Jan. 9, 2013; doi:10.1016/j.neuron.2012.10.032 Contact: Albert S.B. Edge, Harvard Medical School, Boston, Mass. e-mail: albert_edge@meei.harvard.edu</p>

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This week in techniques

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

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

Approach	Summary	Licensing status	Publication and contact information
Assays & screens			
High throughput combinatorial screening to identify genotype-selective combination therapies for melanoma	High throughput combinatorial screening could be useful for identifying genotype-selective combination therapies to treat melanoma. The combinatorial screen tested a curated panel of 150 small molecule chemotherapy or targeted therapies against melanomas with activating mutations in <i>BRAF</i> or <i>Ras</i> or those with wild-type forms of the genes. Inhibition of both epidermal growth factor receptor (EGFR) and protein kinase B (PKB; PKBA; AKT; AKT1) sensitized treatment-resistant <i>BRAF</i> mutant melanomas to Zelboraf vemurafenib. The screen also found that <i>Ras</i> -mutant melanomas were sensitive to the combination of statins and cyclin dependent kinase (CDK) inhibitors. Next steps include running additional animal studies. Roche, Chugai Pharmaceutical Co. Ltd. and Daiichi Sankyo Co. Ltd. market the <i>BRAF</i> inhibitor Zelboraf to treat melanoma.	Unpatented; licensing status not applicable	Held, M.A. <i>et al. Cancer Discov.</i> ; published online Dec. 13, 2012; doi:10.1158/2159-8290.CD-12-0408 Contact: David F. Stern, Yale School of Medicine, New Haven, Conn. e-mail: df.stern@yale.edu
SciBX 6(2); doi:10.1038/scibx.2013.41 Published online Jan. 17, 2013			
Chemistry			
Hydrolysis-resistant proteins with Pictet-Spengler ligations	Pictet-Spengler ligations could be useful for creating hydrolysis-resistant biologics. The Pictet-Spengler ligation forms a hydrolysis-resistant carbon-carbon bond between tryptamine and an aldehyde or ketone. In a protein hydrolysis assay, more than 90% of a stabilized fluorescent protein produced by the Pictet-Spengler ligation remained intact after two days, whereas less than 50% of a fluorescent protein produced using another chemical method remained intact. The ligation reaction generated a HER2 (EGFR2; ErbB2; neu)-targeted antibody-drug conjugate that maintained its target affinity. Next steps could include using the ligation reaction to create additional hydrolysis-resistant variants of existing biologics.	Patent pending; licensing details available from the University of California, Berkeley Office of Technology Licensing	Agarwal, P. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Dec. 13, 2012; doi:10.1073/pnas.1213186110 Contact: Carolyn R. Bertozzi, University of California, Berkeley, Calif. e-mail: crb@berkeley.edu
SciBX 6(2); doi:10.1038/scibx.2013.42 Published online Jan. 17, 2013			
Computational models			
Computational algorithm for designing G protein-coupled receptor (GPCR) ligands against a predefined set of targets	A computational algorithm could be used to design GPCR ligands that modulate a predefined set of targets. Starting from Aricept donepezil, which has moderate dopamine D4 receptor activity and low dopamine D2 receptor activity, an automated algorithm predicted compounds that would have increased D2 receptor activity and blood brain barrier (BBB) permeability. The eight highest-ranked molecules all retained D4 receptor activity and had greater D2 receptor affinity than Aricept, and one compound tested in mice also penetrated the BBB. Next steps include determining whether the method can be used for lead optimization and applied to other target families. Pfizer Inc. and Eisai Co. Ltd. market the acetylcholinesterase (AChE) inhibitor Aricept for Alzheimer's disease (AD).	Patented; licensed to Ex Scientia Ltd.	Besnard, J. <i>et al. Nature</i> ; published online Dec. 12, 2012; doi:10.1038/nature11691 Contact: Andrew L. Hopkins, University of Dundee, Dundee, U.K. e-mail: a.hopkins@dundee.ac.uk
SciBX 6(2); doi:10.1038/scibx.2013.43 Published online Jan. 17, 2013			

