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By *Benjamin Boettner, Associate Editor*

The metabolic enzyme phosphoribosyl pyrophosphate synthetase 2 could represent a tractable way to modulate the notoriously undruggable oncogene MYC.¹ The findings from a **University of California, San Francisco** team are licensed to **Effector Therapeutics Inc.** and provide a clue as to how the company plans to attack protein translation-related mechanisms in cancers.

The UCSF group now plans to identify specific inhibitors of phosphoribosyl pyrophosphate synthetase 2 (PRPS2) and wants to see if the mechanism is present in cancers promoted by oncogenes other than MYC (c-Myc).

MYC is a transcription factor that tumors hijack to upregulate the metabolic machinery that promotes DNA and protein synthesis, glycolysis and glutaminolysis.² The problem is that transcription factors are difficult to target with small molecules or biologics. Indeed, there are only two disclosed molecules in development that target MYC, and both are nucleic acid-based therapies.

A team at UCSF set out to investigate whether protein synthesis and nucleotide synthesis were mechanistically linked downstream of MYC. The group began by asking which metabolic changes were tied to MYC's ability to upregulate protein biosynthesis. In a mouse model of Burkitt lymphoma, nucleotide levels in leukemic B cells were particularly dependent on Myc's ability to trigger protein translation. Additional studies showed that Myc-enhanced protein translation was directly coupled to nucleotide biosynthesis and that the rate-limiting enzyme was Prps2.

PRPS2 adds a pyrophosphate group from ATP to ribose-5-phosphate to generate a nucleotide precursor called 5-phosphoribosyl-1-pyrophosphate (PRPP).

MYC was already known to transcriptionally elevate levels of eukaryotic translation initiation factor 4E (eIF4E), which in turn binds to enhancers in target mRNAs to upregulate their translation. The UCSF team's studies identified the same enhancer element in the 5' portion of the Prps2 mRNA, thus providing a mechanism for its regulation by Myc.

Importantly, genetic knockout of *Prps2* by itself had no physiological or metabolic consequences in mice. However, in the presence of hyperactive Myc, loss of *Prps2* became lethal—it dramatically elevated apoptosis of B lymphocytes in the Myc-driven lymphoma model.

The synthetic lethality of Myc overexpression and *Prps2* loss in mice was recapitulated by knocking down *Prps2* using RNAi.

The reason healthy mice were not affected by the loss of Prps2 is the presence of Prps1, which shares 95% homology with Prps2. The key is

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that Prps1 is not affected by Myc and thus could carry out nucleotide biosynthesis. This also means that small molecule Prps2 inhibitors could provide tumor cell selectivity.

The findings were published in *Cell*. The team was led by Davide Ruggero, a professor in UCSF's Department of Urology.

"Classical high throughput screening has not offered a way to directly target MYC. These findings open up a new space for metabolic drug targets in MYC and perhaps other cancer contexts. As opposed to glycolysis and other metabolic pathways, direct regulators of nucleotide biosynthesis have not been as intensely looked at from a drug discovery perspective," said Neil Jones, senior group leader of discovery bioscience at **Cancer Research Technology**.

He added, "Targeting cancer metabolism often is thwarted by redundancy and rewiring, and the fact that Prps2 is so differently regulated than Prps1 might allow less compensation."

"Targeting cancer metabolism often is thwarted by redundancy and rewiring, and the fact that Prps2 is so differently regulated than Prps1 might allow less compensation."

—Neil Jones,
Cancer Research Technology

Cause and Effector

Ruggero is a cofounder of Effector Therapeutics, and the new paper is one of the first windows into the targets the company is attacking. UCSF has filed a patent on the findings, and the IP is licensed to Effector.

Effector raised \$45 million in a series A round last year. At the time, the company was not discussing its technology, except to say it was developing small molecules that selectively regulate translation of oncogenes.

Effector did not return calls seeking comment.

Ruggero now wants to evaluate the findings in a larger collection of tumor models driven by Myc and other oncogenes.

Zuzana Zachar, director of research at **Cornerstone Pharmaceuticals Inc.**, said that validating PRPS2 as a target will require a better understanding of its role in normal, nontransformed cells. "The lack of gross phenotypic abnormalities in mice does not exclude that Prps2 could perform functions in response to challenges like wounding, infection or involving inflammation," she said.

Cornerstone's CPI-613, a pyruvate dehydrogenase (PDH) inhibitor that interferes with cancer carbohydrate metabolism, is in Phase II testing for multiple cancers.

Both Jones and Heather Christofk said that the cancer cell lethality caused by Myc hyperactivation and Prps2 depletion should be validated in other tumor models that rely on Myc activation, such as some forms of breast cancer.

"An immediate next step to validate PRPS2 is to determine whether its levels are elevated in human cancers and whether this tracks with MYC overexpression or other oncogenes known to result in eIF4E activity," said Christofk, an assistant professor at the Institute for Molecular Medicine at the **University of California, Los Angeles David Geffen School of Medicine**.

“An immediate next step to validate PRPS2 is to determine whether its levels are elevated in human cancers and whether this tracks with MYC overexpression or other oncogenes known to result in eIF4E activity.”

**—Heather Christofk,
University of California,
Los Angeles David Geffen
School of Medicine**

Shokat’s lab to identify PRPS2-specific inhibitors. Shokat, also a cofounder of Effector, is chair of the Department of Cellular and Molecular Pharmacology at UCSF and a **Howard Hughes Medical Institute** investigator.

One key to finding an inhibitor will be getting selectivity for PRPS2 over PRPS1.

“Selective inhibitors of closely related isozymes are challenging to identify. However, lessons from the PI3K [phosphoinositide 3-kinase] field and many other enzyme classes have taught that selective inhibition of a

“Other oncogenic pathways could impinge on the same translational enhancer in the Prps2 mRNA, and it could be part of a larger signature,” added Jones.

Ruggero told *SciBX* that his laboratory is starting to investigate whether the Prps2-based mechanism is conserved in an array of Myc-dependent and Myc-independent tumor models.

Inhibitor search

Ruggero’s team at UCSF is collaborating with Kevan

single isozyme is possible with careful and diligent medicinal chemistry,” said Shokat. “This can be greatly aided by structure-based design.”

Marion Dorsch, VP of biology at cancer metabolism company **Agios Pharmaceuticals Inc.**, agreed that elucidating the structures of PRPS1 and PRPS2 could help guide the design of selective inhibitors. The comparison of the 3D structures of PRPS1 and PRPS2 may reveal exploitable differences between the two enzymes despite the 95% amino acid sequence identity.

“High throughput screening could enhance the probability to identify isoform-selective small molecules with allosteric inhibitory properties. Also, looking for inhibitors acting upstream to modulate PRPS2 vs. PRPS1” could be an approach worth exploring, she said.

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Cancer Research Technology, London, U.K.
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Effector Therapeutics Inc., San Diego, Calif.
Howard Hughes Medical Institute, Chevy Chase, Md.
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Translational tidbits

By Lev Osherovich and Kai-Jye Lou, Senior Writers

Autism Speaks to Google

Patient advocacy group **Autism Speaks** and **Google Inc.** have teamed up to sequence and make accessible the complete genomes of at least 10,000 patients with autism-spectrum disorder and controls. The resulting data set will be the world's largest collection of whole-genome sequence data and will be open to industry and academic researchers searching for clues about the origins of autism-spectrum disorder and possibly other diseases.

Under the Autism Speaks Ten Thousand Genomes Program (AUT10K), Autism Speaks will sequence samples from the Autism Genetics Resource Exchange (AGRE), a repository of biological samples and clinical records

from patients with ASD and their unaffected immediate relatives.

About one-third of the sequences will be from patients, and the rest will be from healthy controls.

Google will organize and host the data on its Google Cloud platform and will provide customized bioinformatic analysis tools to academic and industry researchers interested in probing the data set. Financial terms of the deal are undisclosed.

"We're aiming to assemble the most complete set of genomic data in ASD patients, their siblings and parents," said Autism Speaks CSO Robert Ring. "The database will contain medical information and biomarker analyses as well as sequence data."

Ring said that AUT10K will give researchers an opportunity to test hypotheses about the genetic factors behind ASD, a diverse set of neurodevelopmental disorders caused by a multitude of rare mutations and chromosomal abnormalities.

Table 1. Selected public-private partnerships for May 2014. Last month, the **University of California, San Francisco** launched a project to identify brain signaling pathways associated with anxiety and depression in epilepsy and Parkinson's disease (PD) and design implantable devices that could correct the abnormal brain patterns. The project is one of the first to be launched in support of the U.S.'s Brain Research through Advancing Innovative Neurotechnologies initiative and is funded through the Systems-Based Neurotechnology for Emerging Therapies program from the **U.S. Department of Defense's Defense Advanced Research Projects Agency**. On the pharma side, **Daiichi Sankyo Co. Ltd.** (Tokyo:4568) announced a pair of discovery deals focused on cancer and cardiovascular and metabolic diseases.

