

THIS WEEK

ANALYSIS

COVER STORY

1 **BETting on OncoFusion**

Medivation has licensed a portfolio of BET bromodomain inhibitors that could have better efficacy than the company's castration-resistant prostate cancer drug Xtandi enzalutamide. Medivation got the molecules from OncoFusion as the startup's founders published compelling preclinical data for inhibiting BET in CRPC.

TRANSLATIONAL NOTES

5 **Temple building**

Temple University has teamed up with MorphoSys to bring industry-quality antibody discovery capabilities in-house. The partnership complements the university's medicinal chemistry expertise while expanding the company's access to discovery-stage research.

TARGETS & MECHANISMS

6 **TLR4 on the surface of scleroderma**

BioLineRx's deal with the University of Colorado could give the biotech a disease-modifying therapy for cutaneous fibrosis in patients with diffuse systemic scleroderma. It remains unclear whether the university's TLR4 inhibitors will work in other tissues affected by the disease.

TOOLS

8 **Zapping hearing loss**

An Australian team has devised a method for treating hearing loss by delivering gene therapy to the inner ear. The technique uses electric fields generated by an implantable device to electroporate a transgene into damaged cochlear cells.

THE DISTILLERY

10 **This week in therapeutics**

Alleviating autoimmune conditions such as MS with low-dose CXCL11; treating influenza A by inhibiting PTGES; reversing muscular atrophy by increasing mTORC1 signaling with the tomato-derived natural product tomatidine; and more...

18 **This week in techniques**

Native chemical ligation for generating reversible covalent peptide bonds; a mouse model of acute thrombotic thrombocytopenic purpura; TRPC5-containing extracellular vesicles as a marker of chemotherapy resistance in breast cancer; and more...

INDEXES

21 **Company and institution index**21 **Target and compound index**

BETting on OncoFusion

By Kai-Jye Lou, Senior Writer

Medivation Inc. has licensed a portfolio of BET bromodomain inhibitors that could have better efficacy than the company's castration-resistant prostate cancer drug Xtandi enzalutamide and could provide the biotech with a new way to disrupt androgen receptor signaling. The company got the molecules from **OncoFusion Therapeutics Inc.** on the same day the startup's founders published compelling preclinical data for inhibiting BET in the indication.¹

Under the April 23 deal, Medivation will have exclusive, worldwide rights to selected BET inhibitors. In return, OncoFusion is eligible to receive undisclosed up-front payments and milestones plus royalties.

Also that day, a **University of Michigan Medical School** team led by OncoFusion cofounder Arul Chinnaiyan published a study in *Nature* identifying a previously unknown molecular interaction between BET bromodomain-containing proteins and the androgen receptor (AR).

Chinnaiyan is a professor of pathology and urology at the medical school and an investigator at the **Howard Hughes Medical Institute**.

In AR⁺ human CRPC cell lines, the research tool BET bromodomain inhibitor JQ1 caused more potent suppression of AR-mediated gene transcription than Xtandi, which is a small molecule AR antagonist.

In addition to blocking AR-mediated gene transcription, JQ1 also inhibited the activity and expression of two known oncogenes: *v-ets erythroblastosis virus E26 oncogene homolog (ERG)* and *c-Myc (MYC)*.

Importantly, Chinnaiyan's group replicated the *in vitro* results with a clinical-stage BET bromodomain inhibitor called GSK525762 (formerly I-BET762).

In mice with metastatic CRPC, JQ1 decreased tumor volume and weight compared with Xtandi.

Bromodomain inhibition also showed a safety advantage. Healthy mice treated with Xtandi for 30 days developed abnormal prostate morphology and showed shrinkage of prostate tissues, whereas those treated with JQ1 or vehicle did not.

Chinnaiyan noted that OncoFusion's own BET inhibitors also have been tested and have shown similar or better results than those reported in the *Nature* paper, but he declined to provide details.

"What makes this particular story interesting is the characterization and mechanistic analysis of this molecular pathway showing how BET is involved in the transcription of AR-regulated genes," said Robert Sims, director of biology at **Constellation Pharmaceuticals Inc.**

Constellation's lead BET bromodomain inhibitor, CPI-0610,

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PO Box 1246
San Carlos, CA 94070-1246
T: +1 650 595 5333Chicago
20 N. Wacker Drive, Suite 1465
Chicago, IL 60606-2902
T: +1 312 755 0798United 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
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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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is in a Phase I trial to treat progressive lymphomas.

“Based on the proposed mechanism, the advantage of using BET inhibitors compared to current AR-based therapies is targeting AR-dependent signaling from two angles—the recruitment of AR to DNA as well as recruitment of BRD4 [bromodomain containing 4] and transcriptional machinery to AR-BRD4-occupied genes,” wrote Olena Barbash in an e-mail to SciBX.

Barbash is an investigator in oncology R&D at **GlaxoSmithKline plc** and a coauthor on a study published in 2013 demonstrating the ability of GSK525762 to decrease *MYC* expression as well as cell proliferation and tumor burden in prostate cancer models.²

“The data published in the study are quite robust, and we are clearly excited about the results,” said Medivation president and CEO David Hung. “We’ve also had the opportunity to look at some additional unpublished data showing that bromodomain inhibition represents a very interesting therapeutic approach that warrants the investment.”

Hung said that JQ1’s dearth of effects on normal prostate tissues suggests the potential to use BET bromodomain inhibitors in patients with earlier stage disease. He declined to say what specific indications Medivation plans to pursue with the BET inhibitors.

GlaxoSmithKline’s GSK525762 is in Phase I testing to treat NUT midline carcinoma or other epithelial cancers. The pharma was not

“What makes this particular story interesting is the characterization and mechanistic analysis of this molecular pathway showing how BET is involved in the transcription of AR-regulated genes.”

—Robert Sims,
Constellation Pharmaceuticals Inc.

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Figure 1. Blocking androgen signaling in castration-resistant prostate cancer.

Nearly all pathways associated with the transition from androgen-dependent to castration-resistant prostate cancer (CRPC) include reactivation of signaling pathways that involve the androgen receptor (AR). In prostate cancer cells, testosterone-bound ARs form dimers that translocate into the nucleus, in which they get recruited to target gene loci on DNA along with an RNA polymerase to initiate the transcription of AR-regulated genes.

At least two targeted therapies are marketed to treat CRPC that can block androgen signaling after first-line androgen ablation therapies are no longer effective. The more upstream-targeted drug is **Johnson & Johnson's** Zytiga abiraterone acetate (green circle), a small molecule inhibitor of cytochrome P450 17 α -hydroxylase/C17, 20 lyase (CYP17) [a]. The lyase is responsible for converting testosterone precursors such as dehydroepiandrosterone (DHEA) into testosterone, so inhibiting its function decreases the amount of testosterone available to bind to ARs.

The other drug is **Medivation Inc.'s** Xtandi enzalutamide (blue circle). The drug blocks AR signaling by competing with testosterone for binding to AR [b], which inhibits the translocation of AR into the nucleus [c] and prevents recruitment of nuclear AR to DNA [d].

As reported in Asangani *et al.*, researchers identified a new molecular interaction between AR and BET bromodomain-containing proteins such as BRD2, BRD3 and BRD4. The group found that blocking the AR and BRD2/3/4 interactions with the BET bromodomain inhibitor JQ1 (yellow circle) blocks the co-recruitment of AR and the BET bromodomain-containing proteins to DNA [e]. This results in decreased expression of multiple AR-regulated genes and also inhibits the activity of two known oncogenes: *v-ets erythroblastosis virus E26 oncogene homolog (ERG)* and *c-Myc (MYC)*.

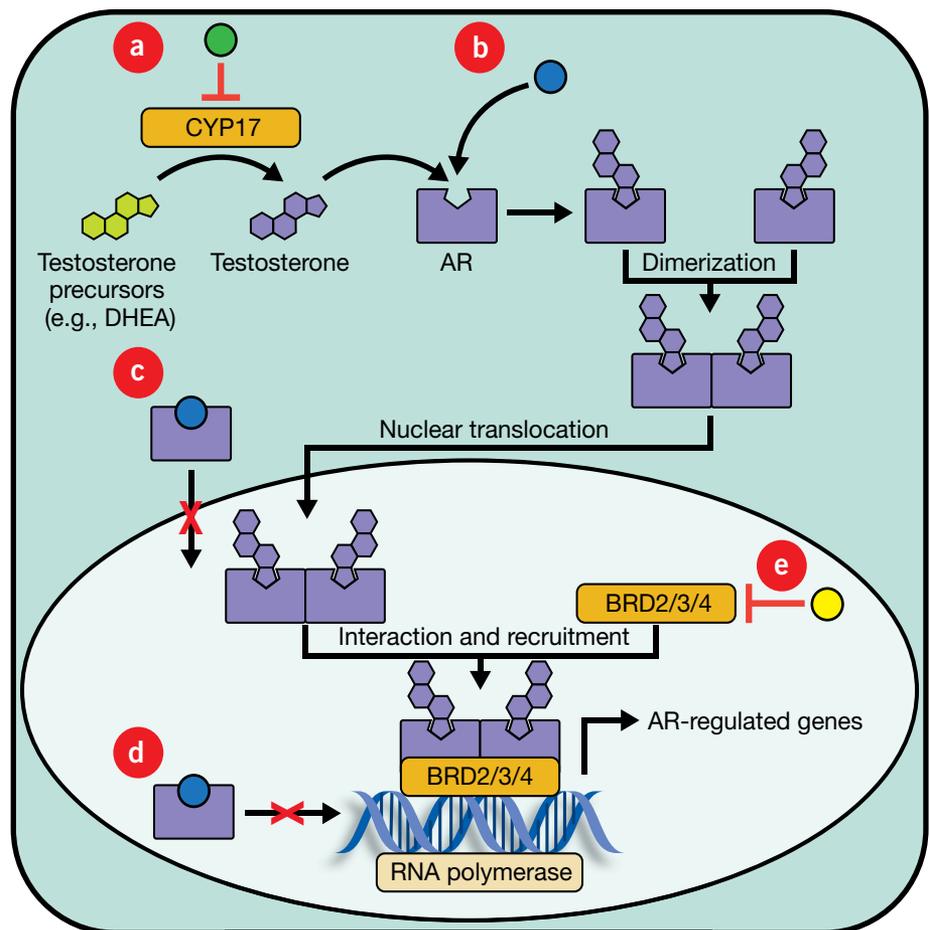
involved in the *Nature* study and is not disclosing whether it has plans to develop GSK525762 in CRPC.

