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A team from Weill Cornell Medical College has found a unifying feature of triple-negative breast cancers—overactivation of the transcription factor X-box binding protein 1. Blocking expression of the target decreases tumor formation and relapse in mice, but more druggable targets upstream of it might be better suited for further development.

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By *Chris Cain, Senior Writer*

Two European teams have pinpointed the DNA-protective enzyme 7,8-dihydro-8-oxoguanine triphosphatase as a chemically tractable target whose inhibition kills cancer cells by accelerating DNA damage.<sup>1,2</sup> Both groups have identified collections of small molecule inhibitors of the enzyme—one of which is an isomer of cancer drug Xalkori crizotinib—and both are looking to partner with industry.

The compounds could be useful to treat a range of tumor types, including *K-Ras* (*KRAS*)-mutant cancers.

The normal role of 7,8-dihydro-8-oxoguanine triphosphatase (*NUDT1*; *MTH1*) is to prevent DNA damage by cleaving oxidized dATP or dGTP, which can accumulate and inappropriately incorporate into the genome if left unchecked.

Recent studies have shown that *MTH1* is overexpressed in Ras-dependent cancers and can suppress oxidative damage. That finding suggested that inhibiting the target could be lethal to tumor cells.<sup>3</sup>

Thomas Helleday, a professor at the **Karolinska Institute**, became interested in *MTH1* in cancer based in part on these earlier publications and his team's long-standing work on DNA-repair pathways.

"We wanted to find a DNA-repair target that could be more generally applicable to cancer by looking at phenotype instead of genotype and building on our knowledge that cancers have a higher load of DNA damage than normal cells," he told *SciBX*.

His team therefore started searching for candidate DNA-repair proteins that were not generally essential for cell growth but could be particularly important for cancer cell survival. *MTH1* fit the bill.

In cancer cell lines, shRNA against *MTH1* inhibited cell growth and decreased the incorporation of oxidized nucleotides compared with control shRNA. Expressing an shRNA-resistant, wild-type copy of *MTH1* restored cell growth, whereas expressing a catalytically dead mutant did not.

The researchers then synthesized small molecule inhibitors of the target, which Helleday's lab had previously helped crystallize in the course of studying DNA-repair pathways in normal cells.<sup>4</sup>

*In vitro*, the best compounds inhibited *MTH1* with low nanomolar potency, and crystal structures identified their binding site on the protein. In a series of cancer cell lines and in xenograft mice with breast cancer, colon cancer or drug-resistant melanoma cells, one of the best compounds decreased growth compared with vehicle.

To confirm that the effect of the compounds was due to their engagement with *MTH1* and not an off-target effect, Helleday's group

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expressed the bacterial homolog of *MTH1*, mutT, which is not inhibited by the compounds, in cancer cells. This reversed the cytotoxic effect of the compounds.

“This is the ultimate proof of an on-target effect,” Helleday told *SciBX*.

Results were published in *Nature*.

**Same target, different routes**

A team led by Giulio Superti-Furga did not set out to interrogate MTH1 at all and came upon it while attempting to determine the target of a 15-year-old compound that had been synthesized by Schering-Plough Corp., SCH51344.

Schering-Plough was acquired by **Merck & Co. Inc.** in 2009, and SCH51344 never entered clinical development for undisclosed reasons.

“For many years we had been building up the capability to identify targets from phenotypic screens using an unbiased chemical proteomic approach,” said Superti-Furga, who is CEO and scientific director of the **Research Center for Molecular Medicine of the Austrian Academy of Sciences (CeMM)**. “We searched the literature for interesting hits and found this compound, which was particularly active against Ras-transformed cells and which had an unknown mechanism of action that was not thought to be through MAP kinase signaling.”

His team synthesized a modified version of SCH51344 that could be affinity purified and then used mass spectrometry of cell lysates to fish out its targets. The top hits turned out to be MTH1 and adenosine kinase.

Inhibiting adenosine kinase had no effect on SCH51344-sensitive cells, suggesting that the compound was most likely killing cells by inhibiting MTH1. Indeed, the team confirmed that knockdown of *MTH1* killed Ras-transformed cancer cells.

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Superti-Furga then reached out to Helleday's group to ask for the protocols and reagents for the *in vitro* assays that would be needed to confirm SCH51344 as an inhibitor of MTH1 catalytic activity, unaware that Helleday's team also was pursuing the target.

Helleday told *SciBX*, "Giulio told us the story of how his team fished out the target with proteomics, so we sent our biochemist to his lab with the assays, and it turned out to be MTH1. It was a nice independent validation of the target."

### Xalkori surprise

The CeMM lab began screening for inhibitors of MTH1 in collaboration with Stefan Knapp, a professor of structural biology at the University of Oxford and principal investigator of epigenetics and chemical biology at the Structural Genomics Consortium. The hypothesis was that existing kinase inhibitors, which often mimic ATP and thus are structurally related to MTH1's nucleotide substrates, might also act on the target.

The top hit from the screen was **Pfizer Inc.**'s Xalkori, an inhibitor of anaplastic lymphoma kinase (ALK) and c-Met receptor tyrosine kinase that is marketed to treat ALK-fusion-positive non-small cell lung cancer (NSCLC).

Although the compound exhibited reproducible activity within batches ordered from chemical suppliers, it had widely variable activity from batch to batch.

After exhaustive testing, the team found that the (*S*) enantiomer of crizotinib inhibited MTH1 with low nanomolar potency. The (*R*) enantiomer—which is what Pfizer markets as Xalkori—did not inhibit MTH1.

"This is where serendipity stepped in again," said Superti-Furga. "If we hadn't received an optically impure crizotinib batch from one vendor and instead used only clinical-grade crizotinib given to patients, we would not have seen this result."

In collaboration with Knapp, the team solved the structures of the (*R*) and (*S*) forms of the compound bound to MTH1. The structures showed that the (*R*) form adopts an unfavorable entropic interaction with the protein that precludes activity.

A proteomic approach then showed that although (*S*)-crizotinib potently targets MTH1 in *KRAS*-mutant colon carcinoma cells, it did not exhibit any significant affinity toward ALK, c-Met or any other kinase target of (*R*)-crizotinib.

"I've been doing these kinds of assays for 15 years, and the result was incredibly dramatic," said Superti-Furga. "Usually with kinase inhibitors you get a gradient of hits, some kinases bind a compound better than others, and then there is a tail. What was remarkable with (*S*)-crizotinib was that it is not binding to kinases at all, and *in vitro* studies confirmed this."

Superti-Furga was cofounder, scientific director and SVP of biology at proteomics company Cellzome AG before joining CeMM in 2004. **GlaxoSmithKline plc** acquired Cellzome in 2012.

In xenograft mice with *KRAS*-mutant tumors, (*S*)-crizotinib decreased tumor growth compared with (*R*)-crizotinib or vehicle.

Results were published in *Nature* alongside Helleday's work.

### Clinical moves

Both teams are continuing to synthesize and optimize MTH1 inhibitors and are seeking development partners.

Helleday's compounds are covered by composition-of-matter patent applications, which are held by a foundation in his name. He hopes to partner or license the compounds to fund work in his lab.

"The people who work with me, half have come from industry; it is quite different from other labs. We have six teams: a basic science team, a medicinal chemistry team, a biochemistry team, *in vivo* pharmacology, biology and *in vitro* pharmacology. I want to make sure the funds flow back to the people who did the work," he said.

He continued, "We are good at derisking a target, and we can make great small molecules, but our competence is not in regulatory affairs or in GMP production or GLP toxicology. We have almost 100 people involved in this project, but we don't want to go into areas where we do not have the appropriate expertise."

Both Superti-Furga and Helleday said that *Mth1*-mutant mice are healthy, which is a promising sign from a safety standpoint. They acknowledged that additional safety work will need to flesh out side effects that could arise from chronic disruption of a DNA-repair pathway.

Superti-Furga said that his lab is looking to either partner with a pharmaceutical company or start a company with venture backing. His team has filed a patent application covering the use of (*S*)-crizotinib to treat cancer susceptible to MTH1 inhibition.

He told *SciBX* that he has synthesized additional compounds covered by composition-of-matter patents.

Superti-Furga said that he contacted Pfizer to discuss the findings prior to publication, but a confidential disclosure agreement was never entered into and no detailed discussions took place. He has not spoken to Pfizer since the publication of the papers.

Pfizer declined requests for comment.

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### COMPANIES AND INSTITUTIONS MENTIONED

**GlaxoSmithKline plc** (LSE:GSK; NYSE:GSK), London, U.K.  
**Karolinska Institute**, Stockholm, Sweden  
**Merck & Co. Inc.** (NYSE:MRK), Whitehouse Station, N.J.  
**Pfizer Inc.** (NYSE:PFE), New York, N.Y.  
**Research Center for Molecular Medicine of the Austrian Academy of Sciences**, Vienna, Austria  
**Structural Genomics Consortium**, Oxford, U.K.  
**University of Oxford**, Oxford, U.K.

# Translational tidbits

By Kai-Jye Lou, Senior Writer

**AstraZeneca plc** had a busy March, announcing five new public-private partnerships and the launch of its Open Innovation website to list additional partnership opportunities (see Table 1, “Selected public-private partnerships for March 2014”).

One of the public-private partnerships (PPPs) was a five-year alliance with the U.K.’s **Medical Research Council (MRC)** to give academic researchers access to more than two million of the pharma’s molecules.

MRC will select and fund up to 15 screening projects per year. Topics for prospective projects are expected to cover a range of therapeutic areas and diseases and will not be restricted to AstraZeneca’s areas of focus—cancer, cardiovascular and metabolic diseases, respiratory disorders, inflammation and autoimmune diseases.

Project proposals will be sourced from U.K. scientists based at academic or noncommercial research institutions, including MRC. Initial projects may start as early as 2015.

The pharma will have the first option to license rights to any resulting drug discovery programs.

The partners also plan to form the AstraZeneca MRC U.K. Centre for Lead Discovery at the pharma’s Cambridge Biomedical Campus. The center is expected to open in 2016.

Financial details were not disclosed.

AstraZeneca and MRC previously partnered in December 2011 to

provide academic researchers with MRC grant funding and access to 22 of the pharma’s discontinued compounds free of charge to carry out mechanistic studies in new indications.<sup>1</sup> MRC awarded £7 million (\$11.3 million) in funding to 15 research projects in October 2012.

Also in March, AstraZeneca signed a memorandum of understanding with the **Korea Health Industry Development Institute** to provide support for 12 early stage translational research projects from Korean oncology investigators.

Scientists will receive research funding from the pharma and will have priority access to a list of its compounds for preclinical evaluation. The investigators also will have access to technological advice and collaboration opportunities with AstraZeneca.