Source: *BioCentury Archives*

Companies	Institutions	Business area	Disclosed value	Purpose
Cubist Pharmaceuticals Inc. (NASDAQ:CBST)	NIH; Rutgers University; The Rockefeller University	Infectious disease	Up to \$26 million	Develop antibiotics against drug-resistant bacteria
None	Cornell University; Lawrence Livermore National Laboratory; New York University; University of California, Berkeley; University of California, San Francisco; U.S. Department of Defense	Neurology	Up to \$26 million	Understand and repair disrupted brain circuitry to treat mental illnesses
AstraZeneca plc (LSE:AZN; NYSE:AZN)	MRC Laboratory of Molecular Biology	Pharmaceuticals	Up to £9 million (\$15.1 million)	Fund preclinical projects at the two organizations to better understand disease biology
Berg Pharma LLC	Medical University of South Carolina	Autoimmune disease	Undisclosed	Identify new therapeutic pathways and biomarkers to treat lupus
Crown Bioscience Inc.	National Resource Center of Mutant Mice	Supply/service	Unavailable	Develop mouse models for cancer research
Daiichi Sankyo	MRC Technology	Cancer; cardiovascular disease; endocrine/metabolic disease	Undisclosed	Identify and select drug targets sourced from academia for cancer and cardiovascular and metabolic diseases
	Sanford-Burnham Medical Research Institute	Cardiovascular disease; endocrine/metabolic disease	Undisclosed	Discover treatments for cardiovascular-metabolic diseases
Debiopharm Group	Yale University	Autoimmune disease; inflammation	Undisclosed	Discover and develop oral inhibitors of macrophage migration inhibitory factor (MIF)
Enigma Diagnostics Ltd.	Chinese Center for Disease Control and Prevention	Infectious disease; diagnostics	Undisclosed	Develop point-of-care molecular diagnostic technology for infectious disease pathogens
None	Cell Therapy Catapult; Great Ormond Street Hospital; Royal Free Hospital; University College London	Transplantation	Undisclosed	Develop a tissue repair product for babies with esophageal atresia using stem cells from amniotic fluid and a donor scaffold
Nuvilex Inc. (OTCQB:NVLX)	University of Northern Colorado	Cancer	Undisclosed	Develop cannabis-based cancer treatments that use Nuvilex's Cell-in-a-Box, cellulose-based, live-cell encapsulation technology
RaQualia Pharma Inc. (JASDAQ:4579)	Kyoto University	Gene/cell therapy	Unavailable	Identify a small molecule that could induce differentiation and proliferation of induced pluripotent stem cells into immune cells
Sanofi (Euronext:SAN; NYSE:SNY)	Foundation Fighting Blindness	Ophthalmic disease	Unavailable	Share information and expertise that could help identify and advance development of potential therapies for inherited retinal diseases

Previous microarray studies and exome sequencing efforts by academics have yielded a long list of inherited and spontaneous mutations and copy number variations that account for up to 30% of ASD cases. According to Ring, unlocking the rare sequence variants behind the remaining 70% of cases requires a deeper dive into the genome.

“Understanding the full complexity behind autism has not been possible just with microarrays and exome sequencing, which miss a lot of the action in the wider genome,” said Ring.

For example, he said, noncoding DNA and epigenetic control of gene expression could be potential players in ASD that may have been missed by prior genomic studies.

“Whether through inherited *de novo* mutations or through epigenetic interactions with the environment, genetics is the fundamental driver of disease,” said Ring. “If you want to move this field forward, mapping the complete genomic variation in ASD is the best investment you can make. The immediate goal of the program is to get through 10,000 genomes, which is considered by statistical geneticists to be the right number to distinguish the many different forms of ASD,” Ring added.

Ring said that in the last few years Autism Speaks ran a pilot project to sequence 100 whole genomes from the AGRE collection. The work was done through contracts with Chinese sequencing company **BGI** and its subsidiary Complete Genomics Inc.

Although obtaining genomic sequences proved relatively cheap and easy, making sense of the sequences proved technically challenging because of the vast size of the accumulated data set.

“We realized we needed partners to address the storage and computational problems with these data,” said Ring. Thus, Autism Speaks partnered with Google Genomics, part of Google’s cloud computing business unit, to manage the mountain of data.

David Glazer, engineering director at Google Genomics, said that the company’s data-handling technology will allow researchers “to store, process, explore and collaborate on data analysis” without clogging up their computers with raw data.

Glazer said that his team has built tools for genomic data analysis in the past, but the scale of data from AUT10K—Google Genomics’ first publically disclosed project—dwarfs previous sequencing efforts. “I don’t know of a similarly sized genomic database,” said Glazer.

He said that the computational challenges “are a lot more than trivial but are a lot less than groundbreaking” for Google’s computers, which routinely handle considerably more data for its search engine services.

Ring said that AUT10K has already sequenced 1,000 genomes, with another 2,000 in the pipeline. The project aims to open a web portal to allow researchers to access the data set by early 2015. All data will be anonymized and accessible to qualified researchers.

Ring noted that because AUT10K will include full sequences from thousands of controls and patients with ASD, the data could be useful to researchers interested in diseases besides ASD.

“If you look at cancer, diabetes or Alzheimer’s disease, you won’t find a program that is trying to achieve this scale of whole-genome sequencing,” said Ring. “Every field will be watching this program.”

Getting BRAIN under way

Researchers at the **University of California, San Francisco** have launched one of the first projects in support of the U.S.’s Brain Research through Advancing Innovative Neurotechnologies (BRAIN) initiative.

The five-year study involves determining how neural circuits become dysregulated in neuropsychiatric disorders and developing miniature implantable stimulation devices that strengthen alternative circuits to correct or bypass the dysregulation.

The multi-institutional study will include researchers at **Cornell University**, **Lawrence Livermore National Laboratory**, **New York University** and the **University of California, Berkeley**.

The project’s initial focus will be on anxiety and depression in patients with Parkinson’s disease (PD) or intractable epilepsy. The first step is studies to record activity from various brain regions.

The **Defense Advanced Research Projects Agency** of the **U.S. Department of Defense** will provide \$12 million in initial funding for the project through its Systems-Based Neurotechnology for Emerging Therapies program, with up to an additional \$14 million based on undisclosed milestones.

The BRAIN initiative was announced by the Obama administration in 2013 as a public-private partnership to give “scientists the tools they need to get a dynamic picture of the brain in action and better understand how we think and how we learn and how we remember.”¹

The **NIH** committed \$40 million to the BRAIN initiative in FY14. The White House requested \$110 million for the initiative in its FY15 budget request.

Earlier this month, an NIH working group proposal called for \$4.5 billion in federal funding over 10 years starting in FY16 to achieve the initiative’s goals, with \$400 million annually from FY16 to FY20 and then \$500 million annually from FY21 to FY25.

Public-private partnership roundup

Another quiet month on the public-private partnership front includes several new deals in Asia. **Daiichi Sankyo Co. Ltd.** announced a pair of discovery deals focused on cancer and cardiovascular and metabolic diseases; **RaQualia Pharma Inc.** announced a partnership with **Kyoto University** in the areas of gene and cell therapy; U.K.-based **Enigma Diagnostics Ltd.** announced a deal with the **Chinese Center for Disease Control and Prevention** for infectious disease and diagnostics (*see Table 1*, “Selected public-private partnerships for May 2014”).

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Autism Speaks, New York, N.Y.
BGI, Shenzhen, China
Chinese Center for Disease Control and Prevention, Beijing, China
Cornell University, Ithaca, N.Y.
Daiichi Sankyo Co. Ltd. (Tokyo:4568), Tokyo, Japan
Defense Advanced Research Projects Agency, Washington, D.C.
Enigma Diagnostics Ltd., Salisbury, U.K.
Google Inc. (NASDAQ:GOOG), Mountain View, Calif.
Kyoto University, Kyoto, Japan
Lawrence Livermore National Laboratory, Livermore, Calif.
National Institutes of Health, Bethesda, Md.
New York University, New York, N.Y.
RaQualia Pharma Inc. (JASDAQ:4579), Nagoya, Japan
University of California, Berkeley, Calif.
University of California, San Francisco, Calif.
U.S. Department of Defense, Washington, D.C.

CXCR2 antibodies for antitumor immunity

By Lauren Martz, Staff Writer

A **National Cancer Institute** team has found a new chemokine-regulated pathway of tumor immune evasion that could account for some patients' resistance to checkpoint inhibitor-based therapies.¹ By blocking CXC chemokine receptor 2, the team prevented migration of myeloid-derived suppressor cells and increased the efficacy of programmed cell death 1–targeting mAbs in a mouse model of rhabdomyosarcoma.

The researchers are now planning to test anti-CXC chemokine receptor 2 (CXCR2; IL8RB) antibodies in combination with other cancer immunotherapies.

Signaling via programmed cell death 1 (PDCD1; PD-1; CD279) or its ligand, programmed cell death 1 ligand 1 (PD-L1; B7-H1; CD274), normally serves to control excessive immune responses by damping down T cell activity. But in cancer, overactivation of the PD-1 pathway suppresses the antitumor effects of T cells, thus allowing cancer cells to escape immune regulation.

Although mAbs against PD-1 and PD-L1, so-called checkpoint inhibitors, are poised to become the newest class of cancer immunotherapies to enter the market,² they are still only effective in about 34% of patients with melanoma and about 35% of patients with non-small cell lung cancer (NSCLC).

The most advanced compounds include the PD-1 antibodies pembrolizumab from **Merck & Co. Inc.** and nivolumab from **Bristol-Myers Squibb Co.**, which are under FDA review for metastatic melanoma and NSCLC, respectively. Both antibodies are also in Phase I to III testing for other cancers. **AstraZeneca plc** and **Roche** have the PD-L1–targeting antibodies, MEDI4736 and MPDL3280A, respectively, in Phase III trials for NSCLC and in earlier phases for other cancers.

