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By Benjamin Boettner, Associate Editor

A **University of California, San Francisco** team has uncovered a pathway for regulating absorption of fatty acids that could yield new targets for treating obesity. MFGE8, an integrin ligand, controls the uptake of fat in the gut and other tissues by co-opting a phosphoinositide 3-kinase signaling module better known for its involvement in insulin action.¹ The team is working on inhibitors of the ligand or its receptors for use in obesity.

The findings provide a new way to stop fatty acids from getting into cells—a strategy for fighting obesity that has proved relatively intractable to date.

Roche's Xenical orlistat inhibits the lipase enzyme that releases fatty acids from dietary fats and thus decreases their absorption in the gut. However, although the compound has been marketed for obesity in the U.S. since 2007, it has limited efficacy and unpleasant side effects.

More recently, efforts have focused on the transporter proteins CD36 (GPIV) and solute carrier family 27 fatty acid transporter member 1 (SLC27A1; FATP1), which shuttle fatty acids into cells.

Arteria S.A. has a CD36 inhibitor in preclinical development for dyslipidemia.

Now, a team led by Kamran Atabai at UCSF has focused on the regulation of the transporters rather than on the proteins themselves and has found that MFGE8 (lactadherin; HMFGE) acts as a master regulator of fatty acid uptake.

Atabai is an assistant professor in the UCSF Department of Medicine and a principal investigator at UCSF's Cardiovascular Research Institute and Lung Biology Center.

Milking the fat connection

Atabai's team identified MFGE8 in 2005. It is an integrin ligand that binds the integrin $\alpha_v\beta_3$ and integrin $\alpha_v\beta_3$ (CD51/CD61) receptor complexes.² Subsequent gene association and expression studies pointed to a connection between MFGE8 and obesity.^{3,4}

The researchers saw a connection between CD36 and MFGE8 because both showed overlapping functions in inflammatory pathways and were associated with obesity. As CD36 mediates fatty acid uptake into cells, they thought MFGE8 might act in concert with the transporter to control fat absorption.

In vitro, they found that adding recombinant MFGE8 (rMFGE8) to adipocytes increased fatty acid uptake compared with no treatment or with adding a mutant version of MFGE8 unable to bind to integrin receptors.

Conversely, *Mfge8* knockout in mice decreased fatty acid uptake



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in isolated adipocytes, liver cells, intestinal enterocytes and cardiac myocytes compared with wild-type *Mfge8* expression.

Furthermore, *Mfge8* knockout mice fed a high-fat diet did not develop obesity and were more sensitive to insulin than wild-type mice. The *Mfge8* knockout mice also had lower intracellular triglyceride levels than wild-type mice and had signs of reduced fatty acid transport.

Antibodies against the individual integrin α_v and β_3 receptor subunits disrupted *Mfge8* signaling and prevented r*Mfge8* from increasing uptake of fatty acid into adipocytes, enterocytes and hepatocytes.

The results provided a clear link between MFGE8 and fatty acid absorption from the gut into the blood and various tissues.

The team then investigated the mechanism by which MFGE8 controls fatty acid uptake and found that the MFGE8 pathway converged on a phosphoinositide 3-kinase (PI3K)-based signaling module that is a known player in the insulin receptor pathway.

In addition to PI3K, the module includes protein kinase B (PKB; PKBA; AKT; AKT1) and TBC1 domain family member 4 (TBC1D4; AS160), a regulator of glucose transporter trafficking.

Activation of the pathway triggers translocation of CD36 and FATP1 from intracellular vesicles to the plasma membrane, in which the transporters mediate the uptake of fatty acids into the cytoplasm.

Despite utilizing the same signaling module, MFGE8 and insulin produce different outcomes. Whereas MFGE8 causes translocation of fatty acid transporters to the cell surface, insulin uses the pathway to translocate a glucose transporter, solute carrier family 2 facilitated glucose transporter member 4 (SLC2A4; GLUT4), thus controlling glucose uptake.

Results were published in *Nature Medicine*.

Atabai is following up the study by looking for additional clinical evidence to support the MFGE8 connection with obesity. The team is prospectively collecting adipose tissue from patients with obesity in order to study MFGE8 levels and is performing a comprehensive genetic SNP analysis.

Where MFGE8 meets insulin

Lex Van der Ploeg, CSO of **Rhythm Pharmaceuticals Inc.**, sees the MFGE8 findings as a promising step forward for obesity therapeutics.

“The ability to regulate fatty acid absorption, through a divergent pathway that can also control glucose uptake, may provide a long-awaited opportunity in therapeutics focused on the direct inhibition of fatty acid uptake and possibly other nutrients,” he told *SciBX*.

Rhythm’s RM-493, a small peptide melanocortin 4 receptor (MC4R) agonist, is in Phase II testing for obesity. It is partnered with **Ipsen Group**.

“The ability to regulate fatty acid absorption, through a divergent pathway that can also control glucose uptake, may provide a long-awaited opportunity in therapeutics focused on the direct inhibition of fatty acid uptake and possibly other nutrients.”

—Lex Van der Ploeg,
Rhythm Pharmaceuticals Inc.

William Holland told *SciBX* that the connection between insulin and MFGE8 is likely to have an important impact on the field.

“It is amazing that the signaling machinery typically used by insulin—PI3K/AKT/AS160—is harnessed by MFGE8 to regulate lipid uptake. How this is done in a context that minimally alters glucose uptake is remarkable,” he said.

Because the goal is to limit lipid uptake, he added, it will be necessary to understand the process well to avoid exacerbating insulin signaling.

Holland is an assistant professor at **The University of Texas Southwestern Medical Center** and works on lipid signaling in metabolic disease.

According to Atabai, the increased insulin sensitivity in the high-fat diet-fed, *Mfge8* knockout mice suggests that blocking MFGE8 signaling could improve glucose control, too.

In obese individuals, he said, “MFGE8-induced fat absorption could induce insulin resistance, and inhibiting MFGE8-dependent fat absorption could enhance insulin sensitivity and ameliorate type 2 diabetes.”

Thomas Hughes told *SciBX*, “The findings might point to new strategies to stimulate glucose transport by way of integrin inhibition. Such approaches could lead to a new class of insulin sensitizers.”

Hughes is president and CEO of **Zafgen Inc.**, which has beloranib in Phase II testing for the orphan obesity disease Prader-Willi syndrome. The compound is an inhibitor of methionine aminopeptidase 2 (MetAP2). Zafgen holds exclusive worldwide rights, outside Korea, for development and commercialization of beloranib. The company licensed the compound from **Chong Kun Dang Pharmaceutical Corp.**

However, according to Atabai, although his laboratory is developing antibodies against MFGE8, there might be unwanted effects of MFGE8 inhibition because of its involvement in other processes related to apoptosis and autoimmune functions.

Matthew Rodeheffer added that global MFGE8 inhibition could create problems by depriving other tissues of energy-delivering fatty acids. He suggested that the issue might be avoided by blocking MFGE8 locally in adipose tissue to prevent effects in other cells such as cardiomyocytes.

An alternative, he said, would be to block MFGE8 locally in the gut,

“It is amazing that the signaling machinery typically used by insulin—PI3K/AKT/AS160—is harnessed by MFGE8 to regulate lipid uptake.”

**—William Holland,
The University of Texas
Southwestern Medical Center**

through which fatty acids initially gain access to the body via enterocytes in the gut lining.

Rodeheffer is an assistant professor of comparative medicine and of molecular, cellular and developmental biology at **Yale University**. He is an expert on adipocyte development.

Holland was cautious about a local treatment in the gut.

“Many lipids, particularly long-chain, saturated fatty acids, are very proinflammatory in the gut. Strong and chronic MFGE8

inhibition and concomitant elevation of these species therefore could have unwanted consequences,” he told *SciBX*.

Atabai told *SciBX* that he thinks blocking the pathway via integrin receptors might produce a better safety profile. His team will focus on local enteric and global integrin $\alpha_v\beta_5$ blockade because it is safer in animals than integrin $\alpha_v\beta_3$ inhibition, which produces diverse effects.

UCSF has filed a provisional patent on the findings. The IP is available for licensing.