The pharma’s Oncology iMed group will review and select four project preproposals by May. Preproposals are abridged proposals that summarize a research project and include project aims, a preliminary budget estimate, expected key deliverables and milestones.

Together with other companies, AstraZeneca also is involved in the **Innovative Medicines Initiative (IMI)**’s GetReal project aimed at helping companies generate real-world data for payers during the drug development process, along with the clinical data necessary for regulatory approval. IMI formally launched the project last month.

**GlaxoSmithKline plc** and **University Medical Center Utrecht** are leading GetReal, which has a budget of €16.3 million (\$22.7 million), including €8 million (\$11.1 million) from IMI and €6 million (\$8.3 million) of in-kind contributions from consortium members.

The last two PPPs announced by AstraZeneca involve a pair of three-year oncology partnerships by its **MedImmune LLC** unit.

**Table 1. Selected public-private partnerships for March 2014. AstraZeneca plc** (LSE:AZN; NYSE:AZN) had a busy March. The pharma is embarking on a broad, five-year screening campaign with the U.K.’s **Medical Research Council (MRC)** and participating in the **Innovative Medicines Initiative (IMI)**’s GetReal project, and its **MedImmune LLC** biologics unit announced a pair of cancer deals to advance the development of immunotherapies and tumor-targeted therapies. Infectious diseases also had a strong showing last month, with a quartet of public-private partnerships that could get up to \$52.1 million in new support.

Source: *BioCentury Archives*

| Companies  | Institutions   | Business area      | Disclosed value                | Purpose   |
|--|--|--------------------|--------------------------------|---|
| <b>Emergent BioSolutions Inc.</b> (NYSE:EBS); <b>Mapp Biopharmaceutical Inc.</b> ; <b>Zalgen Labs LLC</b>  | <b>Ben-Gurion University of the Negev</b> ; <b>NIH</b> ; <b>Public Health Agency of Canada</b> ; <b>The Scripps Research Institute</b> ; <b>Uganda Virus Research Institute</b> ; <b>The University of Texas Medical Branch</b> ; <b>University of Wisconsin–Madison</b> ; <b>U.S. Army Medical Research Institute of Infectious Diseases</b> ; <b>Yeshiva University</b>  | Infectious disease | Up to \$28 million             | Consortium to develop immunotherapies for filoviruses and arenaviruses that cause severe hemorrhagic fever  |
| <b>Amgen Inc.</b> (NASDAQ:AMGN); <b>AstraZeneca</b> ; <b>Bayer AG</b> (Xetra:BAYN); <b>Boehringer Ingelheim GmbH</b> ; <b>Bristol-Myers Squibb Co.</b> (NYSE:BMJ); <b>Eli Lilly and Co.</b> (NYSE:LLY); <b>GlaxoSmithKline plc</b> (LSE:GSK; NYSE:GSK); <b>Johnson &amp; Johnson</b> (NYSE:JNJ); <b>LASER Analytica</b> ; <b>Merck &amp; Co. Inc.</b> (NYSE:MRK); <b>Merck KGaA</b> (Xetra:MRK); <b>Novartis AG</b> (NYSE:NVS; SIX:NOVN); <b>Novo Nordisk A/S</b> (CSE:NVO; NYSE:NVO); <b>Roche</b> (SIX:ROG; OTCQX:RHHBY); <b>Sanofi</b> (Euronext:SAN; NYSE:SNY); <b>Takeda Pharmaceutical Co. Ltd.</b> (Tokyo:4502) | <b>University Medical Center Utrecht</b> ; <b>University Medical Center Groningen</b> ; <b>Health Care Insurance Board of the Netherlands</b> ; <b>EMA</b> ; <b>EORTC</b> ; <b>French National Authority for Health</b> ; <b>London School of Hygiene &amp; Tropical Medicine</b> ; <b>National Institute for Health and Care Excellence</b> ; <b>University of Ioannina</b> ; <b>University of Berne</b> ; <b>University of Leicester</b> ; <b>International Alliance of Patients’ Organizations</b> ; <b>IMI</b> | Pharmaceuticals    | €16.3 million (\$22.7 million) | GetReal project to help companies generate real-world data for payers during drug development process and clinical data necessary for regulatory approval |

(Continues on p. 5)

**Table 1. Selected public-private partnerships for March 2014.** (Continued)

| Companies  | Institutions   | Business area             | Disclosed value                 | Purpose  |
|--|--|---------------------------|---------------------------------|--|
| Japan BCG Laboratory Ltd.; Astellas Pharma Inc. (Tokyo:4503); Dainippon Sumitomo Pharma Co. Ltd. (Tokyo:4506); Eisai Co. Ltd. (Tokyo:4523); Merck KGaA | Aeras; Drugs for Neglected Diseases initiative; Liverpool School of Tropical Medicine; National Institute of Biomedical Innovation; Swiss Tropical and Public Health Institute; TI Pharma; University of Liverpool | Infectious disease        | \$12.5 million                  | Four partnerships to develop drugs and vaccines to treat schistosomiasis, Chagas disease, parasitic roundworms and tuberculosis                |
| None   | Fred Hutchinson Cancer Research Center; NIH; The Rockefeller University; Seattle Biomedical Research Institute; Seattle Children's Hospital; University of Washington  | Infectious disease        | \$9.8 million                   | Consortium to develop a vaccine to elicit broadly neutralizing antibodies against HIV-1  |
| 4SC AG (Xetra:VSC)   | Heidelberg University Hospital   | Infectious disease        | €1.3 million (\$1.8 million)    | Partnership to conduct preclinical testing of small molecule antimalarial compound   |
| Bicoll Group   | Charité–University Hospital Berlin; German Federal Ministry of Education and Research  | Neurology                 | Over €1 million (\$1.4 million) | EPICLEAP project to evaluate traditional Chinese medicine pharmaceutical recipes to identify therapeutic leads                                 |
| Advaxis Inc. (NASDAQ:ADXS)   | University of California, San Francisco  | Cancer                    | Undisclosed                     | Partnership to evaluate immunotherapy constructs against targets important in effective immunotherapies to treat prostate cancer               |
| AstraZeneca  | Korea Health Industry Development Institute  | Cancer                    | Undisclosed                     | Partnership to establish an oncology research program to support 12 early stage translational research projects from Korean investigators      |
| AstraZeneca  | MRC  | High throughput screening | Undisclosed                     | Partnership to evaluate over two million AstraZeneca molecules over five years   |
| AstraZeneca; MedImmune   | University of Cambridge  | Cancer                    | Undisclosed                     | Partnership to study tumor-targeted therapies, including antibody-drug conjugates  |
| AstraZeneca; MedImmune   | The University of Texas MD Anderson Cancer Center  | Cancer                    | Undisclosed                     | Partnership to develop immunotherapies for cancer through MD Anderson's Moon Shots Program   |
| Genocea Biosciences Inc. (NASDAQ:GNCA)   | Dana-Farber Cancer Institute; Harvard Medical School; Ludwig Institute for Cancer Research Ltd.  | Cancer                    | Undisclosed                     | Partnership to characterize immune responses stimulated by treatment with melanoma drug Yervoy ipilimumab                                      |
| GlaxoSmithKline  | EMBL-EBI; Wellcome Trust Sanger Institute  | Functional genomics       | Undisclosed                     | Partnership to form the Centre for Therapeutic Target Validation, which will use genome sequencing and big-data tools to research drug targets |
| Insight Genetics Inc.  | Vanderbilt-Ingram Cancer Center  | Pharmacogenetics          | Undisclosed                     | Partnership to identify genetic markers that could help select targeted therapeutics for triple-negative breast cancer                         |
| Ono Pharmaceutical Co. Ltd. (Tokyo:4528)   | Tohoku University; The University of Tokyo   | Pharmaceuticals           | Undisclosed                     | Research collaboration network called Orientem Innovation to identify and develop bioactive lipid-based therapeutics                           |
| Rosetta Genomics Ltd. (NASDAQ:ROSG)  | Rabin Medical Center   | Diagnostics               | Undisclosed                     | Partnership to develop a noninvasive, microRNA-based assay to diagnose chronic allograft dysfunction in kidney transplant recipients           |

The first is between MedImmune and the **University of Cambridge** and will study tumor-targeted therapies, including antibody-drug conjugates. The second PPP pairs MedImmune and **The University of Texas MD Anderson Cancer Center** in an effort to evaluate the company's immunotherapy candidates in clinical settings through MD Anderson's Moon Shots Program.

Financial details of the deals were not disclosed.

In addition to these five PPPs, AstraZeneca launched its Open Innovation website in March. The site lists 47 compounds the pharma is making available to interested parties for clinical, translational research and disease biology studies. The list includes both active and discontinued compounds.

The website includes a way for interested parties to submit proposals to the pharma for grants of up to \$100,000 for target validation partnerships, as well as an R&D Challenges section through which the pharma plans to crowdsource solutions to problems.

Starting in May, the website will begin accepting proposals for projects to identify new molecules and profile their activity in relevant disease biology assays. The external partner will retain rights to the generated data and IP covering compounds evaluated under such projects.

### Hitting infectious diseases

Last month, Japan's **Global Health Innovative Technology Fund** (GHIT Fund) announced its second round of grant awards, which will support projects focused on tuberculosis (TB) and three neglected tropical diseases.

The GHIT Fund is an infectious disease initiative that plans to disburse \$100 million over 5 years to support partnerships between Japanese and non-Japanese companies and research institutions that focus on HIV/AIDS, malaria, TB and neglected tropical diseases.<sup>2</sup>

The initiative was launched in April 2013 and announced its first round of grant awards in November. In the latest round, the GHIT Fund awarded \$12.5 million in aggregate to 4 partnerships.

Japan's **National Institute of Biomedical Innovation**, Create Vaccine Co. Ltd. and **Aeras** are getting \$5.7 million to fund development of a new vaccine candidate for TB. The award is on top of an initial \$700,000 grant to the partnership.

The candidate is targeted to the mucous membranes and is designed to enhance mucosal immunity to prevent bacteria from getting into the lungs. The new funding will support the preclinical work needed to advance the candidate into a Phase I trial.

Create Vaccine is a joint venture between **Dainippon Sumitomo Pharma Co. Ltd.** and **Japan BCG Laboratory Ltd.**

The next three partnerships to receive GHIT Fund grants are focused on neglected tropical diseases.

**Eisai Co. Ltd.** and the **Drugs for Neglected Diseases initiative** are getting \$3.8 million to fund a Phase II trial of benzimidazole in combination with Eisai's E1224 to treat Chagas disease. E1224 is a prodrug of the antifungal ravuconazole.