Recently, researchers have started looking for additional mechanisms of immune evasion to explain why some patients do not respond to checkpoint inhibitors. One area of particular focus is myeloid-derived suppressor cells (MDSCs)—a class of immature myeloid cells that undergo expansion in cancer.

“This is an exciting time in cancer immunotherapy as we are really beginning to understand how to turn the immune system around to attack tumors,” said Raymond DuBois Jr., executive director of the Biodesign Institute at **Arizona State University** and a professor of medicine at the **Mayo Clinic in Arizona**.

“MDSCs contribute to immune evasion by inhibiting T cell trafficking and activation. The suppressor cells also inhibit NK cells and promote regulatory T cell expansion,” he said.

Previous studies have detected MDSC expansion in mouse tumor

models and indicated that blocking expansion may improve antitumor immunity.³ However, attempts to modulate MDSC suppressive activity have been limited by unacceptable toxicity or have failed to translate from mice to humans.^{4,5}

Now, Crystal Mackall and colleagues at the National Cancer Institute have looked for mechanisms controlling MDSC expansion in tumors and found a chemokine pathway—independent of PD-1—that is regulated by CXCR2.

Mackall is chief of the Pediatric Oncology Branch at the National Cancer Institute.

Blocking MDSCs

To create a system for studying PD-1-independent tumor immune evasion, the team used a mouse model of rhabdomyosarcoma to establish conditions in which PD-1 inhibition was ineffective. In the model, an anti PD-1 mAb only modestly decreased tumor growth when given 7 days after tumors were established, whereas it enabled 100% of the mice to survive when administered at the time of tumor inoculation.

Mackall's group hypothesized that there might be additional mechanisms of immune evasion at play when the tumors were established that were overriding the anti-PD-1 mAb's effect and thus tested whether MDSC recruitment was involved.

In the mouse model, the researchers found that numbers of monocytic and granulocytic MDSCs increased in the peripheral blood, spleen and tumor after inoculation with the

cancer cells. When the two MDSC subsets were cocultured with T cells, the granulocytic subset that expressed *Cxcr2* had a higher fraction in the tumor than the monocytic subset and strongly suppressed T cell activation.

Because chemokines control cell migration, the team explored whether the *Cxcr2* pathway could contribute to the influx of MDSCs to the mouse tumors. They looked at levels of chemokine ligands in the tumors and tested whether inhibiting *Cxcr2* signaling or depleting the *Cxcr2* gene from bone marrow could block MDSC migration.

The *Cxcr2* ligands chemokine CXC motif ligand 1 (*Cxcl1*; Gro; *Mgsa*) and *Cxcl2* (*Mip2*) were present at high levels in the blood within the mouse tumors and in supernatant from cultured mouse rhabdomyosarcoma cells.

In a cell migration assay, antibodies blocking CXCR2, CXCL1 or CXCL2 inhibited migration of MDSCs to tumor cells. Similarly, in mice with *Cxcr2*^{-/-} bone marrow, MDSC migration to the tumor and tumor growth were lower than those in mice with wild-type bone marrow following inoculation with rhabdomyosarcoma cells.

The findings suggested that CXCR2 is required to traffic MDSCs to the tumor and that the cancer cells secrete CXCR2 ligands to direct MDSC migration.

Next, the team tested whether the CXCR2-regulated MDSC pathway could synergize with anti-PD-1 immunotherapy. In mice with *Cxcr2*^{-/-} bone marrow, compared with mice with wild-type bone marrow, the anti-PD-1 therapy decreased growth of established rhabdomyosarcoma tumors and increased overall survival. But combining the anti-CXCR2 antibody with the anti-PD-1 antibody decreased the number of MDSCs

“The idea of combining inhibitors of PD-1 signaling and CXCR2, which target separate immune evasion mechanisms, is really attractive because there is real potential for synergistic immunomodulatory activity.”

—Raymond DuBois Jr.,
Arizona State University

in the tumors and tumor growth and increased survival more than either treatment alone.

Finally, the researchers looked for evidence of the chemokine pathway in human cancer. Patients with metastatic sarcoma had higher levels of the CXCR2 ligands CXCL1 and IL-8 (CXCL8) than healthy controls. Higher CXCL8 levels also correlated with shorter survival.

Data were published in *Science Translational Medicine*.

Balancing act

DuBois told *SciBX*, “The idea of combining inhibitors of PD-1 signaling and CXCR2, which target separate immune evasion mechanisms, is really attractive because there is real potential for synergistic immunomodulatory activity. Myeloid cells are not involved in the checkpoint functions.”

Andrea van Elsas, CSO of **BioNovion B.V.**, told *SciBX* that although MDSCs have been known to limit antitumor immunity for some time, until now no one has found a way to translate the findings to the clinic.

“Unlike most of the other targets, inhibition of CXCR2 is known to be feasible using different classes of inhibitors including therapeutic antibodies. Hence, CXCR2 inhibitors can relatively easily be translated to clinical testing in combination with checkpoint blockade to ultimately generate proof of concept for this mode of action.”

BioNovion is developing therapeutic antibodies for cancer immunotherapy including PD-1 antibodies.

Dompe Farmaceutici S.p.A. has the CXCR2 antagonist peparixin in Phase III testing to treat graft rejection. At least three other companies have CXCR2 antagonists in clinical development for inflammatory diseases.

However, balancing the antitumor effects of CXCR2 inhibition with the chemokine’s anti-infective role could be the biggest challenge.

According to van Elsas, although CXCR2 antibodies are already in the clinic, the chemokine receptor is widely expressed, and blocking its other effects could present safety concerns for developing it as a cancer immunotherapy. “For instance, in humans, CXCR2 and one of its ligands, IL-8, play an important role in directing neutrophils to the sites of infection, and CXCR2 has also been linked to angiogenesis,” he said. “Prolonged CXCR2 inhibition may lead to neutropenia and increased susceptibility to infection or other unwanted adverse pharmacology.”

Mackall agreed. “The issue of toxicity is a potential problem. If we are preventing trafficking of the cells into the tumors, might we also be preventing trafficking into inflamed, infectious tissues?” she asked. Despite the potential infection risk, Mackall noted that early clinical studies of CXCR2 antagonists in inflammatory conditions have not shown a lot of toxicity.

van Elsas said that strategies to reduce toxicity could include giving CXCR2 antagonists for a limited amount of time to decrease the chance of a serious infection or administering the compounds directly into the tumor to avoid systemic effects.

Mackall added that it also will be important to carefully characterize the MDSC subsets involved in immune evasion in human cancers.

“We are only knocking out trafficking of one of the MDSC subsets with CXCR2 blockade. CC chemokine receptor ligands are the chemokine axis on the other cell subset, and this is an entirely different class of molecules and potential therapeutics,” she said. “We are also looking into ways to

modulate these cells, as it may be necessary to knock down both types to get a sufficient response in patients or in specific types of cancers.”

However, DuBois noted that selectively targeting the granulocytic subset may have safety advantages. “It appears that CXCR2 is only expressed on the granulocytic subset of MDSCs. This may actually be a good thing because those do seem to be the cells mainly responsible for tolerance in the tumor microenvironment. Only blocking one type of MDSC, if effective, may be less toxic. These studies were done in mice but have not been confirmed in humans yet. We assume that receptor distribution would be the same,” he said.

Broad potential

In addition to combining CXCR2 blockade with adoptive T cell therapies, DuBois expects that the approach could be combined with many other cancer therapies.

“If MDSCs are present in the tumor microenvironment and suppress immunity against the tumor, preventing trafficking of the cells to the tumor should complement other checkpoint inhibitors as well as chemotherapies and other standard therapies. CXCR2 antagonists could even be used as single agents in some cancers. The potential space for CXCR2 antagonists in cancer is really completely wide open for different development paths,” said DuBois.

Mackall agreed that the strategy should apply to other cancers and said that MDSCs are found in essentially every solid tumor.

John Dixon Gray, a senior scientist and manager of the fluorescence-activated cell

sorting core and animal modeling at **Sorrento Therapeutics Inc.**, said, “As we learn more about tumor biology and immune evasion, we have come to appreciate that every cancer is different.”

Barbara Swanson, director of research at Sorrento, added that cancers “would need to be studied for their dependency on PD-1 or overall immunogenicity and CXCR2 before evaluating this potential combination of antibodies.”

Sorrento has antibodies targeting PD-1 and PD-L1 in preclinical testing to treat several cancers.

DuBois added that cancers such as melanoma, renal cell carcinoma (RCC) and NSCLC have a high rate of response to immunomodulators and may be good candidates for this particular combination approach.

Mackall said that although there could be additional indications to test, her team will continue to focus on pediatric tumors such as rhabdomyosarcoma. “We do think that this approach could also apply to other cancer immunotherapy strategies such as adoptive T cell therapy with chimeric antigen receptors, which is being used in my patients. We are planning to test combining CXCR2-blocking strategies with chimeric antigen receptors next,” she said.

Mackall added, “Immunotherapy is really making a big splash in the cancer treatment space. Adoptive T cell therapies with chimeric antigen receptors are being pursued for leukemia, but this approach hasn’t yet worked for solid tumors. We think that this might be due to the dense immunosuppressive environment in solid tumors, and blocking MDSCs may help open new indications for adoptive T cell therapy.”

(Continues on p. 8)

“The issue of toxicity is a potential problem. If we are preventing trafficking of the cells into the tumors, might we also be preventing trafficking into inflamed, infectious tissues?”