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COMPANIES AND INSTITUTIONS MENTIONED

Arteria S.A., Caissargues, France
Chong Kun Dang Pharmaceutical Corp. (KSE:001630), Seoul, South Korea
Ipsen Group (Euronext:IPN; Pink:IPSEY), Boulogne-Billancourt, France
Rhythm Pharmaceuticals Inc., Boston, Mass.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
University of California, San Francisco, Calif.
The University of Texas Southwestern Medical Center, Dallas, Texas
Yale University, New Haven, Conn.
Zafgen Inc., Cambridge, Mass.

A gift for research

By Michael J. Haas, Senior Writer

An anonymous \$275 million gift propels the **Sanford-Burnham Medical Research Institute** more than halfway toward its funding goal for a newly announced 10-year drug development plan that involves speeding the development of preclinical therapies that it hopes to out-license.

Central to the plan will be promoting closer collaborations with existing partners and forming disease-focused teams to expand the internal cross-talk between labs and clinics.

Sanford-Burnham president Kristiina Vuori told *SciBX* that the genesis of the disease-focused teams was a 2010 collaboration between Sanford-Burnham researcher Stephen Gardell and clinician Steven Smith at **The Translational Research Institute for Metabolism and Diabetes**.

The duo have been collaborating to identify markers that reflect subsets of heterogeneous metabolic diseases better than current markers.¹

Gardell's team studies multiple animal models to link metabolic phenotypes to metabolomic profiles, thereby providing a distinct signature for the disease state of each model. Smith's team performs metabolic profiling on muscle and adipose tissues across the spectrum of human metabolic phenotypes—from marathon runners to patients with obesity, diabetes and other metabolic conditions—and looks for markers that define a particular phenotype or disease subset.

The two teams then work together to match a clinical phenotype or disease subset to an appropriate animal model based on shared metabolic markers. The two-way flow of clinical and preclinical data enables the teams to identify and develop markers of metabolic disease that are meaningful in both animal models and humans.

"Gardell and Smith are a duo whose capabilities and research complement one another," Vuori said. "We want to find more opportunities for our researchers to work together like this."

The Translational Research Institute is a 2009 joint venture between Sanford-Burnham and the **Florida Hospital**.

Two-way teams

Under Sanford-Burnham's 10-year plan, integrated disease teams initially will function as informal working groups and will include basic scientists, drug discovery experts and clinicians from Sanford-Burnham and its existing partners.

"Each integrated disease team will focus on developing small molecule therapies targeting a particular disease or pathway," said Vuori, who also is interim CEO of Sanford-Burnham and a professor at the institute's NCI-Designated Cancer Center.

When an integrated disease team evolves into a more formal unit—for instance, when it begins to acquire its own funding—the team will be called a diversified translational laboratory, she said.

"Gardell and Smith are a duo whose capabilities and research complement one another. We want to find more opportunities for our researchers to work together like this."

**—Kristiina Vuori,
Sanford-Burnham Medical
Research Institute**

Vuori said that the first integrated disease teams will form this year. The number of teams and the specific disease focus have not yet been determined, but "we expect they will focus on areas in which we are already active such as cancer, diabetes and obesity, as well as some neurological indications and autoimmune diseases."

Although the institute plans to expand its network of partnerships over the next decade, the first teams will draw on the institute's existing deals with **Sanford Research**, Florida Hospital, the **H. Lee Moffitt Cancer Center & Research Institute** and the **Mayo Clinic**.

In 2007, Sanford-Burnham and Sanford Research founded the Children's Health Research Center to study pediatric and congenital diseases and develop therapies to treat them. Sanford Research itself is a 1998 partnership between the not-for-profit healthcare system **Sanford Health** and the **University of South Dakota**.

In 2012, Sanford-Burnham, Florida Hospital and Moffitt formed the Personalized Medicine Partnership to discover markers that could predict individual responses to drugs for cancer, metabolic diseases and cardiovascular diseases.²

Last year, Sanford-Burnham and Mayo partnered to discover compounds to treat cancer, Alzheimer's disease (AD) and other conditions. The deal built on a year-long pilot phase in which the institute used its high throughput screening technology to analyze Mayo's compound library.

Pharmas, present and future

In addition to promoting two-way communication between the lab and clinic, the 10-year plan also will involve Sanford-Burnham using its small molecule drug discovery platform to validate preclinical candidates that could be licensed to pharmas, Vuori said.

The institute already has deals with three pharmas—**Takeda Pharmaceutical Co. Ltd.**, **Johnson & Johnson** and **Pfizer Inc.**

In 2010, Sanford-Burnham and the Translational Research Institute partnered with Takeda to support the clinical development of an undisclosed obesity compound from the pharma.¹ The two institutes renewed the deal with Takeda last year.³

In 2011, Sanford-Burnham signed a three-year partnership with the Ortho-McNeill-Janssen Pharmaceutical Inc. unit of J&J to develop therapeutics against new targets in AD and other neuropsychiatric indications.⁴

Also in 2011, the institute partnered with Pfizer to discover mechanisms and therapies for undisclosed diseases under the pharma's Global Centers for Therapeutic Innovation initiative.

Through that initiative, Pfizer provides its partners with funding for preclinical and clinical development programs and offers IP and ownership rights in return for options to license exclusive rights to drug candidates. Academic partners have access to the pharma's antibody libraries and research and are eligible for milestones and royalties on advanced programs.⁵

Last year, Sanford-Burnham entered a separate collaboration with Pfizer to identify and validate new drug targets to prevent and treat

“Each integrated disease team will focus on developing small molecule therapies targeting a particular disease or pathway.”

—*Kristiina Vuori,*
Sanford-Burnham Medical
Research Institute

insulin resistance and organ damage in obesity-related diabetes. Under the three-year deal, the pharma is using the institute’s Conrad Prebys Center for Chemical Genomics to conduct high throughput screening for new targets using investigational compounds from Pfizer and a compound library from the NIH.³

To fully fund its 10-year plan, Sanford-Burnham plans to

raise another \$225 million from philanthropists, investors and other sources over the next decade, Vuori said.

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COMPANIES AND INSTITUTIONS MENTIONED

Florida Hospital, Orlando, Fla.

H. Lee Moffitt Cancer Center & Research Institute, Tampa, Fla.

Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.

Mayo Clinic, Rochester, Minn.

National Institutes of Health, Bethesda, Md.

Pfizer Inc. (NYSE:PFE), New York, N.Y.

Sanford-Burnham Medical Research Institute, La Jolla, Calif.

Sanford Health, Fargo, N.D.

Sanford Research, Sioux Falls, S.D.

Takeda Pharmaceutical Co. Ltd. (Tokyo:4502), Osaka, Japan

The Translational Research Institute for Metabolism and Diabetes, Winter Park, Fla.

University of South Dakota, Vermillion, S.D.

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A RIPping target in Gaucher's disease

By C. Simone Fishburn, Senior Editor

Enzyme-replacement therapies are highly effective for most patients with Gaucher's disease but do little for those with the neurological childhood forms of the disease. Now, an Israeli and U.K. team has unlocked the mechanism of nerve destruction in neuronopathic Gaucher's disease and identified receptor-interacting serine-threonine kinase 3 as a new target.¹

The team is investigating possibilities for generating inhibitors of the protein kinase that cross the blood-brain barrier (BBB).

Gaucher's disease is caused by glucocerebrosidase (GBA; GCCase) deficiency, which leads to accumulation of sphingolipids in lysosomes. In normal cells, GCCase breaks down the lipid glucosylceramide (GlcCer). Mutations in *GCCase* produce catalytically inactive or unstable enzyme, which results in accumulation of unmetabolized glucosylceramide.

Type I Gaucher's disease is the most common form and does not have a neurological component. Neuronopathic Gaucher's disease is divided into Types II and III.

Type II (infantile) Gaucher's disease affects newborns and is usually fatal within one to three years of birth.

Type III (juvenile) has a slower onset and often appears in early childhood with symptoms of abnormal eye movement followed later by seizures. The disease progresses more slowly than Type II Gaucher's disease, with patients generally living into their teens or twenties and sometimes longer.

Together, Types II and III affect about 5% of patients with Gaucher's disease in Western countries but are substantially more prevalent in Asian countries including the Indian subcontinent, China, Japan and Korea.

Companies have taken two main approaches to treating Gaucher's disease—enzyme replacement therapy (ERT) and substrate reduction therapy (SRT)—with the common goal of preventing the buildup of lipids (see Table 1, “Gaucher's disease pipeline”).