BETting on safety, against resistance

Despite being labeled castration resistant, CRPC cells often remain dependent on androgen signaling for their survival, and multiple studies have shown that the transition to castration-resistant disease is associated with reactivation of signaling pathways that involve the AR.^{3,4}

Xtandi is one of two approved drugs for CRPC that work by restoring the blockade of androgen signaling after standard androgen deprivation therapies have failed. The other is **Johnson & Johnson's** Zytiga abiraterone acetate.

In its 4Q13 earnings report, Medivation said that partner **Astellas Pharma Inc.** reported \$161.9 million in global sales for Xtandi, up 282% from \$57.4 million in the same period in 2012. The biotech reports its 1Q14 sales figures this week.



Barbash noted that “combinations of BET inhibitors with current therapies in CRPC as well as novel targeted agents could offer greater efficacy or resensitization of resistant tumors to current agents.”

BET bromodomain inhibitors would work downstream of Zytiga and Xtandi by blocking the recruitment of AR to BET bromodomain proteins, which would in turn inhibit the transcription of AR-regulated genes (see Figure 1, “Blocking androgen signaling in castration-resistant prostate cancer”).

“They show that these BET inhibitors could induce tumor growth inhibition and tumor shrinkage, but what we don’t know at this time is how long the effect could last,” said Howard Scher, chief of the genitourinary oncology service and chair in urologic oncology at the **Memorial Sloan-Kettering Cancer Center**. “We also don’t know what changes would be associated with resistance to these compounds.” He also cautioned that as the prostate cancer space becomes more crowded, it will get more difficult for newer drug candidates to show improvements in survival over standard of care.

Barbash and GlaxoSmithKline’s Anastasia Wyce both noted that studies to evaluate potential therapeutic combinations with BET bromodomain in CRPC models will help guide further development of these compounds in the prostate cancer space. Wyce is an investigator in biology at the pharma.

Chinnaiyan said that his group at the University of Michigan Medical School is working out additional details of the activity of BET bromodomain inhibitors in prostate as well as in other cancers. He said that the work could aid the development of companion diagnostics to identify patients who would be responsive to BET bromodomain inhibitors.

The **University of Michigan** has filed a patent application covering the composition of matter of its BET bromodomain inhibitors. The IP has been to OncoFusion.

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COMPANIES AND INSTITUTIONS MENTIONED

Astellas Pharma Inc. (Tokyo:4503), Tokyo, Japan
Constellation Pharmaceuticals Inc., Cambridge, Mass.
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Howard Hughes Medical Institute, Chevy Chase, Md.
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Medivation Inc. (NASDAQ:MDVN), San Francisco, Calif.
Memorial Sloan-Kettering Cancer Center, New York, N.Y.
OncoFusion Therapeutics Inc., Ann Arbor, Mich.
University of Michigan, Ann Arbor, Mich.
University of Michigan Medical School, Ann Arbor, Mich.



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Temple building

By Chris Cain, Senior Writer

The **Temple University School of Pharmacy** has teamed up with **MorphoSys AG** to bring industry-quality antibody technology in-house. The partnership expands MorphoSys' access to early stage research and adds to the toolkit of discovery capabilities at the **Moulder Center for Drug Discovery Research at Temple University**.

The center was founded in 2009 with a donation from Lonnie Moulder, a university alumnus and CEO of **Tesaro Inc.**

Center director Magid Abou-Gharbia told *SciBX* that the center's strategy has been to focus on building in-house medicinal chemistry capabilities while partnering with outside universities—and in some cases small companies—to gain access to new targets.

Abou-Gharbia also is associate dean for research and a professor of medicinal chemistry at Temple.

"We started with a vision to have a fully integrated drug discovery center, founded with a strength in chemistry and drug design. Most drug discovery centers in academia are founded by biologists and focus on the disease interests of the founder. Our strength in chemistry and drug design allows us to be highly flexible in the disease that we study and the biology that we study," he said

In 2011, the center entered into a discovery partnership with the target-rich but chemistry-poor **University of Rochester Medical Center**.¹ The partners expanded the deal in 2012 to include a \$500,000 research fund called the Drug Discovery Pilot Award Program that provides grants to researchers conducting either exploratory screening studies or lead optimization.

The Rochester partnership has resulted in IP covering compounds against an undisclosed target that were developed as part of a three-way collaboration with the **University of Nebraska Medical Center**.

More recently, the Moulder center has partnered with **The Wistar Institute** to pursue cancer targets and with **The Johns Hopkins University School of Medicine** to pursue targets in neuroscience and drug addiction. Abou-Gharbia said that the center now has nine academic and nine industry collaborators.

He highlighted two industry collaborations: one with **Shifa Biomedical Corp.** to develop a small molecule inhibitor of proprotein convertase subtilisin/kexin type 9 (PCSK9) and one with **Cortendo AB** to develop compounds to treat type 2 diabetes and Cushing's disease.

At least 10 companies are developing PCSK9 inhibitors to lower low-density lipoprotein cholesterol levels in a variety of lipid disorders. There are three antibodies against the target in Phase III testing.

Antibody up

On the heels of the small molecule deals, Abou-Gharbia said that the next logical step was to expand the center's biologic capabilities. To do this, he recruited Jon Condra in September 2012 to head a new Biotherapeutics Discovery Unit.

Condra previously was head of phage display technologies in the biologics department of **Merck & Co. Inc.**'s research labs. He also is an associate professor of pharmaceutical biotechnology at Temple.

Condra's first order of business was to identify a technology Temple could rely on for antibody production.

MorphoSys CEO Simon Moroney told *SciBX* that Condra's prior experience with the company's HuCAL phage-display technology gave the biotech confidence in Temple's ability to make the most of a partnership.

In exchange for a first option on any antibodies produced using its technology, MorphoSys will install its Ylanthia phage-display platform at the Moulder center. Ylanthia is MorphoSys' successor to HuCAL and is designed to reduce the time needed for lead optimization.²

Condra said that the ability to rapidly develop molecules was a key reason he looked to bring Ylanthia in house. "It's easy to get antibodies that bind targets, but then you spend a great deal of time trying to optimize them. What MorphoSys has done is to optimize the antibodies for developability, which will greatly improve our chances of success."

The Moulder center will independently run discovery activities using the Ylanthia platform. MorphoSys will provide technical assistance and will not have a hand in selecting programs.

Moroney said that the company is comfortable with a hands-off approach because Moulder is an applied research institute with a more translational focus than most institutions. This is the first time MorphoSys has installed its phage-display system at an academic center.

He also noted that MorphoSys has been looking for ways to expand its early discovery capabilities. "Discovery is one of the hardest things in the industry, and there aren't any companies, not even pharma, who can do it on their own. We have a discovery group in-house, but of course it is limited, so we look for any way we can work productively with groups that have the potential to discover therapeutic antibodies against new targets," he said.

"This is the kind of partnership we would do again, in a selected, targeted way, at applied sites that are interested in drug development," Moroney added.

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COMPANIES AND INSTITUTIONS MENTIONED

Cortendo AB, Gothenburg, Sweden
The Johns Hopkins University School of Medicine, Baltimore, Md.
Merck & Co. Inc. (NYSE:MRK), Whitehouse Station, N.J.
MorphoSys AG (Xetra:MOR; Pink:MPSYF), Martinsried, Germany
Moulder Center for Drug Discovery Research at Temple University, Philadelphia, Pa.
Shifa Biomedical Corp., Malvern, Pa.
Temple University School of Pharmacy, Philadelphia, Pa.
Tesaro Inc. (NASDAQ:TSRO), Waltham, Mass.
University of Nebraska Medical Center, Omaha, Neb.
University of Rochester Medical Center, Rochester, N.Y.
The Wistar Institute, Philadelphia, Pa.

TLR4 on the surface of scleroderma

By Lauren Martz, Staff Writer

BioLineRx Ltd.'s deal with the **University of Colorado** could give the biotech a disease-modifying therapy for cutaneous fibrosis in patients with diffuse systemic scleroderma.¹ It is still unclear whether the university's toll-like receptor 4 inhibitors will work in other tissues affected by the disease.

There are no marketed disease-modifying drugs for diffuse systemic scleroderma. The diffuse form of the autoimmune disease affects about a third of patients and involves an inflammatory and fibrotic skin component in addition to systemic inflammation and fibrosis of the lungs and other organs.

The diffuse form is generally more aggressive and progresses from inflammation to fibrosis more quickly than limited systemic scleroderma. Standard care includes immunosuppression and anti-inflammatory therapeutics as well as symptomatic treatments.

Scleroderma's etiology is unknown, although previous studies have provided a few hints. For example, a group including a member of the Northwestern team showed that transforming growth factor- β (TGF β ; TGF β) acts as a trigger for the fibroblast activation and cutaneous fibrosis that occurs in patients with scleroderma.²

Other groups have shown that the fibronectin extra domain A (FnEDA) splice variant is upregulated in skin lesions from patients with scleroderma³ and that toll-like receptor 4 (TLR4) ligands and signaling occur in skin and lung biopsies from patients with scleroderma.^{4,5} FnEDA typically is absent in healthy adult tissues and upregulated during injury.

With those clues in mind, John Varga and colleagues have built a clearer mechanistic picture of the disease and showed that FnEDA signaling through TLR4 plays a role in the fibrotic feed-forward loop in cutaneous scleroderma.