Benzimidazole is a generic antiparasitic drug used to treat Chagas

disease but is poorly tolerated in adults and frequently fails to cure chronic infections.

**Astellas Pharma Inc.**, **TI Pharma**, **Merck KGaA** and the **Swiss Tropical and Public Health Institute** are getting \$1.9 million to fund the development and registration of a pediatric formulation of Merck's schistosomiasis drug Cesol praziquantel.

The partners have produced test batches of two new praziquantel formulations—racemate praziquantel and levo-praziquantel. Both formulations will be tested first in adults and followed with taste tests in children. Missing clinical data, pill size and bitter taste have all been factors that hamper the use of Cesol in infants and young children.

Finally, Eisai, the **Liverpool School of Tropical Medicine** and the **University of Liverpool** are getting \$1.1 million to investigate new compounds to treat *Wolbachia* bacterial infections. The partners will focus on compounds from 2 chemical groups known to have potential as anti-infectives and run a 12-month, head-to-head comparison study.

The partners are aiming to identify a single candidate for drug development within two years.

Overall, PPPs that focus on infectious diseases had a strong showing in March, taking in almost 70% of the \$76.2 million in new support for PPPs disclosed that month.

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### COMPANIES AND INSTITUTIONS MENTIONED

**Aeras**, Rockville, Md.

**Astellas Pharma Inc.** (Tokyo:4503), Tokyo, Japan

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

**Dainippon Sumitomo Pharma Co. Ltd.** (Tokyo:4506), Osaka, Japan

**Drugs for Neglected Diseases initiative**, Geneva, Switzerland

**Eisai Co. Ltd.** (Tokyo:4523), Tokyo, Japan

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

**Global Health Innovative Technology Fund**, Tokyo, Japan

**Innovative Medicines Initiative**, Brussels, Belgium

**Japan BCG Laboratory Ltd.**, Tokyo, Japan

**Korea Health Industry Development Institute**, Gangoe-myeon, South Korea

**Liverpool School of Tropical Medicine**, Liverpool, U.K.

**Medical Research Council**, London, U.K.

**MedImmune LLC**, Gaithersburg, Md.

**Merck KGaA** (Xetra:MRK), Darmstadt, Germany

**National Institute of Biomedical Innovation**, Osaka, Japan

**Swiss Tropical and Public Health Institute**, Basel, Switzerland

**TI Pharma**, Leiden, the Netherlands

**University Medical Center Utrecht**, Utrecht, the Netherlands

**University of Cambridge**, Cambridge, U.K.

**University of Liverpool**, Liverpool, U.K.

**The University of Texas MD Anderson Cancer Center**, Houston, Texas

# Expanding into new (bromo)domains

By Michael J. Haas, Senior Writer

The **Neomed Institute** has begun development of its first cancer therapeutic, a bromodomain containing 4 inhibitor from **Epigenetix Inc.** that the not-for-profit organization thinks could have a selectivity advantage over competing molecules.

Bromodomain-containing proteins are a class of epigenetic regulators. These domains bind to histones in which lysine residues are modified by an acetyl group to regulate chromatin remodeling and gene transcription.<sup>1,2</sup> Two independent papers in *Nature* in 2010 first showed the potential druggability of bromodomains by identifying JQ1 and I-BET as selective inhibitors of the BET bromodomain family, which includes bromodomain containing 2 (BRD2), BRD3 and BRD4.<sup>3,4</sup>

According to Mounia Azzi, Neomed's director of scientific affairs, the institute in-licensed the BRD4 inhibitor program from Epigenetix because the biotech's structure-based design approach identified new inhibitors with good selectivity, cellular permeability and activity in multiple cancer models.

Neomed will lead development through human proof of concept. **IntelliSyn**—a medicinal chemistry company located at the institute—will conduct the initial drug discovery work, and CROs will run drug metabolism, pharmacokinetics and toxicity studies, Azzi said.

Epigenetix decided to partner with Neomed because “the institute provides us access to financing and pharma expertise that we would have needed to obtain—one way or another—to develop the BRD4 program,” said Joseph Collard, the biotech's cofounder and CEO. He also is a cofounder of IntelliSyn. “Plus, we have other programs, so we aren't out-licensing our one and only program.”

After the BRD4 inhibitors, Epigenetix's next most advanced program is in lead identification and targets oxytocin receptor (OXTR) to treat autism, Collard said.

The partners expect to identify a lead compound within six to eight months and have not yet selected a lead indication.

Financial details were not disclosed, but Azzi said that Neomed and

Epigenetix will share any proceeds from out-licensing the BRD4 program. Neomed's pharma partners will have options to in-license the project at certain undisclosed milestones.

Neomed was founded in 2012 by the Quebec government, **AstraZeneca plc** and **Pfizer Inc.** to provide funding for academic labs and biotechs to develop therapeutics to human proof of concept and then out-license them.<sup>5</sup>

Johnson & Johnson Innovation LLC and Janssen Labs units of **Johnson & Johnson** joined Neomed last December.<sup>6</sup> The institute is still seeking a fourth pharma partner, President and CEO Max Fehlmann said.

None of the three pharmas has a disclosed BRD4 inhibitor program.

At least six other companies have BET bromodomain inhibitors in the clinic (see **Table 1**, “Clinical bromodomains”).

Although the BRD4 inhibitor is Neomed's first asset that directly treats cancer, the institute was not specifically looking for an early stage cancer project, Azzi said. Instead, the partnership evolved from Neomed's and Epigenetix's link through IntelliSyn, which had been working with the biotech on the bromodomain program.

As a result of that link, “Epigenetix presented the project to Neomed, and we saw value in the program,” she said. Moreover, “IntelliSyn has the right expertise on epigenetic targets—specifically, BRD inhibitors—to develop it.”

Neomed's pipeline includes three compounds that were donated by AstraZeneca after the pharma wound down its neurology R&D in Montreal and elsewhere in 2012:<sup>5</sup> NEO1940, an agonist of cannabinoid CB<sub>1</sub> receptor (CNR1) and CNR2, is in Phase I testing to treat cancer cachexia; NEO6860, a transient receptor potential vanilloid 1 (TRPV1; VR1) antagonist, is in preclinical testing to treat osteoarthritis (OA) pain; and a purinergic receptor P2X ligand-gated ion channel 3 (P2X3) antagonist is in preclinical development for painful bladder syndrome/interstitial cystitis and OA pain.

In September, Neomed in-licensed technology from the **University of Sherbrooke** to develop inhibitors of type II transmembrane serine proteases, a family of enzymes involved in the replication of influenza

“The institute provides us access to financing and pharma expertise that we would have needed to obtain—one way or another—to develop the BRD4 program.”  
—Joseph Collard, Epigenetix Inc.

**Table 1. Clinical bromodomains.** At least six companies have compounds that inhibit bromodomains, including the bromodomain containing 2 (BRD2), BRD3 and BRD4 members of the BET bromodomain family, in clinical testing to treat cancer and other diseases.

Source: *BCIQ: BioCentury Online Intelligence*

| Company   | Product            | Description   | Status  |
|---|--------------------|---|---|
| Zenith Epigenetics Corp. subsidiary of <b>Resverlogix Corp.</b> (TSX:RVX) | RVX-208            | Inhibitor of BRD4 and other members of the BET bromodomain family   | Phase II for atherosclerosis and diabetes; Phase I for Alzheimer's disease (AD) |
| <b>Constellation Pharmaceuticals Inc.</b>                                 | CPI-0610           | Bromodomain inhibitor   | Phase I for lymphoma  |
| <b>GlaxoSmithKline plc</b> (LSE:GSK; NYSE:GSK)                            | GSK525762 (525762) | Bromodomain inhibitor   | Phase I for NUT midline carcinoma (NMC)   |
| <b>Mitsubishi Tanabe Pharma Corp.</b> (Tokyo:4508); <b>Oncoethix S.A.</b> | OTX015 (Y-803)     | Synthetic small molecule inhibitor of BRD2, BRD3 and BRD4   | Phase I for hematological malignancies  |
| <b>Tensha Therapeutics Inc.</b>   | TEN-010            | Small molecule inhibitor selective for the BET bromodomain family (BRD2, BRD3, BRD4 and bromodomain testis specific (BRDT)) | Phase I for solid tumors  |

virus. Because the enzymes are host factors—not viral proteins—the inhibitors should target multiple subtypes of the influenza virus to treat infection and prevent the virus from developing resistance, Fehlmann said.

Haas, M.J. *SciBX* 7(15); doi:10.1038/scibx.2014.420  
Published online April 17, 2014

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**Epigenetix Inc.**, Miami, Fla.  
**IntelliSyn**, Montreal, Quebec, Canada  
**Johnson & Johnson** (NYSE:JNJ), New Brunswick, N.J.  
**Neomed Institute**, Montreal, Quebec, Canada  
**Pfizer Inc.** (NYSE:PFE), New York, N.Y.  
**University of Sherbrooke**, Sherbrooke, Quebec, Canada



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# Unfolding triple-negative breast cancer

By Benjamin Boettner, Associate Editor

A team from Weill Cornell Medical College has found a unifying feature of triple-negative breast cancers—overactivation of the transcription factor X-box binding protein 1—that could open the door to new therapies for this notoriously hard-to-treat disease.<sup>1</sup> Although blocking expression of this target, which is involved in the unfolded protein response, decreases tumor formation and relapse in mice, more druggable targets upstream of it might be better suited for further development.

Triple-negative breast cancers lack expression of estrogen receptor, progesterone receptor and HER2 (EGFR2; ErbB2; neu) and thus do not respond to hormonal or HER2-directed therapy.<sup>2</sup>

Instead, patients receive chemotherapy—which typically produces a good initial response. However, a significant proportion of patients relapse, and the cancer often metastasizes.

Triple-negative cancers represent about 10%–20% of invasive breast cancers and are among the most aggressive types of breast cancer.

In 1999 Laurie Glimcher—who was then at the Harvard School of Public Health—coauthored a transcriptional study on multiple myeloma (MM) that showed upregulation of X-box binding protein 1 (XBP1), a protein associated with a cellular stress response to improper protein folding, in this cancer.<sup>3</sup> Results from other labs corroborated the findings in MM and further showed involvement of the pathway in various other tumors.<sup>4</sup>

Now, Glimcher and colleagues have tied the unfolded protein response to triple-negative breast cancer.

Glimcher is dean and a professor of medicine at Weill Cornell.

The team also included researchers from the University of California, Los Angeles, The University of North Carolina at Chapel Hill, Tongji University, Sichuan Agricultural University, Brigham and Women's Hospital, Boston Children's Hospital and the Dana-Farber Cancer Institute.

## X-box on

The unfolded protein response is part of the cellular adaptive response to stress. In normal cells the response is activated when improperly folded proteins accumulate in the endoplasmic reticulum following exposure to stimuli such as hypoxia.