ERT involves recombinant enzymes that replace the defective GCCase. These enzymes do not cross the BBB and thus are not used in Types II and III disease.

SRT compounds prevent accumulation of the sphingolipids by inhibiting the synthesis of GCCase substrates. These therapies can cross the BBB but have not shown efficacy in

neuronopathic Gaucher's disease.

Although the pathway from defective GCCase to lysosomal accumulation of lipids is well understood, little is known about the downstream part of the process, in which the lipid accumulation causes the cellular toxicity that underlies the disease.

A group headed by Tony Futerman at the **Weizmann Institute of Science** decided to look at how the buildup of lipids in lysosomes causes nerve cell destruction in Types II and III Gaucher's disease.

Futerman is a professor of biochemistry and director of The Nella and Leon Benozziyo Center for Neurological Diseases at Weizmann. His lab collaborated on the study with researchers at the **University of Cambridge** and **University of Oxford**.

“The key question for the field has been how the process of storing lipids in Gaucher's causes cell death. This paper gets to the heart of that.”

—Neil Weinreb,
National Gaucher Foundation Inc.

Ripping ahead

In two mouse models of neuronopathic Gaucher's disease, the researchers found that the disease was not caused by apoptosis of neurons but by a different, less-extensively studied process called necroptosis.

Two of the most important proteins in necroptosis, receptor-interacting serine-threonine kinase 1 (Ripk1; Rip1) and Ripk3 (Rip3), were upregulated in symptomatic Gaucher's disease mice compared with controls.

The team also found higher RIPK1 levels in a postmortem human brain from a patient with Type II disease than in an age-matched control. The researchers were unable to test RIPK3 levels as they did not have a specific RIPK3 antibody.

Table 1. Gaucher's disease pipeline. Selected compounds on the market or in clinical development for Type I Gaucher's disease.

Source: BCIQ: BioCentury Online Intelligence

| Company | Product | Description | Type of therapy | Status |
|--|---------------------------------|---|--|-----------|
| Genzyme Corp.; Sanofi (Euronext:SAN; NYSE:SNY) | Cerezyme imiglucerase | Recombinant glucocerebrosidase (GBA; GCCase) (rGCCase) | Enzyme replacement therapy (ERT) | Marketed |
| Genzyme; Sanofi | Ceredase alglucerase | Alglucerase enzyme | ERT | Marketed |
| Protalix BioTherapeutics Inc. (NYSE-M:PLX; Tel Aviv:PLX); Pfizer Inc. (NYSE:PFE) | Elelyso alfataliglycerase | Plant cell- expressed rGCCase | ERT | Marketed |
| Shire plc | Vpriv velaglucerase alfa | rGCCase | ERT | Marketed |
| Actelion Ltd. (SIX:ATLN); UCB Group (Euronext:UCB) | Zavesca miglustat | Glucosyltransferase inhibitor | Substrate reduction therapy (SRT) | Marketed |
| Genzyme; Sanofi | Cerdelga eliglustat tartrate | Glucosylceramide synthase inhibitor | SRT | Phase III |
| Isu Abxis Co. Ltd. (KOSDAQ:086890) | ISU302 | Biosimilar Cerezyme | ERT | Phase III |
| Protalix BioTherapeutics | PRX-112 | Plant cell- expressed rGCCase (oral) | ERT | Phase I |
| ExSAR Corporation | EXR-202 ^A | GCCase-binding chaperone | Not applicable | Phase I |

^AThe indication for EXR-202 may include neuronopathic Gaucher's disease.

Increased Ripk1 and Ripk3 expression also occurred in a mouse model of another neuronal lysosomal storage disease—Krabbe disease. However, levels were not altered in animal models of other lysosomal storage diseases including Niemann-Pick disease type C1, GM1 gangliosidosis and Sandhoff disease, despite the fact that some of these involve neuronal pathways.

Because *Ripk1* knockout mice did not survive more than three days, the team focused on RIPK3.

The most direct evidence of a central role for RIPK3 came when the team treated *Ripk3*^{-/-} knockout mice with a chemical that induces Gaucher's disease and found that the animals did not develop the disease.

The mice showed none of the weight loss or decreased motor coordination seen in the wild-type mice that received the compound. Knockouts lived for more than 100 days on average compared with an upper limit of 40 days for the symptomatic mice.

In addition, whereas the neuronopathic Gaucher's disease mice had increased signs of systemic inflammation in the liver and spleen, the chemical caused no such effects in the *Ripk3*-deficient mice. In contrast to the *Ripk1*^{-/-} mice, the *Ripk3*^{-/-} knockouts showed no overt pathology in their development or overall health.

Results were published in *Nature Medicine*.

Futerman told *SciBX* that the data suggest RIPK3 has two pivotal effects in the disease. The first is to cause nerve cell death via necroptosis, and the second is to promote inflammation in both the CNS and systemic organs.

From target to clinic

According to Neil Weinreb, the paper represents a conceptual breakthrough for neuronopathic Gaucher's disease. "The key question for the field has been how the process of storing lipids in Gaucher's causes cell death. This paper gets to the heart of that," he told *SciBX*. "If you can block the storage of lipids in lysosomes and neutralize their activity, that would be very good. This is the first major step in that direction."

Weinreb, a clinical Gaucher's disease practitioner, is a member of the board of the **National Gaucher Foundation Inc.** and regional coordinator of the International Collaborative Gaucher Group, which runs the Gaucher Registry.

Futerman told *SciBX* that the initial challenge will be to synthesize RIPK3 inhibitors with pharmaceutical properties. According to Futerman, commercially available RIPK inhibitors do not cross the BBB and have half-lives of under an hour.

"We are very intrigued with the findings and are interested in validating the target—and if it is a major contributor in Gaucher's, Krabbe and other diseases, then we'd be interested in looking for antagonists as therapeutics," said Seng Cheng, head of research and early development in the rare diseases division at the **Genzyme Corp.** unit of **Sanofi**.

Cheng said that a key experiment would be to develop an

antagonist and test it in an animal model. But he added that antisense oligonucleotides or RNAi could also be used in Gaucher's disease models to bolster the case for RIPK3.

However, finding the best translational path might not be simple because the patient population is so small, and electing whether to test proof of concept in Type II or Type III disease is complex.

Weinreb thinks that RIPK3 inhibitors might be better suited for Type III Gaucher's disease than Type II because its slower onset could increase the chance of starting treatment before excessive neuronal damage has occurred.

However, Norman Barton, VP of R&D at **Shire plc**, told *SciBX* that it will be hard to find appropriate endpoints for a clinical trial in patients with Type III disease because it progresses much more slowly than Type II.

The endpoints used in Type I disease would not be relevant for Types II and III.

Cheng said that Genzyme has joined with physicians and others in the field to develop outcome measures for neuronopathic Gaucher's disease and said that finding a biomarker would be a real boost.

According to Barton, patients with Type II disease would be a better population for demonstrating proof of concept if they can be identified early enough. In that group, the progression of the disease could

enable any positive effect of a RIPK3 inhibitor to be detected more definitively and more rapidly.

Barton said that any attempts to achieve proof-of-concept for either Type II or Type III Gaucher's disease would likely require a partnership with a global commercial organization.

"But a large organization would not want to go solo on developing a RIPK3 inhibitor. They would want it to be a risk-shared activity involving an alliance with an academic center and venture people," he told *SciBX*.

According to Barton, rare diseases generally require alliances to move programs forward. The small numbers of patients, complexity of clinical trials and significant financial investment all contribute to a high risk that is better shared between multiple parties.

Cheng agreed that a multiparty effort is needed to take the findings forward as designing the right trials and finding patients for rare diseases can be difficult for a single company to do successfully. He said that Genzyme traditionally operates by including patients, a foundation and a commercial partner.

Gregory Macres, founder of the **Children's Gaucher Research Fund**, which focuses on neuronopathic Gaucher's disease and supported the *Nature Medicine* study, said that his organization is seeking ways to participate in such a consortium.

A provisional patent application has been filed in the U.S. by **Yeda Research and Development Company Ltd.**, the technology transfer company of the Weizmann Institute. The IP is available for licensing.

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"We are very intrigued with the findings and are interested in validating the target—and if it is a major contributor in Gaucher's, Krabbe and other diseases, then we'd be interested in looking for antagonists as therapeutics."

—Seng Cheng, Genzyme Corp.