Varga is director of the Northwestern Scleroderma Program and a professor of medicine-rheumatology and dermatology at the **Northwestern University Feinberg School of Medicine**. The team also included a researcher from the **University of Michigan**.

In 48 patients with diffuse cutaneous scleroderma, serum FnEDA levels were 5-fold higher than those in 16 healthy controls. FnEDA mRNA levels in skin lesion biopsies from 20 patients were 3-fold higher than those in 8 healthy controls. In normal human foreskin fibroblasts, incubation with TGF β triggered fibrosis and induced 30-fold increases in FnEDA mRNA and 9-fold increases in protein levels.

In mouse models of cutaneous fibrosis, knockout of *Fneda* decreased dermal thickening and collagen accumulation compared with no

alteration. These findings suggested that FnEDA is both increased and required for cutaneous fibrosis during scleroderma.

In fibroblast monolayers and human skin models, incubation with FnEDA increased collagen levels, wound healing and skin thickness, whereas pretreatment with a TLR4 inhibitor, siRNA targeting TLR4 or genetic knockout of the receptor prevented the profibrotic effects of FnEDA.

Finally, in a mouse model of cutaneous fibrosis, subcutaneous injection of a TLR4 inhibitor decreased skin thickness and collagen deposition compared with no treatment and prevented muscle necrosis.

Based on these findings, the researchers proposed that FnEDA signaling through TLR4 facilitates a loop that maintains the fibrotic state in the skin of patients with scleroderma.

The researchers proposed that FnEDA is upregulated upon a fibrotic trigger and is recognized by TLR4. Activation of TLR4 then stimulates an inflammatory reaction at the site, causing the release of more FnEDA.

Data were published in *Science Translational Medicine*.

Therapeutic development

Varga told *SciBX* that one of his next steps is developing TLR4 inhibitors.

"We are pursuing studies to identify specific, novel TLR4 inhibitors with maximal efficacy and optimal drug-like properties including stability and low toxicity," he said.

He noted that the TLR4 inhibitor used in the paper is no longer being pursued in the clinic, but his team is now working with a new class of orally available, highly selective TLR4 inhibitors with a distinct mechanism of inhibitory activity.

BioLineRx has an option to license lead compound T5342126. The molecule was developed by Varga's collaborator Hang Hubert Yin, an associate professor at the **University of Colorado at Boulder**.

"BioLineRx is currently in early stages with this compound, assessing dose regimens and safety in animal models. Next stages will include process development as well as safety and distribution requirements," said CSO Leah Klapper.

She added that the company is exploring several potential indications for the inhibitor.

"TLR4 is involved in the actual fibrosis process and therefore specifically targets the problem and not only affects the immune system. It is upstream in the cascade of fibrosis, enabling efficient modulation of the cascade," said Klapper. "Most importantly, TLR4 is suggested to be a part of the mechanism responsible for the persistent chronic fibrosis

as opposed to targets that only trigger fibrosis, suggesting a unique beneficial intervention."

Luke Evnin, chairman of the **Scleroderma Research Foundation** and managing director of **MPM Capital**, agreed. "This work provides insights into how we can break into the feed-forward loop that characterizes fibrosis. Once initiated, pathologic fibrosis progresses to a maintenance state, but there are hints that the body continues to run a process to resolve the fibrosis. Breaking into the feed-forward loop by

"This work provides insights into how we can break into the feed-forward loop that characterizes fibrosis. Once initiated, pathologic fibrosis progresses to a maintenance state, but there are hints that the body continues to run a process to resolve the fibrosis. Breaking into the feed-forward loop by blocking TLR4 signaling could allow the body to start resolving some of the pathology on its own."

**—Luke Evnin,
Scleroderma Research Foundation**

blocking TLR4 signaling could allow the body to start resolving some of the pathology on its own,” he said.

He added, “This is exciting because it suggests that intervening, even late once fibrosis has progressed, could have an impact for patients.”

Cutaneous limitations

An unanswered question is whether TLR4 also underlies fibrosis in other organs.

“Systemic scleroderma is not a local disease. It is accurate that part of the problem is localized to the skin, but there is also fibrosis of other organs that causes very serious complications for patients,” noted Evnin. Thus, he wanted to see the researchers study the role of TLR4 in other organs.

Varga told *SciBX* that his team is planning to evaluate the new compounds in a series of complementary models that recapitulate key features of scleroderma including fibrosis, autoimmunity and vasculopathy. He said that even if TLR4 is only at work in the skin, the program is well worth pursuing.

“Topical application of our compound is an extremely appealing strategy since it is expected to be able to hit the target—activated myofibroblasts within the fibrotic dermis—without systemic exposure,” said Varga. “We expect the topical approach to local therapy can avoid issues of immunomodulation and potential immunosuppression by a systemically absorbed TLR inhibitor.”

Varga told *SciBX* that in addition to designing new TLR4 inhibitors, his team is developing a companion diagnostic to identify patients most likely to benefit from TLR4 inhibitors.

“We have already succeeded in defining a provisional TLR signature based on genomewide microarray analysis of genes whose expression

is modulated by TLR and have identified patient subsets with a strong TLR signature in skin biopsies,” he said.

Northwestern University and the University of Colorado have filed a patent application covering the use of TLR inhibitors to treat scleroderma. A separate patent covering the chemical structure of the lead TLR4 inhibitor has been issued to the University of Colorado, and BioLineRx has an exclusive option to license the IP.

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Contact: Swati Bhattacharyya, Northwestern University Feinberg School of Medicine, Chicago, Ill.
e-mail: s-bhattacharyya@northwestern.edu
Contact: John Varga, same affiliation as above
e-mail: j-varga@northwestern.edu
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COMPANIES AND INSTITUTIONS MENTIONED

BioLineRx Ltd. (Tel Aviv:BLRX; NASDAQ:BLRX), Jerusalem, Israel

MPM Capital, South San Francisco, Calif.

Northwestern University, Chicago, Ill.

Northwestern University Feinberg School of Medicine, Chicago, Ill.

Scleroderma Research Foundation, San Francisco, Calif.

University of Colorado, Denver, Colo.

University of Colorado at Boulder, Boulder, Colo.

University of Michigan, Ann Arbor, Mich.

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Zapping hearing loss

By Lev Osherovich, Senior Writer

The most advanced cochlear implants for hearing loss lack frequency resolution and dynamic range, causing recipients to perceive sounds as loud, monotonous and robotic. An Australian team may have solved those problems with a combination product that uses electric fields generated by a cochlear implant to electroporate a gene therapy into the cells of damaged inner ears.¹

Hearing device maker **Cochlear Ltd.** has an option to license the technology.

Profound hearing loss can be caused by congenital absence of—or damage to—hair cells in the cochlea, a spiral structure in the inner ear that decodes sound waves into neurological impulses.

Patients with total hearing loss can benefit from cochlear implants, which are multielectrode arrays inserted into the cochlea. The implants encode sound into electrical impulses that mimic the activation of hair cells.

However, replacing hair cell function with an electrical implant solves only half of the problem in patients who lose their hearing later in life. The other half is the loss of trophic factors that promote or maintain neuronal connections to the ear.

Ordinarily, trophic factors such as brain-derived neurotrophic factor (BDNF) are produced by mesenchymal cells in the inner ear and stimulate the growth of neuronal connections. In damaged ears, the production of BDNF is limited, causing nearby neurons to atrophy and disconnect from the cochlear lining.

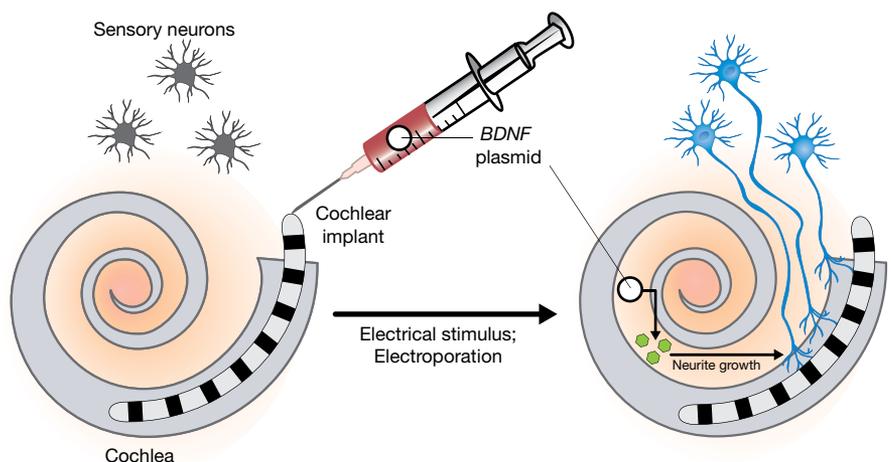
Thus, restoring trophic factor production in the inner ear has been a major goal for enhancing the performance and useful lifespan of cochlear implants.

“The idea of delivering neurotrophins to the inner ear has been around for a while. The hope has been that this would increase survival of neurons,” said Allen Ryan, a professor of surgery at the **University of California, San Diego**.

Current methods to deliver trophic factors include osmotic pumps, which act as extended-release reservoirs, or gene therapy using viral vectors. Ryan said that these approaches have yielded few benefits in animal models of hearing loss.

Figure 1. Gene therapy by cochlear implant.

Cochlear implants are multielectrode arrays that treat severe forms of hearing loss caused by the absence of mechanosensory hair cells. Pinyon et al. adapted a cochlear implant marketed by **Cochlear Ltd.** to deliver a plasmid encoding *brain-derived neurotrophic factor* (BDNF), a growth factor that promotes sensory neuron growth. Activation of selected electrodes along the implanted array led to localized plasmid delivery to cochlear tissue near the activated electrodes. BDNF production and neurite outgrowth occurred near the regions that received plasmid but not in other parts of the cochlea.



“People put in an osmotic pump and they see growth of neurites, which are small projections from neuronal bodies that connect to adjacent cells and develop into synapses,” said Ryan. “The problem with pumps is that they eventually run out of the trophic factor, and then the neurites die.”