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Drug delivery			
pH (low) insertion peptides (pHLIPs) for drug delivery to ischemic myocardium	<p>pHLIPs could be useful for delivering imaging agents or therapeutics to ischemic regions of the heart that have lower pH values than nonischemic regions. pHLIPs are water-soluble polypeptides derived from the bacteriorhodopsin C helix. In mice with ischemia in different regions of the heart, injection of dye-conjugated pHLIPs increased fluorescence signal in ischemic regions compared with nonischemic regions. In isolated mouse hearts subjected to ischemia, dye-loaded pHLIP-coated liposomes increased fluorescence signal compared with that in nonischemic hearts. Next steps include evaluating the pHLIP technology to deliver imaging and therapeutic agents in additional models of ischemia.</p> <p>SciBX 6(2); doi:10.1038/scibx.2013.44 Published online Jan. 17, 2013</p>	Covered by multiple issued and pending patents; use of radionuclide-labeled pHLIPs as a diagnostic tool for imaging of acidic tissues licensed to General Electric Co.; other diagnostic applications and all therapeutic applications available for licensing	<p>Sosunov, E.A. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Dec. 17, 2012; doi:10.1073/pnas.1220038110 Contact: Oleg A. Andreev, University of Rhode Island, Kingston, R.I. e-mail: andreev@mail.uri.edu Contact: Donald M. Engelman, Yale University, New Haven, Conn. e-mail: donald.engelman@yale.edu</p>
pH (low) insertion peptides (pHLIPs) for delivery of gold nanoparticles to tumors	<p>pHLIPs could be used to target gold nanoparticles to tumors, which tend to have lower pH than normal tissue. pHLIPs are water-soluble polypeptides derived from the bacteriorhodopsin C helix. In mice with human cervical cancer tumors, intratumoral injection of pHLIP-conjugated gold nanoparticles led to a sixfold increase in gold accumulation in tumor tissues compared with injection of nonconjugated gold nanoparticles. Next steps include developing nanoparticle coatings that could further increase bioavailability and tumor targeting and reduce accumulation in off-target tissues.</p> <p>SciBX 6(2); doi:10.1038/scibx.2013.45 Published online Jan. 17, 2013</p>	Patented; use of radionuclide-labeled pHLIPs as a diagnostic tool for imaging of acidic tissues licensed to General Electric Co.; other diagnostic applications and all therapeutic applications available for licensing	<p>Yao, L. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Dec. 24, 2012; doi:10.1073/pnas.1219665110 Contact: Oleg A. Andreev, University of Rhode Island, Kingston, R.I. e-mail: andreev@mail.uri.edu Contact: Donald M. Engelman, Yale University, New Haven, Conn. e-mail: donald.engelman@yale.edu</p>
Drug platforms			
Chimeric antigen receptors (CARs) that require dual-antigen binding for activation	<p>T cells engineered to express a CAR and a chimeric co-stimulatory receptor could enhance the tumor specificity of targeted T cell therapies. T cells expressing CARs can trigger a tumor antigen-specific immune response but also can cause toxicity if the targeted antigen is not exclusively expressed by tumor cells. To increase specificity, T cells were engineered to carry a CAR that induces T cell activation only when a second co-stimulatory receptor engages with another tumor-specific antigen. In a mouse model of prostate cancer, T cells engineered to bind both prostate stem cell antigen (PSCA) and prostate-specific membrane antigen (PSMA; FOLH1; GCPII) decreased the growth of PSCA⁺/PSMA⁺ tumors but not the growth of tumors expressing only one of the two antigens. Next steps include developing additional strategies to increase the safety of the T cell therapy.</p> <p>SciBX 6(2); doi:10.1038/scibx.2013.46 Published online Jan. 17, 2013</p>	Patent application filed; available for licensing	<p>Kloss, C.C. <i>et al. Nat. Biotechnol.</i>; published online Dec. 16, 2012; doi:10.1038/nbt.2459 Contact: Michel Sadelain, Memorial Sloan-Kettering Cancer Center, New York, N.Y. e-mail: m-sadelain@ski.mskcc.org</p>
Direct conversion of quiescent cardiomyocytes into pacemaker cells	<p>A gene therapy approach for direct conversion of quiescent cardiomyocytes into pacemaker cells could be useful for treating arrhythmias. In cultured rat ventricular myocytes, adenoviral vector expression of <i>T-box 18</i> (<i>Tbx18</i>) resulted in the formation of monolayers of spontaneously beating cells. In guinea pigs, cardiac injection of the adenovirus vector encoding <i>Tbx18</i> led to pacemaker activity at the site of injection, whereas injection of the same vector encoding a control protein did not. Next steps include validating the results in a large animal model and evaluating the safety and pharmacokinetics of the vector.</p> <p>SciBX 6(2); doi:10.1038/scibx.2013.47 Published online Jan. 17, 2013</p>	Patent and licensing status undisclosed	<p>Kapoor, N. <i>et al. Nat. Biotechnol.</i>; published online Dec. 16, 2012; doi:10.1038/nbt.2465 Contact: Eduardo Marbán, Cedars-Sinai Medical Center, Los Angeles, Calif. e-mail: eduardo.marban@cshs.org</p>