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COMPANIES AND INSTITUTIONS MENTIONED

Children's Gaucher Research Fund, Granite Bay, Calif.

Genzyme Corp., Cambridge, Mass.

National Gaucher Foundation Inc., Tucker, Ga.

Sanofi (Euronext:SAN; NYSE:SNY), Paris, France

Shire plc (LSE:SHP; NASDAQ:SHPG), Dublin, Ireland

University of Cambridge, Cambridge, U.K.

University of Oxford, Oxford, U.K.

Weizmann Institute of Science, Rehovot, Israel

Yeda Research and Development Company Ltd., Rehovot, Israel

Micromanaging the microenvironment

By Tracey Baas, Senior Editor

A Massachusetts team has designed an *in vivo* shRNA screen to discover immunosuppressive tumor targets that can be blocked to improve the efficacy of T cell immunotherapies.¹ The screening system shows that current checkpoint inhibitors are barely scratching the surface of potential targets to modulate and may enable new directions in immunotherapy enhancement.

Targets for modulating immune responses, such as CTLA-4 (CD152) and programmed cell death 1 (PDCD1; PD-1; CD279), are typically identified *in vitro* and tested in animal models later in the discovery process. The Massachusetts team thought it would be useful to identify targets directly in animals to account for the complex interactions of immune cells within tissues.

CTLA-4 and PD-1 are immunological checkpoint proteins. Signaling through these proteins can lead to T cell exhaustion and allow tumors to evade the immune response.

Yervoy ipilimumab, a human mAb against CTLA-4 from **Bristol-Myers Squibb Co.**, is the first checkpoint inhibitor to reach the market. The antibody was approved to treat metastatic melanoma in 2011. Bristol-Myers and **Ono Pharmaceutical Co. Ltd.** have the most advanced PD-1 antibody, nivolumab, which is in Phase III testing for metastatic melanoma, non-small cell lung cancer (NSCLC) and renal cell carcinoma (RCC).

The Massachusetts group used two separate shRNA libraries—one focused on genes associated with dysfunctional T cells and the other on kinase and phosphatase genes. The hypothesis was that when the shRNAs were introduced into T cells, only a small subset of the nucleic acids would restore T cell proliferation within the tumor microenvironment.

The result would be an enriched population of those shRNA-expressing T cells within the tumors.

Mice were injected with melanoma antigen-specific T cells infected with multiple shRNAs. Seven days later, T cells were purified from tumors and secondary lymphoid tissue.

Deep sequencing of the shRNAs found in T cells purified from tumors and secondary lymphoid organs identified the over-represented shRNAs (see Figure 1, “*In vivo* shRNA discovery of immunotherapy targets”).

The researchers identified 43 genes with shRNAs that were increased more than fourfold in tumors compared with spleens. The set included new targets as well as genes known to inhibit T cell receptor (TCR) signaling or function.

Next, the targets were validated in the same system using antigen-specific T cells infected with only a single shRNA for each target gene. The goal was to directly determine which shRNAs increased T cell accumulation in tumors.

In mice, the researchers identified shRNAs targeting seven genes that led to a tenfold increase in T cell accumulation in tumors compared with spleens.

These genes included *Ppp2r2d* (protein phosphatase 2 regulatory subunit B δ), *Perk* (eukaryotic translation initiation factor 2 α kinase 3; *Eif2ak3*), *Arhgap5* (rho GTPase activating protein 5), *Smad2* (Smad family member 2; *Madh2*), *Akap8l* (α -kinase anchor protein 8-like), *ribokinase (Rbks)* and *Erg2* (potassium channel Kv11.2; *Kcnh6*).

The greatest difference in accumulation was observed for *Ppp2r2d*.

In the melanoma mouse model, tumor antigen-specific T cells expressing *Ppp2r2d*-targeting shRNA increased T cell proliferation, survival and function compared with T cells expressing a control shRNA. Compared with mice given the control shRNA T cells, mice given the *Ppp2r2d* shRNA T cells had decreased tumor volume and increased survival.

Results were published in *Nature*. The team included researchers from the **Dana-Farber Cancer Institute, Massachusetts Institute of Technology, Broad Institute of MIT and Harvard, Novartis Institutes for BioMedical Research and Genomics Institute of the Novartis Research Foundation**.

Surprise players

Corresponding author Kai Wucherpfennig said that the *in vivo* assay is a first attempt to find previously unknown genes that could be regulated to help T cells circumvent the immunosuppressive tumor microenvironment.

“For future modification to our system, we are thinking about including fluorescent reporters for expression of cytokines such as interferon- γ (IFNG; IFN- γ) and cytotoxic molecules such as granzyme B (GrB; GZMB) and perforin 1 (PRF1) so that we might discover genes that control these critical T cell effector functions,” added Wucherpfennig, a professor of neurology at **Harvard Medical School** and a professor in the Department of Cancer Immunology and AIDS at Dana-Farber.

Drew Pardoll, a professor of oncology and co-director of the cancer immunology and hematopoiesis program at

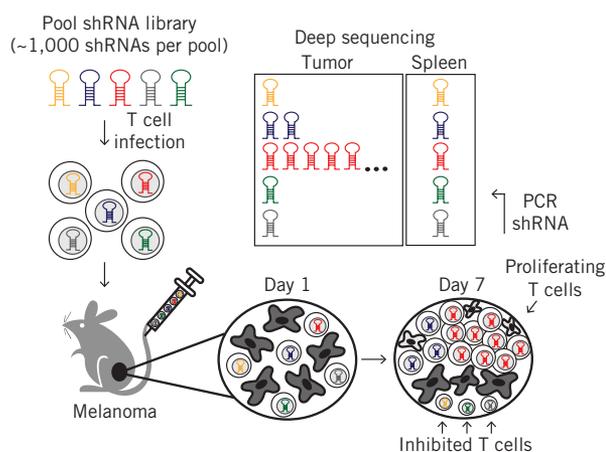


Figure 1. *In vivo* shRNA discovery of immunotherapy targets. T cells infected with shRNA libraries were injected into mice with melanoma. Several days later, T cells were purified from tumors and secondary lymphoid tissue. Deep sequencing then identified shRNAs that enabled T cells to preferentially accumulate and proliferate in tumors more so than in spleens. (Figure based on Figure 1 in ref. 1.)

The Johns Hopkins University School of Medicine, said that the screening strategy is a good way to identify truly unexpected targets relative to conventional screening procedures.

“What I really like about the screen is that most of the genes identified are not on the list of the usual suspects,” said Pardoll. “Their method emphasizes that current checkpoint inhibitors being developed for immunotherapy are barely scratching the surface of what is available to modulate therapeutically. The team will ultimately have to demonstrate, using multiple targets identified in their screening approach, that knockdown or inhibition of the targets enhances T cell antitumor activity.”

Going forward, Wucherpennig said that the team wants to find additional targets and include human tumors in xenotransplant mouse models. “Subcutaneous tumors are imperfect models, but they provide information regarding interactions between tumor cells, immune cells and stromal cells that *in vitro* screening methods cannot,” he said.

Sriram Sathy, director of target and biomarker discovery at cancer immunotherapy company **Jounce Therapeutics Inc.**, said that human tumors “display a high degree of heterogeneity in the composition of T cell infiltrates. To expand on these results, these analyses need to be extended to additional tumor models. Ideally, models where tumor rejection antigens that have been modified by the immune system would be included to help solidify these findings.”

Tibor Keler, CSO and SVP at antibody and immunomodulation company **Celldex Therapeutics Inc.**, said that it would be important to link the findings of the Massachusetts team to clinical situations.

“For example, are these proteins regulated in tumor-infiltrating T cells in patient tumor samples?” asked Keler. “Are they differentially expressed in tumor-infiltrating T cells of patients with a good outcome relative to those with a poor outcome?”

“Ultimately, validation will require translation to the human setting, which could be partially addressed in a humanized mouse model of

“What I really like about the screen is that most of the genes identified are not on the list of the usual suspects. Their method emphasizes that current checkpoint inhibitors being developed for immunotherapy are barely scratching the surface of what is available to modulate therapeutically.”

—Drew Pardoll,
The Johns Hopkins University
School of Medicine

cancer,” continued Keler. “This would provide a better understanding of the regulation of a target in a human disease setting.”