“Getting genes into the ear is tricky,” continued Ryan. “Doing this in such a way as to avoid an immunological response, and delivering enough of the viral vector, is a challenge.”

Now, a team from **The University of New South Wales** led by professor of neurology and neuromuscular diseases Gary Housley has solved the problem of how to deliver trophic factors to the inner ear.

The team adapted electroporation—a well-known technique for introducing foreign material into cells using a brief burst of high-voltage electricity—to deliver a plasmid encoding *BDNF* into specific portions of the cochlea that are in contact with a cochlear implant.

“What we have done is targeted delivery adjacent to the neural interface,” said Housley. “This creates a gradient of BDNF that stimulates regeneration of the neural processes” that enable hearing.

Housley’s technique improves on previous trophic factor delivery strategies and provides a high degree of spatial control over where the transgene goes.

Genetic engin-ear-ing

Housley’s team began by modifying the electrical parameters of an off-the-shelf device from Cochlear to provide brief but powerful electrical pulses at specific spots along an eight-electrode array inserted into the cochlear spiral (see Figure 1, “Gene therapy by cochlear implant”).

Housley’s team inserted the modified implant into the ears of deaf guinea pigs and then bathed the cochlea with a solution containing a plasmid encoding human *BDNF* along with a GFP reporter.

Activation of individual electrodes along the implant led to electroporation of the plasmid into nearby mesenchymal tissue. After two weeks, nearby cells expressed both the *BDNF* and *GFP* transgenes.

The transgenic BDNF produced by transfected mesenchymal cells promoted the growth of neurites from nearby spiral ganglion neurons toward the electroporated cells.

BDNF transgene expression led to better implant performance than no transgene expression. In an electrophysiological assay of implant responsiveness, animals with implants that received the *BDNF* transgene

showed a lower threshold for activation—and thus greater sensitivity—than animals with conventional implants.

The improved implant performance “reflects a graded, progressive increase in the number of nerve fibers,” said Housley. “We’ve expanded the dynamic range of the nerve response.”

Results were reported in *Science Translational Medicine* and are covered by patents filed by **NewSouth Innovations Pty. Ltd.**, the technology transfer arm of the university.

Cochlear contributed materials and expertise to the academic team’s work through an **Australian Research Council**–sponsored Linkage Project, a translational R&D scheme that helps Australian companies and researchers collaborate on preclinical studies.

Hear today, gone tomorrow?

M. Charles Liberman, a professor of otology and laryngology at **Harvard Medical School**, said that the study is the first practical demonstration of localized gene therapy using electrical stimulation. “This is the first time that integration of electroporation into bionic interfaces—in this case the cochlear implant—has been demonstrated,” he said.

Liberman added that lowering the threshold of activation for cochlear implants could open paths to miniaturizing cochlear implants, which currently include bulky power supplies that sit behind the patients’ outer ears.

“They show that they can reduce the electrical threshold for excitation needed to stimulate fibers in the vicinity, leading to higher sensitivity,” he said. “Lower threshold reduces power consumption, which gets you closer to devices without external power supplies.”

Housley also suspects that electroporation of *BDNF* could improve the ability of patients to distinguish signals from each electrode, leading to better frequency resolution in existing devices. Alternatively, the technology could be used to increase the number of electrodes and thus the number of distinguishable frequencies in next-generation devices.

“As it is, today’s implants have up to 30 electrodes, but in effect you get only 6–8 channels,” said Ryan. This is because the relatively high electronic currents needed to activate each electrode tend to spread to adjacent regions of the cochlea and limit the resolution of sound frequencies.

The lower activation thresholds made possible by stronger local neuronal connections “mean there’s an opportunity to use much lower stimulus levels,” said Housley. “This also increases the number of electrodes we could use without current spread.”

Housley and Cochlear SVP and CSO Jim Patrick cautioned that the technology needs considerable preclinical work. One major question

is whether the effects of the *BDNF* transgene expression will be long lasting.

“This work is just starting,” said Patrick. “In their paper, Housley’s team showed good short-term improvement, but longer-term effects would be needed for this to be clinically useful.”

Along these lines, Ryan said that a next step would be constructing a more robust gene expression vector than the plasmid used by Housley’s team. He suggested repeating the experiment with a permanent gene-editing technique such as clustered, regularly interspaced short palindromic repeats (CRISPR).

Another question is whether *BDNF* is the best trophic factor for the job. Housley said that his team started with *BDNF* because it is a known entity. Liberman thinks a different growth factor—neurotrophin 3 (*NTF3*)—may have a more potent effect on neurite regeneration than *BDNF*.

“Our data show that in the cochlea, *NTF3* is really more relevant than *BDNF*,” said Liberman. “If you did this with *NTF3*, you would get more bang for the buck.”

Housley said that experiments with *NTF3* transgene electroporation are under way.

Liberman also wanted to know whether *BDNF* transgenes could improve hearing function throughout the entire cochlea and not just in the accessible portion studied by Housley.

Housley said that his team has yet to test hearing function of treated animals using behavioral assays, so it is unclear how the improved electrophysiological functioning his team observed affects perception of sound.

Patrick noted that the company is interested in adjunct therapies to enhance the performance of its products.

Osherovich, L. *SciBX* 7(18); doi:10.1038/scibx.2014.513
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Contact: Gary D. Housley, The University of New South Wales, Sydney, New South Wales, Australia
e-mail: g.housley@unsw.edu.au

COMPANIES AND INSTITUTIONS MENTIONED

Australian Research Council, Canberra, Australian Capital Territory, Australia

Cochlear Ltd., Sydney, New South Wales, Australia

Harvard Medical School, Boston, Mass.

NewSouth Innovations Pty. Ltd., Sydney, New South Wales, Australia

University of California, San Diego, La Jolla, Calif.

The University of New South Wales, Sydney, New South Wales, Australia

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
Autoimmune disease				
Autoimmune disease; multiple sclerosis (MS)	Chemokine CXC motif ligand 11 (CXCL11)	<p>Mouse studies suggest low doses of CXCL11 could be useful for treating autoimmune conditions such as MS. In a mouse model of experimental autoimmune encephalomyelitis (EAE), a Cxcl11-Ig fusion molecule induced remission and prevented relapse, whereas a Cxcl10 (Ip-10)-Ig fusion molecule, control IgG or saline did not. In an EAE mouse model with <i>Cxcl11</i> deficiency, treatment with low doses of Cxcl11 suppressed development of EAE, whereas saline treatment did not. Next steps could include evaluating CXCL11-based therapies in additional models of autoimmune disease.</p> <p>SciBX 7(18); doi:10.1038/scibx.2014.514 Published online May 8, 2014</p>	<p>Patented; available for licensing from Technion-Israel Institute of Technology Contact: Orit Shaked, Technion-Israel Institute of Technology, Haifa, Israel e-mail: oshaked@tx.technion.ac.il</p>	<p>Zohar, Y. <i>et al. J. Clin. Invest.</i>; published online April 8, 2014; doi:10.1172/JCI71951 Contact: Nathan Karim, Technion-Israel Institute of Technology, Haifa, Israel e-mail: nkarin10@gmail.com</p>
Inflammatory bowel disease (IBD)	CD1D; IL-10; signal transducer and activator of transcription 3 (STAT3)	<p>Mouse studies suggest epithelial CD1D could help protect against intestinal inflammation in IBD. In a mouse model of chemical-induced colitis, intestinal epithelial cell-specific knockout of <i>Cd1d</i> increased disease severity and mortality compared with no alteration. In the mice, intestinal epithelial <i>Cd1d</i> protected against intestinal inflammation through the activation of Stat3 and Stat3-dependent transcription of the anti-inflammatory cytokine Il-10 and also reinforced expression of <i>Cd1d</i> itself. Next steps could include developing a strategy to selectively upregulate intestinal epithelial CD1D signaling.</p> <p>SciBX 7(18); doi:10.1038/scibx.2014.515 Published online May 8, 2014</p>	<p>Patent and licensing status unavailable</p>	<p>Olszak, T. <i>et al. Nature</i>; published online April 6, 2014; doi:10.1038/nature13150 Contact: Richard S. Blumberg, Harvard Medical School, Boston, Mass. e-mail: rblumberg@partners.org Contact: Sebastian Zeissig, same affiliation as above e-mail: szeissig@1.med.uni-kiel.de</p>
Cancer				
Breast cancer	Eukaryotic translation initiation factor 2 α kinase 3 (EIF2AK3; PERK)	<p>Primary tumor, cell culture and mouse studies suggest PERK inhibitors could help treat breast cancer. In primary breast tumors and in human breast cancer cell lines, markers of epithelial-to-mesenchymal transition (EMT) were associated with upregulation of the PERK signaling pathway. In human breast cancer cell lines that underwent EMT, a research compound that inhibited PERK decreased cell growth and migration compared with vehicle. In mice injected with a metastatic mammary cancer cell line, pretreatment with the PERK inhibitor decreased tumor burden in the lungs compared with vehicle pretreatment. Next steps could include testing the PERK inhibitor in additional tumor types.</p> <p>SciBX 7(18); doi:10.1038/scibx.2014.516 Published online May 8, 2014</p>	<p>Patent and licensing status unavailable</p>	<p>Feng, Y. <i>et al. Cancer Discov.</i>; published online April 4, 2014; doi:10.1158/2159-8290.CD-13-0945 Contact: Piyush B. Gupta, Whitehead Institute for Biomedical Research, Cambridge, Mass. e-mail: pgupta@wi.mit.edu</p>