**—Crystal Mackall,
National Cancer Institute**

Collateral tumor damage

By Tracey Baas, Senior Editor

Australian researchers are taking a new approach to attacking brain cancer—raising T cells against antigens from the cytomegalovirus frequently found in gliomas rather than against tumor targets.¹ The approach has shown efficacy in patients, and the next steps include applying the method to larger cohorts and identifying the best cytomegalovirus epitopes to be used to activate T cells.

Glioblastoma multiforme (GBM) is an aggressive malignancy, with median survival of less than 15 months and a 5-year survival rate below 10%.^{2,3} Standard care includes surgical resection, radiotherapy and chemotherapy.

The link between GBM and virus surfaced more than a decade ago, when researchers reported that cytomegalovirus (CMV) was found in a majority of human gliomas. The presence of virus was first considered an opportunistic infection because of the immunosuppressive environment of the tumor, but mounting evidence suggested that it contributed to disease progression.⁴⁻⁶

CMV was unlikely to be a causal agent, as placing the virus in culture with healthy cells did not give rise to gliomas.

In 2008, a team at the **University of California, Los Angeles** reported that a patient vaccinated with autologous dendritic cells pulsed with tumor lysate experienced a robust expansion of CMV-specific but not tumor-specific T cells.⁷ The patient's glioblastoma tissue was later shown to be infected with CMV.

The study suggested that an immune response against a viral antigen was more easily accomplished than inducing an immune response against tumor antigens.

“One of the advantages of using immunotherapy—T cells or vaccines—to target CMV antigens in tumors is that it is not requisite that the viral antigen is a driver of tumor biology or that the virus is undergoing a productive replicative life cycle for the immune system to attack and kill a tumor cell expressing the targeted antigen.”

—Duane Mitchell,
University of Florida College of
Medicine

Four years later, a team at the **QIMR Berghofer Medical Research Institute** decided to treat GBM using T cells that target CMV antigens isolated from patients' tumor-infiltrating lymphocytes. The institute was previously known as the Queensland Institute of Medical Research (QIMR).

In the group's one-patient, proof-of-concept study, *ex vivo* expansion of the patient's endogenous, CMV-specific T cells, which were then returned to the patient in combination with temozolomide, led to long-term, disease-free survival.⁸

Now, the researchers have data from a larger cohort of patients.

The team collected and expanded CMV-specific T cells from 13 patients with recurrent GBM undergoing standard therapy. Two patients died from disease before receiving adoptive T cell therapy. In the 11 patients who received infusions of autologous, CMV-specific T cells plus radiotherapy, temozolomide and other standard treatments, median overall survival was about 57 weeks. Of the 11 treated, 4 were progression free at the end of the study and remain so to date, which is now between 10 months and over 4 years after T cell therapy.

However, the number of CMV-specific T cells did not correlate with overall or

progression-free survival (PFS).

Thus, the researchers set out to identify T cell expression profiles that might provide prognostic value. To do so, the group compared profiles from patients with short vs. long PFS. Seven genes were found with significant expression differences, including T cell transcription factors, cytokines such as interferon- γ (IFNG; IFN- γ), chemokines and checkpoint markers such as CTLA-4 (CD152).

Results were published in *Cancer Research*. The QIMR Berghofer team was led by Rajiv Khanna, a professor and director of the institute's Centre for Immunotherapy and Vaccine Development.

(Continues on p. 9)

(Continued from “CXCR2 antibodies for antitumor immunity,” p. 7)

Mackall said that the findings are not patented and the licensing status is not applicable.

Martz, L. *SciBX* 7(24); doi:10.1038/scibx.2014.693
Published online June 19, 2014

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Arizona State University, Phoenix, Ariz.
AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K.
BioNovion B.V., Oss, the Netherlands
Bristol-Myers Squibb Co. (NYSE:BMJ), New York, N.Y.
Dompe Farmaceutici S.p.A., Milan, Italy
Mayo Clinic in Arizona, Scottsdale, Ariz.
Merck & Co. Inc. (NYSE:MRK), Whitehouse Station, N.J.
National Cancer Institute, Bethesda, Md.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
Sorrento Therapeutics Inc. (NASDAQ:SRNE), San Diego, Calif.

One bird, two stones

Khanna's team is starting a Phase II trial of autologous, CMV-specific T cell therapy to treat primary glioblastoma. The primary endpoints of the trial are the safety and tolerability of the adoptive transfer of CMV-specific, cytotoxic T cells and PFS. Secondary endpoints include overall survival.

In the long term, Khanna said, a therapeutic vaccine based on the CMV epitopes may be a better approach than using engineered T cells because the latter are more cumbersome.

"We have an ongoing CMV vaccine program based on our IP that has successfully completed preclinical studies, and now the CMV vaccine is moving toward a Phase I clinical trial," he added.

Regardless of modality, other researchers wanted to see data in larger groups of patients.

"Their exciting results will now have to be confirmed in larger trials, as well as in patients with newly diagnosed tumors who have a better chance of extended survival with this therapy than recurrent glioblastoma patients," said Cecilia Söderberg-Nauclér, a professor of medicine at the **Karolinska Institute**.

Söderberg-Nauclér also suggested further examination of the CMV-specific epitopes that may be able to activate CMV-specific T cells in nonresponders. "It is possible that special cancer-associated CMV strains are present in these GBM patients and that the antigenic epitopes are different from those known to be produced by well-characterized CMV strains found in normal tissues," she noted. "Thus, CMV strains in glioblastoma need to be defined in more depth."

"One of the advantages of using immunotherapy—T cells or vaccines—to target CMV antigens in tumors is that it is not requisite that the viral antigen is a driver of tumor biology or that the virus is undergoing a productive replicative life cycle for the immune system to attack and kill a tumor cell expressing the targeted antigen," said Duane Mitchell, co-director of the Preston A. Wells Jr. Center for Brain Tumor Therapy, director of the University of Florida Brain Tumor

"Their exciting results will now have to be confirmed in larger trials, as well as in patients with newly diagnosed tumors who have a better chance of extended survival with this therapy than recurrent glioblastoma patients."

**—Cecilia Söderberg-Nauclér,
Karolinska Institute**

Immunotherapy Program and an associate professor in the Department of Neurosurgery at the **University of Florida College of Medicine**.

"A central question with respect to CMV-directed immunotherapy is whether the low levels of viral antigens expressed within these tumors will be sufficient to mediate clinically meaningful responses in a significant number of patients," noted Mitchell. "Additional clinical studies are needed to address this issue, but I believe this is a promising area for future research."

The findings have been patented by QIMR Berghofer and the IP, which includes CMV epitopes and the strategy for T cell-based adoptive immunotherapy, is available for licensing for its potential application in CMV-associated diseases including glioblastoma.

**Baas, T. *SciBX* 7(24); doi:10.1038/scibx.2014.694
Published online June 19, 2014**

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Karolinska Institute, Stockholm, Sweden
QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia
University of California, Los Angeles, Calif.
University of Florida College of Medicine, Gainesville, Fla.