Michael Briskin, VP of discovery research at Jounce, noted that “targeting the gene product of *Ppp2r2d* with antibodies or small molecules will be challenging because it is expressed intracellularly and is part of a complex regulatory network. *Ppp2r2d* might be more interesting from an adoptive T cell therapy perspective, where knockdown of *Ppp2r2d* could be included.”

In their *Nature* manuscript, the team proposed that “the efficacy of such T-cell-based therapies could be enhanced by shRNA-mediated silencing of genes that inhibit T-cell function in the tumor microenvironment.”

The patent and licensing status of the findings are not disclosed.

Baas, T. *SciBX* 7(6); doi:10.1038/scibx.2014.162
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1. Zhou, P. *et al. Nature*; published online Jan. 29, 2014; doi:10.1038/nature12988
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COMPANIES AND INSTITUTIONS MENTIONED

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Broad Institute of MIT and Harvard, Cambridge, Mass.
Celldex Therapeutics Inc. (NASDAQ: CLDX), Needham, Mass.
Dana-Farber Cancer Institute, Boston, Mass.
Genomics Institute of the Novartis Research Foundation, San Diego, Calif.
Harvard Medical School, Boston, Mass.
The Johns Hopkins University School of Medicine, Baltimore, Md.
Jounce Therapeutics Inc., Cambridge, Mass.
Massachusetts Institute of Technology, Cambridge, Mass.
Novartis Institutes for BioMedical Research, Cambridge, Mass.
Ono Pharmaceutical Co. Ltd. (Tokyo: 4528), Osaka, Japan

This week in therapeutics

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

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

| Indication | Target/marker/pathway | Summary | Licensing status | Publication and contact information |
|---------------|--|--|--|--|
| Cancer | | | | |
| Breast cancer | Signal transducer and activator of transcription 5 (STAT5) | Human tissue sample and mouse studies suggest inhibiting STAT5 could help reduce the risk of breast cancer associated with late-age pregnancy. Mice that had been pregnant had greater numbers of tumors and levels of Stat5 in precancerous lesions than unmated mice. In precancerous lesion-bearing mice that had been pregnant, a Stat5 inhibitor decreased tumor incidence and increased tumor-free survival compared with vehicle. Tissue from patients with breast cancer who had been pregnant had higher numbers of STAT5 ⁺ lesions compared with patients who had never been pregnant. Next steps could include designing specific inhibitors of STAT5 and testing them in preclinical models of pregnancy-associated breast cancer. The STAT5 inhibitor used in the study, StemMed Ltd.'s C188-9, is in preclinical testing in breast cancer. SciBX 7(6); doi:10.1038/scibx.2014.163 Published online Feb. 13, 2014 | Patented by Baylor College of Medicine; licensed to StemMed | Haricharan, S. <i>et al. eLife</i> ; published online Dec. 31, 2013; doi:10.7554/eLife.00996 Contact: Yi Li, Baylor College of Medicine, Houston, Texas e-mail: liy@bcm.edu |
| Cancer | Aldehyde dehydrogenase 3 family member A1 (ALDH3A1) | <i>In vitro</i> studies suggest ALDH3A1 inhibitors could help sensitize cancers to cyclophosphamide or related compounds. ALDH3A1 is overexpressed on some cancer cells and can lead to drug resistance by detoxifying phosphamide-based therapeutics. Enzyme kinetic and crystallographic studies identified an inhibitor that bound the aldehyde-binding pocket of ALDH3A1 and had selectivity for ALDH3A1 over other closely related enzymes. In human lung adenocarcinoma or glioblastoma cells expressing ALDH3A1, compared with primary human lung fibroblasts that did not express the enzyme, the inhibitor increased chemosensitivity to the cyclophosphamide analog mafosfamide. Next steps include evaluating toxicology and pharmacology of ALDH3A1 inhibitors. Cyclophosphamide is a generic chemotherapeutic. SciBX 7(6); doi:10.1038/scibx.2014.164 Published online Feb. 13, 2014 | Provisional patent application filed; available for licensing | Parajuli, B. <i>et al. J. Med. Chem.</i> ; published online Jan. 4, 2014; doi:10.1021/jm401508p Contact: Thomas D. Hurley, Indiana University School of Medicine, Indianapolis, Ind. e-mail: thurley@iu.edu |
| Cancer | Choline kinase- α (CHKA) | <i>In vitro</i> studies identified a CHKA inhibitor that could help treat cancers. An asymmetrical, bicationic inhibitor of CHKA that interacts with the choline-binding site exclusively and opens an adjacent binding site had about 200-fold selectivity for CHKA over CHKB. In human cervical carcinoma cells, the inhibitor induced apoptosis and decreased cell proliferation compared with vehicle. Next steps include testing the inhibitor <i>in vivo</i> and improving selectivity. SciBX 7(6); doi:10.1038/scibx.2014.165 Published online Feb. 13, 2014 | Patent application filed; available for licensing | Ruiz, B. <i>et al. J. Med. Chem.</i> ; published online Jan. 4, 2014; doi:10.1021/jm401665x Contact: Ana Conejo-García, University of Granada, Granada, Spain e-mail: aconejo@ugr.es |
| Cancer | Glutathione peroxidase 4 (GPX4) | <i>In vitro</i> and mouse studies suggest inhibiting GPX4 could help treat cancer by inducing ferroptosis. Ferroptosis is a form of iron-dependent, nonapoptotic cell death. In cancer cells treated with multiple small molecule inducers of ferroptosis, metabolomic and chemoproteomic profiling identified inhibition of GPX4 as a common mechanism of cell death. In mice with fibrosarcoma or oncogene-expressing fibroblast xenografts, the ferroptosis inducers inhibited tumor growth and decreased size of established tumors compared with vehicle. In a panel of cancer cell lines, renal cell carcinomas and diffuse large B cell lymphomas (DLBCLs) were especially sensitive to GPX4-mediated ferroptotic cell death. Next steps include testing the ferroptotic agents in additional cancer models. SciBX 7(6); doi:10.1038/scibx.2014.166 Published online Feb. 13, 2014 | Patent applications filed covering compounds, their use in treating cancer and methods related to evaluating ferroptosis; unlicensed; availability undisclosed | Yang, W.S. <i>et al. Cell</i> ; published online Jan. 16, 2014; doi:10.1016/j.cell.2013.12.010 Contact: Brent R. Stockwell, Columbia University, New York, N.Y. e-mail: bstockwell@columbia.edu |

This week in therapeutics (continued)

