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Two independent teams at UCSF and Harvard have found an immune-regulated pathway for beige fat formation and a hormone, METRN1, that activates it. Ember Therapeutics has an option to license the molecule, which could represent a new way to treat obesity.

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A UNC Chapel Hill team has found a way to block multiple pain receptors by antagonizing the lipid kinase PIP5K1C. Although a PIP5K1C inhibitor alleviates chronic pain in multiple mouse models, the lethality of PIP5K1C mutations suggests that titrating the right dose will be key for safety.

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No disease-modifying therapy has been developed to date for Parkinson's disease. Independent teams in Europe and the U.S. have now found that the dopamine transporter VMAT2 has a potentially causative role in the disease—figuring out how to enhance its activity is the next challenge.

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A Harvard University team has shown that low-power laser treatment could be used to noninvasively drive dental stem cell differentiation and tissue regeneration in rats. What remains to be determined is whether the approach can restore function in human teeth and whether it will work in other tissue types.

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Going immune on beige fat

By Kai-Jye Lou, Senior Writer

Since its founding in 2010, **Ember Therapeutics Inc.** has been exploiting the biology of brown and beige fat to treat metabolic diseases, including obesity and type 2 diabetes. Now, the biotech has an option to license the hormone meteorin glial cell differentiation regulator-like, one of the first molecules found to activate a newly identified immune system-regulated pathway responsible for driving the formation of beige fat.^{1,2}

Beige adipocytes and their brown adipocyte cousins are mitochondria-rich cells that metabolize triglycerides to generate heat. Beige adipocytes are found interspersed within white adipose tissue, whereas brown adipocytes are found in concentrated depots but only at trace levels in adults. Beige and brown adipocytes are more metabolically active than white adipocytes, which store energy as triglycerides.

Various stimuli, such as cold exposure, are known to promote the formation of beige adipocytes in white fat—a process known as browning.

Antiobesity therapeutics based on increasing the amount of brown fat have received more attention from industry as the biology and regulation of brown fat are better understood than that of beige fat.³

New data concurrently published in a pair of studies in *Cell* show that the immune system is a key regulator of beige fat generation and thermogenesis. The findings could spark efforts to develop therapies that focus on increasing the amount of beige fat.

“Brown adipose tissue is well innervated by sympathetic neurons, and past studies have already demonstrated the role of the sympathetic nervous system in regulating its formation and activity,” said Ember CSO Jasbir Sehra. “White adipose tissue, on the other hand, has less innervation, so the lingering question prior to these two papers has been how white adipose tissue gets stimulated to form beige fat.”

In one study, a group at the **University of California, San Francisco** led by Ajay Chawla teased out the components of the pathway by which cold exposure drives the development of beige fat. Chawla is an associate professor at the Cardiovascular Research Institute at UCSF.

The UCSF researchers used a series of knockout mice to show that cold exposure-induced formation of beige fat depends on eosinophils, IL-4 (BSF1) and IL-13 signaling, the downstream transcription factor signal transducer and activator of transcription 6 (STAT6) and monocyte recruitment to adipose tissues via CC chemokine receptor 2 (CCR2; CD192) signaling.

The recruited monocytes differentiate into macrophages and are activated by IL-4 and IL-13. Macrophage activation increases the

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expression of tyrosine hydroxylase, which is the key rate-limiting enzyme that catalyzes catecholamine synthesis (see Figure 1, “Pathway for driving beige fat formation”). Catecholamines induce thermogenesis activity and the generation of beige adipocytes in white adipose tissue.

In mice with diet-induced obesity, i.p. injection of Il-4 increased beige fat mass and decreased total body mass and fat mass compared with vehicle injection. In the obese mice, Il-4 also improved several measures of obesity-related metabolic dysfunction such as glucose homeostasis and insulin sensitivity.

“We’ve identified a core mechanism that animals are using to recruit beige fat mass,” said Chawla.

In the other study, a group led by Bruce Spiegelman identified meteorin glial cell differentiation regulator-like (METRNL) as a key mediator of the heat-

generating activity of beige fat. In mice, an adenoviral vector that induced overexpression of *Metrnl* in the liver increased thermogenesis from beige fat and decreased whole-body fat content compared with a control vector. *Metrnl* overexpression also induced the expression of multiple anti-inflammatory genes.

Spiegelman is a professor of cell biology and medicine at the Dana-Farber Cancer Institute and Harvard Medical School. He is a cofounder of Ember and chair of its scientific advisory board.

In a mouse model of obesity, vector-induced *Metrnl* overexpression improved glucose tolerance and increased whole-body energy expenditure.

Analyses of mouse adipose tissues suggested that *Metrnl* induces the generation of beige adipocytes in white adipose tissue and thermogenesis activity via the same pathway described by Chawla’s group.

“We’ve identified a core mechanism that animals are using to recruit beige fat mass.”
—Ajay Chawla,
University of California,
San Francisco

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Figure 1. Pathway for driving beige fat formation.

Cold stimulus promotes beige fat formation and thermogenesis, but the pathways involved in such processes were unclear. The recently hypothesized immune system–mediated pathway for driving these processes could yield new ways to treat obesity, type 2 diabetes and related metabolic disorders.

Through this pathway, cold stimulus triggers recruitment of CC chemokine receptor 2 (CCR2; CD192)⁺ monocytes to white adipose tissues, where they differentiate into macrophages. Cold stimulus also induces eosinophils in those tissues to release type 2 cytokines, such as IL-4 (BSF1) and IL-13 (small yellow circles).

The cytokines induce alternative activation of macrophages. This process leads to increased expression of tyrosine hydroxylase in myeloid cell populations found in white adipose tissues, including the macrophages themselves.

The increased expression of tyrosine hydroxylase results in more secretion of catecholamines (small purple circles) from myeloid cells, which in turn drives the formation of beige adipocytes and increases their thermogenesis activity.

Whether these beige adipocytes are formed from white adipocytes or some precursor cell population in white adipose tissue has not been determined.

At least two points of intervention (red dashed arrows) have been identified. As reported in Rao *et al.*, the hormone meteorin glial cell differentiation regulator-like (METRNL) (gray circles) can induce expression of IL-4 and IL-13 and promote beige fat formation and thermogenesis activity. Separately, Qiu *et al.* report that infusion of IL-4 itself has similar effects.

Chawla noted that although the identified molecules themselves are probably not yet ready for therapeutic development, the findings “do suggest that one may want to engage in more rigorous studies to understand the described pathway and then move toward the development of new antiobesity therapies.”

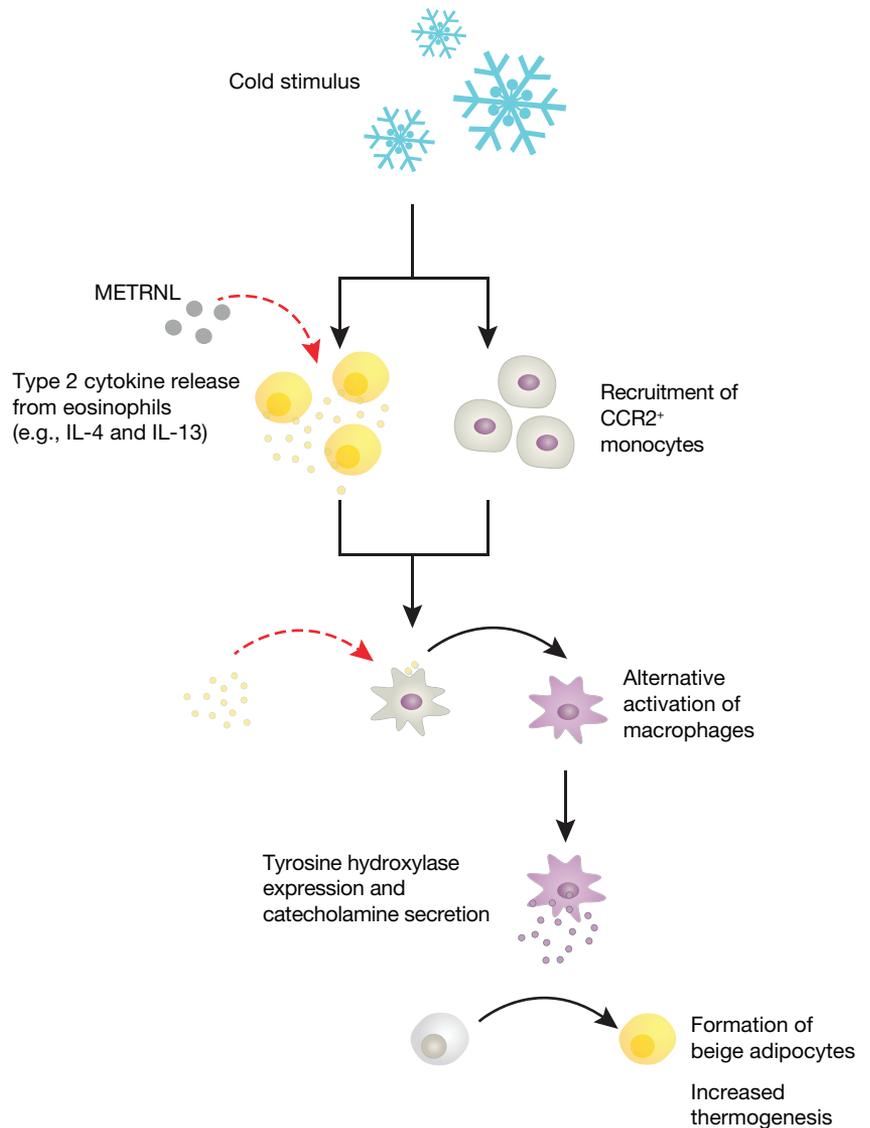
“The reported findings represent major steps toward the realization of a therapeutic that works by increasing beige fat,” added Seehra.