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This week in therapeutics

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

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

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Autoimmune disease				
Multiple sclerosis (MS)	G protein-coupled receptor 109A (GPR109A; HM74A; HCAR2)	<p>Mouse studies suggest GPR109A activation is the mechanism of action for Tecfidera dimethyl fumarate and that activating GPR109A could help treat MS. In an experimental autoimmune encephalomyelitis (EAE) mouse model of MS, Tecfidera delayed CNS neutrophil infiltration and disease onset in <i>Gpr109a</i>⁺ mice but not in <i>Gpr109a</i> knockouts. Next steps include testing GPR109A agonists in mouse models of MS.</p> <p>Biogen Idec Inc. markets Tecfidera, an oral formulation of dimethyl fumarate that activates the nuclear factor (erythroid-derived 2)-like 2 (NFE2L2; NRF2) pathway, to treat MS.</p> <p>SciBX 7(24); doi:10.1038/scibx.2014.695 Published online June 19, 2014</p>	Unpatented; available for licensing	<p>Chen, H. <i>et al. J. Clin. Invest.</i>; published online May 1, 2014; doi:10.1172/JCI72151</p> <p>Contact: Markus Schwaninger, University of Luebeck, Luebeck, Germany e-mail: markus.schwaninger@pharma.uni-luebeck.de</p>
Multiple sclerosis (MS)	Prostaglandin E2 receptor EP2 subtype (prostanoid EP2 receptor; PTGER2); RAR-related orphan receptor C (RORC; ROR γ)	<p>Studies in human samples and mice suggest inhibiting PTGER2 could help treat MS. In T helper type 17 (Th17) cells from healthy subjects, overexpression of <i>PTGER2</i> or siRNA knockdown of the PTGER2 inhibitor <i>RORC</i> induced a pathogenic inflammatory phenotype. In Th17 cells from patients with MS, <i>PTGER2</i> expression was higher than that in cells from healthy subjects. Next steps could include testing PTGER2 inhibitors in models of MS.</p> <p>SciBX 7(24); doi:10.1038/scibx.2014.696 Published online June 19, 2014</p>	Patent and licensing status unavailable	<p>Kofler, D.M. <i>et al. J. Clin. Invest.</i>; published online May 8, 2014; doi:10.1172/JCI72973</p> <p>Contact: David A. Hafler, Yale School of Medicine, New Haven, Conn. e-mail: david.hafler@yale.edu</p> <p>Contact: David M. Kofler, same affiliation as above e-mail: david.kofler@yale.edu</p>
Multiple sclerosis (MS)	Sphingosine 1-phosphate lyase (S1P lyase)	<p>SAR and rat studies suggest S1P lyase antagonists could help treat MS. <i>In vitro</i> screening identified S1P lyase inhibitors, and subsequent optimization yielded an orally available compound with high selectivity that inhibited the enzyme with an IC₅₀ value of 210 nM. In rats with experimental autoimmune encephalomyelitis (EAE), the optimized S1P lyase inhibitor decreased neuroinflammation compared with vehicle control. Researchers did not disclose next steps, which could include further optimization of the lead inhibitor and evaluating the compound in additional animal models of MS.</p> <p>Lexicon Pharmaceuticals Inc. has the indirect S1P lyase antagonist LX2931 in Phase II testing to treat rheumatoid arthritis (RA) and in preclinical development for Duchenne muscular dystrophy (DMD).</p> <p>SciBX 7(24); doi:10.1038/scibx.2014.697 Published online June 19, 2014</p>	Patent and licensing status undisclosed	<p>Weiler, S. <i>et al. J. Med. Chem.</i>; published online May 8, 2014; doi:10.1021/jm500338n</p> <p>Contact: Sven Weiler, Novartis Institutes for BioMedical Research, Basel, Switzerland e-mail: sven.weiler@novartis.com</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Cancer				
Breast cancer	Granulocyte macrophage colony-stimulating factor (GM-CSF; CSF2); chemokine CC motif ligand 18 (CCL18); phosphatidylinositol transfer protein membrane associated family member 3 (PITPNM3)	Mouse and human sample studies suggest blocking secreted GM-CSF or CCL18 could help prevent breast cancer metastasis. In a humanized mouse model of metastatic breast cancer, a neutralizing antibody against tumor cell-secreted GM-CSF reduced numbers of tumor-associated macrophages (TAMs), inhibited metastasis and prolonged metastasis-free survival. In the same model, a neutralizing antibody against TAM-secreted CCL18 reduced epithelial-to-mesenchymal transition of tumor cells, inhibited metastasis and prolonged metastasis-free survival. In human breast cancer samples or patient data collections, high GM-CSF expression correlated with elevated numbers of stromal CCL18 ⁺ cells or higher tumor grade and poor prognosis. Next steps include developing antibodies and identifying small molecules able to inhibit the CCL18 receptor PITPNM3. SciBX 7(24); doi:10.1038/scibx.2014.698 Published online June 19, 2014	Patent application filed; licensing status undisclosed	Su, S. <i>et al. Cancer Cell</i> ; published online May 12, 2014; doi:10.1016/j.ccr.2014.03.021 Contact: Erwei Song, Sun Yat-sen University, Guangzhou, China e-mail: songew@mail.sysu.edu.cn
Cancer	Aldehyde dehydrogenase (ALDH); c-Met proto-oncogene (MET; HGFR); epidermal growth factor receptor 1 (EGFR; HER1; ErbB1)	Cell culture and mouse studies suggest ALDH inhibitors could help treat cancer. In human cancer cell lines expressing MET or EGFR1, the acquisition of resistance to inhibitors was associated with upregulation of ALDH. In multiple kinase-dependent cancer cell lines, an ALDH inhibitor plus an inhibitor of the respective kinase increased cell death compared with either agent alone. In mice bearing EGFR1-dependent xenograft lung tumors, an ALDH inhibitor plus an EGFR1 inhibitor decreased tumor growth and increased time to tumor recurrence compared with an EGFR1 inhibitor alone. Ongoing work includes testing ALDH inhibitors in mouse models of other cancers. Tekmira Pharmaceuticals Corp. has TKM-ALDH2, an siRNA targeting aldehyde dehydrogenase 2 family mitochondrial (ALDH2) formulated using lipid nanoparticle delivery technology, in preclinical testing to treat addiction. SciBX 7(24); doi:10.1038/scibx.2014.699 Published online June 19, 2014	Patent and licensing status undisclosed	Raha, D. <i>et al. Cancer Res.</i> ; published online May 8, 2014; doi:10.1158/0008-5472.CAN-13-3456 Contact: Jeff Settleman, Genentech Inc., San Francisco, Calif. e-mail: settleman.jeffrey@gene.com
Cancer	Eukaryotic translation initiation factor 4E (eIF4E)	<i>In vitro</i> studies have identified an inhibitor of eIF4E that could help treat cancer. A derivative of a tricyclic 2-(4-(3,4-dichlorophenyl)thiazol-2-yl) was synthesized that was threefold more potent in competitive binding to eIF4E than the parent compound. In a human melanoma cell line, the new compound inhibited proliferation with an IC ₅₀ of 5.1 μM. Next steps include further optimization of structural and functional aspects of the eIF4E inhibitor. SciBX 7(24); doi:10.1038/scibx.2014.700 Published online June 19, 2014	Patent application filed by Harvard University; licensed to a private entity; available for partnering	Mahalingam, P. <i>et al. J. Med. Chem.</i> ; published online May 14, 2014; doi:10.1021/jm401733v Contact: Michael Chorev, Brigham and Women's Hospital, Boston, Mass. e-mail: michael_chorev@hms.harvard.edu