| Indication | Target/marker/pathway | Summary | Licensing status | Publication and contact information |
|------------|---|---|--|---|
| Cancer | IL-6; IL-6 signal transducer (IL-6ST; gp130; CD130); JAK kinase (JAK); signal transducer and activator of transcription 3 (STAT3) | <i>In vitro</i> studies suggest two marketed drugs could inform the design of inhibitors that block the IL-6-CD130 interaction and help treat cancer. Fragment-based drug design and virtual screening identified raloxifene and bazedoxifene as potential inhibitors of the IL-6-CD130 interaction that activates JAK and STAT3 signaling. In a CD130 ⁺ human pancreatic cancer cell line, both drugs reduced viability at micromolar IC ₅₀ values. In an estrogen receptor-negative human breast cancer cell line, the drugs reduced viability at micromolar IC ₅₀ values. Ongoing work includes optimizing the two drugs for potency against the IL-6-CD130 interaction. Eli Lilly and Co. and Takeda Pharmaceutical Co. Ltd. market Evista raloxifene, a selective estrogen receptor modulator (SERM), to treat osteoporosis and breast cancer. Ligand Pharmaceuticals Inc. and Pfizer Inc. market the SERM Conbriza bazedoxifene to treat osteoporosis. SciBX 7(6); doi:10.1038/scibx.2014.167 Published online Feb. 13, 2014 | Unpatented; unlicensed; available for partnering | Li, H. <i>et al. J. Med. Chem.</i> ; published online Jan. 23, 2014; doi:10.1021/jm401144z Contact: Chenglong Li, The Ohio State University, Columbus, Ohio e-mail: li.728@osu.edu |
| Cancer | Inhibitor of apoptosis (IAP); toll-like receptor 3 (TLR3); TLR9 | <i>In vitro</i> and mouse studies suggest combining IAP inhibitors with oncolytic viruses or TLR agonists could help treat cancer. In human and mouse cancer cell lines, an IAP antagonist plus an oncolytic virus, TLR3 agonist or TLR9 agonist decreased cell viability synergistically compared with any agent alone. In mice with mammary or xenograft colorectal tumors, the combination therapy decreased tumor growth and increased survival compared with any agent alone. Ongoing work includes discussing plans with undisclosed partners for a Phase I trial of an IAP inhibitor and an oncolytic virus in patients with cancer. At least six companies have IAP inhibitors in Phase II or earlier development to treat cancer. SciBX 7(6); doi:10.1038/scibx.2014.168 Published online Feb. 13, 2014 | Patent application filed by Children's Hospital of Eastern Ontario; licensing status undisclosed | Beug, S.T. <i>et al. Nat. Biotechnol.</i> ; published online Jan. 26, 2014; doi:10.1038/nbt.2806 Contact: Robert G. Korneluk, Children's Hospital of Eastern Ontario Research Institute, Ottawa, Ontario, Canada e-mail: bob@arc.cheo.ca |
| Cancer | Interferon- β (IFN β); IFN- β) | Mouse studies suggest directly coupling antibodies to IFN- β could help treat cancer. In multiple mouse models of breast cancer, the anti-epidermal growth factor receptor (EGFR) antibody Erbitux cetuximab fused to IFN- β decreased tumor growth compared with Erbitux alone. In mice with melanoma, an anti-programmed cell death 1 ligand 1 (CD274 molecule; PD-L1; B7-H1) antibody that blocks inhibitory T cell signaling increased the efficacy of the fusion antibody compared with either antibody alone. Next steps include increasing the half-life of the IFN- β -coupled antibody. Eli Lilly and Co., Bristol-Myers Squibb Co. and Merck KGaA market Erbitux to treat colorectal cancer and head and neck cancer. At least five companies have therapeutic antibodies against PD-L1 in Phase II or earlier development to treat cancer. SciBX 7(6); doi:10.1038/scibx.2014.169 Published online Feb. 13, 2014 | Patent application filed; available for licensing | Yang, X. <i>et al. Cancer Cell</i> ; published online Jan. 13, 2014; doi:10.1016/j.ccr.2013.12.004 Contact: Yang-Xin Fu, Institute of Biophysics, Chinese Academy of Sciences, Beijing, China e-mail: yfu@uchicago.edu |
| Cancer | Ras homolog family member J (RHOJ) | Studies in mice suggest antagonizing RHOJ could help treat cancer by disrupting the tumor vasculature. In multiple mouse models of solid tumors, <i>Rhoj</i> knockout decreased tumor growth, tumor vascularization and metastasis compared with <i>Rhoj</i> expression. A combination of a VEGF inhibitor and a fibronectin-targeting liposome carrying <i>Rhoj</i> -specific siRNA reduced peri- and intratumor vascularization and growth more potently than either agent alone. Next steps include identifying small molecule RHOJ antagonists. SciBX 7(6); doi:10.1038/scibx.2014.170 Published online Feb. 13, 2014 | Patent pending; available for licensing | Kim, C. <i>et al. Cancer Cell</i> ; published online Jan. 13, 2014; doi:10.1016/j.ccr.2013.12.010 Contact: Gou Young Koh, Korea Advanced Institute of Science and Technology, Daejeon, South Korea e-mail: gykoh@kaist.ac.kr Contact: Akiyoshi Uemura, Kobe University Graduate School of Medicine, Kobe, Japan e-mail: aumura@med.kobe-u.ac.jp |

This week in therapeutics (continued)

| Indication | Target/marker/pathway | Summary | Licensing status | Publication and contact information |
|------------------------------------|--|---|---|--|
| Cancer | RNA polymerase I (Pol I) | <i>In vitro</i> studies identified a small molecule that causes the degradation of the RPA194 catalytic subunit of Pol I and could help treat cancer. A small molecule with broad anticancer activity preferentially bound GC-rich ribosomal DNA, inhibited transcription by Pol I and caused degradation of RPA194 in cancer cell lines. In the cell lines, the molecule inhibited ribosomal RNA synthesis, and reduced cell viability was correlated with lower levels of RPA194. Next steps include testing the compound in animal models. Senhwa Biosciences Inc. has the Pol I inhibitor CX-5461 in Phase I testing to treat cancer. SciBX 7(6); doi:10.1038/scibx.2014.171 Published online Feb. 13, 2014 | Patented; available for licensing | Peltonen, K. <i>et al. Cancer Cell</i> ; published online Jan. 13, 2014; doi:10.1016/j.ccr.2013.12.009 Contact: Marikki Laiho, University of Helsinki, Helsinki, Finland e-mail: mlaiho1@jhmi.edu |
| Glioblastoma | Epidermal growth factor receptor variant III (EGFRvIII); prominin 1 (PROM1; CD133) | Studies in patient samples and mice suggest a bispecific antibody targeting EGFRvIII and CD133 could help treat glioblastoma. In samples from patients with glioblastoma, CD133 and EGFRvIII were often coexpressed. In a mouse model of glioblastoma, intracranially implanted cells coexpressing CD133 and EGFRvIII led to greater tumor formation than cells expressing CD133 alone. In the mouse model, a bispecific antibody targeting CD133 and EGFRvIII inhibited tumor formation and increased survival compared with antibodies targeting either protein alone or IgG. Next steps include scaling up production of the bispecific antibody for additional efficacy tests in the intracranial model of glioblastoma. ImmunoCellular Therapeutics Ltd. has ICT-121, an antibody targeting CD133, in Phase I testing to treat brain cancer. Celldex Therapeutics Inc.'s CDX-110, a vaccine targeting EGFRvIII, is in Phase III testing to treat glioblastoma. SciBX 7(6); doi:10.1038/scibx.2014.172 Published online Feb. 13, 2014 | Patent filed covering bispecific antibody and application to identify stem cells; available for licensing | Emler, D.R. <i>et al. Cancer Res.</i> ; published online Dec. 23, 2013; doi:10.1158/0008-5472.CAN-13-1407 Contact: Albert J. Wong, Stanford University, Stanford, Calif. e-mail: ajwong@stanford.edu |
| Prostate cancer | G protein-coupled receptor kinase 3 (GRK3; ADRBK2) | Mouse and human sample studies suggest inhibiting ADRBK2 could help suppress prostate cancer growth and metastasis. In mice orthotopically transplanted with human prostate cancer cells, shRNA against <i>ADRBK2</i> decreased primary tumor growth compared with control shRNA, whereas overexpression of <i>ADRBK2</i> increased primary tumor growth and metastasis to the lung and lymph nodes compared with overexpression of green fluorescent protein. In human prostate tumor samples, elevated ADRBK2 expression correlated with malignancy, visceral metastasis and microvascular proliferation. Next steps include investigating ADRBK2's mechanism of action and identifying small molecule inhibitors of ADRBK2. SciBX 7(6); doi:10.1038/scibx.2014.173 Published online Feb. 13, 2014 | Patent status undisclosed; unavailable for licensing | Li, W. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Jan. 13, 2014; doi:10.1073/pnas.1320638111 Contact: Ed Harlow, Harvard Medical School, Boston, Mass. e-mail: eharlow@hms.harvard.edu Contact: Wenliang Li, The University of Texas Health Science Center at Houston, Houston, Texas e-mail: wenliang.li@uth.tmc.edu |
| Endocrine/metabolic disease | | | | |
| Metabolic disease | Unknown | Studies in cell culture and mice suggest β -aminoisobutyric acid could be useful for treating metabolic disease. β -Aminoisobutyric acid is secreted into the bloodstream by muscles during exercise. In a human induced pluripotent stem (iPS) cell model of adipocyte differentiation, β -aminoisobutyric acid increased differentiation into brown adipose tissue compared with vehicle control. In mice, β -aminoisobutyric acid-treated drinking water improved glucose tolerance and decreased body fat compared with untreated drinking water. Next steps could include testing β -aminoisobutyric acid in mouse models of obesity and type 2 diabetes. SciBX 7(6); doi:10.1038/scibx.2014.174 Published online Feb. 13, 2014 | Patent and licensing status undisclosed | Roberts, L.D. <i>et al. Cell Metab.</i> ; published online Jan. 7, 2014; doi:10.1016/j.cmet.2013.12.003 Contact: Robert E. Gerszten, Harvard Medical School, Boston, Mass. e-mail: rgerszten@partners.org |