Ember already is developing molecules that promote the formation of brown fat and/or the browning of white fat.

Seehra said that Ember is interested in METRNL but declined to say whether the company has active programs related to the hormone.

Figuring out therapies

The new data could spur efforts to investigate other immune system components as therapeutics that promote the development of beige fat.



“Understanding the types of immune cells and how they are regulated in fat will now be important.”

—Patrick Seale,
Perelman School of Medicine at
the University of Pennsylvania

“Figuring out whether there are specific immune components that could serve as targets for therapy opens up an interesting new area,” said Patrick Seale, an assistant professor in the Department of Cell and

Developmental Biology at the **Perelman School of Medicine at the University of Pennsylvania**.

“Understanding the types of immune cells and how they are regulated in fat will now be important.” Seale said that previous efforts to promote beige fat development have primarily focused on manipulating the fat cells themselves or targeting CNS pathways.

“What these new studies describe is an entirely new pathway that promotes the formation of

beige adipocytes, and I think every step of this pathway should be reviewed for potential therapeutic purpose,” said Sven Enerbäck, a professor of medical genetics at the **University of Gothenburg** and a member of Ember’s scientific advisory board.

He said that it will be important to determine the extent to which the activated macrophages could maintain catecholamine production and to

find the identity of the downstream catecholamine-activated precursor cells that give rise to beige adipocytes.

“These studies provide an excellent starting point for the development of new therapies but also raise questions on what the signaling pathway could be doing in other tissues,” said Jorge Plutzky. “The question that needs to be addressed is: can you modulate the pathway in a manner that does not have adverse outcomes?”

Plutzky is director of The Vascular Disease Prevention Program at **Brigham and Women’s Hospital**. He also is an associate professor at Harvard Medical School and a member of Ember’s scientific advisory board.

Spiegelman said that it appears the components of the newly described pathway could be manipulated to promote beige fat development, but he added that it is too early to say whether such manipulation could be achieved in a manner that mitigates potential side effects.

The tractability of METRNL and IL-4 as drugs in their own right also remains unclear.

“A fair amount of work still needs to be done to understand how [METRNL] works at the molecular level before one can come up

with a form of the protein with the appropriate pharmacokinetic properties to allow it to be developed as a therapeutic,” said Seehra. “Until you know what the receptors are, coming up with molecular forms of [METRNL] that could be delivered therapeutically is challenging.”

Seale added that it will be important to determine how

METRNL expression is regulated in fat and muscle tissues.

Spiegelman’s group is trying to identify the receptor for METRNL. As the hormone also showed an anti-inflammatory effect, his group is evaluating whether METRNL could have utility in other diseases such as exercise-induced muscle damage and muscular dystrophy.

As for IL-4, Chawla noted that it might be difficult to develop the cytokine as a therapy for obesity and related metabolic conditions

because it regulates many aspects of immunity, such as B cell and T cell proliferation.

“You probably wouldn’t want to have some of these aspects chronically turned on,” Chawla told *SciBX*. He noted that if antiobesity strategies based on IL-4 were to be pursued, “you will want to develop something that is selective, short-lived and targeted to the specific tissue.”

Chawla said that his group is conducting studies to identify additional cell types and signaling networks that could be important to the described pathway for regulating beige fat. He added that it also will be important for others to develop and evaluate proof-of-concept molecules that target various points of the pathway.

Dana-Farber has filed a patent application covering the results related to METRNL. The findings described by the UCSF group are unpatented.

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“The reported findings represent major steps toward the realization of a therapeutic that works by increasing beige fat.”

—*Jasbir Seehra,*
Ember Therapeutics Inc.

The pain of PIP₂

By Amy Donner, Senior Editor

A team from **The University of North Carolina at Chapel Hill** has shown that phosphatidylinositol-4-phosphate 5-kinase type 1 γ regulates signaling by diverse pain receptors and has identified a small molecule antagonist that targets it.¹ Although the compound alleviates chronic pain in multiple mouse models, the lethality of homozygous mutations of the kinase in mice and humans highlights the need for repeat-dosing studies to better characterize the safety of the approach.

Pain is triggered by the action of specialized sensory neurons known as nociceptors, which are found in skin, muscle and other tissues and are activated by noxious stimuli, including excess heat, chemical stress or physical stress.² Nociceptors detect these inputs by expressing proteins that transmit a signal from the site of the insult to the CNS, causing pain. For example, the nociceptor-expressed ion channel TRPV1 (transient receptor potential vanilloid 1; VR1) is activated by temperature or chemical stresses, triggering a signaling cascade that leads to the sensation of pain.

Although distinct receptors are responsible for detecting different stimuli, a common feature of nociception is that inflammation or injury can sensitize cells to these inputs. Indeed, most non-opioid drugs that are approved to treat pain rely on blocking inflammatory signaling rather than acting on any individual receptor.

A UNC team led by Mark Zylka and Jian Jin set out to identify and target additional pathways that could broadly modulate the activity of pain receptors.

Zylka told *SciBX*, “Tissue injury causes the release of diverse molecules that activate receptors on sensory neurons and cause pain. Given this molecular diversity, efforts to treat pain by blocking individual receptors have failed.”

Zylka is an associate professor of cell biology and physiology at UNC, and Jin is associate director of medicinal chemistry in the Center for Integrative Chemical Biology and Drug Discovery and an associate professor of chemical biology, medicinal chemistry and pharmacology at **The University of North Carolina at Chapel Hill Eshelman School of Pharmacy**.

Zylka’s team zeroed in on the synthesis of phosphatidylinositol 4,5-bisphosphate (PIP₂), a lipid that had previously been shown to regulate signaling by pain receptors. PIP₂ is generated in part by the activity of lipid kinases, but the identity of the kinase or kinases responsible for PIP₂’s synthesis in neurons of the dorsal root ganglia (DRG), in which pain signals originate, was not known.

“We sought to determine which lipid kinase was responsible for generating PIP₂ in pain-sensing neurons, with the idea that inhibiting this kinase might reduce the levels of PIP₂ and reduce signaling through pain-producing receptors,” Zylka said.

A top candidate was phosphatidylinositol-4-phosphate 5-kinase type 1 γ (PIP5K1C), which had previously been shown to be expressed in the brain of mice and whose knockout decreased PIP₂ levels in the brain by ~50% compared with wild-type expression.^{3,4} Thus, Zylka’s team set out to test whether PIP5K1C contributes to PIP₂ production in the DRG.