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Production of antibody-toxin fusion immunotoxins in algae	<p><i>In vitro</i> and mouse studies suggest algae chloroplasts could be used to produce anticancer immunotoxin fusion proteins. Genetically engineered green algae chloroplasts were used to produce an immunotoxin fusion protein that combined a eukaryotic endotoxin and an antibody domain targeting B cell-specific CD22. The algae-produced immunotoxin-induced death of human B cell lymphoma cells but not normal human B or T cells. In a mouse xenograft model of human lymphoma, the algae-produced immunotoxins inhibited tumor progression and increased survival compared with the antibody domain alone. Next steps include designing a new fusion protein for testing in large animal models.</p> <p>At least six companies have antibodies targeting CD22 in Phase II testing or earlier to treat various cancers.</p> <p>SciBX 6(2); doi:10.1038/scibx.2013.48 Published online Jan. 17, 2013</p>	Patent application filed; licensed to Sapphire Energy Inc., a biofuels company	<p>Tran, M. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online Dec. 10, 2012; doi:10.1073/pnas.1214638110 Contact: Stephen P. Mayfield, University of California, San Diego, La Jolla, Calif. e-mail: smayfield@ucsd.edu</p>
Targeting ventral tegmental area (VTA) dopaminergic neurons to treat depression	<p>Targeting a subset of dopaminergic neurons could be useful for reducing depression-related behaviors. In mice, optogenetic induction of a phasic firing pattern in VTA dopaminergic neurons in mice increased susceptibility to social defeat stress and depression-related behaviors compared with induction of a tonic firing pattern. In mice and rats, optogenetic inhibition of VTA dopaminergic neurons increased depression-related behaviors compared with no inhibition. Next steps could include developing pharmacological agents to modulate the activity of VTA neurons.</p> <p>SciBX 6(2); doi:10.1038/scibx.2013.49 Published online Jan. 17, 2013</p>	Patent and licensing status for both studies unavailable	<p>Chaudhury, D. <i>et al. Nature</i>; published online Dec. 12, 2012; doi:10.1038/nature11713 Contact: Ming-Hu Han, Mount Sinai School of Medicine, New York, N.Y. e-mail: ming-hu.han@mssm.edu</p> <p>Tye, K.M. <i>et al. Nature</i>; published online Dec. 12, 2012; doi:10.1038/nature11740 Contact: Karl Deisseroth, Stanford University, Stanford, Calif. e-mail: deissero@stanford.edu</p>