This week in therapeutics (continued)

| Indication | Target/marker/pathway | Summary | Licensing status | Publication and contact information |
|-------------------------------------|--|--|---|---|
| Obesity | Lactadherin (MFGE8; HMFG); integrin $\alpha_v\beta_3$; integrin $\alpha_v\beta_3$ (CD51/CD61) | <p>Mouse studies suggest inhibiting MFGE8 could help reduce fat uptake and treat obesity. In <i>Mfge8</i> knockout mice fed a high-fat diet, insulin sensitivity increased and weight gain and total body fat decreased compared with what was seen in wild-type mice fed a high-fat diet. In mice treated with recombinant Mfge8, injection of antibodies blocking the Mfge8 receptors integrin α_v or integrins β_5 or β_3 decreased serum, hepatic and enterocyte triglyceride contents compared with control antibody. Next steps include developing antibodies against human MFGE8 and investigating local and systemic integrin $\alpha_v\beta_5$ inhibition in mouse models of obesity (see <i>Curb your fatty acids</i>, page 1).</p> <p>SciBX 7(6); doi:10.1038/scibx.2014.175 Published online Feb. 13, 2014</p> | Provisional patent application filed; available for licensing | <p>Khalifeh-Soltani, A. <i>et al. Nat. Med.</i>; published online Jan. 19, 2014; doi:10.1038/nm.3450</p> <p>Contact: Kamran Atabei, University of California, San Francisco, Calif. e-mail: kamran.atabai@ucsf.edu</p> |
| Infectious disease | | | | |
| HIV/AIDS | HIV gp120 | <p>Mouse studies suggest combining antiretroviral therapy with an HIV gp120-targeting immunotoxin could help eliminate chronic HIV infection. In a mouse model of HIV with humanized bone marrow, liver and thymus, a combination of three antiretroviral therapies reduced but did not eliminate viral RNA, and addition of an anti-gp120 immunotoxin further decreased tissue levels of viral RNA by specifically eliminating virus-infected cells. Next steps could include testing the combination in primate models.</p> <p>SciBX 7(6); doi:10.1038/scibx.2014.176 Published online Feb. 13, 2014</p> | Patent and licensing status unavailable | <p>Denton, P.W. <i>et al. PLoS Pathog.</i>; published online Jan. 9, 2014; doi:10.1371/journal.ppat.1003872</p> <p>Contact: J. Victor Garcia, The University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, N.C. e-mail: victor_garcia@med.unc.edu</p> |
| Musculoskeletal disease | | | | |
| Osteoporosis | Lysophosphatidic acid receptor 1 (LPA1; EDG2; LPA1) | <p><i>In vitro</i> and mouse studies suggest LPAR1 antagonists could help treat osteoporosis. In mouse models of the indication, bone levels of <i>Lpar1</i> were higher than those in healthy control mice, and LPAR1 antagonists decreased bone loss compared with vehicle. In bone marrow cells from normal mice, <i>Lpar1</i> levels correlated with markers of osteoclast differentiation, and <i>Lpar1</i> deficiency or inhibition decreased osteoclast differentiation compared with normal <i>Lpar1</i> expression or vehicle. Planned work includes testing bone levels of LPAR1 in patients with osteoporosis. Bristol-Myers Squibb Co.'s BMS-986202 (formerly AM152), an oral LPAR1 antagonist, is in Phase I testing to treat pulmonary fibrosis. The company also has another oral LPAR1 antagonist, AM095, in preclinical testing to treat scleroderma. Kyowa Hakko Kirin Co. Ltd. and Debiopharm Group have Debio 0719, a selective inhibitor of LPAR1 and LPAR3 (EDG7; LPA3), in preclinical testing to treat cancer.</p> <p>SciBX 7(6); doi:10.1038/scibx.2014.177 Published online Feb. 13, 2014</p> | Unpatented; unlicensed; available for partnering | <p>David, M. <i>et al. J. Biol. Chem.</i>; published online Jan. 15, 2014; doi:10.1074/jbc.M113.533232</p> <p>Contact: Olivier Peyruchaud, Institut National de la Santé et de la Recherche Médicale (INSERM) U1033, Lyon, France e-mail: olivier.peyruchaud@inserm.fr</p> |
| Neurology | | | | |
| Amyotrophic lateral sclerosis (ALS) | Matrix metalloproteinase 9 (MMP9) | <p>Mouse studies suggest inhibiting MMP9 could help treat ALS. In patients with ALS and in mouse models, slow motor neurons and neurons regulating eye movement and sexual function were resistant to neurodegeneration. In mouse models of ALS, levels of <i>Mmp9</i> in these neurons were lower than those in fast motor neurons lost during disease progression. In the models, genetic inactivation of <i>Mmp9</i> or intracerebroventricular administration of a research-grade MMP9 inhibitor delayed the onset of disease symptoms, decreased loss of motor functions and increased survival compared with unmodified <i>Mmp9</i> expression or vehicle. Ongoing work includes confirming the proneurodegenerative role of MMP9 in patients with ALS.</p> <p>SciBX 7(6); doi:10.1038/scibx.2014.178 Published online Feb. 13, 2014</p> | Unpatented; unlicensed | <p>Kaplan, A. <i>et al. Neuron</i>; published online Jan. 22, 2014; doi:10.1016/j.neuron.2013.12.009</p> <p>Contact: Christopher E. Henderson, Columbia University Medical Center, New York, N.Y. e-mail: ch2331@columbia.edu</p> |

This week in therapeutics (continued)

| Indication | Target/marker/pathway | Summary | Licensing status | Publication and contact information |
|------------|-----------------------|--|---|---|
| Epilepsy | Estrogen receptor | <p>Mouse studies suggest estradiol or related drugs could be used to treat infantile spasms syndrome (ISS). Estradiol mediates long-term gene expression changes through the estrogen receptor. In a mouse model of ISS with deficient interneuron development, estradiol given in an early postnatal window decreased motor spasms and seizures compared with vehicle or treatment at a later time. In the mice treated in the early window, neuropeptide Y (Npy)⁺ cortical interneuron and choline acetyltransferase-positive striatal interneuron numbers were restored. Next steps include studies to refine dosing levels, duration and timing of estradiol treatment.</p> <p>More than 20 companies market ligands for the estrogen receptor for various indications.</p> <p><i>SciBX</i> 7(6); doi:10.1038/scibx.2014.179 Published online Feb. 13, 2014</p> | Unpatented; mouse model available for licensing from Baylor College of Medicine | <p>Olivetti, P.R. <i>et al. Sci. Transl. Med.</i>; published online Jan. 22, 2014; doi:10.1126/scitranslmed.3007231</p> <p>Contact: Jeffrey L. Noebels, Baylor College of Medicine, Houston, Texas e-mail: jnoebels@bcm.edu</p> |