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Cancer	Programmed cell death 1 (PDCD1; PD-1; CD279)	<p>Mouse studies suggest PD-1 inhibitors could help improve the efficacy of dendritic cell (DC)-activating cancer vaccines. In a mouse model of melanoma, an experimental, DC-activating cancer vaccine plus an anti-PD-1 mAb caused tumor regression, whereas vaccine alone only inhibited tumor growth. Next steps could include evaluating the combination in a clinical trial.</p> <p>Bristol-Myers Squibb Co. and Ono Pharmaceutical Co. Ltd. have the PD-1 antibody nivolumab under FDA review to treat advanced melanoma and non-small cell lung cancer (NSCLC).</p> <p>Merck & Co. Inc. has the PD-1 antibody MK-3475 (formerly lambrolizumab) under FDA review to treat advanced melanoma.</p> <p>At least four other companies have antibodies against PD-1 in Phase II or earlier testing to treat cancers.</p> <p>SciBX 7(24); doi:10.1038/scibx.2014.701 Published online June 19, 2014</p>	Patent and licensing status unavailable	<p>Fu, J. <i>et al. Cancer Res.</i>; published online May 8, 2014; doi:10.1158/0008-5472.CAN-13-2685</p> <p>Contact: Young J. Kim, The Johns Hopkins University School of Medicine, Baltimore, Md. e-mail: ykim76@jhmi.edu</p>
Chronic lymphocytic leukemia (CLL); mantle cell lymphoma (MCL); multiple myeloma (MM)	Endoplasmic reticulum to nucleus signaling 1 (ERN1; IRE1); Bruton's tyrosine kinase (Btk)	<p>Cell culture and mouse studies suggest inhibiting IRE1 and Btk could help treat CLL, MCL and MM. Chemical synthesis and <i>in vitro</i> testing of chromenone analogs identified compounds that inhibited the activity of IRE1's RNase domain with nanomolar to low micromolar potency. In a transgenic mouse model of CLL, one lead inhibitor decreased CLL cell levels in peripheral blood compared with vehicle. In CLL cells from the mouse models and human CLL, MCL and MM cell lines, the IRE1 inhibitor plus the Btk inhibitor Imbruvica ibrutinib caused more potent growth inhibition than either agent alone. Ongoing work includes testing IRE1 inhibitors and ibrutinib in mouse models of B cell lymphoma.</p> <p>Pharmacyclics Inc. and Johnson & Johnson market Imbruvica to treat CLL and MCL. The compound is in Phase III testing to treat B cell lymphoma and non-Hodgkin's lymphoma (NHL) and Phase II testing to treat MM and lymphoma.</p> <p>Celgene Corp. has the covalent small molecule Btk inhibitor AVL-292 (CC-292) in Phase I testing to treat CLL and B cell lymphoma.</p> <p>Ono Pharmaceutical Co. Ltd. has the Btk inhibitor ONO-4059 in Phase I testing to treat B cell lymphoma.</p> <p>SciBX 7(24); doi:10.1038/scibx.2014.702 Published online June 19, 2014</p>	For findings from both studies, patent application filed by the H. Lee Moffitt Cancer Center & Research Institute; available for licensing	<p>Ranatunga, S. <i>et al. J. Med. Chem.</i>; published online April 21, 2014; doi:10.1021/jm5002452</p> <p>Tang, C.-H.A. <i>et al. J. Clin. Invest.</i>; published online May 8, 2014; doi:10.1172/JCI73448</p> <p>Contact: Chih-Chi Andrew Hu, H. Lee Moffitt Cancer Center & Research Institute, Tampa, Fla. e-mail: chih-chi.hu@moffitt.org</p> <p>Contact: Juan R. Del Valle, same affiliation as above e-mail: juan.delvalle@moffitt.org</p>
Glioma	Not applicable	<p>Cell-based and mouse studies suggest a chimeric vesicular stomatitis virus (VSV)-based oncolytic virus could help treat glioma. The VSV glycoprotein in wild-type VSV was replaced with a variant glycoprotein from lymphocytic choriomeningitis virus to create rVSV(GP). In multiple tumor cell lines, rVSV(GP) had cytotoxic potency comparable to that of wild-type VSV. In mice, rVSV(GP) did not elicit neurotoxicity associated with wild-type VSV. In a mouse model of human glioma, rVSV(GP) increased survival compared with wild-type VSV. Next steps could include IND-enabling safety studies.</p> <p>SciBX 7(24); doi:10.1038/scibx.2014.703 Published online June 19, 2014</p>	Patent and licensing status unavailable	<p>Muik, A. <i>et al. Cancer Res.</i>; published online May 8, 2014; doi:10.1158/0008-5472.CAN-13-3306</p> <p>Contact: Dorothee von Laer, Medical University Innsbruck, Innsbruck, Austria e-mail: dorothee.von-laer@i-med.ac.at</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Leukemia	Spleen tyrosine kinase (SYK)	<p>Studies in human samples and mice suggest inhibiting SYK could help treat high-risk B cell acute lymphoblastic leukemia (B-ALL). In the human B-ALL samples, the SYK inhibitor fostamatinib decreased proliferation compared with vehicle. In a mouse xenograft model of high-risk human B-ALL, fostamatinib decreased leukemic burden at the injection site and disease dissemination from bone to spleen, liver, kidney and CNS compared with vehicle. Next steps include evaluating SYK inhibitors in combination with first-line chemotherapies to treat B-ALL in xenograft models.</p> <p>Rigel Pharmaceuticals Inc.'s fostamatinib disodium is in Phase II testing to treat idiopathic thrombocytopenic purpura.</p> <p>At least eight other companies have SYK inhibitors in Phase II or earlier testing to treat various indications, including hematologic malignancies.</p> <p>SciBX 7(24); doi:10.1038/scibx.2014.704 Published online June 19, 2014</p>	Unpatented; licensing status not applicable	<p>Perova, T. <i>et al. Sci. Transl. Med.</i>; published online May 14, 2014; doi:10.1126/scitranslmed.3008661</p> <p>Contact: Jayne S. Danska, The Hospital for Sick Children, Toronto, Ontario, Canada e-mail: jayne.danska@sickkids.ca</p>
Liver cancer	Transmembrane 4 L six family member 5 (TM4SF5)	<p>Studies in patient samples, cell culture and mice suggest antagonizing TM4SF5 could help treat hepatocellular carcinoma (HCC). In patient samples, HCC expressed TM4SF5, whereas normal liver tissue did not. In a human liver cell line expressing TM4SF5, an anti-TM4SF5 mAb inhibited cell migration and suppressed cell growth compared with IgG control or vehicle. In xenograft and syngeneic mouse models of HCC, i.p. injection of the mAb decreased tumor progression compared with IgG control injection. Next steps could include evaluating different isotypes of the anti-TM4SF5 mAb in additional preclinical studies.</p> <p>SciBX 7(24); doi:10.1038/scibx.2014.705 Published online June 19, 2014</p>	Patent and licensing status unavailable	<p>Kwon, S. <i>et al. Cancer Res.</i>; published online May 6, 2014; doi:10.1158/0008-5472.CAN-13-2730</p> <p>Contact: Younghee Lee, Chungbuk National University, Chungcheongbuk-do, South Korea e-mail: yhl4177@cbnu.ac.kr</p>
Pancreatic cancer	IL-17; IL-17 receptor (IL17R; IL17RA)	<p>Human sample and mouse studies suggest inhibiting IL-17 signaling could help treat pancreatic cancer. Chronic pancreatitis accelerates pancreatic cancer, and chronic inflammation can induce pancreatic intraepithelial neoplasias (PanINs). In human tissue arrays, IL17R expression was greater in pancreatic lesions, including PanINs, than normal acinar tissue. In a mouse model of inducible pancreatitis that progresses to PanIN, IL-17 was expressed in Cd4⁺ T cells, and depletion of Cd4⁺ T cells delayed progression. In the mice, a cocktail of anti-IL17R and anti-IL-17 mAbs decreased PanINs on the pancreas surface and the number of advanced PanINs compared with saline. Next steps include neutralizing IL-17 signaling in more advanced metastatic disease models and identifying patients that would benefit from IL-17 inhibition.</p> <p>Amgen Inc., AstraZeneca plc and Kyowa Hakko Kirin Co. Ltd. have brodalumab, a humanized mAb against IL17R, in Phase III or earlier testing to treat autoimmune and inflammatory indications.</p> <p>At least seven companies have antibodies against IL-17 in Phase II or earlier testing to treat various indications.</p> <p>SciBX 7(24); doi:10.1038/scibx.2014.706 Published online June 19, 2014</p>	Unpatented; licensing status not applicable	<p>McAllister, F. <i>et al. Cancer Cell</i>; published online May 12, 2014; doi:10.1016/j.ccr.2014.03.014</p> <p>Contact: Steven D. Leach, The Johns Hopkins University, Baltimore, Md. e-mail: leachs@mskcc.org</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Cardiovascular disease				
Hypertension	Epoxide hydrolase	<p>Mouse studies identified a soluble epoxide hydrolase-dependent mechanism by which a Mediterranean diet protects against hypertension. Mediterranean diet components form nitro fatty acids, which inhibit soluble epoxide hydrolase. In mice expressing a mutant soluble epoxide hydrolase insensitive to nitro fatty acids, vasodilation induced by nitro fatty acids was impaired. In a mouse model of angiotensin II-induced hypertension, wild-type mice were protected against hypertension and cardiac hypertrophy by nitro fatty acids, but mice expressing mutant soluble epoxide hydrolases were not. In wild-type mouse hearts, gavage with Mediterranean dietary components inhibited soluble epoxide hydrolase activity. Next steps could include further defining the relationship between the extent of soluble epoxide hydrolase inhibition and lowering blood pressure.</p> <p>SciBX 7(24); doi:10.1038/scibx.2014.707 Published online June 19, 2014</p>	Patent and licensing status unavailable	<p>Charles, R.L. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online May 19, 2014; doi:10.1073/pnas.1402965111</p> <p>Contact: Philip Eaton, Kings College London, London, U.K. e-mail: philipeaton@kcl.ac.uk</p>
Ischemia/reperfusion injury	Tumor necrosis factor receptor superfamily member 11b (TNFRS11B; OPG); receptor activator of NF-κB ligand (RANKL; TNFSF11)	<p><i>In vitro</i> and mouse studies suggest RANKL could help reduce ischemic brain damage following stroke. OPG, which binds RANKL and inhibits signaling through RANK (TNFRSF11A; CD265), is upregulated following stroke. In mice, <i>Opg</i> knockout or intracerebroventricular injection of Rankl decreased infarct volume and cerebral edema following middle cerebral artery occlusion compared with no knockout or injection of a control protein. In the mice with cerebral artery occlusion, a Rankl-neutralizing antibody increased infarct volume compared with a control protein. In neurons cocultured with microglia, RANKL inhibited lipopolysaccharide (LPS)-induced inflammatory cytokines and neuronal cell death. Next steps include assessing the effects of systemic RANKL delivery on ischemic injury.</p> <p>SciBX 7(24); doi:10.1038/scibx.2014.708 Published online June 19, 2014</p>	Patent application filed; available for licensing	<p>Shimamura, M. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online May 20, 2014; doi:10.1073/pnas.1400544111</p> <p>Contact: Ryuichi Morishita, United Graduate School of Child Development, Osaka, Japan e-mail: morishit@cgt.med.osaka-u.ac.jp</p>
Dermatology				
Itch	Endothelin 1 (EDN1; ET1); endothelin A receptor; endothelin converting enzyme 1 (ECE1)	<p>Mouse and human studies suggest inhibiting endothelin A receptor could help treat itch. In skin samples from mice with pruritic chronic dermatitis and patients with the pruritic skin disorder prurigo nodularis, endothelin A receptor, ET1 and ECE1 were expressed and co-localized in peripheral nerves, suggesting the endothelin A signaling pathway is involved in itch. In a mouse model of chronic itch, an endothelin A receptor inhibitor decreased scratching behavior and chronic dermatitis compared with no treatment. Next steps include further investigating the role of the ET1 and endothelin A receptor pathway in models of histamine-independent itch.</p> <p>SciBX 7(24); doi:10.1038/scibx.2014.709 Published online June 19, 2014</p>	Patent application filed; available for licensing	<p>Kido-Nakahara, M. <i>et al. J. Clin. Invest.</i>; published online May 8, 2014; doi:10.1172/JCI67323</p> <p>Contact: Martin Steinhoff, University College Dublin, Dublin, Ireland e-mail: martin.steinhoff@ucd.ie</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Endocrine/metabolic disease				
Diabetes	Glycerol-3-phosphate dehydrogenase 2 mitochondrial (GPD2)	Rodent and <i>in vitro</i> studies suggest inhibiting GPD2 can help treat type 2 diabetes. In rat mitochondrial lysates, metformin was shown to inhibit the redox shuttle enzyme GPD2. In rats and mice, an antisense oligonucleotide targeting <i>Gpd2</i> or knockout of <i>Gpd2</i> blocked metformin-mediated effects on glucose homeostasis, endogenous glucose production and cellular redox state. Next steps could include developing pharmacological GPD2 inhibitors. SciBX 7(24); doi:10.1038/scibx.2014.710 Published online June 19, 2014	Patent and licensing status unavailable	Madiraju, A.K. <i>et al. Nature</i> ; published online May 21, 2014; doi:10.1038/nature13270 Contact: Gerald I. Shulman, Yale School of Medicine, New Haven, Conn. e-mail: gerald.shulman@yale.edu
Diabetes	Insulin degrading enzyme (IDE)	Mouse and <i>in vitro</i> studies suggest inhibiting IDE could help treat type 2 diabetes. Library screening, chemical synthesis and <i>in vitro</i> testing identified a macrocyclic compound that bound to a noncatalytic site of IDE and inhibited the enzyme with a nanomolar IC ₅₀ value. In a mouse model of diet-induced obesity, i.p. delivery of the compound increased liver and plasma levels of insulin, glucagon and amylin compared with vehicle. The compound also increased the duration of amylin-regulated gastric emptying and improved glucose tolerance. Next steps could include evaluating the compound in other models of type 2 diabetes. SciBX 7(24); doi:10.1038/scibx.2014.711 Published online June 19, 2014	Patent application filed; unlicensed	Maianti, J.P. <i>et al. Nature</i> ; published online May 21, 2014; doi:10.1038/nature13297 Contact: David R. Liu, Harvard University , Cambridge, Mass. e-mail: drliu@fas.harvard.edu
Diabetes	Protectin DX (PDX)	Mouse studies suggest PDX could help treat type 2 diabetes. In mice, PDX decreased blood glucose levels following lipid infusion compared with vehicle and protected against lipid-induced insulin resistance. In obese diabetic mice, PDX decreased blood glucose levels compared with vehicle and improved insulin sensitivity. Next steps include testing the antidiabetic effects of PDX in humans. SciBX 7(24); doi:10.1038/scibx.2014.712 Published online June 19, 2014	Patent application filed; available for licensing	White, P.J. <i>et al. Nat. Med.</i> ; published online May 11, 2014; doi:10.1038/nm.3549 Contact: André Marette, Laval University, Quebec City, Quebec, Canada e-mail: andre.marette@criucpq.ulaval.ca
Hematology				
Sickle cell disease	Sphingosine kinase 1 (SPHK1); sphingosine 1-phosphate receptor	Human and mouse studies suggest inhibiting SPHK1 could help treat sickle cell disease. In red blood cells (RBCs) and plasma from patients and a mouse model of sickle cell disease, sphingosine 1-phosphate (S1P) levels and activity of the S1P-producing enzyme SPHK1 were higher than what was seen in samples from healthy individuals and normal mice. In RBCs from patients and mice, an SPHK1 inhibitor decreased the hallmark hypoxia-induced sickling behavior compared with vehicle or an S1P receptor antagonist. In the mouse model, the SPHK1 inhibitor decreased S1P levels in RBCs and the severity of multiple disease symptoms compared with vehicle. Next steps could include elucidating the mechanism by which S1P signaling leads to sickling behavior in RBCs. SciBX 7(24); doi:10.1038/scibx.2014.713 Published online June 19, 2014	Patent and licensing status unavailable	Zhang, Y. <i>et al. J. Clin. Invest.</i> ; published online May 16, 2014; doi:10.1172/JCI74604 Contact: Yang Xia, The University of Texas Medical School at Houston, Houston, Texas e-mail: yang.xia@uth.tmc.edu