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cancer	BRAF; solute carrier family 31 copper transporters member 1 (SLC31A1; CTR1)	Cell culture and mouse studies suggest copper chelation could help treat cancers with oncogenic BRAF mutations. In mouse embryonic fibroblasts or melanoma cells expressing BRAF V600E, <i>Ctrl1</i> ^{-/-} cells had less growth than <i>Ctrl1</i> ^{+/+} cells. In mouse models of BRAF-mutant lung cancer, <i>Ctrl1</i> knockout or the copper chelator tetrathiomolybdate (TTM) decreased tumorigenesis and increased survival compared with no alteration or with vehicle. Ongoing studies include a Phase I clinical trial assessing the efficacy of the copper chelator trientine with the BRAF inhibitor vemurafenib. Roche, Daiichi Sankyo Co. Ltd. and Chugai Pharmaceutical Co. Ltd. market Zelboraf vemurafenib to treat melanoma. Valeant Pharmaceuticals International Inc. and Kadmon Corp. LLC market Syprine trientine hydrochloride to treat Wilson's disease. SciBX 7(18); doi:10.1038/scibx.2014.517 Published online May 8, 2014	Provisional patent application filed; unlicensed	Brady, D.C. <i>et al. Nature</i> ; published online April 9, 2014; doi:10.1038/nature13180 Contact: Chris M. Counter, Duke University School of Medicine, Durham, N.C. e-mail: chris.counter@duke.edu
Cancer	Cartilage matrix protein matrilin 1 (MATN-1; CMP)	<i>In vitro</i> , chick embryo and mouse studies suggest MATN-1 could help treat cancer by inhibiting angiogenesis. <i>In vitro</i> , recombinant human MATN-1 inhibited endothelial cell proliferation with an IC ₅₀ value of about 75 nM and inhibited endothelial cell migration with an IC ₅₀ value of about 10 nM. In a chick embryo-based model of angiogenesis, human MATN-1 decreased neovascularization compared with vehicle. In a mouse model of fracture healing, <i>Matn-1</i> knockout mice healed faster than wild-type mice. Next steps could include testing MATN-1 in mouse models of cancer. SciBX 7(18); doi:10.1038/scibx.2014.518 Published online May 8, 2014	Patent and licensing status undisclosed	Foradori, M.J. <i>et al. J. Biol. Chem.</i> ; published online April 1, 2014; doi:10.1074/jbc.M113.529982 Contact: Marsha A. Moses, Boston Children's Hospital, Boston, Mass. e-mail: marsha.moses@childrens.harvard.edu
Cancer	Histone deacetylase 1 (HDAC1); HDAC3	<i>In vitro</i> and mouse studies have identified inhibitors selective for HDAC1 and HDAC3 that could help treat cancer. <i>In vitro</i> , the most potent <i>N</i> -hydroxycinnamamide-based derivatives had low nanomolar potency against HDAC1 and HDAC3 and low micromolar potency against other HDACs. In a panel of solid and hematological tumor cells, the most potent and selective dual inhibitor blocked proliferation better than a nonselective HDAC inhibitor. In mice with subcutaneous lymphoma xenografts, the most potent dual inhibitor decreased tumor growth more than a nonselective inhibitor. Next steps include additional structural optimization of the compounds. SciBX 7(18); doi:10.1038/scibx.2014.519 Published online May 8, 2014	Patent application filed; available for licensing	Li, X. <i>et al. J. Med. Chem.</i> ; published online April 2, 2014; doi:10.1021/jm401877m Contact: Wenfang Xu, Shandong University, Shandong, China e-mail: xuwenf@gmail.com Contact: Yingjie Zhang, same affiliation as above e-mail: zhangyingjie@sdu.edu.cn

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cancer	Ring finger protein 31 (RNF31; HOIP)	Cell culture studies suggest inhibiting the E3 ubiquitin ligase HOIP could increase cancer sensitivity to platinum-based chemotherapeutics such as cisplatin. In an siRNA screen using a human osteosarcoma cell line, HOIP was identified as a suppressor of cisplatin-induced cytotoxicity. In a panel of human cancer cell lines including those known to be cisplatin resistant, siRNA against HOIP increased sensitivity to cisplatin compared with control siRNA. Next steps include determining whether HOIP abundance or activity directly correlates with resistance to platinum-based therapy. SciBX 7(18); doi:10.1038/scibx.2014.520 Published online May 8, 2014	Unpatented; licensing status undisclosed	MacKay, C. <i>et al. Cancer Res.</i> ; published online March 31, 2014; doi:10.1158/0008-5472.CAN-13-2131 Contact: Arno F. Alpi, University of Dundee, Dundee, U.K. e-mail: a.f.alpi@dundee.ac.uk
Cancer	V-region immunoglobulin-containing suppressor of T cell activation (VISTA)	Cell culture and mouse studies suggest inhibiting VISTA could help treat cancer. In cultured human CD4 ⁺ and CD8 ⁺ T cells, a VISTA-Ig fusion protein decreased anti-CD3 mAb-induced T cell proliferation compared with control Ig. In multiple mouse xenograft tumor models, a VISTA mAb decreased tumor growth and increased the number of effector T cells in the tumor compared with control antibody. In a mouse model of melanoma, the VISTA mAb increased T cell tumor infiltration compared with control antibody and delayed tumor progression. Next steps include testing anti-VISTA mAbs alone or in combination with other therapeutics in additional tumor models. SciBX 7(18); doi:10.1038/scibx.2014.521 Published online May 8, 2014	Findings from both studies patented; licensed to ImmuneNext Inc. and Johnson & Johnson	Lines, J.L. <i>et al. Cancer Res.</i> ; published online April 1, 2014; doi:10.1158/0008-5472.CAN-13-1504 Contact: J. Louise Lines, King's College London, London, U.K. e-mail: janet.lines@kcl.ac.uk Le Mercier, I. <i>et al. Cancer Res.</i> ; published online April 1, 2014; doi:10.1158/0008-5472.CAN-13-1506 Contact: Li Wang, Geisel School of Medicine at Dartmouth, Lebanon, N.H. e-mail: li.wang@dartmouth.edu
Liver cancer	VEGF-A	<i>In vitro</i> and mouse studies suggest hepatocellular carcinoma (HCC) with amplifications in VEGF-A may be particularly susceptible to Nexavar sorafenib. In mice with HCC and in human tumor samples, VEGF-A was amplified in a subset of tumors. In a mouse model of HCC, Nexavar induced an antitumor response specifically in the Vegf-a-amplified tumor subset. In a retrospective analysis of patients with HCC treated with Nexavar, survival was improved in those with VEGF-A amplifications. Next steps include validation in an additional cohort. Nexavar sorafenib, which targets VEGF receptor (VEGFR) and other kinases, is marketed by Amgen Inc. and Bayer AG to treat various cancers. SciBX 7(18); doi:10.1038/scibx.2014.522 Published online May 8, 2014	Patent application filed; licensing negotiations under way with an undisclosed biotech in Israel	Horwitz, E. <i>et al. Cancer Discov.</i> ; published online March 31, 2014; doi:10.1158/2159-8290.CD-13-0782 Contact: Eli Pikarsky, The Hebrew University Hadassah Medical School, Jerusalem, Israel e-mail: peleli@hadassah.org.il

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Pancreatic cancer	Nuclear factor of activated T cells cytoplasmic calcineurin-dependent 1 (NFATc1)	<i>In vitro</i> and mouse studies suggest inhibiting NFATc1 could help treat pancreatic cancers. In transgenic mice expressing proinflammatory, mutant <i>NFATc1</i> and oncogenic, mutant <i>K-Ras</i> (<i>KRAS</i>), pancreatic tumors developed and survival was decreased compared with that in mice expressing only one of the two mutant genes. In <i>Kras</i> -mutant mice, inhibition of NFATc1 decreased pancreatic epithelial cell proliferation compared with no inhibition and prevented a marker of neoplastic transformation called acinar-to-ductal metaplasia. Next steps include identifying a strategy to specifically inhibit NFATc1 in cancer cells. SciBX 7(18); doi:10.1038/scibx.2014.523 Published online May 8, 2014	Findings unpatented; licensing status not applicable	Baumgart, S. <i>et al. Cancer Discov.</i> ; published online April 2, 2014; doi:10.1158/2159-8290.CD-13-0593 Contact: Volker Ellenrieder, University Medical Center Goettingen, Goettingen, Germany e-mail: ellenrie@med.uni-marburg.de
Pancreatic cancer	Platelet derived growth factor receptor B (PDGFRB; PDGFR1; CD140B)	Studies in mice and human samples suggest inhibiting PDGFRB could help prevent pancreatic cancer metastasis. In mice injected with metastasis-prone pancreatic cancer cells, shRNA knockdown or pharmacological inhibition of Pdgfrb with crenolanib or Gleevec imatinib decreased metastatic spread compared with no alteration or inhibition. In human pancreatic ductal adenocarcinoma samples, elevated levels PDGFRB correlated with poor disease-free survival and decreased time to relapse. Next steps could include evaluating pharmacological PDGFRB inhibitors in additional pancreatic cancer models. Novartis AG markets Gleevec, a BCR-ABL tyrosine kinase inhibitor, to treat chronic myelogenous leukemia (CML), acute lymphoblastic leukemia (ALL) and gastrointestinal stromal tumors (GISTs). Arog Pharmaceuticals LLC's crenolanib is in Phase II testing to treat acute myelogenous leukemia (AML) and Phase I to treat brain cancer. SciBX 7(18); doi:10.1038/scibx.2014.524 Published online May 8, 2014	Patent and licensing status unavailable	Weissmueller, S. <i>et al. Cell</i> ; published online April 10, 2014; doi:10.1016/j.cell.2014.01.066 Contact: Scott W. Lowe, Memorial Sloan-Kettering Cancer Center, New York, N.Y. e-mail: lowes@mskcc.org