A key player in the pathway is endoplasmic reticulum to nucleus signaling 1 (ERN1; IRE1), a kinase and endoribonuclease in the endoplasmic reticulum membrane that senses misfolded proteins. Activated IRE1 splices a short inhibitory sequence out of the *XBP1* mRNA transcript, which triggers translation of *XBP1* to an active transcription factor that turns on a battery of genes to normalize protein folding.

To see what role XBP1 plays in different types of breast cancer, the

researchers scanned a panel of breast cancer cell lines for the activation status of *XBP1*. They discovered that the spliced, active form was on average about twice as prevalent in triple-negative breast cancer cell lines than other breast cancer cell lines.

Next, the team used shRNA to deplete *XBP1* mRNA in a mouse xenograft model of triple-negative breast cancer and found that *XBP1* knockdown decreased tumor growth, angiogenesis and metastasis to the lung compared with no alteration.

shRNA-mediated *XBP1* knockdown also interfered with tumor formation and extended survival in mice transplanted with patient-derived triple-negative primary cells.

Glimcher's group then investigated whether XBP1 is connected to the high relapse rate in triple-negative breast cancer.

By combining the chemotherapeutic doxorubicin with shRNA-mediated inhibition of *XBP1*, the researchers produced greater growth inhibition in the patient-derived cells than that seen using either agent alone and prevented or delayed relapse of the tumors in mice.

In triple-negative breast cancer, relapses can be triggered by tumor-initiating cells that have a characteristic CD44<sup>high</sup>/CD24<sup>low</sup> surface marker expression.

Silencing *XBP1* decreased the fraction of CD44<sup>high</sup>/CD24<sup>low</sup> in a population of transformed breast cells and interfered with their potential to form mammospheres, a readout for tumor-initiating potential.

Finally, the team searched for genes regulated by *XBP1* activation in triple-negative cells and identified *hypoxia-inducible factor 1α* (*HIF1A*; *HIF1α*) as a pivotal component of XBP1's tumorigenic pathway.

An extensive chromatin immunoprecipitation analysis coupled with high throughput sequencing (ChIP-seq) revealed XBP1 binding sites at a significant number of loci that coincided with binding sites for HIF1α.

Other studies had previously linked hyperactivated HIF1α with triple-negative breast cancer and had shown it to be required for maintenance of the CD44<sup>high</sup>/CD24<sup>low</sup> cell signature.<sup>5–7</sup>

Here, Glimcher's study connected XBP1, HIF1α and tumor formation by showing that XBP1 reinforced HIF1α activity in mammospheres *in vitro* and in triple-negative breast cancer xenografts *in vivo*.

The team concluded that *XBP1* activation promotes tumor formation in triple-negative

breast cancers by acting through HIF1α.

The findings were published in *Nature*.

## Unfolding targets

Glimcher told *SciBX* that the next step is to extend the studies' validation using multiple preclinical models with patient-derived xenografts representing major triple-negative breast cancer subtypes and with genetically engineered mouse models bearing mutations seen in human triple-negative breast cancers.

Connie Eaves agreed that the interesting findings need additional validation because the data in Glimcher's paper were based on breast cancer cell lines and only one patient's tumor.

"It will be crucial to examine the pathway and the effects of its manipulation in primary tumor cells from multiple patients including

**"It will be crucial to examine the pathway and the effects of its manipulation in primary tumor cells from multiple patients including a full spectrum of triple-negative breast cancers and non-triple-negative cancers."**

—Connie Eaves, BC Cancer Agency

a full spectrum of triple-negative breast cancers and non-triple-negative cancers,” she said.

Eaves is a professor of medical genetics at the **BC Cancer Agency’s** Terry Fox Laboratory and works on hematopoietic and breast stem cells in cancer.

In addition, Glimcher and Eaves agreed that the next step is to identify the optimal therapeutic target in the XBP1 pathway.

Glimcher told *SciBX*, “While XBP1 is a transcription factor, and

traditionally transcription factors have been difficult to target with small molecules, IRE1 is a viable drug target.” She added that her team is planning to study IRE1 inhibitors in preclinical and genetic models.

Eric Chevet agreed that IRE1 could be a good target to investigate in triple-

negative breast cancer. He added that several IRE1 inhibitors are in development.

Chevet is a researcher at the **Institut National de la Santé et de la Recherche Médicale** (INSERM) at the **University of Bordeaux Segalen**. He is studying the unfolded protein response in normal and pathological processes.

**MannKind Corp.** has the IRE1 inhibitors MKC204 and MKC-3946 in preclinical testing for MM. **Ruga Corp.** has STF-08310, an IRE1 inhibitor, in preclinical testing for MM and breast cancer.

However, Chevet cautioned that IRE1 has other activities in addition to *XBP1* splicing. It helps degrade a pool of mRNAs in a process called regulated IRE1-dependent decay (RIDD) and cleaves premature microRNAs. Both these activities “can have proapoptotic effects that may run opposite to survival-promoting *XBP1* splicing,” he said.

“Finding agents that uncouple IRE1’s *XBP1* from its RIDD activity could give the overall best net effects. So far, no small molecules with this potential have been described, but peptide studies have shown that this is possible,” he added.

Ruga CEO Raymond Tabibiazar agreed that IRE1’s multiple activities make it a challenging pharmacological target.

“It is also known that proteasome inhibitors like Velcade bortezomib increase the unfolded protein response,” he said. “Thus, it is tempting to speculate what happens if triple-negative breast cancers are treated

with proteasome inhibitors. Would this push them over the edge and kill them?”

That approach, according to Tabibiazar, would be opposite to inhibiting *XBP1*. Instead, it would amplify *XBP1* activation—and theoretically produce the same result.

Chevet also noted, “Another potentially very specific target could be the elusive ligase that completes the IRE1-initiated splicing reaction on *XBP1*, which so far has not been identified.”

Glimcher told *SciBX* that her lab is exploring the upstream signals that activate the IRE1- and *XBP1*-controlled sensor mechanism in response to hypoxia in triple-negative breast cancer cells, which could reveal additional therapeutic entry points.

Weill Cornell Medical College has filed a patent application on the findings. The licensing status is unavailable.

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**Boston Children’s Hospital**, Boston, Mass.  
**Brigham and Women’s Hospital**, Boston, Mass.  
**Dana-Farber Cancer Institute**, Boston, Mass.  
**Harvard School of Public Health**, Boston, Mass.  
**Institut National de la Santé et de la Recherche Médicale**, Bordeaux, France  
**MannKind Corp.** (NASDAQ:MNKD), Valencia, Calif.  
**Ruga Corp.**, Palo Alto, Calif.  
**Sichuan Agricultural University**, Ya’an, China  
**Tongji University**, Shanghai, China  
**University of Bordeaux Segalen**, Bordeaux, France  
**University of California, Los Angeles**, Calif.  
**The University of North Carolina at Chapel Hill**, Chapel Hill, N.C.  
**Weill Cornell Medical College**, New York, N.Y.

**“While XBP1 is a transcription factor, and traditionally transcription factors have been difficult to target with small molecules, IRE1 is a viable drug target.”**

—Laurie Glimcher,  
Weill Cornell Medical College

## This week in therapeutics

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

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

| Indication   | Target/marker/pathway   | Summary  | Licensing status                        | Publication and contact information   |
|--|---|--|---|---|
| <b>Cancer</b>  |   |  |   |   |
| Acute myelogenous leukemia (AML)   | Casein kinase 1 $\alpha$ (CSNK1A; CKI- $\alpha$ )             | Mouse and cell culture studies suggest inhibiting CKI- $\alpha$ could help treat AML. In a mouse model of AML, shRNA against Cki- $\alpha$ decreased leukemic cell growth and increased survival compared with control shRNA. In irradiated mice, transplantation of a mixture of human AML and normal hematopoietic stem cells that had been pretreated with a small molecule CKI- $\alpha$ inhibitor resulted in decreased leukemic growth compared with transplantation of cells pretreated with vehicle and did not impair normal hematopoiesis. Next steps could include testing additional CKI- $\alpha$ inhibitors in animal AML models.  | Patent and licensing status unavailable | Järås, M. <i>et al. J. Exp. Med.</i> ; published online March 10, 2014; doi:10.1084/jem.20131033<br><b>Contact:</b> Benjamin L. Ebert, Harvard Medical School, Boston, Mass.<br>e-mail: <a href="mailto:bebert@partners.org">bebert@partners.org</a>  |
| <b>SciBX 7(15); doi:10.1038/scibx.2014.422<br/>Published online April 17, 2014</b> |   |  |   |   |
| Acute myelogenous leukemia (AML)   | DNA (cytosine-5-)-methyltransferase 3 $\alpha$ (DNMT3A) R882H | <i>In vitro</i> studies suggest targeting DNMT3A R882H could be useful for treating AML. The R882H mutation in DNMT3A is commonly found in AML, but the functional consequence of this mutation has been unclear. A series of cellular assays showed that DNMT3A R882H had 80% lower methyltransferase activity than wild-type DNMT3A and resulted in greater than expected loss of global DNA methylation when coexpressed with wild-type enzyme. In a human cell line, coexpression of R882H-mutant and wild-type DNMT3A showed that the mutant inhibits the wild-type enzyme by blocking its ability to form active tetramers, suggesting the R882H mutation acts in a dominant-negative manner. Next steps could include developing pharmacological agents that block the dominant-negative activity of DNMT3A R882H without affecting the wild-type methyltransferase.  | Patent and licensing status unavailable | Russler-Germain, D.A. <i>et al. Cancer Cell</i> ; published online March 18, 2014; doi:10.1016/j.ccr.2014.02.010<br><b>Contact:</b> Timothy J. Ley, Washington University in St. Louis, St. Louis, Mo.<br>e-mail: <a href="mailto:timley@wustl.edu">timley@wustl.edu</a>  |
| <b>SciBX 7(15); doi:10.1038/scibx.2014.423<br/>Published online April 17, 2014</b> |   |  |   |   |
| Breast cancer  | Fas receptor (CD95)   | <i>In vitro</i> and mouse studies suggest blocking CD95 signaling could help treat breast cancer. CD95 signaling can promote apoptosis in some cells, but constitutive CD95 expression in breast cancer cells is associated with resistance to CD95-induced apoptosis and increased inflammation. In mice with orthotopic breast tumor xenografts, shRNA knockdown of <i>Cd95</i> decreased tumor growth and metastasis and increased survival compared with no alteration. In these mice, <i>Cd95</i> knockdown suppressed tumor growth by decreasing cancer-related inflammation and proinflammatory cytokine levels. Next steps could include testing CD95 inhibition in additional animal models of cancer. Topotarget A/S' APO010, a fusion protein derived from the Fas ligand (TNF superfamily, member 6; FASL), is in Phase I testing to treat cancer. At least two other companies have CD95-targeted therapies in preclinical development. | Patent and licensing status unavailable | Liu, Q. <i>et al. J. Biol. Chem.</i> ; published online March 13, 2014; doi:10.1074/jbc.M113.525014<br><b>Contact:</b> Xuetao Cao, Second Military Medical University, Shanghai, China<br>e-mail: <a href="mailto:caoxt@immunol.org">caoxt@immunol.org</a><br><b>Contact:</b> Qiuyan Liu, same affiliation as above<br>e-mail: <a href="mailto:liuqy@immunol.org">liuqy@immunol.org</a> |
| <b>SciBX 7(15); doi:10.1038/scibx.2014.424<br/>Published online April 17, 2014</b> |   |  |   |   |