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Infectious disease				
Tuberculosis	DNA gyrase	<i>In vitro</i> and mouse studies identified a series of N-linked aminopiperidine DNA gyrase inhibitors that could help treat tuberculosis infection. <i>In vitro</i> , the aminopiperidines inhibited DNA gyrase via a mechanism from fluoroquinolone antibiotics. In <i>Mycobacterium tuberculosis</i> culture, the aminopiperidines killed both fluoroquinolone-sensitive and fluoroquinolone-resistant strains. In mouse models of acute and chronic tuberculosis infection, the aminopiperidines decreased bacterial burden in the lung compared with fluoroquinolone antibiotics or vehicle. Researchers did not disclose next steps, which could include testing the compounds in additional animal models of tuberculosis infection.	Patent and licensing status undisclosed	Hameed P, S. <i>et al. J. Med. Chem.</i> ; published online May 8, 2014; doi:10.1021/jm500432n Contact: Shahul Hameed P, AstraZeneca India Pvt. Ltd., Bangalore, India e-mail: shahul.mehar@astrazeneca.com
SciBX 7(24); doi:10.1038/scibx.2014.714 Published online June 19, 2014				
Inflammation				
Asthma	Chemokine CC motif ligand 20 (CCL20; MIP3A)	Mouse studies suggest the heparan sulfate-binding monosaccharide 2,4-O-disulfated iduronic acid (Di-S-IdoA) could help treat asthma. In a mouse model of antigen-induced asthma, knockout of the heparan sulfate synthase exostosin glycosyltransferase 1 (Ext1) decreased lymphocyte recruitment to the lungs and airway hyperresponsiveness compared with no alteration. Nasal inhalation or i.v. Di-S-IdoA, which blocks the interaction between heparan sulfate and CCL20, decreased T lymphocyte recruitment to the mouse lungs compared with saline. Next steps could include testing the monosaccharide in additional asthma models.	Patent and licensing status unavailable	Nonaka, M. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online May 16, 2014; doi:10.1073/pnas.1319870111 Contact: Minoru Fukuda, Sanford-Burnham Medical Research Institute, La Jolla, Calif. e-mail: minoru@sanfordburnham.org
SciBX 7(24); doi:10.1038/scibx.2014.715 Published online June 19, 2014				
Neurology				
Alzheimer's disease (AD)	α -Melanocyte stimulating hormone (α -MSH); β -amyloid ($A\beta$)	Mouse studies suggest α -MSH could help treat AD. In mice with established $A\beta$ pathology and behavioral deficits, i.p. injection of α -MSH prevented the development of spatial memory deficits, whereas vehicle did not. Next steps could include testing α -MSH in additional models of AD and at different stages of the disease. Clinuvel Pharmaceuticals Ltd's CUV9900, an α -MSH analog, is in preclinical development for dermatology indications.	Patent and licensing status unavailable	Ma, K. & McLaurin, J. <i>J. Neurosci.</i> ; published online May 14, 2014; doi:10.1523/JNEUROSCI.5075-13.2014 Contact: JoAnne McLaurin, University of Toronto, Toronto, Ontario, Canada e-mail: j.mclaurin@utoronto.ca
SciBX 7(24); doi:10.1038/scibx.2014.716 Published online June 19, 2014				
Alzheimer's disease (AD)	Serotonin (5-HT) transporter (SLC6A4; SERT)	Mouse and human studies suggest selective serotonin reuptake inhibitors (SSRIs) could help prevent AD. In three-month-old mice expressing human amyloid precursor protein (APP) and presenilin 1 (PSEN1; PS1) and free of β -amyloid ($A\beta$)-related pathology, the SSRI Celexa citalopram caused dose-dependent decreases in $A\beta$ levels in brain and interstitial fluid within 24 hours. In a cohort of 23 healthy human subjects between ages 18 and 50, citalopram decreased $A\beta$ levels in cerebrospinal fluid by 37% compared with placebo. Next steps could include developing strategies to identify human subjects with high baseline levels of $A\beta$ that could benefit from SSRIs. Citalopram is marketed by H. Lundbeck A/S and Forest Laboratories Inc. to treat depression.	Patent and licensing status unavailable	Sheline, Y.I. <i>et al. Sci. Transl. Med.</i> ; published online May 14, 2014; doi:10.1126/scitranslmed.3008169 Contact: Yvette I. Sheline, University of Pennsylvania, Philadelphia, Pa. e-mail: sheline@mail.med.upenn.edu
SciBX 7(24); doi:10.1038/scibx.2014.717 Published online June 19, 2014				

This week in therapeutics (continued)

Indication	Target/marker/pathway	Summary	Licensing status	Publication and contact information
Huntington's disease (HD)	Huntingtin (HTT); translocase of inner mitochondrial membrane 23 homolog (TIMM23; TIM23)	<p>Mouse and cell culture studies suggest increasing TIM23 activity or mitochondrial protein import could help treat HD. In cell culture, mutant Htt interacted with Tim23 and inhibited mitochondrial protein import, resulting in neuronal cell death. In mutant Htt-expressing primary mouse neurons, lentivirus-mediated overexpression of the Tim23 complex rescued the mitochondrial protein import defect and decreased cell death compared with overexpression of a control gene. Next steps could include screening for pharmacological compounds that increase TIM23 activity and mitochondrial protein transport.</p> <p>SciBX 7(24); doi:10.1038/scibx.2014.718 Published online June 19, 2014</p>	Patent and licensing status unavailable	<p>Yano, H. <i>et al. Nat. Neurosci.</i>; published online May 18, 2014; doi:10.1038/nn.3721</p> <p>Contact: Robert M. Friedlander, University of Pittsburgh, Pittsburgh, Pa. e-mail: friedlanderr@upmc.edu</p>