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This week in techniques

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

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

| Approach | Summary | Licensing status | Publication and contact information |
|---|--|---|---|
| Assays & screens | | | |
| <i>In vivo</i> shRNA screen to identify immunosuppressive tumor targets | <i>In vivo</i> shRNA screens could be used to identify immunosuppressive tumor targets to enhance T cell immunotherapy. In melanoma-bearing mice injected with T cells expressing an shRNA library, deep sequencing determined that shRNA targeting <i>protein phosphatase 2 regulatory subunit Bδ</i> (<i>Ppp2r2d</i>) increased T cell accumulation in tumors compared with in spleens. In the mice, T cells expressing <i>Ppp2r2d</i> -targeting shRNA showed greater tumor infiltration, proliferation and survival, and also greater mouse survival, than T cells expressing a control shRNA. Next steps could include testing T cells that express a chimeric antigen receptor (CAR) plus <i>PPP2R2D</i> -targeting shRNA in animal models of cancer (see <i>Micromanaging the microenvironment</i> , page 9). | Patent and licensing status undisclosed | Zhou, P. <i>et al. Nature</i> ; published online Jan. 29, 2014; doi:10.1038/nature12988 Contact: Kai W. Wucherpfennig, Dana-Farber Cancer Institute, Boston, Mass. e-mail: kai_wucherpfennig@dfci.harvard.edu |
| | SciBX 7(6); doi:10.1038/scibx.2014.180 Published online Feb. 13, 2014 | | |
| Computational models | | | |
| Mathematical model of dynamic radiation response in glioma cells predicts schedule to improve radiation therapy | Mouse studies suggest a mathematical model can improve radiation schedules for treating cancer. The model considers radiation-resistant and radiation-sensitive cells, allows time-dependent, bidirectional flow between these states and is based on a linear quadratic formula. In a mouse model of platelet-derived growth factor-driven glioma, the optimized radiation schedule increased survival compared with a standard schedule. Next steps include testing the scheduling predictions in a clinical trial and extending the analysis to additional cancer types. | Unpatented; unlicensed | Leder, K. <i>et al. Cell</i> ; published online Jan. 30, 2014; doi:10.1016/j.cell.2013.12.029 Contact: Franziska Michor, Dana-Farber Cancer Institute, Boston, Mass. e-mail: michor@jimmy.harvard.edu Contact: Eric C. Holland, Fred Hutchinson Cancer Research Center, Seattle, Wash. e-mail: eholland@fhcrc.org |
| | SciBX 7(6); doi:10.1038/scibx.2014.181 Published online Feb. 13, 2014 | | |
| Disease models | | | |
| Gut microbe-associated phenotypes in mice receiving human fecal microbiota | A systems biology approach to studying mouse recipients of human gut microbes could aid the development of microbiota-associated disease models. Cultured fecal microbiota from a healthy human donor contained 17 different bacterial species. In gnotobiotic mice receiving 1 of 94 distinct combinations of up to 11 of the 17 species, systems-level analyses identified individual or groups of bacterial species that contributed to host phenotypes including colonic T _{reg} populations, adiposity and gut levels of short-chain fatty acids. Future studies could include examining phenotypes in mice receiving cultured microbiota from patients with metabolic or intestinal diseases. | Patent and licensing status unavailable | Faith, J.J. <i>et al. Sci. Transl. Med.</i> ; published online Jan. 22, 2014; doi:10.1126/scitranslmed.3008051 Contact: Jeffrey I. Gordon, Washington University in St. Louis School of Medicine, St. Louis, Mo. e-mail: jgordon@wustl.edu |
| | SciBX 7(6); doi:10.1038/scibx.2014.182 Published online Feb. 13, 2014 | | |
| Modeling the effect of hyperactive mast cells in inflammatory disease | Mice with hyperactive mast cells could help model inflammatory diseases. In cell culture, <i>tumor necrosis factor-α-induced protein 3</i> (<i>TNFAIP3</i> ; <i>A20</i>) depletion enhanced lipopolysaccharide (LPS)- and IL-33 (NF-HEV)-induced mast cell activation. In mice, <i>A20</i> depletion in mast cells induced a sensitized state without eliciting spontaneous inflammation. In mouse models of asthma, allergic asthma and rheumatoid arthritis (RA), <i>A20</i> depletion in mast cells exacerbated inflammatory responses. In mouse models of multiple sclerosis (MS), <i>A20</i> depletion in mast cells had no effect. Next steps include finding methods to stabilize <i>A20</i> protein to reduce inflammation and studying the role of hyperinflammatory mast cells in cancer. | Unpatented; licensing status not applicable | Heger, K. <i>et al. PLoS Biol.</i> ; published online Jan. 14, 2014; doi:10.1371/journal.pbio.1001762 Contact: Marc Schmidt-Supprian, Max Planck Institute of Biochemistry, Martinsried, Germany e-mail: supprian@biochem.mpg.de |
| | SciBX 7(6); doi:10.1038/scibx.2014.183 Published online Feb. 13, 2014 | | |

This week in techniques (continued)

| Approach | Summary | Licensing status | Publication and contact information |
|---|---|--|---|
| Mouse models of epilepsy and anxiety | A study in mice suggests neuron type-specific perturbation of glycine receptor $\alpha 3$ (GLRA3) could help model epilepsy and neuropsychiatric disease. RNA editing can lead to a gain-of-function mutation in <i>GLRA3</i> that is associated with drug-resistant temporal lobe epilepsy. Mice expressing a transgenic, gain-of-function <i>Gla3</i> variant in glutamatergic neurons showed signs of epilepsy including elevated electrophysiological activity and defects in memory and cognitive function. Mice expressing transgenic, gain-of-function <i>Gla3</i> in interneurons of inhibitory circuits had greater anxiety but normal cognition compared with controls not expressing the transgene. Next steps include testing glycine receptor-modulating compounds in these transgenic mice. | Unpatented; licensing status not applicable | Winkelmann, A. <i>et al. J. Clin. Invest.</i> ; published online Jan. 16, 2014; doi:10.1172/JCI71472 Contact: Jochen C. Meier, Max Delbrueck Center for Molecular Medicine, Berlin, Germany e-mail: jochen.meier@mdc-berlin.de |
| SciBX 7(6); doi:10.1038/scibx.2014.184 Published online Feb. 13, 2014 | | | |
| Drug platforms | | | |
| Engineered Fc γ -receptor engagement enhances broadly neutralizing antibodies (bNAbs) against influenza A virus | Mouse studies suggest bNAbs engineered to activate Fc γ -receptors on immune cells could help prevent influenza infection. bNAbs that bind the invariant stalk region of hemagglutinin (HA) were modified with Fc regions designed to bind a subset of Fc γ -receptors on immune cells that activate an antiviral response. In a mouse model of lethal influenza infection, the engineered bNAbs increased survival and decreased viral titers in the lung compared with antibodies containing Fc regions that engaged inhibitory Fc γ -receptors or were deficient in Fc γ -receptor binding. In humanized mice exclusively expressing human Fc γ -receptors, an engineered HA stalk-specific bNAb increased survival after viral infection compared with an unmodified bNAb. Next steps could include building Fc portions into therapeutic bNAbs that enable interactions with activating Fc γ -receptors in the host. | Patent and licensing status unavailable | DiLillo, D.J. <i>et al. Nat. Med.</i> ; published online Jan. 12, 2014; doi:10.1038/nm.3443 Contact: Jeffrey V. Ravetch, The Rockefeller University, New York, N.Y. e-mail: ravetch@rockefeller.edu |
| SciBX 7(6); doi:10.1038/scibx.2014.185 Published online Feb. 13, 2014 | | | |
| Systematic evolution of ligands by exponential enrichment (SELEX) incorporating artificially expanded genetic information systems (AEGIS) nucleotides | SELEX using AEGIS-incorporating libraries could help identify aptamers with strong binding to cellular targets. SELEX involves screening libraries of nucleic acid molecules for binding to targets, then amplifying and sequencing the binders. SELEX with a nucleotide-based library created with the four standard nucleic acids plus two artificially constructed AEGIS nucleotides identified an aptamer that bound to a breast cancer cell line with a lower dissociation constant than a standard SELEX aptamer. Next steps could include applying the method to other targets. | Patent application filed; nonexclusively licensed to undisclosed companies; available for licensing | Sefah, K. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Dec. 30, 2013; doi:10.1073/pnas.1311778111 Contact: Steven A. Benner, Foundation for Applied Molecular Evolution, Gainesville, Fla. e-mail: sbenner@ffame.org |
| SciBX 7(6); doi:10.1038/scibx.2014.186 Published online Feb. 13, 2014 | | | |
| Transformation-associated recombination (TAR)-based method to capture large, biosynthetic bacterial gene clusters | A TAR-based approach to isolate bacterial gene clusters could aid the synthesis of natural products including antibiotics. In yeast, TAR was used to assemble a contiguous 67 kb region from the marine actinomycete <i>Saccharomonospora</i> sp. that contained 20 transcriptionally silent open reading frames including a biosynthetic gene cluster. Subsequent deletion of an inhibitory gene, heterologous expression in a model biosynthetic host and structural characterization identified the cluster's product as taromycin A, an antibiotic similar to Cubicin daptomycin. Next steps include streamlining the TAR-based approach for high throughput screening of biosynthetic microbial gene clusters. Cubist Pharmaceuticals Inc. markets Cubicin to treat bacteremia and skin and skin structure infections. | Patent application filed; available for licensing from the University of California, San Diego Contact: Dominic Montisano, University of California, San Diego, La Jolla, Calif. e-mail: dfmontisano@ucsd.edu | Yamanaka, K. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; published online Jan. 21, 2014; doi:10.1073/pnas.1319584111 Contact: Bradley S. Moore, University of California, San Diego, La Jolla, Calif. e-mail: bmoore@ucsd.edu |
| SciBX 7(6); doi:10.1038/scibx.2014.187 Published online Feb. 13, 2014 | | | |

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