## This week in therapeutics (continued)

| Indication      | Target/marker/pathway  | Summary  | Licensing status                            | Publication and contact information  |
|-----------------|--|--|---|--|
| Cancer          | miR-BART9  | <i>In vitro</i> and mouse studies suggest blocking Epstein-Barr virus (EBV) miR-BART9 could help treat EBV-associated cancers. miR-BART9 expression was higher in EBV-associated nasopharyngeal carcinoma (NPC) samples and in EBV <sup>+</sup> NPC cell lines than in healthy control samples or EBV <sup>-</sup> NPC cell lines. In EBV <sup>+</sup> NPC cells, an anti-miR-BART9 oligomer decreased migration and invasiveness compared with a scrambled oligomer control. In mice, EBV <sup>-</sup> NPC cells engineered to overexpress <i>miR-BART9</i> showed increased metastasis compared with EBV <sup>-</sup> NPC cells that overexpressed a control gene. Next steps could include testing miR-BART9 inhibition in additional animal models of EBV-associated cancers.<br><br><b>SciBX 7(15); doi:10.1038/scibx.2014.425</b><br><b>Published online April 17, 2014</b>          | Patent and licensing status unavailable     | Hsu, C.-Y. <i>et al. PLoS Pathog.</i> ; published online Feb. 27, 2014; doi:10.1371/journal.ppat.1003974<br><b>Contact:</b> Hua-Chien Chen, Chang Gung University, Taoyuan, Taiwan<br>e-mail: <a href="mailto:hcchen@mail.cgu.edu.tw">hcchen@mail.cgu.edu.tw</a><br><b>Contact:</b> Shu-Jen Chen, same affiliation as above<br>e-mail: <a href="mailto:sjchen@mail.cgu.edu.tw">sjchen@mail.cgu.edu.tw</a>                  |
| Cancer          | Signal transducer and activator of transcription 3 (STAT3)       | <i>In vitro</i> and mouse studies identified a STAT3-specific binding peptide that could help treat cancer. Peptides made up of a $\beta$ -hairpin-forming tryptophan zipper region and a target-binding site of randomized amino acids were used to generate a peptide library. A phage display-based screen of the library detected a peptide that bound STAT3 with a $K_d$ value of 231 nM. In three mouse models of cancer, the peptide conjugated to a cell-penetrating peptide decreased tumor burden compared with saline or a scrambled peptide. Next steps could include testing the peptide in additional animal models of cancer.<br>At least five companies have STAT3 inhibitors in Phase I/II or earlier testing to treat various cancers.<br><br><b>SciBX 7(15); doi:10.1038/scibx.2014.426</b><br><b>Published online April 17, 2014</b>                                   | Patent and licensing status unavailable     | Kim, D. <i>et al. Cancer Res.</i> ; published online Feb. 27, 2014; doi:10.1158/0008-5472.CAN-13-2187<br><b>Contact:</b> Sangyong Jon, Korea Advanced Institute of Science and Technology, Daejeon, South Korea<br>e-mail: <a href="mailto:syjon@kaist.ac.kr">syjon@kaist.ac.kr</a>  |
| Cancer          | Tubulin  | <i>In vitro</i> and human studies suggest paclitaxel induces cell death by promoting the formation of abnormal multipolar spindles that lead to chromosomal missegregation during mitosis. In cultured breast cancer cell lines, clinically relevant concentrations of paclitaxel promoted multipolar spindle formation and resulted in chromosomal missegregation during mitosis followed by cell death. In tumor biopsies from patients treated with paclitaxel, the number of cells with multipolar spindles increased compared with what was seen with no treatment, and the presence of multipolar spindles correlated with tumor regression. Next steps include identifying a biomarker to select patients who will respond to paclitaxel. Paclitaxel is a generic chemotherapeutic.<br><br><b>SciBX 7(15); doi:10.1038/scibx.2014.427</b><br><b>Published online April 17, 2014</b> | Unpatented; licensing status not applicable | Zasadil, L.M. <i>et al. Sci. Transl. Med.</i> ; published online March 26, 2014; doi:10.1126/scitranslmed.3007965<br><b>Contact:</b> Beth A. Weaver, University of Wisconsin-Madison, Madison, Wis.<br>e-mail: <a href="mailto:baweaver@wisc.edu">baweaver@wisc.edu</a>  |
| Cervical cancer | PC4 and SFRS1-interacting protein (PSIP1; LEDGF; p75; LEDGF/p75) | Studies in cell culture and patient samples suggest inhibiting <i>LEDGF</i> expression could help treat HPV <sup>+</sup> cervical cancers. In human HPV <sup>+</sup> cervical cancer cells, siRNA against <i>LEDGF</i> increased sensitivity to genotoxic therapies, including radiation and camptothecin, compared with control siRNA. In human cervix biopsies, <i>LEDGF</i> expression was higher in HPV <sup>+</sup> lesions than in normal samples. Next steps could include developing <i>LEDGF</i> inhibitors.<br><br><b>SciBX 7(15); doi:10.1038/scibx.2014.428</b><br><b>Published online April 17, 2014</b>  | Patent and licensing status unavailable     | Leitz, J. <i>et al. PLoS Pathog.</i> ; published online March 6, 2014; doi:10.1371/journal.ppat.1003957<br><b>Contact:</b> Felix Hoppe-Seyler, German Cancer Research Center, Heidelberg, Germany<br>e-mail: <a href="mailto:hoppe-seyler@dkfz.de">hoppe-seyler@dkfz.de</a><br><b>Contact:</b> Karin Hoppe-Seyler, same affiliation as above<br>e-mail: <a href="mailto:k.hoppe-seyler@dkfz.de">k.hoppe-seyler@dkfz.de</a> |

## This week in therapeutics (continued)

| Indication                    | Target/marker/pathway                         | Summary   | Licensing status                        | Publication and contact information  |
|-------------------------------|---|---|---|--|
| Ovarian cancer                | Ras-related associated with diabetes (RRAD)   | Human sample, cell culture and mouse studies suggest increasing RRAD activity could help treat ovarian cancer. In human ovarian cancer tissue, methylation of the RRAD promoter was greater and RRAD expression was lower than those in normal tissue. In cultured human ovarian cancer cells, a demethylating agent led to partial demethylation of the RRAD promoter and increased RRAD expression compared with no treatment. In mice, injection of various RRAD-overexpressing human ovarian cancer cells resulted in no tumor formation or decreased tumor formation compared with injection of matched cell lines with normal RRAD expression. Next steps could include screening for pharmacological agents that increase RRAD activity.<br><br><b>SciBX 7(15); doi:10.1038/scibx.2014.429</b><br><b>Published online April 17, 2014</b>   | Patent and licensing status unavailable | Wang, Y. <i>et al. J. Biol. Chem.</i> ; published online March 19, 2014; doi:10.1074/jbc.M113.527671<br><b>Contact:</b> Zhong Sheng Sun, Beijing Institutes of Life Science, Chinese Academy of Sciences, Beijing, China<br>e-mail: <a href="mailto:zhongshengsun@yeah.net">zhongshengsun@yeah.net</a><br><b>Contact:</b> Kai-Fu Tang, Wenzhou Medical University, Wenzhou, China<br>e-mail: <a href="mailto:tangkaifu@hotmail.com">tangkaifu@hotmail.com</a>            |
| <b>Cardiovascular disease</b> |   |   |   |  |
| Cardiovascular disease        | Transmembrane 6 superfamily member 2 (TM6SF2) | Studies in human samples and mice suggest inhibiting TM6SF2 could help lower total cholesterol levels. In 5,771 Norwegians, genomewide assessment of coding variants identified an association between the rs58542926 SNP in <i>TM6SF2</i> and low total cholesterol levels. In mice, <i>Tm6sf2</i> overexpression in the liver increased total cholesterol compared with overexpression of a control gene. In mice, shRNA against <i>Tm6sf2</i> decreased total cholesterol levels compared with control shRNA. Next steps could include identifying carriers of the rs58542926 SNP in clinical trials of lipid-modulating therapies.<br><br><b>SciBX 7(15); doi:10.1038/scibx.2014.430</b><br><b>Published online April 17, 2014</b>  | Patent and licensing status unavailable | Holmen, O.L. <i>et al. Nat. Genet.</i> ; published online March 16, 2014; doi:10.1038/ng.2926<br><b>Contact:</b> Cristen J. Willer, University of Michigan, Ann Arbor, Mich.<br>e-mail: <a href="mailto:cristen@umich.edu">cristen@umich.edu</a><br><b>Contact:</b> Kristian Hveem, Norwegian University of Science and Technology, Levanger, Norway<br>e-mail: <a href="mailto:kristian.hveem@ntnu.no">kristian.hveem@ntnu.no</a>                                       |
| <b>Dental disease</b>         |   |   |   |  |
| Periodontitis                 | IL-17A; IL-23                                 | Patient and mouse studies suggest inhibiting IL-17A or IL-23 could help treat the severe periodontitis that develops in patients who have leukocyte adhesion deficiency type I (LAD I). In patients with LAD I who have periodontitis, gum levels of IL-17A were higher than those in patients with periodontitis alone. In mouse models of LAD I with periodontitis, gingival levels of IL-23- and IL-17a-producing T cells correlated with loss of periodontal bone. In the mice, a rat antibody against IL-23 or IL-17a decreased periodontal bone loss compared with an inactive control antibody. Next steps include testing whether IL-23 and IL-17A drive periodontitis in other diseases involving defective neutrophil recruitment.<br>Novartis AG's secukinumab (AIN457), a human IgG1 mAb targeting IL-17A, is under review to treat psoriasis; in Phase III testing to treat psoriatic arthritis, rheumatoid arthritis (RA) and ankylosing spondylitis; and in Phase II trials to treat multiple sclerosis (MS).<br>Eli Lilly and Co.'s ixekizumab (LY2439821), a humanized mAb against IL-17A, is in Phase III testing to treat psoriasis and psoriatic arthritis and Phase I trials to treat RA.<br>Merck & Co. Inc.'s tildrakizumab (MK-3222), an anti-IL-23 antibody, is in Phase III testing to treat psoriasis.<br><br><b>SciBX 7(15); doi:10.1038/scibx.2014.431</b><br><b>Published online April 17, 2014</b> | Unpatented; available for partnering    | Moutsopoulos, N.M. <i>et al. Sci. Transl. Med.</i> ; published online March 26, 2014; doi:10.1126/scitranslmed.3007696<br><b>Contact:</b> Niki M. Moutsopoulos, National Institutes of Health, Bethesda, Md.<br>e-mail: <a href="mailto:nmoutsop@mail.nih.gov">nmoutsop@mail.nih.gov</a><br><b>Contact:</b> George Hajishengallis, University of Pennsylvania School of Dental Medicine, Philadelphia, Pa.<br>e-mail: <a href="mailto:geoh@upenn.edu">geoh@upenn.edu</a> |