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This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Prostate cancer	Androgen receptor; bromodomain containing 4 (BRD4)	<p>Mouse and cell culture studies suggest BRD4 inhibitors could be more effective than androgen receptor antagonists at treating castration-resistant prostate cancer (CRPC). In a human CRPC cell line, the BRD4 inhibitor JQ1 caused more potent suppression of androgen receptor-mediated gene transcription than the androgen receptor antagonist Xtandi enzalutamide. In a mouse xenograft model of human CRPC, JQ1 caused more potent tumor growth inhibition than Xtandi or vehicle. Next steps include developing a strategy to identify patients that would respond to BET bromodomain inhibitors in prostate and other cancers.</p> <p>Medivation Inc. and Astellas Pharma Inc. market Xtandi to treat prostate cancer.</p> <p>The corresponding author is a cofounder of OncoFusion Therapeutics Inc., which is collaborating with Medivation to evaluate OncoFusion's preclinical BET bromodomain inhibitors in undisclosed cancers and other indications.</p> <p>At least four other companies have BET bromodomain inhibitors in Phase I testing to treat various cancers.</p> <p>JQ1 is a research reagent (<i>see BETting on OncoFusion, page 1</i>).</p> <p>SciBX 7(18); doi:10.1038/scibx.2014.525 Published online May 8, 2014</p>	Composition-of-matter patents filed; licensed to Medivation	<p>Asangani, I.A. <i>et al. Nature</i>; published online April 23, 2014; doi:10.1038/nature13229</p> <p>Contact: Arul M. Chinnaiyan, University of Michigan Medical School, Ann Arbor, Mich. e-mail: arul@umich.edu</p>
Sarcoma	EPH receptor B4 (EPHB4); platelet derived growth factor receptor B (PDGFRB; PDGFR1; CD140B)	<p>Patient sample and mouse studies suggest inhibiting PDGFRB cross talk with EPHB4 could help treat alveolar rhabdomyosarcoma (aRMS). In aRMS cells from human patients and mouse models, EPHB4 and PDGFRB were upregulated. In human and mouse aRMS cells, <i>EPHB4</i>- and <i>PDGFRB</i>-targeting siRNA or the dual inhibitor Sprycel dasatinib decreased viability compared with nonspecific siRNA or the PDGFRB inhibitor Gleevec imatinib. In a mouse orthotopic model of aRMS, dasatinib increased survival compared with imatinib or vehicle. Next steps include working with partner VasGene Therapeutics Inc. to validate the findings in mice with human tumor xenografts.</p> <p>Bristol-Myers Squibb Co. and Otsuka Pharmaceutical Co. Ltd. market Sprycel, a small molecule inhibitor of BCR-ABL tyrosine kinase and Src kinase, to treat acute lymphoblastic leukemia (ALL) and chronic myelogenous leukemia (CML).</p> <p>Novartis AG markets Gleevec, a BCR-ABL tyrosine kinase inhibitor, to treat CML, ALL and gastrointestinal stromal tumors (GISTs).</p> <p>SciBX 7(18); doi:10.1038/scibx.2014.526 Published online May 8, 2014</p>	Findings unpatented; licensing status not applicable	<p>Aslam, M.I. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online April 14, 2014; doi:10.1073/pnas.1403608111</p> <p>Contact: Charles Keller, Oregon Health & Science University, Portland, Ore. e-mail: keller@ohsu.edu</p> <p>Contact: Jeffrey W. Tyner, same affiliation as above e-mail: tynerj@ohsu.edu</p> <p>Contact: Brian J. Druker, same affiliation as above e-mail: drukerb@ohsu.edu</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Endocrine/metabolic disease				
Diabetes; obesity	Nicotinamide <i>N</i> -methyltransferase (NNMT)	Mouse studies suggest inhibiting NNMT activity in adipose tissue could help treat obesity and type 2 diabetes. Mice with insulin resistance had higher levels of <i>Nnmt</i> mRNA in adipose tissue than mice lacking insulin resistance. In mice, <i>Nnmt</i> -targeting antisense oligonucleotides protected against high-fat diet-induced diabetes by increasing energy expenditure compared with a nontargeting antisense oligonucleotide. Next steps could include testing NNMT inhibition in additional models of metabolic diseases. SciBX 7(18); doi:10.1038/scibx.2014.527 Published online May 8, 2014	Patent and licensing status unavailable	Kraus, D. <i>et al. Nature</i> ; published online April 9, 2014; doi:10.1038/nature13198 Contact: Barbara B. Kahn, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Mass. e-mail: bkahn@bidmc.harvard.edu
Glycosphingolipid storage disorders	Galactosidase β 1 (GLB1); ganglioside GM1 (GM1)	Feline studies suggest intracranial delivery of adeno-associated viral (AAV) vectors encoding GLB1 could help treat GM1 gangliosidosis. GM1 gangliosidosis is an autosomal recessive lysosomal storage disorder caused by a GLB1 deficiency that results in accumulation of GM1 in neuronal tissues and leads to progressive neurodegeneration and death. In a feline model of GM1 gangliosidosis, bilateral intracranial injection of AAV1 or AAVrh8 vectors encoding feline GLB1 into the thalamus and deep cerebellar nuclei resulted in near-normal GLB1 activity in the CNS and decreased both GM1 levels in CNS tissues and neuromuscular impairments compared with no treatment. In the treated felines, mean survival was over 38 months versus 5 months for untreated controls. Next steps include running safety studies in mice and nonhuman primates and preparing an IND submission to the FDA. SciBX 7(18); doi:10.1038/scibx.2014.528 Published online May 8, 2014	Patent application filed; licensing status unavailable	McCurdy, V.J. <i>et al. Sci. Transl. Med.</i> ; published online April 9, 2014; doi:10.1126/scitranslmed.3007733 Contact: Douglas R. Martin, Auburn University, Auburn, Ala. e-mail: martidr@auburn.edu
Infectious disease				
Influenza virus	Microsomal prostaglandin E synthase-1 (PTGES; mPTGES-1)	Mouse studies suggest inhibiting PTGES could help treat influenza A virus infection. In mice infected with influenza A, <i>Ptges</i> knockout increased macrophage, monocyte and dendritic cell numbers in the lungs and increased T cell numbers in lungs and lymph nodes compared with no alteration. In mice lacking T and B cells, adoptive transfer of <i>Ptges</i> -deficient, influenza-infected macrophages led to a lower viral load and a stronger antiviral interferon response than adoptive transfer of infected wild-type macrophages. In wild-type mice, an inhibitor of PTGES decreased viral load and increased survival compared with saline. Next steps include testing a selective PTGES inhibitor in humans. SciBX 7(18); doi:10.1038/scibx.2014.529 Published online May 8, 2014	Findings unpatented; licensing status not applicable	Coulombe, F. <i>et al. Immunity</i> ; published online April 10, 2014; doi:10.1016/j.immuni.2014.02.013 Contact: Maziar Divangahi, McGill University, Montreal, Quebec, Canada e-mail: maziar.divangahi@mcgill.ca