In adult wild-type mice, Pip5k1c was expressed in nearly all DRG neurons. In *Pip5k1c* mice lacking one copy of the gene, PIP₂ levels in

DRG neurons were ~50% lower than those in wild-type mice, whereas PIP₂ levels in the spinal cord and brain were comparable between the two groups, suggesting that Pip5k1c is responsible for PIP₂ production specifically in the DRG.

Next, Zylka’s team tested whether modulating the expression of *Pip5k1c* could alleviate pain. In *Pip5k1c*^{+/-} mice, signaling downstream of lysophosphatidic acid (LPA), which activates neuropathic pain; 17-phenyl trinor prostaglandin E₂ (17-PT PGE₂), which activates inflammatory pain; and capsaicin, which activates thermal pain, was lower than that seen in wild-type mice. In these mice, pain-associated behaviors induced by LPA, 17-PT PGE₂ or capsaicin injection were also decreased.

In multiple mouse models of chronic pain with insults initiated at distinct anatomical locations, *Pip5k1c* depletion reduced pain.

Finally, the team sought to test whether pharmacological inactivation of PIP5K1C could treat pain. To do this, Zylka collaborated with Jin and Stephen Frye to generate a small molecule inhibitor of the kinase. Frye is director of the Center for Integrative Chemical Biology and Drug Discovery and a professor of chemical biology and medicinal chemistry at UNC’s Eshelman School of Pharmacy.

An *in vitro* kinase activity screen of 5,000 compounds identified a lead, UNC3230, with a K_d of about 0.2 μ M against PIP5K1C. The compound was largely selective for PIP5K1C in a panel of 148 kinases.

In cultured murine DRG neurons, UNC3230 decreased LPA-induced calcium signaling compared with vehicle. In mouse models of inflammatory and neuropathic pain, intrathecal or intraplantar injection of UNC3230 dose-dependently inhibited pain-associated behavior, whereas an inactive analog did not.

The study was published in *Neuron*.

“Using a trifecta of pain models, the authors show substantial analgesic activity,” said pain expert William Schmidt. “Turning off pain signals before they reach the CNS will hopefully have less or different side effects from available drugs.” Schmidt is president of **NorthStar Consulting LLC**, VP of clinical and regulatory for **Centrexion Corp.**, VP of clinical and regulatory for **Api Genesis LLC** and VP of clinical development at **EicOsis LLC**. Centrexion, EicOsis and Api Genesis are developing non-opioid therapeutics to treat pain.

“Novel, druggable targets for neuropathic pain are rare opportunities. We hope our work motivates drug discovery efforts,” said Frye.

Taking PIP₂ to the clinic

Although the study provides proof of concept for a new druggable player in pain signaling, additional safety studies are needed given the chronic use of pain drugs and the central role that PIP5K1C plays in synaptic function.³

Schmidt told *SciBX* that he was excited about the discovery of a putative new target in pain but emphasized that this is only the beginning of validation for PIP5K1C as a clinically relevant target.

“The convergence point idea is a strength as long as they can demonstrate that being at this position in these pathways will not interrupt other critical functions. They’ve done a reasonable job so far but with limited models,” noted Schmidt. “They haven’t evaluated their hypothesis in higher species, and they haven’t had a chance to evaluate other types of functions that might be critical to the normal animal.”

He added, “They’ve done single-dose studies, and validation requires repeat-dose studies. They will also need to move from experimental pain

models to pathological pain models and to use additional animal models. They have studied the effectiveness of their compound for up to seven days in each pain state, but they need to extend the studies and address administration, progressing to oral or parenteral delivery.”

Zylka said that a key next step is to develop PIP5K1C inhibitors with better solubility

and oral bioavailability. “This will entail medicinal chemistry optimization of our existing inhibitor and several others that we identified in our initial screen,” he noted.

Frye agreed that solubility is the key hurdle they will need to overcome and added, “We will be working in other templates, so reproducing the observed effects with a different chemotype would further support PIP5K1C as a target in pain.”

In addition to expanded validation studies, Schmidt suggested that human populations with mutations in *PIP5K1C* could be tapped as a resource for exploring the viability of the target. “It would be interesting to evaluate a human cohort with heterozygosity [in *PIP5K1C*], looking at pain, cardiovascular and gastrointestinal function. This could help them rule out side effects that have been seen with other types of drugs,” he said.

The UNC scientists detected no differences between adult *Pip5k1c*^{+/-} mice and wild-type mice in assays that assessed general motor function. The scientists also detected no defects in synaptic transmission or synaptic vesicle trafficking in the *Pip5k1c*^{+/-} mice.

“Using a trifecta of pain models, the authors show substantial analgesic activity. Turning off pain signals before they reach the CNS will hopefully have less or different side effects from available drugs.”

—William Schmidt,
NorthStar Consulting LLC

One potential cause for concern is the association between homozygous mutations in *PIP5K1C* and lethal contractural syndrome type 3.⁵ The syndrome is lethal at or around birth and is characterized by joint contractures and muscle atrophy.

“Homozygous mutations are lethal in animals and humans,” said Schmidt. “Could you develop this type of musculoskeletal impairment with a small molecule antagonist in an adult? This could limit the dose or the timing of administration to temporary applications.”

Schmidt emphasized that the consequences of inhibiting PIP5K1C remain to be evaluated in more detail. “If it doesn’t have adverse effects, wonderful. If it does, they might consider ways to limit access of a drug to critical organs, perhaps by targeted administration.”

Patent applications covering the PIP5K1C inhibitors and the application of PIP5K1C inhibitors for treating pain have been filed and are available for licensing from UNC’s Office of Technology Development.

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Priming the PD pump

By Lev Osherovich, Senior Writer

The precise cause of neurodegeneration in Parkinson's disease remains unknown, and as a result no one has been able to develop a truly disease-modifying therapy. Now, independent teams in Europe and the U.S. have found that the dopamine transporter VMAT2 has a potentially causative role in the disease^{1,2}—figuring out how to enhance its activity is the next challenge.

PD involves degeneration of nigrostriatal dopaminergic neurons, leading to insufficient dopamine levels in brain circuits that influence cognition and motor function. Symptomatic therapies for PD work by raising dopamine levels at synapses of affected neurons but do not arrest the degeneration of dopaminergic neurons. Eventually, the drugs become ineffective.

Genetic studies suggest 5%–10% of PD cases are caused by mutations in genes involved in metabolism and intracellular transport, but the origin of most cases is unclear or idiopathic.

One leading hypothesis about the origins of idiopathic PD relates to dopamine itself. Because dopamine is highly reactive and can damage intracellular proteins, the neurotransmitter must be stored inside intracellular vesicles until it is ready to be released at synapses. Researchers have long suspected that one potential cause of PD is a breakdown among cellular systems that protect neurons from intracellular dopamine. The result is acceleration of neurodegeneration.

“There are probably multiple mechanisms that work to protect against dopamine, which undergoes spontaneous oxidation and free-radical formation in the cytoplasm,” said Robert Edwards, a professor of neurology at the **University of California, San Francisco**.

Chief among these dopamine-detoxifying mechanisms is VMAT2 (vesicular monoamine transporter 2; SLC18A2), which pumps dopamine from the cytoplasm into synapse-bound vesicles. In the 1990s, Edwards cloned VMAT2 while searching for ways to counteract the toxic effect of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a dopamine-like toxin used in rodent models of PD.³

Since then, PD researchers have debated whether diminished VMAT2 activity plays a central role in disease or whether the transporter is merely a secondary participant that gets overwhelmed when cytoplasmic dopamine levels rise due to other factors.

Now, a team led by Christian Piffl, an associate professor of pharmacology at the **Medical University of Vienna**, has found the best evidence to date of

compromised VMAT2 function in the brains of patients with idiopathic PD.

“This is as close as possible with current techniques to see if there are changes in VMAT2 activity in people with disease,” said David Sulzer, a professor of

psychiatry, neurology and pharmacology at **Columbia University**. “They are looking at brains from people preserved just hours after they’ve died.”

Meanwhile, a team led by Gary Miller, a professor of environmental

health and associate dean for research at the **Emory University Rollins School of Public Health**, has shown that VMAT2 overexpression enhances dopamine sequestration and protects mice from MPTP toxicity.