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Technology Enterprise and		at Chapel Hill	2	HSPB5	11	PPARGC1A4	11
Commercialization	9	University of Pennsylvania	5	I		Prostate-specific membrane	
D		W		ID1	9	antigen	14
Daiichi Sankyo Co. Ltd.	4,13	Washington University in		Inavir	4	Prostate stem cell antigen	14
Dana-Farber Cancer Institute	2	St. Louis School of Medicine	1	Influenza A virus matrix		Protein kinase B	13
Dynamix Pharmaceuticals			protein 2	4	Protein kinase C	10
Ltd.	6	Target and compound index		Inhibitor of DNA binding 1	9	PSCA	14
E		A		Isoxazole	4	PSMA	14
Eisai Co. Ltd.	14	Acetylcholinesterase	13	Isoxazoline	4	Pyruvate	5
Eli Lilly and Co.	7	Acetyl-CoA	6	J		Pyruvate kinase M1 isozyme	5
Ex Scientia Ltd.	14	AChE	13	JAK-2	9	Pyruvate kinase M2 isozyme	5
G		ADP	5	Janus kinase-2	9	Q	
Genentech Inc.	1	AKT	13	L		Quinpirole	11
General Electric Co.	14	AKT1	13	Lactate	6	R	
Gilead Sciences Inc.	4	Amantadine	4	Laninamivir	4	RAFT1	9
GlaxoSmithKline plc	1,4	Amyloid precursor protein	7	Lapatinib	1	Ras	13
H		APP	7	LECT2	11	Relenza	4
Harvard Medical School	7	Aricept	13	Leukocyte cell-derived		Rimantadine	4
I		ATP	5	chemotaxin 2	11	S	
Inception 3 Inc.	8,12	B		M		Semagacestat	7
InfluMedix Inc.	4	<i>BRAF</i>	13	M2	4	Serine	10
K		Bruton's tyrosine kinase	9	MALT1	9	SHH	8
Keio University School of		BTK	9	Mammalian target of		SIAL1	4
Medicine	7	C		rapamycin	9	Sonic hedgehog homolog	8
M		CAR	14	MI-2	9	Statin	13
Massachusetts Eye and Ear		CD22	15	Midostaurin	10	Staurosporine	10
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Massachusetts Institute of		Chimeric antigen receptor	14	Mucosa associated lymphoid		Tamiflu	4
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Memorial Sloan-Kettering		Citrate	6	gene 1	9	<i>Tbx18</i>	14
Cancer Center	2	CRYAB	11	N		TGFB	8
N		Crystallin α B	11	Neratinib	1	TGF- β	8
NanoViricides Inc.	4	CXCL4	11	Neu	1,13	Thioridazine	9
Northwestern University	4	Cyclin dependent kinase	13	NEU1	4	TP-1454	6
Novartis AG	5,10	D		Neuraminidase	4	Transforming growth factor- β	8
O		Dexamethasone	8	NOTCH1	7,12	Trastuzumab	1
Oregon Health & Science		DNX-03047	6	Notch 1	7,12	Tykerb	1
University	7	Donepezil	13	O		U	
Otonomy Inc.	8	Dopamine D2 receptor	11,13	Oseltamivir	4	Undecaprenyl diphosphate	
P		Dopamine D4 receptor	13	OTO-104	8	synthase	10
Pfizer Inc.	3,14	E		OTO-201	8	UppS	10
PolyMedix Inc.	11	EGFR	2,10,13	Oxadiazole	4	V	
Puma Biotechnology Inc.	1	EGFR2	1,13	P		Vemurafenib	13
R		Epidermal growth factor		PEP	5	W	
Roche	1,4,8,13	receptor	2,10,13	Perjeta	1	Wingless-type MMTV	
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