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Influenza virus	Sialic acid	<p>Mouse studies suggest multivalent peptides made up of carbohydrate-binding modules could be used to prevent influenza virus infection. Sialic acid-interacting peptides were generated from carbohydrate-binding modules from <i>Streptococcus pneumoniae</i> and <i>Vibrio cholerae</i> sialidase, with or without an oligomerization domain from <i>Pseudomonas aeruginosa</i>. In a mouse model of influenza virus challenge, prophylactic intranasal delivery of a peptide seven days before challenge led to pulmonary expression of IL-1β, interferon-γ (Ifng; Ifnγ) and tumor necrosis factor-α (Tnf-α) and enabled survival of all mice. Next steps include testing the peptides in ferret models of influenza infection and conducting toxicology studies.</p> <p>SciBX 7(18); doi:10.1038/scibx.2014.530 Published online May 8, 2014</p>	<p>Patent application filed; available for licensing or partnering from The University of St. Andrews Contact: Ewan Chirnside, University of St. Andrews, Fife, U.K. phone: +44 (0)1334 467223 e-mail: ec36@st-andrews.ac.uk</p>	<p>Connaris, H. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online April 14, 2014; doi:10.1073/pnas.1404205111 Contact: Robert G. Webster, St. Jude Children's Research Hospital, Memphis, Tenn. e-mail: robert.webster@stjude.org</p>
Musculoskeletal disease				
Muscular atrophy	Mammalian target of rapamycin complex 1 (mTORC1)	<p>Cell culture and mouse studies suggest the tomato-derived natural product tomatidine could help treat muscular atrophy by increasing mTORC1 signaling. In cultured human cancer cells, tomatidine produced an mRNA signature that negatively correlated with that of muscular atrophy. In mice, tomatidine increased mTorC1 signaling, skeletal muscle fiber size and grip strength compared with no treatment. Next steps include developing tomatidine derivatives to treat age-related muscular atrophy.</p> <p>SciBX 7(18); doi:10.1038/scibx.2014.531 Published online May 8, 2014</p>	<p>Patent application filed; licensed to Emmyon Inc.; available for partnering</p>	<p>Dyle, M.C. <i>et al. J. Biol. Chem.</i>; published online April 9, 2014; doi:10.1074/jbc.M114.556241 Contact: Christopher M. Adams, The University of Iowa, Iowa City, Iowa e-mail: christopher-adams@uiowa.edu</p>
Ophthalmic disease				
Age-related macular degeneration (AMD)	IL-18	<p>Mouse studies suggest recombinant IL-18 could help treat AMD. Knockout of IL-18 in mice results in AMD-like pathological neovascularization in the eye. In a mouse model of laser-induced choroidal neovascularization (CNV), intravitreal injection or systemic treatment with recombinant human IL-18 attenuated CNV neovascularization without affecting retinal pigment epithelial cell integrity. In the same mouse model, intravitreal injection of an anti-VEGF antibody plus subcutaneous injection of IL-18 increased CNV suppression compared with injection of the anti-VEGF antibody alone. Next steps include conducting further safety studies before designing a clinical study to treat AMD.</p> <p>SciBX 7(18); doi:10.1038/scibx.2014.532 Published online May 8, 2014</p>	<p>Patent application filed covering use of IL-18 for CNV secondary to AMD; IP covered under an option agreement with GlaxoSmithKline plc</p>	<p>Doyle, S.L. <i>et al. Sci. Trans. Med.</i>; published online April 2, 2014; doi:10.1126/scitranslmed.3007616 Contact: Matthew Campbell, Smurfit Institute of Genetics at Trinity College Dublin, Dublin, Ireland e-mail: matthew.campbell@tcd.ie Contact: Sarah L. Doyle, Trinity College Dublin, Dublin, Ireland e-mail: sarah.doyle@tcd.ie</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Pulmonary disease				
Pulmonary fibrosis	NADPH oxidase 4 (NOX4)	<p>Mouse studies suggest inhibiting NOX4 could help treat age-related lung fibrosis. In aged mice with chemically induced pulmonary fibrosis, siRNA against <i>Nox4</i> or pharmacological inhibition with the small molecule GKT137831 increased fibrosis resolution and the recovery of body weight compared with control siRNA or no inhibition. Next steps include conducting further studies of GKT137831 and identifying additional NOX4 inhibitors to treat fibrosis.</p> <p>Genkyotex S.A.'s dual NOX1 and NOX4 inhibitor, GKT137831, is in Phase II testing to treat diabetic nephropathy and preclinical development for liver and pulmonary fibrosis.</p> <p>SciBX 7(18); doi:10.1038/scibx.2014.533 Published online May 8, 2014</p>	Unpatented; licensing status not applicable	<p>Hecker, L. <i>et al. Sci. Transl. Med.</i>; published online April 9, 2014; doi:10.1126/scitranslmed.3008182</p> <p>Contact: Victor J. Thannickal, The University of Alabama at Birmingham, Birmingham, Ala. e-mail: vjthan@uab.edu</p> <p>Contact: Louise Hecker, same affiliation as above e-mail: lhecker@uab.edu</p>
Transplantation				
Graft rejection	IL-7; IL-7 receptor (CD127)	<p>Mouse studies suggest inhibiting IL-7 signaling could help prevent graft rejection. In a mouse model of diabetes, injection of an IL-7 receptor–blocking antibody starting 3 weeks before transplantation of pancreatic islets and continuing for 90 days post-transplantation increased graft survival and decreased formation and activation of donor-specific memory T cells compared with no treatment or with injection of the antibody at the time of transplantation. In a skin transplantation mouse model, IL-7 receptor blockade following T cell depletion prolonged graft survival to 58 days from 30 days. Next steps include testing safety and immunological features of an anti–human IL-7 receptor mAb in nonhuman primates.</p> <p>SciBX 7(18); doi:10.1038/scibx.2014.534 Published online May 8, 2014</p>	Patent application filed covering anti–IL-7 receptor mAbs; licensing status undisclosed	<p>Mai, H.-L. <i>et al. J. Clin. Invest.</i>; published online April 1, 2014; doi:10.1172/JCI66287</p> <p>Contact: Jean-Paul Soullillou, Institut National de la Santé et de la Recherche Médicale (INSERM) UMR 1064, Nantes, France e-mail: soullillou@yahoo.fr</p>
Various				
Autoimmune disease; infectious disease	Negative regulator of reactive oxygen species (NRROS)	<p><i>In vitro</i> and mouse studies suggest inhibiting NRROS could help treat infectious diseases and suggest enhancing its expression could help treat autoimmune diseases. In mice challenged with <i>Listeria monocytogenes</i>, <i>Nrros</i> knockout increased survival and decreased levels of bacteria in liver and spleen compared with no alteration. In a mouse model of autoimmune encephalomyelitis (EAE), bone marrow–specific <i>Nrros</i> deficiency resulted in increased disease severity and mortality compared with what was seen in nondeficient controls. Next steps include additional studies to elucidate the NRROS signaling pathway.</p> <p>SciBX 7(18); doi:10.1038/scibx.2014.535 Published online May 8, 2014</p>	Patent and licensing status unavailable	<p>Noubade, R. <i>et al. Nature</i>; published online April 13, 2014; doi:10.1038/nature13152</p> <p>Contact: Wenjun Ouyang, Genentech Inc., South San Francisco, Calif. e-mail: ouyang.wenjun@gene.com</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
Assays & screens			
Identification of small molecule protein inhibitors with laser-assisted detection of specific binding	A laser-based system could help identify new small molecule inhibitors of various proteins. The system directs a laser at adjacent wells in a 384-well plate, with one well containing a small molecule and immobilized target protein and the other well containing only the small molecule. Specific small molecule-protein binding resulted in a detectable difference between the wavelengths of light reflected back to the system by photonic sensors in the two adjacent wells. Using carbonic anhydrase II (CAII) as the target protein, the system correctly distinguished the nanomolar CAII inhibitor dorzolamide from 47 other compounds that do not specifically bind CAII. Ongoing work has increased the sensitivity of the system for small molecule-protein binding and will be reported in a forthcoming publication. SciBX 7(18); doi:10.1038/scibx.2014.536 Published online May 8, 2014	Patented; available for licensing	Zhang, M. <i>et al. J. Am. Chem. Soc.</i> ; published online April 10, 2014; doi:10.1021/ja500636p Contact: Brian T. Cunningham, University of Illinois at Urbana-Champaign, Urbana, Ill. e-mail: bcunning@illinois.edu Contact: Paul J. Hergenrother, same affiliation as above e-mail: hergenro@illinois.edu
Chemistry			
Native chemical ligation for generating reversible covalent peptide bonds	A new approach for generating reversible covalent peptide bonds could be useful for synthesizing pharmacological agents, such as therapeutic peptides. The approach uses chemoselective, native chemical ligation at the non-natural amino acid <i>N</i> -(methyl)-cysteine. The approach was used to form reversible peptide bonds between amino acids without the use of enzyme catalysis. Next steps include using the method to synthesize pharmacological agents. SciBX 7(18); doi:10.1038/scibx.2014.537 Published online May 8, 2014	Patent application filed; available for licensing	Ruff, Y. <i>et al. J. Am. Chem. Soc.</i> ; published online April 18, 2014; doi:10.1021/ja4129845 Contact: Nicolas Giuseppone, University of Strasbourg, Charles Sadron Institute, Centre National de la Recherche Scientifique (CNRS), Strasbourg, France e-mail: giuseppone@unistra.fr
Disease models			
Mouse model of acute thrombotic thrombocytopenic purpura (TTP)	A mouse model of acute TTP could be useful for studying disease pathophysiology and evaluating candidate therapies. von Willebrand factor (Vwf)-deficient mice were injected with a vector encoding a mutant Vwf that is resistant to proteolytic cleavage, and the mice rapidly developed multiple markers of acute TTP including thrombocytopenia, renal dysfunction and schistocytes in blood samples. Next steps could include using the mice to evaluate acute TTP therapeutics. SciBX 7(18); doi:10.1038/scibx.2014.538 Published online May 8, 2014	Patent and licensing status unavailable	Morioka, Y. <i>et al. Blood</i> ; published online April 8, 2014; doi:10.1182/blood-2013-10-531392 Contact: Nicolas Prévost, Kyoto University, Kyoto, Japan e-mail: nprevost@cp.kyoto-u.ac.jp
Mouse model of early T cell precursor acute lymphoblastic leukemia (ETP-ALL) with IL-7 receptor (CD127) mutation	A mouse model of ETP-ALL could help identify new therapeutics for the disease. In immature thymocytes, expression of a mutant form of CD127 found in pediatric cases of ETP-ALL blocked differentiation of thymocytes early in development. In irradiated mice, transplantation of thymocytes expressing mutant Cd127, but not wild-type Cd127, caused lethal leukemia with similar gene expression patterns as the human pediatric cancers. In the ETP-ALL mouse model, the Janus kinase-1 (JAK-1) and JAK-2 inhibitor Jakafi ruxolitinib increased survival compared with vehicle. Next steps could include using the model to identify other therapeutics for ETP-ALL. Incyte Corp. and Novartis AG market Jakafi to treat myeloproliferative disorder. SciBX 7(18); doi:10.1038/scibx.2014.539 Published online May 8, 2014	Patent and licensing status unavailable	Treanor, L.M. <i>et al. J. Exp. Med.</i> ; published online March 31, 2014; doi:10.1084/jem.20122727 Contact: Brian P. Sorrentino, St. Jude Children's Research Hospital, Memphis, Tenn. e-mail: brian.sorrentino@stjude.org