“When you impair the storage of dopamine, it’s bad,” said Miller. He added that it was not clear until now that extra VMAT2 could increase the ability of neurons to sequester dopamine and ameliorate disease.

Smoking gun

Piffl’s team measured dopamine levels and VMAT2 activity in brain lysates from six patients with idiopathic PD and four healthy controls. The lysates were harvested shortly after death, before dopamine-laden intracellular vesicles could dissipate.

“The question was whether we could study the pumping efficiency of VMAT2,” said Piffl. Working with lysates from fresh brain tissue, “we were surprised to find that vesicular transport was still active” in these patients. The team found that overall levels of dopamine and VMAT2 in patients with PD were markedly lower than those in healthy controls because dopaminergic cells degenerated.

The researchers then used pharmacological methods to show that the remaining VMAT2 was unable to function normally in patients with PD, unlike VMAT2 from healthy controls that showed normal functional activity. “Parallel studies of dopamine uptake and binding showed that in PD the VMAT2 transporter is not working as efficiently as in healthy controls,” said Piffl.

Results were reported in *The Journal of Neuroscience* and are not patented.

Sulzer said that the results support the hypothesis that PD is caused by mislocalization of dopamine from intracellular vesicles to the cytoplasm resulting from insufficient VMAT2 activity. “It does now look like PD patients have reduced levels of dopamine transport,” said Sulzer.

The next step is to understand how VMAT2 activity becomes compromised in PD. Piffl said that his team has ruled out some simple possibilities such as defective vesicular proton gradients. The group now is looking for cellular factors that differentially regulate VMAT2’s activity in patients with PD versus controls.

“The most important question is why isn’t VMAT2 working,” said Piffl. “There is no evidence that levels of the protein are affected. We can speculate that there are post-translational modifications to the pump, but none have been found yet.”

Edwards cautioned that Piffl’s findings do not prove that compromised VMAT2 activity is the sole cause of idiopathic PD because there could be other ways to increase cytoplasmic dopamine besides inactivating VMAT2.

Going to the VMAT

Whereas Piffl’s findings imply that increasing VMAT2 activity could have a therapeutic effect, Miller’s mouse findings show this is indeed the case.

“The most important question is why isn’t VMAT2 working. There is no evidence that levels of the protein are affected. We can speculate that there are post-translational modifications to the pump, but none have been found yet.”

— Christian Piffl,
Medical University of Vienna

“A small molecule that turns on VMAT2 production or increases its activity is what’s needed.”

— David Sulzer, Columbia University

Miller's team overexpressed murine Vmat2 in the dopaminergic regions of mouse brains and saw increased dopamine transport into synaptic vesicles in *ex vivo* brain lysates compared with what was seen with endogenous Vmat2 expression. The engineered mice stored and secreted more dopamine than controls, mimicking the prodopaminergic effects of PD therapies such as L-dopa.

Vmat2 overexpression increased locomotion and decreased anxiety in mouse behavioral assays, as would be expected from raising dopamine levels. Miller's Vmat2-enriched mice also proved more resistant to MPTP toxicity than wild-type animals, likely because the now-abundant transporter could safely dispose of the toxin into vesicles.

The findings were reported in the *Proceedings of the National Academy of Sciences* and are not patented.

Altogether, Miller's results show that elevating VMAT2 activity could stimulate intracellular vesicular transport as a way to detoxify dopamine. "People said that the vesicles were maximally full and increasing dopamine transport wouldn't do anything, but our data clearly show that this is not the case," said Miller.

"Miller shows that artificial overexpression of VMAT2 is protective against MPTP toxicity, which is the best available model for PD," said Pifl. "Increased dopamine sequestration by extra VMAT2 might thus be protective."

Sulzer said that Miller's results are in line with previous findings by Edwards' and Sulzer's teams indicating that overexpression of VMAT2 protects against high levels of L-dopa, which is metabolized into dopamine.⁴

What's uncertain is how to enhance VMAT2 activity in patients. Miller's overexpression approach is unlikely to work in the clinic, so "a small molecule that turns on VMAT2 production or increases its activity is what's needed," said Sulzer. Toward this goal, Miller's team is screening for positive allosteric modulators of VMAT2 *in vitro*.

Last year, Sulzer's team reported fluorescent VMAT2 activity probes that could be useful for drug discovery.⁵

No companies are known to be developing VMAT2 agonists, but several VMAT2 antagonists are marketed or in clinical development for a range of neurological indications.

Another question is whether enhancing VMAT2 activity would work in all cases of PD or just a subset of idiopathic cases. "We don't know if this would work in the genetic forms of disease," Sulzer noted. Further studies with postmortem brain tissue from a variety of PD patients using Pifl's methods could help answer this question.

Osherovich, L. *SciBX* 7(26); doi:10.1038/scibx.2014.755
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Emory University Rollins School of Public Health, Atlanta, Ga.
Medical University of Vienna, Vienna, Austria
University of California, San Francisco, Calif.

Regenerative light touch

By Benjamin Boettner, Associate Editor

Regenerative approaches to tooth repair often involve the use of invasive and complex procedures such as cell transplantation or the controlled delivery of growth factors. A **Harvard University** team believes that it has identified a simpler solution—low-power laser treatment—that can induce stem cell differentiation in dental tissue.¹

It remains to be seen whether the approach can restore functional dentin in human teeth and the extent to which it can induce differentiation in additional cell types.

Most common dental restoration procedures rely on the use of inert biocompatible materials, such as mineral composites combined with adhesive resins, the purpose of which are to directly replace the function of natural teeth. These biomaterials have been engineered to release factors that can induce the regeneration of dentin, which is a calcified tissue that is produced by specialized cells called odontoblasts that reside within tooth pulp.

For advanced procedures in which more substantial tissue regeneration is needed, such as dental implantation or periodontitis treatment, cell grafting techniques have been developed. However, placing the cells into the correct anatomical context and getting them to survive or differentiate has been challenging.

The precise mechanisms by which these methods can drive tooth regeneration are not clearly understood, but one key factor is transforming growth factor- β 1 (TGFB1), which has been shown to preserve adult tooth structure.² It is deposited as a latent, inactive form in the extracellular environment; once it is activated, it drives the differentiation of stem cells.^{3,4}

Now, a team at the **Wyss Institute for Biologically Inspired Engineering at Harvard University** has shown that even in the absence of any grafting material, low-power lasers can differentiate some dental stem cells into odontoblasts through the activation of TGFB1.

Low-power lasers had previously been anecdotally linked to stem cell regeneration in multiple cell types and also are commonly used in nonregenerative dental procedures like polymer cross-linking and tooth whitening. The Harvard team wanted to investigate whether the method could directly affect the function of dental stem cells.

The investigators first sought to test whether a low-power laser could improve tooth structure in rats with mechanically exposed tooth pulp. Rats whose exposed teeth were treated with a low-power laser for 5 minutes and then covered with a filling had greater production of tertiary dentin at 12 weeks than rats who did not receive light treatment.

To pinpoint the mechanism underlying dentin production, the team analyzed primary human dental stem cells exposed to a low-power laser. In cell culture, the laser light elevated levels of reactive oxygen species, which led to the activation of latent TGFB1. This release triggered a signaling cascade that induced the differentiation of mesenchymal stem cells into odontoblasts and promoted the production of tertiary dentin.

Blocking the cascade *in vitro* or *in vivo* using TGFB1 receptor inhibitors or using TGFB1 knockout mice prevented dentin formation,

nauling down the requirement of TGFB1 for the light-induced effect.

Results were published in *Science Translational Medicine*. The team was led by David Mooney, a professor of bioengineering at the **Harvard University School of Engineering and Applied Sciences** and a core faculty member at the Wyss Institute.

Gianpaolo Papaccio, director of the Department of Experimental Medicine at the **Second University of Naples**, told *SciBX*, “These findings are of great interest because they represent a fundamental step in overcoming complications related to the grafting of stem cells. They provide a basis for future clinical treatment strategies.”

Anibal Diogenes, an assistant professor of endodontics at **The University of Texas Health Science Center at San Antonio**, noted, “Dentists already use lasers for disinfection and curing dental materials. Thus, this technology is very likely to transfer easily to clinical practice. Hopefully, this technique will allow for better preservation of pulp vitality, increasing the predictability and success of direct and indirect pulp capping procedures following caries [cavity] removal.”