## This week in therapeutics (continued)

| Indication  | Target/marker/pathway  | Summary   | Licensing status                                  | Publication and contact information  |
|---|--|---|---|--|
| <b>Inflammation</b>                                       |  |   |   |  |
| Asthma  | Potassium channel Kv1.3 (KCNA3)                              | Rat studies suggest KCNA3 antagonists could be useful for treating asthma. In a rat model of allergen-induced asthma, injection of the peptide-based KCNA3 inhibitor ShK-186 decreased airway inflammation, airway hyper-responsiveness and T helper type 2 (Th2) lymphocyte function compared with vehicle injection. Next steps could include evaluating ShK-186 in additional animal models of asthma.<br><br>Airmid Inc. and Kineta Inc. have ShK-186 in Phase I testing to treat multiple sclerosis (MS), lupus and psoriatic arthritis. conoGenetix biosciences GmbH has the KCNA3 antagonists cgtx_A and cgtx_F/cgtx_G in preclinical development to treat MS and rheumatoid arthritis (RA). | Patent and licensing status unavailable           | Koshy, S. <i>et al. J. Biol. Chem.</i> ; published online March 18, 2014; doi:10.1074/jbc.M113.517037<br><b>Contact:</b> Christine Beeton, Baylor College of Medicine, Houston, Texas<br>e-mail: <a href="mailto:beeton@bcm.edu">beeton@bcm.edu</a>  |
| <b>Neurology</b>  |  |   |   |  |
| Alzheimer's disease (AD)                                  | RE1-silencing transcription factor (REST; NRSE)              | Studies in human samples and mice suggest activating REST could help protect against age-related neurodegeneration. In postmortem samples from patients with AD, REST expression was lower than that in samples from aged subjects without AD. In mice, CNS-specific <i>Rest</i> knockout led to progressive age-related neurodegeneration compared with no alteration. In cultured human neuronal cells, moderate REST overexpression decreased oxidative stress-induced death compared with no overexpression. Next steps could include developing pharmacological REST activators.   | Patent and licensing status unavailable           | Lu, T. <i>et al. Nature</i> ; published online March 19, 2014; doi:10.1038/nature13163<br><b>Contact:</b> Bruce A. Yankner, Harvard Medical School, Boston, Mass.<br>e-mail: <a href="mailto:bruce_yankner@hms.harvard.edu">bruce_yankner@hms.harvard.edu</a>  |
| Alzheimer's disease (AD); frontal temporal dementia (FTD) | Microtubule-associated protein- $\tau$ (MAPT; tau; FTDP-17)  | Mouse studies suggest inhibiting the oligomeric extracellular form of tau could help treat tauopathies associated with AD and FTD. In a mouse model of FTD, an intracerebroventricular or i.v. injection of a polyclonal antibody targeting oligomeric tau decreased brain levels of oligomeric tau and increased locomotion and memory performance compared with injection of control IgG or antibodies that target monomeric tau or tau in neurofibrillary tangles. Next steps include further characterizing sequences and humanization potential of the oligomeric tau-targeting antibodies and testing them in additional mouse models.  | Patent application filed; available for licensing | Castillo-Carranza, D.L. <i>et al. J. Neurosci.</i> ; published online March 19, 2014; doi:10.1523/JNEUROSCI.3192-13.2014<br><b>Contact:</b> Rakez Kaye, The University of Texas Medical Branch, Galveston, Texas<br>e-mail: <a href="mailto:rakayed@utmb.edu">rakayed@utmb.edu</a>   |
| <b>Various</b>  |  |   |   |  |
| Autoimmune disease; inflammation                          | Platelet/endothelial cell adhesion molecule 1 (PECAM1; CD31) | <i>In vitro</i> and mouse studies suggest increasing CD31 signaling could help treat inflammatory and autoimmune diseases. In mice, a CD31 agonist decreased dendritic cell maturation and migration compared with vehicle. In a mouse model of experimental autoimmune encephalomyelitis (EAE), adoptive transfer of dendritic cells treated with a CD31 peptide led to decreased production of inflammatory cytokines and lower disease severity compared with transfer of immature dendritic cells. Ongoing studies include development of shorter peptides as drug candidates for chronic inflammatory diseases.  | Patents filed; available for licensing            | Clement, M. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online March 10, 2014; doi:10.1073/pnas.1314505111<br><b>Contact:</b> Giuseppina Caligiuri, Institut National de la Santé et de la Recherche Médicale (INSERM), Paris, France<br>e-mail: <a href="mailto:giuseppina.caligiuri@inserm.fr">giuseppina.caligiuri@inserm.fr</a> |

## This week in therapeutics (continued)

| Indication                          | Target/marker/pathway                            | Summary  | Licensing status                        | Publication and contact information  |
|-------------------------------------|--|--|---|--|
| Autoimmune disease; inflammation    | Tumor necrosis factor- $\alpha$ (TNF- $\alpha$ ) | <p>Mouse and <i>in vitro</i> culture studies identified a small molecule TNF-<math>\alpha</math> inhibitor that could be useful for treating autoimmune and inflammatory diseases. In a murine cell line, the small molecule suppressed TNF-<math>\alpha</math>-induced cell death and expression of proinflammatory cytokines with potency comparable to that of a neutralizing mAb against TNF-<math>\alpha</math>. <i>In vitro</i> assays showed that the small molecule bound directly to human TNF-<math>\alpha</math> with high affinity. In a mouse model of hepatitis, the small molecule decreased liver inflammation and increased survival compared with vehicle. Next steps could include developing optimized derivatives of the identified TNF-<math>\alpha</math> inhibitor and evaluating them in additional models of autoimmune and inflammatory diseases.</p> <p><b>SciBX 7(15); doi:10.1038/scibx.2014.436</b><br/>Published online April 17, 2014</p> | Patent and licensing status unavailable | <p>Ma, L. <i>et al. J. Biol. Chem.</i>; published online March 14, 2014; doi:10.1074/jbc.M113.521708<br/><b>Contact:</b> Jiayi Zhou, Chinese Academy of Medical Sciences, Tianjin, China<br/>e-mail: <a href="mailto:zhoujx@ihcams.ac.cn">zhoujx@ihcams.ac.cn</a></p>                |
| Stroke; ischemia/reperfusion injury | IL-21  | <p>Mouse studies suggest inhibiting IL-21 signaling could help prevent ischemia/reperfusion injury in stroke. In mice, cerebral ischemia/reperfusion injury increased <i>Il-21</i> expression compared with no injury. In a mouse model of cerebral ischemia/reperfusion injury, knockout of <i>Il-21</i> or treatment with an IL-21 decoy receptor decreased neuronal injury compared with no alteration or saline treatment. Next steps could include testing IL-21 inhibitors in combination with antithrombotic drugs in models of ischemic stroke. Novo Nordisk A/S has a recombinant human mAb against IL-21 in Phase II testing to treat Crohn's disease and Phase I trials to treat lupus.</p> <p><b>SciBX 7(15); doi:10.1038/scibx.2014.437</b><br/>Published online April 17, 2014</p>   | Patent and licensing status unavailable | <p>Clarkson, B.D.S. <i>et al. J. Exp. Med.</i>; published online March 10, 2014; doi:10.1084/jem.20131377<br/><b>Contact:</b> Zsuzsanna Fabry, University of Wisconsin–Madison, Madison, Wis.<br/>e-mail: <a href="mailto:zfabry@facstaff.wisc.edu">zfabry@facstaff.wisc.edu</a></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   |
|--|---|--|---|
| <b>Assays &amp; screens</b>  |   |  |   |
| A refined, allele-specific quantitative PCR assay called Intplex for analysis of circulating cell-free DNA (cfDNA) mutations   | Intplex could be used to characterize small, highly fragmented, tumor-derived cfDNA for diagnostic applications. Current cfDNA sequencing methods have difficulty determining the presence of point mutations in fragments smaller than 100 base pairs. In tumor tissue samples from patients with metastatic colorectal cancer, tumor tissue analysis methods detected <i>K-Ras</i> ( <i>KRAS</i> ) mutations in 36 of 95 samples and the <i>BRAF V600E</i> mutation in 5 of 95 samples. In plasma samples from the same patients, Intplex detected <i>KRAS</i> mutations in 37 of 95 samples and <i>BRAF V600E</i> mutations in 5 of 95 samples, giving a concordance of 96% and 100%. Ongoing work includes using Intplex to characterize samples from larger patient cohorts. | Patented; exclusively licensed to an undisclosed company             | Thierry, A.R. <i>et al. Nat. Med.</i> ; published online March 23, 2014; doi:10.1038/nm.3511<br><b>Contact:</b> Alain R. Thierry, Montpellier Cancer Research Institute, Montpellier, France<br>e-mail: <a href="mailto:alain.thierry@inserm.fr">alain.thierry@inserm.fr</a>  |
|  | <b>SciBX 7(15); doi:10.1038/scibx.2014.438</b><br>Published online April 17, 2014   |  |   |
| Tumor endothelial marker (TEM)-expressing circulating endothelial cells (CECs) as a blood-based marker to detect tumors and monitor response to antiangiogenic therapy | Studies in human samples and mice suggest TEM <sup>+</sup> CECs could help detect the presence of tumors and monitor tumor response to antiangiogenic therapy. Mice with human non-small cell lung cancer (NSCLC) xenografts had higher numbers of plexin domain containing 1 (PLXDC1; TEM7) <sup>+</sup> CECs in blood than mice without xenografts. In the mouse xenograft model, antiangiogenic drugs decreased the number of TEM7 <sup>+</sup> CECs in blood compared with vehicle. In patients undergoing tumor resection, TEM <sup>+</sup> CEC numbers in blood samples taken after surgery were lower than those in samples taken before resection. Next steps could include assessing TEM <sup>+</sup> CEC numbers in a larger patient cohort.                            | Patent and licensing status unavailable                              | Mehran, R. <i>et al. Cancer Res.</i> ; published online March 13, 2014; doi:10.1158/0008-5472.CAN-13-2044<br><b>Contact:</b> John V. Heymach, The University of Texas MD Anderson Cancer Center, Houston, Texas<br>e-mail: <a href="mailto:jheykach@mdanderson.org">jheykach@mdanderson.org</a>   |
|  | <b>SciBX 7(15); doi:10.1038/scibx.2014.439</b><br>Published online April 17, 2014   |  |   |
| <b>Chemistry</b>   |   |  |   |
| Isoacyl dipeptides to increase insulin yield from chemical synthesis   | Chemical synthesis of insulin using isoacyl dipeptides could improve yield of the hormone. Synthesis of insulin—a protein composed of two peptide chains—is inefficient, with yields generally less than 15%. Incorporation of an isoacyl dipeptide into the insulin A chain improved purification of the peptide and enabled on-resin intramolecular disulfide bond formation. Incorporation of an isoacyl dipeptide in the insulin B chain increased yield compared with no isoacyl dipeptide. Subsequent ligation of the two chains produced insulin with an overall yield of 24%. Next steps could include further optimizing the synthesis process.  | Patent and licensing status unavailable                              | Liu, F. <i>et al. Angew. Chem. Int. Ed.</i> ; published online March 11, 2014; doi:10.1002/anie.201310735<br><b>Contact:</b> Fa Liu, Eli Lilly & Co., Indianapolis, Ind.<br>e-mail: <a href="mailto:liufx@lilly.com">liufx@lilly.com</a>  |
|  | <b>SciBX 7(15); doi:10.1038/scibx.2014.440</b><br>Published online April 17, 2014   |  |   |
| <b>Drug platforms</b>  |   |  |   |
| Binary nylon-3 copolymers containing cationic and hydrophobic subunits for antimicrobial activity  | <i>In vitro</i> studies identified binary nylon-3 copolymers containing cationic and hydrophobic subunits that could help treat and prevent bacterial infections. Nylon-3 copolymers were designed to mimic antibacterial host-defense peptides by modulating the arrangement of backbone components and subunits. The copolymer with the highest potency against prokaryotic cells versus eukaryotic cells showed strong antibacterial activity against <i>Escherichia coli</i> and methicillin-resistant <i>Staphylococcus aureus</i> . Resistance against the copolymer was not observed through 10 cell-culturing passages. Next steps include evaluating the polymers as antimicrobial agents on surfaces of implantable devices.  | Patent applications filed covering polymers; available for licensing | Liu, R. <i>et al. J. Am. Chem. Soc.</i> ; published online March 7, 2014; doi:10.1021/ja500367u<br><b>Contact:</b> Samuel H. Gellman, University of Wisconsin–Madison, Madison, Wis.<br>e-mail: <a href="mailto:gellman@chem.wisc.edu">gellman@chem.wisc.edu</a><br><b>Contact:</b> Kristyn S. Masters, same affiliation as above<br>e-mail: <a href="mailto:kmasters@wisc.edu">kmasters@wisc.edu</a> |
|  | <b>SciBX 7(15); doi:10.1038/scibx.2014.441</b><br>Published online April 17, 2014   |  |   |