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Single amyloid precursor protein (APP) knock-in mouse models of Alzheimer's disease (AD)	Mice that express humanized <i>APP</i> with various knock-in mutations could be useful as models for studying AD pathophysiology and evaluating therapies. The mice were engineered to express humanized <i>APP</i> with knock-in mutations called Swedish, Beyreuther/Iberian or Arctic. Mice with Swedish and Beyreuther mutations showed high levels of β -amyloid 42 ($A\beta_{42}$) compared with mice that had Swedish mutations alone or no mutation and showed $A\beta$ deposits at 6 months and memory impairments at 18 months. Mice with all three knock-in mutations had levels of $A\beta_{42}$ and $A\beta$ deposits similar to those in mice with Swedish and Beyreuther mutations alone but also showed subcortical amyloidosis, higher levels of microgliosis and astrogliosis and more rapid onset of memory impairments, which parallels disease pathophysiology seen in patients carrying the Arctic mutation. Next steps include using the mice to identify molecular targets to stop or decelerate $A\beta$ deposition in the brain for early prevention of AD and creating similar nonhuman primate AD models. SciBX 7(18); doi:10.1038/scibx.2014.540 Published online May 8, 2014	The APP knock-in mouse model containing the Beyreuther/Iberian mutation is patented; available for nonexclusive licensing from the RIKEN Technology Transfer Office Contact: Ryosuke Furubayashi, RIKEN Brain Science Institute, Saitama, Japan e-mail: ryosuke.furubayashi@riken.jp	Saito, T. <i>et al. Nat. Neurosci.</i> ; published online April 13, 2014; doi:10.1038/nn.3697 Contact: Takaomi C. Saito, RIKEN Brain Science Institute, Saitama, Japan e-mail: saito@brain.riken.jp
Drug delivery			
Brain-derived neurotrophic factor (BDNF) gene therapy delivered to the inner ear using cochlear implants	A study in guinea pigs suggests delivering gene therapy to the inner ear using cochlear implants could improve the ability of the implants to aid hearing. In a guinea pig model of deafness, an electronic cochlear implant that delivered plasmid cDNA encoding human BDNF by electroporation increased neurite outgrowth, neuron density and hearing compared with implants that delivered a plasmid cDNA control. Next steps include optimizing the duration of gene therapy delivery and testing other neurotrophic factors delivered by this method (<i>see Zapping hearing loss, page 8</i>). SciBX 7(18); doi:10.1038/scibx.2014.541 Published online May 8, 2014	Patent pending; available for licensing	Pinyon, J.L. <i>et al. Sci. Transl. Med.</i> ; published online April 23, 2014; doi:10.1126/scitranslmed.3008177 Contact: Gary D. Housley, The University of New South Wales, Sydney, New South Wales, Australia e-mail: g.housley@unsw.edu.au
Drug platforms			
Crystal structure of exonuclease-resistant flavivirus RNA	The crystal structure of an exonuclease-resistant flavivirus RNA could help guide the design of new therapies to treat flaviviral infections. <i>In vitro</i> , an X-ray crystal structure of an exonuclease-resistant Murray Valley encephalitis (MVE) virus RNA revealed a ring-like conformation on one of its sides formed by nucleotides 33–49. In a human cell line, infection with MVE viral strains with point mutations that disrupt the viral RNA ring structure eliminated or decreased the formation of subgenomic flavivirus RNA—a marker of pathogenicity—compared with infection with the wild-type virus. Next steps include screening for small molecules that disrupt the activity of flavivirus RNA. SciBX 7(18); doi:10.1038/scibx.2014.542 Published online May 8, 2014	Invention disclosure filed; available for licensing from the University of Colorado Denver Contact: David Poticha, University of Colorado Denver, Aurora, Colo. e-mail: david.poticha@cu.edu	Chapman, E.G. <i>et al. Science</i> ; published online April 18, 2014; doi:10.1126/science.1250897 Contact: Jeffrey S. Kieft, University of Colorado Denver, Aurora, Colo. e-mail: jeffrey.kieft@ucdenver.edu

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Markers			
Transient receptor potential cation channel subfamily C member 5 (TRPC5)-containing extracellular vesicles as a marker of chemotherapy resistance in breast cancer	<p>Studies in patient samples, mice and cell culture suggest TRPC5-containing extracellular vesicles could help predict chemotherapy resistance in breast cancer. In coculture of chemoresistant and chemosensitive human breast cancer cell lines, TRPC5-containing extracellular vesicles were shown to enter chemosensitive cells and increase their resistance to chemotherapy. In cell culture and a mouse xenograft model of chemoresistant human breast cancer, siRNA against <i>TRPC5</i> decreased the release of TRPC5-containing extracellular vesicles compared with scrambled siRNA. In samples from 26 patients with breast cancer who received anthracycline- and taxane-based chemotherapy, samples from patients with a complete or partial response had lower TRPC5 expression than those from patients with progressive or stable disease. Next steps include validating TRPC5-containing vesicles as a biomarker of chemotherapy response and developing a quantitative assay for TRPC5-containing vesicles in peripheral blood.</p> <p><i>SciBX</i> 7(18); doi:10.1038/scibx.2014.543 Published online May 8, 2014</p>	<p>Patented; available for licensing from Jiangnan University Contact: Zheng Jing, Jiangnan University, Wuxi, China e-mail: jingzheng@jiangnan.edu.cn</p>	<p>Ma, X. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online April 14, 2014; doi:10.1073/pnas.1400272111 Contact: Jian Jin, Jiangnan University, Wuxi, China e-mail: jinjian31@126.com Contact: Xin Ma, same affiliation as above e-mail: maxin@jiangnan.edu.cn</p>

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Company and institution index

A		R					
Amgen Inc.	12	RIKEN	19	Cartilage matrix protein		Jakafi	18
Arog Pharmaceuticals LLC	13	Roche	11	matrilin 1	11	Janus kinase-1	18
Astellas Pharma Inc.	3,14			CD127	17,18	JQ1	1,14
Australian Research Council	9	S		CD140B	13,14		
		Scleroderma Research		CD1D	10	K	
B		Foundation	6	CD3	12	<i>K-Ras</i>	13
Bayer AG	12	Shifa Biomedical Corp.	5	CD4	12	<i>KRAS</i>	13
BioLineRx Ltd.	6			CD8	12	M	
Bristol-Myers Squibb Co.	14	T		Chemokine CXC motif		Mammalian target of	
		Technion-Israel Institute of		ligand 11	10	rapamycin complex 1	16
C		Technology	10	Cisplatin	12	MATN-1	11
Chugai Pharmaceutical		Temple University School of		CMP	11	Microsomal prostaglandin E	
Co. Ltd.	11	Pharmacy	5	CPI-0610	1	synthase-1	15
Cochlear Ltd.	8	Tesaro Inc.	5	Crenolanib	13	mPGES-1	15
Constellation Pharmaceuticals				CTR1	11	mTORC1	16
Inc.	1	U		Cxcl10	10	<i>MYC</i>	1
Cortendo AB	5	University of California,		CXCL11	10		
		San Diego	8	CYP17	3	N	
D		University of Colorado		Cytochrome P450 17		NADPH oxidase 4	17
Daiichi Sankyo Co. Ltd.	11	Denver	19	α -hydroxylase/C17, 20 lyase	3	Negative regulator of reactive	
		University of Colorado	6			oxygen species	17
E		University of Colorado at		D		Neurotrophin 3	9
Emmyon Inc.	16	Boulder	6	Dasatinib	14	Nexavar	12
		University of Michigan		Dorzolamide	18	NFATc1	13
G		Medical School	1			Nicotinamide <i>N</i> -	
Genkyotex S.A.	17	University of Michigan	4,6	E		methlyltransferase	15
GlaxoSmithKline plc	2,16	University of Nebraska		E3 ubiquitin ligase	12	NNMT	15
		Medical Center	5	EIF2AK3	10	NOX1	17
H		University of New South Wales	8	Enzalutamide	1,14	NOX4	17
Harvard Medical School	9	University of Rochester		EPH receptor B4	14	NRROS	17
Howard Hughes Medical		Medical Center	5	EPHB4	14	NTF3	9
Institute	1	University of St. Andrews	16	<i>ERG</i>	1	Nuclear factor of activated T	
				Eukaryotic translation		cells cytoplasmic calcineurin-	
I		V		initiation factor 2 α kinase 3	10	dependent 1	13
ImmuNext Inc.	12	Valeant Pharmaceuticals				P	
Incyte Corp.	18	International Inc.	11	F		PCSK9	5
		VasGene Therapeutics Inc.	14	Fibronectin extra domain A	6	PDGFR1	13,14
J				FnEDA	6	PDGFRB	13,14
Jiangnan University	20	W				PERK	10
Johns Hopkins University		Wistar Institute	5	G		Platelet derived growth	
School of Medicine	5		Galactosidase β 1	15	factor receptor B	13,14
Johnson & Johnson	3,12	Target and compound index		Ganglioside GM1	15	Proprotein convertase	
		A		GKT137831	17	subtilisin/kexin type 9	5
K		AAV1	15	GLB1	15	PTGES	15
Kadmon Corp. LLC	11	AAVrh8	15	Gleevec	13,14		
		Abiraterone acetate	3	GM1	15	R	
M		Amyloid precursor protein	19	GSK525762	1	Ring finger protein 31	12
Medivation Inc.	1,14	Androgen	3			RNF31	12
Memorial Sloan-Kettering		Androgen receptor	1,14	H		Ruxolitinib	18
Cancer Center	4	APP	19	HDAC	11		
Merck & Co. Inc.	5	AR	1	HDAC1	11	S	
MorphoSys AG	5	ARN-509	3	HDAC3	11	Sialic acid	16
Moulder Center for Drug				Histone deacetylase 1	11	Signal transducer and	
Discovery Research at		B		HOIP	12	activator of transcription 3	10
Temple University	5	β -Amyloid 42	19	HuCAL	5	SLC31A1	11
MPM Capital	6	BCR-ABL tyrosine kinase	13,14			Solute carrier family 31 copper	
		BDNF	8,19	I		transporters member 1	11
N		BET bromodomain	1	I-BET762	1	Sorafenib	12
NewSouth Innovations		BRAF	11	Ifn γ	16	Sprycel	14
Pty. Ltd.	9	Brain-derived neurotrophic		Ifng	16	Src	14
Northwestern University	7	factor	8,19	IL-10	10	STAT3	10
Northwestern University		BRD2	3	IL-18	16	Syprine	11
Feinberg School of		BRD3	3	IL-1 β	16		
Medicine	6	BRD4	2,14	IL-7	17	T	
Novartis AG	13,14,18	Bromodomain containing 4	2,14	IL-7 receptor	17,18	T5342126	6
				Imatinib	13,14	Tetrathiomolybdate	11
O		C		Interferon- γ	16	TGF β	6
OncoFusion Therapeutics		<i>c-Myc</i>	1	Ip-10	10	TGFB	6
Inc.	1,14	CAII	18			TLR4	6
Otsuka Pharmaceutical		Carbonic anhydrase II	18	J		Tnf- α	16
Co. Ltd.	14			JAK-1	18		
				JAK-2	18		

Toll-like receptor 4	6	TTM	11	VEGF	16	X	
Tomatidine	16	Tumor necrosis factor- α	16	VEGF receptor	12	Xtandi	1,14
Transforming growth factor- β	6	V		VEGF-A	12	Y	
Transient receptor potential cation channel subfamily C member 5	20	<i>V-ets erythroblastosis virus E26 oncogene homolog</i>	1	VEGFR	12	Ylanthia	5
Trientine	11	V-region immunoglobulin-containing suppressor of T cell activation	12	Vemurafenib	11	Z	
Trientine hydrochloride	11			VISTA	12	Zelboraf	11
TRPC5	20			Von Willebrand factor	18	Zytiga	3
				Vwf	18		



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