Tooth complex

Although the ability of a low-power laser to drive stem cell differentiation is striking, the clinical utility of the approach will hinge on whether it can drive dentin formation in human teeth and direct the differentiation of additional types of dental stem cells at precisely targeted locations.

Frederic Michon, a team leader at the **University of Helsinki's** Institute of Biotechnology who studies dental stem cell populations, told *SciBX* that the usefulness of the approach might be limited to repairing damage located at the pulp-dentin interface.

“The method is focusing on dental pulp, which is specifically derived from mesenchymal stem cells. Other essential tooth tissues are generated by other stem cell lineages,” he said. The effectiveness of low-power lasers in differentiating other cell lineages was not tested in the study.

Jeremy Mao, co-director of the Center for Craniofacial Regeneration at the **Columbia University College of Dental Medicine**, agreed that the method needs to be tested in other dental tissues but was optimistic it could be broadly effective. “Beyond punctured pulp, there might be a potential for laser activation of latent TGFB1 for other types of tooth regeneration, such as root formation,” he said.

It also remains to be tested whether laser exposure will drive dentin formation in human cells. “Rat teeth are different from those in humans in that they are continuously regenerated. The translation to humans must necessarily first pass through *in vitro* experiments conducted on human primary dental cells,” said Papaccio.

Although human dental stem cells were observed to switch on dentin-producing genes when exposed to a low-power laser, actual dentin deposition was only shown in rodent cell culture and teeth.

In addition, Papaccio said that the functionality of the dentin being produced remains in question. “The approach leads to tertiary dentin formation, which is usually produced by dental stem cells during tooth injury, and it is only organized in a sparse, irregular pattern that resembles the ‘woven bone structure,’ which is not a true dentin; collagen fibers are arranged irregularly in the form of interlacing networks. Overall, it remains to be seen whether this technique can generate compact dentin resistant to mechanical stress.”

Praveen Arany agreed. “Future attempts need to focus on organizing newly generated tissue in a normal, tubular pattern using better

“Since we know that very low power has no effect while higher power has a detrimental response, outlining the therapeutic sweet spot is going to be key to translating this approach.”

**—Praveen Arany,
National Institutes of Health**

dose of the laser treatment could improve the method. “Since we know that very low power has no effect while higher power has a detrimental response, outlining the therapeutic sweet spot is going to be key to translating this approach.” He is developing additional assays that can accurately monitor and predict the effect of low-power laser therapy.

Ophir Klein, an associate professor in the departments of orofacial sciences and pediatrics at the **University of California, San Francisco**, said that more exhaustive monitoring of pathways affected by laser exposure would be required to convince him of the safety of the approach and could be used to help optimize its efficacy.

“The study focused on a single pathway, and while it is clear that the effects are mediated to a large extent by TGF β 1, it is likely that there are additional effects. Thus, an unbiased approach that examines a broader array of signals will be an important next step, as it is unlikely that the reactive oxygen species generated by the laser are exclusively targeting

technique and perhaps additional cues.” Arany is first author of the study and was at the Wyss Institute. He is now an assistant clinical investigator at the **NIH**.

Mooney added that the effect of low-power light could be further improved. “In our study we only treated once. Treating multiple times may enhance the effect and accelerate the repair process,” he said.

Arany said that modulating the

TGF β 1.” Klein is also an associate professor at the institutes for human genetics and regeneration medicine at UCSF.

A patent has been filed covering the method, and the IP is available for licensing from the Office of Technology Development at Harvard University.

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The University of Texas Health Science Center at San Antonio, San Antonio, Texas
Wyss Institute for Biologically Inspired Engineering at Harvard University, Cambridge, Mass.

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				
Psoriasis	Aryl hydrocarbon receptor (AHR)	<p>Mouse studies suggest agonizing AHR could be useful for treating psoriasis and other inflammatory skin disorders. In a mouse model of chemical-induced psoriasis, <i>Ahr</i> knockout mice developed more severe disease than wild-type mice. An <i>Ahr</i> agonist decreased disease severity compared with no treatment. Next steps could include optimizing and testing nontoxic <i>Ahr</i> agonists in a range of inflammatory skin disorders.</p> <p>SciBX 7(26); doi:10.1038/scibx.2014.757 Published online July 10, 2014</p>	Patent and licensing status undisclosed	<p>Di Meglio, P. <i>et al. Immunity</i>; Published online July 19, 2014; doi:10.1016/j.immuni.2014.04.019 Contact: Brigitta Stockinger, MRC National Institute for Medical Research, London, U.K. e-mail: bstocki@nimr.mrc.ac.uk</p>
Cancer				
Acute myelogenous leukemia (AML)	Glioma-associated oncogene homolog 1 zinc finger protein (GLI1); smoothened (SMO); UDP glucuronosyltransferase 1 family polypeptide A1 (UGT1A1)	<p>Cell culture studies suggest inhibiting SMO or UGT1A1 could prevent drug resistance in AML. Chemotherapy-resistant AML cells had higher UGT1A1 and GLI1 levels than nonresistant cells. In cultured, chemotherapy-resistant AML cells, the SMO inhibitor Erivedge vismodegib, which acts upstream of GLI1, decreased UGT1A1 levels and increased the efficacy of nucleoside chemotherapeutics compared with no treatment. Next steps include identifying UGT1A1 inhibitors and evaluating chemotherapy in combination with SMO inhibitors in an investigator-led clinical trial. Roche's Genentech Inc. unit markets Erivedge to treat basal cell carcinoma (BCC). The drug is in Phase III or earlier testing to treat AML and various solid tumors. At least five other companies have SMO inhibitors in Phase III testing or earlier to treat various cancers.</p> <p>SciBX 7(26); doi:10.1038/scibx.2014.758 Published online July 10, 2014</p>	Patent pending; available for licensing	<p>Zahreddine, H.A. <i>et al. Nature</i>; published online May 28, 2014; doi:10.1038/nature13283 Contact: Katherine L.B. Borden, University of Montreal, Montreal, Quebec, Canada e-mail: katherine.borden@umontreal.ca</p>
Breast cancer	Lysine-specific demethylase 2B (KDM2B; JHDM1B)	<p><i>In vitro</i> and mouse studies suggest inhibiting KDM2B could help treat breast cancer. In multiple breast cancer cell lines, shRNA against <i>KDM2B</i> decreased proliferation compared with control shRNA. In a mouse model of breast cancer, shRNA against <i>KDM2B</i> delayed tumor growth and decreased expression of stem cell markers. Next steps could include developing a KDM2B inhibitor.</p> <p>SciBX 7(26); doi:10.1038/scibx.2014.759 Published online July 10, 2014</p>	Unpatented; licensing status not applicable	<p>Kottakis, F. <i>et al. Cancer Res.</i>; published online May 22, 2014; doi:10.1158/0008-5472.CAN-13-2733 Contact: Philip N. Tsichlis, Tufts Medical Center, Boston, Mass. e-mail: ptsichlis@tuftsmedicalcenter.org</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Cancer	Myeloid-lymphoid or mixed-lineage leukemia (MLL; HRX); heat shock protein 90 (Hsp90)	<i>In vitro</i> and mouse studies suggest inhibiting MLL in combination with HSP90 could help treat cancer. Heat shock transcription factor 1 (HSF1) is induced in response to HSP90 inhibitors and limits their efficacy. In cultured human cancer cell lines, an siRNA targeting <i>MLL</i> , but not siRNAs targeting related genes, downregulated HSF1-dependent gene expression. In a mouse xenograft model of human melanoma, combination of <i>MLL</i> knockdown and an HSP90 inhibitor decreased tumor volume more than vehicle or either treatment alone. Next steps could include testing MLL and HSP90 inhibitors in combination in animal models of cancer. SciBX 7(26); doi:10.1038/scibx.2014.760 Published online July 10, 2014	Patent and licensing status unavailable	Chen, Y. <i>et al. J. Biol. Chem.</i> ; published online May 15, 2014; doi:10.1074/jbc.M114.574053 Contact: Wenlai Zhou, Novartis Institutes for BioMedical Research, Cambridge, Mass. e-mail: wenlai.zhou@novartis.com
Cancer; melanoma	Signal transducer and activator of transcription 3 (STAT3)	<i>In vitro</i> and mouse studies suggest compounds from a class of organometallic STAT3 inhibitors could help treat melanoma and other cancers. Chemical synthesis and <i>in vitro</i> testing of rhodium(III) complexes identified a lead compound that blocked STAT3 dimerization with a nanomolar IC ₅₀ value. In human melanoma cell lines, the lead compound showed cytotoxicity with low micromolar IC ₅₀ values. In mouse xenograft models of melanoma, the compound decreased tumor growth compared with vehicle. Ongoing work includes optimizing the lead compound and testing the other complexes in the series in leukemia, lymphoma and other cancer cell lines. Isis Pharmaceuticals Inc. and AstraZeneca plc have ISIS-STAT3Rx (AZD9150), an antisense inhibitor of STAT3, in Phase I/II testing or earlier to treat various cancers. Otsuka Pharmaceutical Co. Ltd. has OPB-31121, an inhibitor of STAT3, in Phase I testing to treat solid tumors. GLG Pharma LLC has four compounds that inhibit STAT3 activity in preclinical development to treat cancer. SciBX 7(26); doi:10.1038/scibx.2014.761 Published online July 10, 2014	Patent application cofiled by the University of Macau, Kaohsiung Medical University and Hong Kong Baptist University; available for licensing	Ma, D.-L. <i>et al. Angew. Chem. Int. Ed.</i> ; published online May 30, 2014; doi:10.1002/anie.201404686 Contact: Chung-Hang Leung, Institute of Chinese Medical Sciences, University of Macau, Macau, China e-mail: duncanleung@umac.mo Contact: Hui-Min David Wang, Kaohsiung Medical University, Kaohsiung City, Taiwan e-mail: davidw@kmu.edu.tw Contact: Dik-Lung Ma, Hong Kong Baptist University, Hong Kong, China e-mail: edmondma@hkbu.edu.hk