## This week in techniques (continued)

| Approach   | Summary   | Licensing status  | Publication and contact information  |
|--|---|---|--|
| Clustered, regularly interspaced short palindromic repeats (CRISPR)-based genome editing platform to treat genetic liver disease   | <p>Mouse studies suggest CRISPR-based genome editing could be used to treat tyrosinemia type I (TTI), a fatal disease resulting from mutation of <i>fumarylacetoacetate hydrolase (FAH)</i> and accumulation of toxic metabolites. A compound that acts upstream of FAH called 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC) can keep <i>Fah5981SB</i>-mutant mice alive. In a <i>Fah5981SB</i> mouse model of hereditary TTI, tail vein injection of a <i>Fah</i>-correcting, single-stranded DNA (ssDNA) donor, a CRISPR-associated 9 (Cas9)-expressing ssDNA and a <i>Fah</i>-targeting single-guide RNA restored <i>Fah</i> mRNA to up to 36% of wild-type levels, resulted in widespread patches of <i>Fah</i><sup>+</sup> hepatocytes and prevented weight loss upon NTBC withdrawal. Next steps include testing the CRISPR platform in large-animal studies and developing delivery systems.</p> <p><b>SciBX 7(15); doi:10.1038/scibx.2014.442</b><br/> <b>Published online April 17, 2014</b></p>  | Multiple patent applications filed; licensing discussions in progress   | <p>Yin, H. <i>et al. Nat. Biotechnol.</i>; published online March 30, 2014; doi:10.1038/nbt.2884<br/> <b>Contact:</b> Daniel G. Anderson, Massachusetts Institute of Technology, Cambridge, Mass.<br/> e-mail: <a href="mailto:dgander@mit.edu">dgander@mit.edu</a></p>  |
| Mice with directed integration of human immunoglobulin transgenes to produce chimeric antibodies with fully human variable domains | <p>Transgenic mice that produce chimeric antibodies with human variable domains could be used for therapeutic antibody discovery. Previous development of transgenic mice with humanized immunoglobulins was limited by size of and random integration of human transgenes. In mouse embryonic stem cells, the entire human immunoglobulin variable-gene repertoire was inserted into the corresponding mouse loci using bacterial artificial chromosome-based targeting vectors. The resulting transgenic mice had functional immune systems that, when inoculated with human IL-6 receptor (CD126), produced antibodies with a wide range of binding affinities for the antigen. Ongoing work includes testing in clinical studies a high-affinity anti-CD126 antibody in which the mouse constant domain has been exchanged with the human constant domain.</p> <p><b>SciBX 7(15); doi:10.1038/scibx.2014.443</b><br/> <b>Published online April 17, 2014</b></p>  | Patented; nonexclusively licensed to Astellas Pharma Inc. to use the mice to discover human mAbs; partnership with Sanofi to discover and commercialize human mAbs; Academic VelocImmune Investigators Program established to provide academics with access to the mice | <p>Macdonald, L.E. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online March 25, 2014; doi:10.1073/pnas.1323896111<br/> Murphy, A.J. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online March 25, 2014; doi:10.1073/pnas.1324022111<br/> <b>Contact:</b> Andrew J. Murphy, Regeneron Pharmaceuticals, Inc., Tarrytown, N.Y.<br/> e-mail: <a href="mailto:andrew.murphy@regeneron.com">andrew.murphy@regeneron.com</a><br/> <b>Contact:</b> George D. Yancopoulos, same affiliation as above<br/> e-mail: <a href="mailto:george@regeneron.com">george@regeneron.com</a></p> |
| <b>Markers</b>   |   |   |  |
| Markers of distinct sonic hedgehog homolog (SHH)-driven medulloblastomas   | <p>Mouse and sequencing studies suggest SHH-driven medulloblastomas in adults, children and infants are molecularly distinct from one another and should be treated using different protocols. Most adults but only about half of pediatric patients with SHH-driven medulloblastomas respond to smoothened (SMO) inhibitors. In SHH-driven medulloblastoma tumor samples from 50 adults, 33 children over 3 years old and 50 infants, sequencing showed that <i>SMO</i> mutations were enriched in adults, <i>suppressor of fused homolog (SUFU)</i> mutations were found almost exclusively in infants and amplifications in both <i>v-myc myelocytomatosis viral related oncogene neuroblastoma derived (MYCN; NMYC)</i> and <i>glioma-associated oncogene homolog 2 zinc finger protein (GLI2)</i> plus <i>p53</i> mutations were enriched in children. In mouse xenograft models, <i>SUFU</i>-mutated and <i>MYCN</i>-amplified SHH-driven medulloblastomas showed resistance to the small molecule SMO inhibitor LDE225. Next steps could include developing a patient screening assay for the gene alterations.</p> <p>Novartis AG has LDE225 in Phase III testing to treat basal cell carcinoma (BCC) and Phase I testing to treat other cancers.</p> <p>Roche's Genentech Inc. unit markets the SMO inhibitor Erivedge vismodegib to treat BCC.</p> <p>At least four other companies have SMO inhibitors in Phase III or earlier testing to treat various cancers.</p> <p><b>SciBX 7(15); doi:10.1038/scibx.2014.444</b><br/> <b>Published online April 17, 2014</b></p> | Patent and licensing status unavailable   | <p>Kool, M. <i>et al. Cancer Cell</i>; published online March 17, 2014; doi:10.1016/j.ccr.2014.02.004<br/> <b>Contact:</b> Marcel Kool, German Cancer Research Center, Heidelberg, Germany<br/> e-mail: <a href="mailto:m.kool@dkfz.de">m.kool@dkfz.de</a></p>   |

## This week in techniques (continued)

| Approach   | Summary  | Licensing status                                     | Publication and contact information  |
|--|--|--|--|
| MicroRNA-155 (miR-155) as a predictive marker of breast cancer response to radiation therapy                           | <i>In vitro</i> and mouse studies suggest miR-155 levels could help predict breast cancer response to radiation therapy. In two independent cohorts of patients with triple-negative breast cancer that received chemotherapy and radiation therapy, elevated miR-155 expression was associated with increased overall survival. In a human triple-negative breast cancer cell line, expression of miR-155 decreased levels of RAD51 homolog (RAD51), a factor involved in DNA repair, and increased sensitivity to ionizing radiation compared with expression of a scrambled oligonucleotide. Next steps include validating the results in larger cohorts.<br><br><b>SciBX 7(15); doi:10.1038/scibx.2014.445</b><br><b>Published online April 17, 2014</b>   | Findings unpatented; licensing status not applicable | Gasparini, P. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online March 10, 2014; doi:10.1073/pnas.1402604111<br><b>Contact:</b> Carlo M. Croce, The Ohio State University, Columbus, Ohio<br>e-mail: <a href="mailto:carlo.croce@osumc.edu">carlo.croce@osumc.edu</a> |
| Mitochondrial DNA (mtDNA) mutations and impaired glucose utilization as markers of sensitivity to biguanides in cancer | Cell culture studies suggest mutations in mtDNA and impaired glucose utilization could be useful as markers to help predict cancer sensitivity to biguanides, which inhibit oxidative phosphorylation. Biguanides such as metformin and phenformin are diabetes drugs that inhibit the growth of some cancers, but markers to predict cancer sensitivity to these drugs have not been discovered. In a panel of human cancer cell lines cultured under low-glucose conditions, metabolic profiling, DNA sequencing and RNAi screening showed that impaired glucose utilization and mutations in mtDNA-encoded genes for the core complex I subunits of mitochondria were associated with increased sensitivity to inhibition of oxidative phosphorylation. In low-glucose culture conditions, cancer cell lines with impaired glucose utilization or those carrying mutations in mtDNA showed 5- to 20-fold increased sensitivity to phenformin compared with control cancer cell lines and an immortalized B cell line. Next steps could include validating these markers of biguanide sensitivity in a larger patient cohort and then developing a patient screening assay. Metformin is a generic drug used to treat type 2 diabetes. Phenformin was previously marketed to treat type 2 diabetes but was withdrawn in 1978 because of a high risk for lactic acidosis.<br><br><b>SciBX 7(15); doi:10.1038/scibx.2014.446</b><br><b>Published online April 17, 2014</b> | Patent and licensing status unavailable              | Birsoy, K. <i>et al. Nature</i> ; published online March 16, 2014; doi:10.1038/nature13110<br><b>Contact:</b> David M. Sabatini, Whitehead Institute for Biomedical Research, Cambridge, Mass.<br>e-mail: <a href="mailto:sabatini@wi.mit.edu">sabatini@wi.mit.edu</a>         |