Other

Poisoning	Hypoxia-inducible factor prolyl hydroxylase 1 (EGLN2; HIF-PH1; PHD1); PHD2 (EGLN1; HIF-PH2); PHD3 (EGLN3; HIF-PH3)	<p>Mouse studies suggest pan-PHD inhibitors could help prevent damage to the GI tract and death resulting from acute radiation exposure. In irradiated mice, knockout of <i>Phd1</i>, <i>Phd2</i> and <i>Phd3</i> in GI tissues or pretreatment with a pan-PHD inhibitor decreased markers of GI toxicity and increased survival compared with no knockout or with vehicle pretreatment. In wild-type mice, the pan-PHD inhibitor improved survival in animals treated after total abdominal irradiation but failed to do so in animals treated after total body irradiation. Ongoing work includes testing additional PHD inhibitors in mice before and after radiation exposure.</p> <p>FibroGen Inc., Astellas Pharma Inc. and AstraZeneca plc have the small molecule PHD inhibitor roxadustat (FG-4592; ASP1517) in Phase III testing to treat anemia in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD).</p> <p>FibroGen and Astellas have the small molecule PHD inhibitor FG-2216 (YM311) in Phase II testing to treat anemia in patients with CKD.</p> <p>Akebia Therapeutics Inc. has the oral PHD inhibitor AKB-6548 in Phase IIb testing to treat anemia in patients with CKD.</p> <p>SciBX 7(24); doi:10.1038/scibx.2014.719 Published online June 19, 2014</p>	Patent application filed; available for licensing	<p>Taniguchi, C.M. <i>et al. Sci. Transl. Med.</i>; published online May 14, 2014; doi:10.1126/scitranslmed.3008523</p> <p>Contact: Amato J. Giaccia, Stanford University, Stanford, Calif. e-mail: giaccia@stanford.edu</p>
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This week in techniques

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

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

Approach	Summary	Licensing status	Publication and contact information
Disease models			
Mouse model of Crohn's disease	<p>Mice with the T300A mutation in <i>autophagy related 16-like 1</i> (<i>Atg16l1</i>) could be useful as a model for studying the biology of Crohn's disease and evaluating therapeutic candidates. In the mouse model, knock-in of a Crohn's disease-associated T300A <i>Atg16l1</i> variant resulted in abnormal intestinal cell morphology and impaired autophagy and led to greater intestinal bacterial replication and higher proinflammatory cytokine production than expression of wild-type <i>Atg16l1</i>. Next steps could include identifying conditions that lead to Crohn's disease pathogenesis in the model.</p> <p>SciBX 7(24); doi:10.1038/scibx.2014.720 Published online June 19, 2014</p>	Patent and licensing status undisclosed	<p>Lassen, K.G. <i>et al. Proc. Natl. Acad. Sci. USA</i>; published online May 12, 2014; doi:10.1073/pnas.1407001111</p> <p>Contact: Ramnik J. Xavier, Broad Institute of MIT and Harvard, Cambridge, Mass. e-mail: xavier@molbio.mgh.harvard.edu</p> <p>Contact: Stuart L. Schreiber, same affiliation as above e-mail: stuart_schreiber@harvard.edu</p>
Drug platforms			
Labeled spherical nucleic acid (SNA) nanoparticle conjugates to study cellular uptake mechanisms and intracellular trafficking	<p>Cell culture studies with labeled SNA nanoparticle conjugates could provide insights into cellular trafficking and improve the design of these agents as drug delivery vehicles. SNA nanoparticle conjugates consisting of a quantum dot core and a fluorescent oligonucleotide shell were synthesized to track intracellular events following uptake. In cultured mouse endothelial cells, the nanoparticles trafficked from early endosomes to late endosomes without entering lysosomes or Golgi bodies, while a small unquantifiable fraction reached the cytosol. In the late endosome, nucleic acid was degraded and cleared from the cell, but the core was retained. Next steps could include designing SNA nanoparticle conjugates with biodegradable cores to minimize cellular toxicity.</p> <p>SciBX 7(24); doi:10.1038/scibx.2014.721 Published online June 19, 2014</p>	Patent and licensing status unavailable	<p>Wu, X.A. <i>et al. J. Am. Chem. Soc.</i>; published online May 19, 2014; doi:10.1021/ja503010a</p> <p>Contact: Chad A. Mirkin, Northwestern University, Evanston, Ill. e-mail: chadnano@northwestern.edu</p>
Imaging			
Hyperspectral stimulated Raman scattering (hsSRS) to image drug interactions in live cells	<p>Cell culture studies suggest the hsSRS imaging approach can be used to study drug-drug interactions in cells. In cultured cell lines, hsSRS revealed that the BCR-ABL tyrosine kinase inhibitors Gleevec imatinib and Tassigna nilotinib accumulated in lysosomes, with nilotinib showing 80 higher accumulation than predicted values based on the drug's chemical properties. In imatinib-treated cell lines, hsSRS imaging data suggested chloroquine could improve the efficacy of imatinib by increasing the cytosolic availability of the cancer drug. Next steps could include improving the sensitivity of the technique so less potent drugs can be studied. Gleevec and Tassigna are marketed by Novartis AG to treat various cancers. Chloroquine is a generic drug used to treat malaria.</p> <p>SciBX 7(24); doi:10.1038/scibx.2014.722 Published online June 19, 2014</p>	Patent and licensing status unavailable	<p>Fu, D. <i>et al. Nat. Chem.</i>; published online May 25, 2014; doi:10.1038/nchem.1961</p> <p>Contact: X. Sunney Xie, Harvard University, Cambridge, Mass. e-mail: xie@chemistry.harvard.edu</p>

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Markers			
Loss of olfaction as an early symptom of cerebral malaria	<p>Mouse studies suggest loss of olfaction could be an early indicator of cerebral malaria infection. In a mouse model of cerebral malaria, MRI showed microbleeding within the olfactory bulb and other pathophysiology including accumulation of Cd8⁺ T cells in local capillaries. In the mice, impaired olfaction developed within four days of infection and was associated with the loss of blood brain barrier integrity and upregulated expression of chemokine CC motif ligand 21 (Ccl21). An antibody against Ccl21 or knockout of its receptor, <i>CC chemokine receptor 7 (Ccr7; Cd197)</i>, increased survival in the mice compared with an isotype control antibody or expression of wild-type <i>Ccr7</i>. Next steps include validating the loss of olfaction as a marker of cerebral malaria infection in nonhuman primates and humans.</p> <p>SciBX 7(24); doi:10.1038/scibx.2014.723 Published online June 19, 2014</p>	Patent application filed; unavailable for licensing	<p>Zhao, H. <i>et al. Cell Host Microbe</i>; published online May 15, 2014; doi:10.1016/j.chom.2014.04.008</p> <p>Contact: Cevayir Coban, Osaka University, Osaka, Japan e-mail: ccoban@biken.osaka-u.ac.jp</p>
Netrin 1 (NTN1) levels to predict invasive disease in medulloblastoma	<p>Studies <i>in vitro</i> and in patient samples suggest NTN1 levels could help predict invasive disease in medulloblastoma. In medulloblastoma cells, siRNA targeting NTN1 or its receptors inhibited cell invasion without altering proliferation. Urine samples from patients with invasive tumors had higher NTN1 levels than samples from patients with noninvasive tumors or healthy subjects. Next steps could include validating the association between NTN1 levels and disease stage in larger patient cohorts.</p> <p>SciBX 7(24); doi:10.1038/scibx.2014.724 Published online June 19, 2014</p>	Patent and licensing status unavailable	<p>Akino, T. <i>et al. Cancer Res.</i>; published online May 8, 2014; doi:10.1158/0008-5472.CAN-13-3116</p> <p>Contact: Michael Klagsbrun, Boston Children's Hospital and Harvard Medical School, Boston, Mass. e-mail: michael.klagsbrun@childrens.harvard.edu</p>

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 α -Melanocyte stimulating hormoneA β

AKB-6548

Aldehyde dehydrogenase

Aldehyde dehydrogenase 2

family mitochondrial

ALDH

ALDH2

Amyloid precursor protein

APP

ASP1517

*Atg16l1**Autophagy related 16-like 1*

AVL-292

B β -Amyloid

B7-H1

BCR-ABL tyrosine kinase

Brodalumab

Bruton's tyrosine kinase

Btk

C

c-Met proto-oncogene

c-Myc

CC chemokine receptor 7

CC-292

CCL18

CCL20

Ccl21

Ccr7

CD152

Cd197

CD265

CD274

CD279

Cd4

Cd8

Celexa

Chemokine CC motif ligand 18

Chemokine CC motif ligand 20

Chemokine CC motif ligand 21

Chemokine CXC motif ligand 1

Chloroquine

Citalopram

CPI-613

CSF2

CTLA-4

CUV9900

CXC chemokine receptor 2

Cxcl1

Cxcl2

CXCL8

CXCR2

D

Dimethyl fumarate

DNA gyrase

E

ECE1

EDN1

EGFR1

EGLN1

EGLN2

EGLN3

eIF4E

Endoplasmic reticulum to

nucleus signaling 1

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Endothelin A receptor

Endothelin converting enzyme 1

Epidermal growth factor

receptor 1

Epoxide hydrolase

ErbB1

ERN1

ET1

Eukaryotic translation initiation

factor 4E

Exostosin glycosyltransferase 1

Ext1

F

FG-2216

FG-4592

Fostamatinib

G

G protein-coupled receptor

109A

Gleevec

Glycerol-3-phosphate

dehydrogenase 2 mitochondrial

GM-CSF

GPD2

GPR109A

Granulocyte macrophage

colony-stimulating factor

Gro

H

HCAR2

Heparan

HER1

HGFR

HIF-PH1

HIF-PH2

HIF-PH3

HM74A

HTT

Huntingtin

Hypoxia-inducible factor prolyl

hydroxylase 1

I

Ibrutinib

IDE

IFN- γ

IFNG

IL-17 receptor

IL-17

IL-8

IL17R

IL17RA

IL8RB

Imatinib

Imbruvica

Insulin degrading enzyme

Interferon- γ

IRE1

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Lambrolizumab

Lipopolysaccharide

LPS

LX2931

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