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Chronic lymphocytic leukemia (CLL)	Bruton's tyrosine kinase (BTK); phospholipase C _{v2} (phosphatidylinositol-specific) (PLCG2)	<p>Studies in human samples identified mutations responsible for resistance to the irreversible BTK inhibitor Imbruvica ibrutinib in patients with CLL that could guide the development of new therapies. Whole-exome sequencing of peripheral blood samples from patients with CLL before and after ibrutinib treatment identified a resistance-associated C481S mutation in BTK that prevented irreversible binding of the drug in five of six patients. In two of six patients, gain-of-function resistance mutations in PLCG2 were identified that induced B cell receptor signaling independent of BTK. Next steps could include designing compounds that could overcome the identified resistance mechanisms.</p> <p>Pharmacyclics Inc. and Johnson & Johnson market Imbruvica to treat CLL and mantle cell lymphoma (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 multiple myeloma (MM) and lymphoma.</p> <p>SciBX 7(26); doi:10.1038/scibx.2014.762 Published online July 10, 2014</p>	Patent and licensing status unavailable	<p>Woyach, J.A. <i>et al. N. Engl. J. Med.</i>; published online May 28, 2014; doi:10.1056/NEJMoa1400029 Contact: John C. Byrd, The Ohio State University, Columbus, Ohio e-mail: john.byrd@osumc.edu</p>
Liver cancer	Purinergic receptor P2Y G protein-coupled 2 (P2RY2; P2Y2)	<p>Cell culture and mouse studies suggest antagonizing P2Y2 could be useful for treating liver cancer. Human hepatocellular carcinoma (HCC) cells had higher P2Y2 levels than normal hepatocytes. In cultured HCC cells, P2Y2-targeting shRNA or a P2Y2 antagonist decreased proliferation and migration compared with control shRNA or vehicle. In a mouse xenograft model of HCC, P2Y2-targeting shRNA or a P2Y2 antagonist decreased tumor growth. Next steps could include identifying potent and selective P2Y2 antagonists.</p> <p>SciBX 7(26); doi:10.1038/scibx.2014.763 Published online July 10, 2014</p>	Patent and licensing status undisclosed	<p>Xie, R. <i>et al. J. Biol. Chem.</i>; published online May 20, 2014; doi:10.1074/jbc.M113.540047 Contact: Biguang Tuo, Zunyi Medical College, Zunyi, China e-mail: tuobiguang@aliyun.com Contact: Hui Dong, same affiliation as above e-mail: h2dong@ucsd.edu</p>
Prostate cancer	Monoamine oxidase A (MAO-A)	<p>Mouse and human sample studies suggest inhibiting MAO-A could help prevent prostate cancer growth and metastasis. In mouse xenograft models of prostate cancer, shRNA against MAO-A or a small molecule inhibitor of MAO-A suppressed metastasis and decreased tumor frequency and growth compared with control shRNA or saline. In human prostate cancer samples, elevated MAO-A levels correlated with higher clinical grade tumors, cancer recurrence and decreased survival. Next steps could include designing small molecule-based strategies to inhibit MAO-A in patients with prostate cancer.</p> <p>Krenitsky Pharmaceuticals Inc. has the reversible MAO-A inhibitor TriRima (KP157) in Phase II testing to treat anxiety and depression.</p> <p>SciBX 7(26); doi:10.1038/scibx.2014.764 Published online July 10, 2014</p>	Patent and licensing status unavailable	<p>Wu, J.B. <i>et al. J. Clin. Invest.</i>; published online May 27, 2014; doi:10.1172/JCI70982 Contact: Leland W.K. Chung, Cedars-Sinai Medical Center, Los Angeles, Calif. e-mail: leland.chung@cshs.org Contact: Haiyen E. Zhou, same affiliation as above e-mail: haiyen.zhou@cshs.org Contact: Jean C. Shih, University of Southern California, Los Angeles, Calif. e-mail: jcshih@usc.edu</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Solid tumors	Phosphoinositide 3-kinase- δ (PI3K δ); phosphoinositide 3-kinase catalytic subunit δ -polypeptide (PI3KCD; p110 δ)	<p>Mouse studies suggest inhibitors of PI3Kδ could help treat solid tumors. In mice bearing breast, lung, melanoma or other solid tumor types, expression of <i>p110δ</i> with an inactivating mutation or use of a selective PI3Kδ inhibitor decreased tumor growth and metastasis and increased survival compared with expression of wild-type <i>p110δ</i> or use of vehicle. Planned work includes clinical testing of a selective PI3Kδ inhibitor in patients with undisclosed solid tumor types. Gilead Sciences Inc. has idelalisib, a small molecule inhibitor of PI3Kδ, in registration to treat chronic lymphocytic leukemia (CLL) and non-Hodgkin's lymphoma (NHL). Takeda Pharmaceutical Co. Ltd. and Infinity Pharmaceuticals Inc. have IPI-145, an oral inhibitor of PI3Kδ and PI3Kγ, in Phase III trials to treat CLL and in Phase II testing to treat NHL, lymphoma, rheumatoid arthritis (RA) and inflammation. Rhizen Pharmaceuticals S.A. and TG Therapeutics Inc. have the PI3Kδ inhibitor RP-5264 (TGR-1202) in Phase II trials to treat CLL, B cell lymphoma and hematological malignancies.</p> <p>SciBX 7(26); doi:10.1038/scibx.2014.765 Published online July 10, 2014</p>	Unpatented; unlicensed	<p>Ali, K. <i>et al. Nature</i>; Published online July 11, 2014; doi:10.1038/nature13444 Contact: Bart Vanhaesebroeck, University College London, London, U.K. e-mail: bart.vanh@ucl.ac.uk</p>
Dermatology				
Wounds	c-Met proto-oncogene (MET; HGFR); hepatocyte growth factor/scatter factor (HGF/SF)	<p><i>In vitro</i> studies suggest allosteric zymogen activator peptides that stimulate MET signaling could help treat wounds and prevent fibrosis. Proteolytic conversion of zymogen-like pro-HGF/SF to its MET-activating form is impaired in some fibrotic diseases. In <i>in vitro</i> wound healing and survival assays, zymogen activator peptides that bind the activation pocket of pro-HGF induced activation of pro-HGF/SF and promoted cell migration and survival by activating MET. Next steps include evaluating the efficacy of the peptides in animal models of aberrant tissue repair such as chronic ulcers or fibrosis. Roche's Genentech Inc. unit declined to disclose details on the status the zymogen activator peptides. ChronTech Pharma AB and Kringle Pharma Inc. have the hepatocyte growth factor peptide ChronSeal in Phase II testing to treat wounds.</p> <p>SciBX 7(26); doi:10.1038/scibx.2014.766 Published online July 10, 2014</p>	Patent and licensing status undisclosed	<p>Landgraf, K.E. <i>et al. Nat. Chem. Biol.</i>; published online May 25, 2014; doi:10.1038/nchembio.1533 Contact: Robert A. Lazarus, Genentech Inc., San Francisco, Calif. e-mail: laz@gene.com Contact: Kyle E. Landgraf, AvidBiotics Corp., South San Francisco, Calif. e-mail: kyle@avidbiotics.com</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Endocrine/metabolic disease				
Obesity	IL-4 (BSF1); IL-13	<p>Mouse studies suggest increasing IL-4 and IL-13 signaling could help treat obesity. In mice, knocking out <i>Il-4</i> and <i>Il-13</i> decreased cold-induced thermogenic activity and remodeling of white adipose tissue into beige and brown adipose tissues compared with no alteration. In mice fed a high-fat diet, IL-4 injections increased beige fat mass and decreased both overall body mass and fat mass compared with vehicle injection. In obese mice, IL-4 injections improved glucose tolerance and insulin sensitivity. Next steps include identifying additional cell types and signaling networks that are important for regulating the generation of beige and brown adipose tissues (<i>see Going immune on beige fat, page 1</i>).</p> <p>SciBX 7(26); doi:10.1038/scibx.2014.767 Published online July 10, 2014</p>	Unpatented; licensing status not applicable	<p>Qiu, Y. <i>et al. Cell</i>; Published online July 5, 2014; doi:10.1016/j.cell.2014.03.066 Contact: Ajay Chawla, University of California, San Francisco, Calif. e-mail: ajay.chawla@ucsf.edu</p>
Hematology				
Bone marrow transplant (BMT)	Chemokine CC motif ligand 21 (CCL21); CCL25	<p>Mouse studies suggest pretreatment of bone marrow cells with CCL21 and CCL25 could enhance T cell reconstitution after transplant. In irradiated mice, the number of thymic endothelial cells and levels of CCL21 and Ccl25 expression in those cells were decreased compared with what was seen in nonirradiated mice. Transplantation of bone marrow cells pretreated with recombinant murine Ccl21 and Ccl25 increased bone marrow homing to the thymus and reconstitution of thymic endothelial cells compared with transplantation of untreated bone marrow cells. Ongoing work includes investigating the effect of CCL21 and CCL25 on T cell reconstitution when bone marrow is transplanted into immunodeficient mice with an implanted human thymus.</p> <p>SciBX 7(26); doi:10.1038/scibx.2014.768 Published online July 10, 2014</p>	<p>Patent application filed covering therapeutic compositions and methods; available for licensing from the University of Pennsylvania Contact: Heather Steinman, University of Pennsylvania, Philadelphia, Pa. e-mail: steinman@ctt.upenn.edu</p>	<p>Zhang, S.L. <i>et al. Blood</i>; published online May 29, 2014; doi:10.1182/blood-2014-01-552794 Contact: Avinash Bhandoora, University of Pennsylvania, Philadelphia, Pa. e-mail: bhandoora@mail.med.upenn.edu</p>
Thrombocytopenia	Secreted protein acidic cysteine-rich (SPARC)	<p>Mouse studies suggest inhibiting the extracellular matrix protein SPARC could help protect hematopoietic stem cells from chemotherapy-associated toxicity. In mice receiving repeated cycles of 5-fluorouracil chemotherapy, <i>Sparc</i>^{-/-} animals had less bone marrow failure and longer survival than wild-type littermates. In the <i>Sparc</i>^{-/-} mice, hematopoietic stem cells had an accelerated return to a quiescent state after chemotherapy. Next steps could include screening for pharmacological inhibitors of SPARC synthesis.</p> <p>SciBX 7(26); doi:10.1038/scibx.2014.769 Published online July 10, 2014</p>	Patent and licensing status unavailable	<p>Ehninger, A. <i>et al. Blood</i>; published online May 15, 2014; doi:10.1182/blood-2013-10-533711 Contact: Andreas Trumpp, German Cancer Research Center, Heidelberg, Germany e-mail: a.trumpp@dkfz-heidelberg.de</p>