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| Drugs for Neglected Diseases initiative           | 5     |          | Mitsubishi Tanabe Pharma Corp.   | 7       | University of Ioannina                                      | 4  | Casein kinase 1 $\alpha$                       | 11 |
| <b>E</b>  |       |          | <b>N</b>   |         | University of Leicester                                     | 4  | CD126  | 17 |
| Eisai Co. Ltd.                                    | 5     |          | National Institute for Health and Care Excellence                          | 4       | University of Liverpool                                     | 5  | CD24   | 9  |
| Eli Lilly and Co.                                 | 4,13  |          | National Institute of Biomedical Innovation                                | 5       | University of North Carolina at Chapel Hill                 | 9  | CD31   | 14 |
| EMBL-EBI  | 5     |          | National Institutes of Health  | 4       | University of Oxford  | 3  | CD44   | 9  |
| Emergent BioSolutions Inc.                        | 4     |          | Neomed Institute   | 7       | University of Sherbrooke                                    | 7  | CD95   | 11 |
| EORTC   | 4     |          | Novartis AG  | 4,13,17 | University of Texas MD Anderson Cancer Center               | 5  | Cesol  | 6  |
| Epigenetix Inc.                                   | 7     |          | Novo Nordisk A/S   | 4,15    | University of Texas Medical Branch                          | 4  | Cgtx_A   | 14 |
| European Medicines Agency                         | 4     |          | <b>O</b>   |         | University of Tokyo   | 5  | Cgtx_F/cgtx_G                                  | 14 |
| <b>F</b>  |       |          | Oncoethix S.A.   | 7       | University of Washington                                    | 5  | CKI- $\alpha$                                  | 11 |
| Fred Hutchinson Cancer Research Center            | 5     |          | Ono Pharmaceutical Co. Ltd.  | 5       | University of Wisconsin-Madison                             | 4  | CNR1   | 7  |
| French National Authority for Health              | 4     |          | <b>P</b>   |         | <b>V</b>  |    | CNR2   | 7  |
| <b>G</b>  |       |          | Pfizer Inc.  | 3,7     | Vanderbilt-Ingram Cancer Center                             | 5  | CPI-0610                                       | 7  |
| Genentech Inc.                                    | 17    |          | Public Health Agency of Canada   | 4       | <b>W</b>  |    | CRISPR-associated 9                            | 17 |
| Genocea Biosciences Inc.                          | 5     |          | <b>R</b>   |         | Weill Cornell Medical College                               | 9  | Crizotinib                                     | 1  |
| German Federal Ministry of Education and Research | 5     |          | Rabin Medical Center   | 5       | Wellcome Trust Sanger Institute                             | 5  | CSNK1A   | 11 |
| GlaxoSmithKline plc                               | 3,4,7 |          | Research Center for Molecular Medicine of the Austrian Academy of Sciences | 2       | <b>Y</b>  |    | dATP   | 1  |
| Global Health Innovative Technology Fund          | 6     |          | Resverlogix Corp.  | 7       | Yeshiva University  | 4  | dGTP   | 1  |
| <b>H</b>  |       |          | Roche  | 4,17    | <b>Z</b>  |    | DNA (cytosine-5-)-methyltransferase 3 $\alpha$ | 11 |
| Harvard Medical School                            | 5     |          | Rockefeller University   | 5       | Zalgen Labs LLC   | 4  | DNMT3A   | 11 |
| Harvard School of Public Health                   | 9     |          | Rosetta Genomics Ltd.  | 5       | .....   |    | Doxorubicin                                    | 9  |
| Health Care Insurance Board of the Netherlands    | 4     |          | Ruga Corp.   | 10      | <b>Target and compound index</b>                            |    | <b>E</b>                                       |    |
| Heidelberg University Hospital                    | 5     |          | <b>S</b>   |         | 2-(2-Nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione   | 17 | E1224  | 6  |
|   |       |          | Sanofi   | 4,17    |   |    | EGFR2  | 9  |
|   |       |          | Scripps Research Institute   | 4       |   |    | Endoplasmic reticulum to nucleus signaling 1   | 9  |
|   |       |          |  |         |   |    | ErbB2  | 9  |
|   |       |          |  |         |   |    | Erivedge                                       | 17 |
|   |       |          |  |         |   |    | ERN1   | 9  |
|   |       |          |  |         |   |    | Estrogen receptor                              | 9  |
|   |       |          |  |         |   |    | <b>F</b>                                       |    |
|   |       |          |  |         |   |    | FAH  | 17 |
|   |       |          |  |         |   |    | Fas ligand                                     | 11 |
|   |       |          |  |         |   |    | Fas receptor                                   | 11 |
|   |       |          |  |         |   |    | FASL   | 11 |
|   |       |          |  |         |   |    | FTDP-17  | 14 |
|   |       |          |  |         |   |    | <i>Fumarylacetoacetate hydrolase</i>           | 17 |

|   |      |  |    |  |    |  |    |
|---|------|--|----|--|----|--|----|
| <b>G</b>  |      | <b>M</b>                               |    |  |    |  |    |
| <i>GLI2</i>   | 17   | MAPT                                   | 14 | Phenformin   | 18 | <i>SUFU</i>  | 17 |
| <i>Glioma-associated oncogene homolog 2 zinc finger protein</i> |      | Metformin                              | 18 | Platelet/endothelial cell adhesion molecule 1      | 14 | <i>Suppressor of fused homolog</i>   | 17 |
| Glucose   | 18   | Methicillin                            | 16 | Plexin domain containing 1                         | 16 | <b>T</b>   |    |
| GSK525762   | 7    | MicroRNA-155                           | 18 | PLXDC1   | 16 | Tau  | 14 |
| <b>H</b>  |      | Microtubule-associated protein- $\tau$ | 14 | Potassium channel Kv1.3                            | 14 | TEM  | 16 |
| HER2  | 9    | miR-155                                | 18 | Praziquantel                                       | 6  | TEM7   | 16 |
| <i>HIF1<math>\alpha</math></i>                                  | 9    | miR-BART9                              | 12 | Progesterone receptor                              | 9  | TEN-010  | 7  |
| <i>HIF1A</i>  | 9    | MK-3222                                | 13 | PSIP1  | 12 | Tildrakizumab  | 13 |
| <i>Hypoxia-inducible factor 1<math>\alpha</math></i>            | 9    | MKC-3946                               | 10 | Purinergic receptor P2X ligand-gated ion channel 3 | 7  | TM6SF2   | 13 |
| <b>I</b>  |      | MKC204                                 | 10 | <b>R</b>   |    | TNF superfamily, member 6  | 11 |
| I-BET   | 7    | MTH1                                   | 1  | RAD51  | 18 | TNF- $\alpha$  | 15 |
| IgG1  | 13   | <i>MYCN</i>                            | 17 | RAD51 homolog                                      | 18 | Transient receptor potential vanilloid 1                                   | 7  |
| IL-17A  | 13   | <b>N</b>                               |    | Ras  | 1  | Transmembrane 6 superfamily member 2                                       | 13 |
| IL-21   | 15   | NEO1940                                | 7  | Ras-related associated with diabetes               | 13 | TRPV1  | 7  |
| IL-23   | 13   | NEO6860                                | 7  | Ras  | 1  | Tubulin  | 12 |
| IL-6 receptor   | 17   | Neu                                    | 9  | Ras-related associated with diabetes               | 13 | Tumor endothelial marker   | 16 |
| Insulin   | 16   | <i>NMYC</i>                            | 17 | Ravunozazole                                       | 6  | Tumor necrosis factor- $\alpha$  | 15 |
| Ipilimumab  | 5    | NRSF                                   | 14 | RE1-silencing transcription factor                 | 14 | <b>V</b>   |    |
| IRE1  | 9    | NTBC                                   | 17 | REST   | 14 | <i>v-Myc myelocytomatosis viral related oncogene neuroblastoma derived</i> | 17 |
| Ixekizumab  | 13   | NUDT1                                  | 1  | RRAD   | 13 | Velcade  | 10 |
| <b>J</b>  |      | Nylon-3                                | 16 | RVX-208  | 7  | Vismodegib   | 17 |
| JQ1   | 7    | <b>O</b>                               |    | <b>S</b>   |    | VR1  | 7  |
| <b>K</b>  |      | OTX015                                 | 7  | SCH51344   | 7  | <b>X</b>   |    |
| <i>K-Ras</i>  | 1,16 | OXTR                                   | 7  | Secukinumab  | 13 | X-box binding protein 1  | 9  |
| KCNA3   | 14   | Oxytocin receptor                      | 7  | SHH  | 17 | Xalkori  | 1  |
| KRAS  | 1,16 | <b>P</b>                               |    | ShK-186  | 14 | XBP1   | 9  |
| <b>L</b>  |      | P2X3                                   | 7  | Signal transducer and activator of transcription 3 | 12 | <b>Y</b>   |    |
| LDE225  | 17   | <i>p53</i>                             | 17 | SMO  | 17 | Y-803  | 7  |
| LEDGF   | 12   | p75                                    | 12 | Smoothened   | 17 | Yervoy   | 5  |
| LEDGF/p75   | 12   | Paclitaxel                             | 12 | Sonic hedgehog homolog                             | 17 |  |    |
| LY2439821   | 13   | PC4 and SFRS1-interacting protein      | 12 | STAT3  | 12 |  |    |
|   |      | PECAM1                                 | 14 | STF-08310  | 10 |  |    |

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