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Hepatic disease				
Nonalcoholic steatohepatitis (NASH)	Transmembrane 6 superfamily member 2 (TM6SF2)	Patient sample and cell culture studies suggest increasing TM6SF2 levels could help treat NASH. In 206 human liver samples, the NASH-associated rs10401969 SNP correlated with decreased expression of <i>TM6SF2</i> and low plasma triglyceride concentrations. In two human hepatic cell lines, siRNA against <i>TM6SF2</i> decreased secretion of triglyceride-rich lipoproteins and increased the number and size of lipid droplets compared with control siRNA. In <i>TM6SF2</i> -overexpressing human hepatic cell lines, lipid droplet size was smaller than that in cells with normal <i>TM6SF2</i> expression. Next steps could include identifying strategies to increase TM6SF2 levels.	Patent and licensing status unavailable	Mahdessian, H. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; Published online July 4, 2014; doi:10.1073/pnas.1323785111 Contact: Ferdinand van't Hooft, Karolinska Institute, Stockholm, Sweden e-mail: ferdinand.vant.hooft@ki.se
Infectious disease				
Tuberculosis	Unknown	<i>In vitro</i> and mouse studies identified an imidazo[1,2- <i>a</i>]pyridine amide (IPA) analog that could help treat drug-resistant tuberculosis. In cultured macrophages, nanomolar concentrations of the optimized IPA analog inhibited replication of a <i>Mycobacterium tuberculosis</i> strain both inside and outside macrophages. In mice infected with the same <i>M. tuberculosis</i> strain, the optimized derivative decreased bacterial burden in the lungs compared with no treatment. Next steps could include further preclinical testing and identifying the target of the optimized IPA.	Patent and licensing status unavailable	Kang, S. <i>et al. J. Med. Chem.</i> ; published online May 28, 2014; doi:10.1021/jm5003606 Contact: Jaeseung Kim, Institute Pasteur Korea, Gyeonggi-do, South Korea e-mail: silanediol@gmail.com Contact: Zaesung No, same affiliation as above e-mail: jsnoh@gstep.re.kr
Neurology				
Alzheimer's disease (AD)	Amyloid precursor protein (APP)	Mouse studies suggest inhibiting production of soluble β -amyloid ($A\beta$) and $A\beta$ oligomers could help treat AD. In a mouse model of AD with inducible APP production, inhibiting APP production or depletion of soluble $A\beta$ improved cognitive performance and increased functional synapses around existing $A\beta$ plaques compared with no treatment. Next steps include identifying a therapeutic that specifically inhibits $A\beta$ production.	Patent and licensing status unavailable	Fowler, S.W. <i>et al. J. Neurosci.</i> ; Published online July 4, 2014; doi:10.1523/JNEUROSCI.0572-14.2014 Contact: Joanna L. Jankowsky, Baylor College of Medicine, Houston, Texas e-mail: jankowsk@bcm.edu

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Alzheimer's disease (AD)	β -Amyloid (A β); fibrinogen	<i>In vitro</i> and mouse studies suggest compounds that block the interaction between A β and fibrinogen could be useful for treating AD. <i>In vitro</i> bead-based screening identified RU-505 as a small molecule that blocked the interaction between A β and fibrinogen. In a mouse model of AD, RU-505 improved cognitive function and decreased neuroinflammation and vascular damage compared with vehicle. Researchers did not disclose next steps, which could include optimization and preclinical development of RU-505.	Patent and licensing status undisclosed	Ahn, H.J. <i>et al. J. Exp. Med.</i> ; published online May 12, 2014; doi:10.1084/jem.20131751 Contact: Sidney Strickland, The Rockefeller University, New York, N.Y. e-mail: strickland@rockefeller.edu
		SciBX 7(26); doi:10.1038/scibx.2014.773 Published online July 10, 2014		
Pain	Phosphatidylinositol-4-phosphate 5-kinase type 1 γ (PIP5K1C)	Mouse studies suggest inhibiting PIP5K1C could help treat chronic pain. In mice, heterozygous knockout of <i>Pip5k1c</i> decreased levels of the pain signaling molecule phosphatidylinositol 4,5-bisphosphate by 50% in dorsal root ganglia compared with no alteration. In three mouse models of chronic pain, heterozygous knockout of <i>Pip5k1c</i> attenuated pain responses. In mice, intrathecal injection of a small molecule PIP5K1C inhibitor decreased hypersensitivity to various types of pain compared with injection of an inactive analog. Next steps include generating orally bioavailable PIP5K1C inhibitors with improved solubility (<i>see The pain of PIP</i> , page 5).	Patent applications filed; available for licensing	Wright, B.D. <i>et al. Neuron</i> ; published online May 21, 2014; doi:10.1016/j.neuron.2014.04.006 Contact: Mark J. Zylka, The University of North Carolina at Chapel Hill, Chapel Hill, N.C. e-mail: zylka@med.unc.edu
		SciBX 7(26); doi:10.1038/scibx.2014.774 Published online July 10, 2014		
Parkinson's disease (PD)	Vesicular monoamine transporter 2 (VMAT2; SLC18A2)	Mouse studies suggest agonizing VMAT2 could be useful for treating PD. In a mouse model of chemically induced PD, overexpression of VMAT2 in dopaminergic neurons increased vesicular capacity for dopamine and synaptic dopamine release and decreased neurotoxicity compared with wild-type VMAT2 expression. Next steps include identifying small molecule activators of VMAT2 and testing them in PD models (<i>see Priming the PD pump</i> , page 7).	Unpatented; licensed status not applicable	Lohr, K.M. <i>et al. Proc. Natl. Acad. Sci. USA</i> ; Published online July 16, 2014; doi:10.1073/pnas.1402134111 Contact: Gary W. Miller, Emory University, Atlanta, Ga. e-mail: gary.miller@emory.edu
		SciBX 7(26); doi:10.1038/scibx.2014.775 Published online July 10, 2014		
Parkinson's disease (PD)	Vesicular monoamine transporter 2 (VMAT2; SLC18A2)	Studies in postmortem patient tissue suggest increasing VMAT2 activity could be useful for treating PD. Dopaminergic brain tissue from patients with PD had lower levels of VMAT2 activity when normalized for VMAT2 protein levels and had decreased vesicular uptake of dopamine compared with brain tissue from healthy controls. Next steps include identifying pharmacological activators or positive modulators of VMAT2 (<i>see Priming the PD pump</i> , page 7).	Unpatented; licensing status not applicable	Pifl, C. <i>et al. J. Neurosci.</i> ; Published online July 11, 2014; doi:10.1523/JNEUROSCI.5456-13.2014 Contact: Christian Pifl, Medical University of Vienna, Vienna, Austria e-mail: christian.pifl@meduniwien.ac.at
		SciBX 7(26); doi:10.1038/scibx.2014.776 Published online July 10, 2014		

This week in therapeutics (continued)

Indication	Target/marker/ pathway	Summary	Licensing status	Publication and contact information
Various				
Obesity; inflammation	Meteorin glial cell differentiation regulator-like (METRNL)	<p>Mouse studies suggest increasing METRNL signaling could help treat obesity and inflammatory diseases. In mice, an adenoviral vector that induced overexpression of <i>Metrn1</i> in the liver increased thermogenesis in brown and beige fat and decreased whole-body fat content compared with control vector. In these mice, hepatic <i>Metrn1</i> overexpression also increased expression of anti-inflammatory genes. In a mouse model of obesity, <i>Metrn1</i> overexpression improved glucose tolerance and increased whole-body energy expenditure compared with normal <i>Metrn1</i> expression. Next steps include identifying the receptors for METRNL and elucidating the molecular pathways affected by the hormone. Ember Therapeutics Inc. is developing oral small molecules that induce brown fat formation as an approach to treat obesity and diabetes (<i>see Going immune on beige fat, page 1</i>).</p> <p><i>SciBX</i> 7(26); doi:10.1038/scibx.2014.777 Published online July 10, 2014</p>	Patent application filed; Ember Therapeutics has an exclusive option to license the technology	<p>Rao, R.R. <i>et al. Cell</i>; Published online July 5, 2014; doi:10.1016/j.cell.2014.03.065 Contact: Bruce Spiegelman, Dana-Farber Cancer Institute, Boston, Mass. e-mail: bruce_spiegelman@dfci.harvard.edu</p>

This week in techniques

THE DISTILLERY brings you this week's most essential scientific findings in techniques, distilled by *SciBX* editors from a weekly review of more than 400 papers in 41 of the highest-impact journals in the fields of biotechnology, the life sciences and chemistry. The Distillery goes beyond the abstracts to explain the commercial relevance of featured research, including licensing status and companies working in the field, where applicable. This week in techniques includes findings about research tools, disease models and manufacturing processes that have the potential to enable or improve all stages of drug discovery and development.

Approach	Summary	Licensing status	Publication and contact information
Disease models			
Crystal structure of human GABA _A receptor	The crystal structure of the human GABA _A receptor could help guide the design of new γ -aminobutyric acid (GABA)-targeted therapies to treat psychiatric disorders. <i>In vitro</i> , the X-ray crystal structure of the human GABA _A receptor bound to the previously unknown agonist benzamidine was solved at a resolution of 3 Å and revealed a complex of 19 different subunits arranged in a homopentameric architecture. The crystal structure also showed that the receptor's neurotransmitter-binding pocket is located between extracellular domains. Next steps include solving the crystal structure of additional heterometric human receptors and evaluating benzamidine derivatives as modulators of such receptors.	Patent application filed; available for licensing from Isis Innovation Ltd. Contact: Louis Pymar, Isis Innovation Ltd., Oxford, U.K. e-mail: louis.pymar@isis.ox.ac.uk	Miller, P.S. & Aricescu, A.R. <i>Nature</i> ; Published online July 8, 2014; doi:10.1038/nature13293 Contact: A. Radu Aricescu, University of Oxford, Oxford, U.K. e-mail: radu@strubi.ox.ac.uk Contact: Paul Miller, same affiliation as above e-mail: paul@strubi.ox.ac.uk
SciBX 7(26); doi:10.1038/scibx.2014.778 Published online July 10, 2014			
Drug platforms			
<i>Glypican 4</i> (<i>GPC4</i>) deficiency to improve embryonic stem cell (ESC)-derived therapies for Parkinson's disease (PD)	Cell replacement therapies for PD derived from <i>GPC4</i> -deficient ESC lines could offer improved safety and efficacy over cells with intact <i>GPC4</i> . Residual, undifferentiated stem cells in stem cell-derived cell therapies can cause teratoma formation. In culture, mouse ESCs expressing a loss-of-function mutant <i>Gpc4</i> showed greater differentiation into dopaminergic neurons than wild-type mouse ESCs. In a rat model of PD, injection of the <i>Gpc4</i> -deficient mouse ESCs into the substantia nigra improved motor function and increased survival compared with injection of wild-type mouse ESCs. Next steps could include evaluating long-term outcomes and tumor risk in rodents receiving transplants of neurons derived from the <i>Gpc4</i> -deficient ESCs.	Patent and licensing status unavailable	Fico, A. <i>et al. J. Neurosci.</i> ; Published online July 11, 2014; doi:10.1523/JNEUROSCI.2501-13.2014 Contact: Harold Cremer, Aix-Marseille University, Marseille, France e-mail: harold.cremer@univ-amu.fr Contact: Rosanna Dono, same affiliation as above e-mail: rosanna.dono@univ-amu.fr
SciBX 7(26); doi:10.1038/scibx.2014.779 Published online July 10, 2014			
Overexpression of yes-associated protein 1 (YAP1) reprograms hepatocytes to progenitors that promote liver regeneration	Cell culture and mouse studies suggest hepatocytes reprogrammed to progenitor cells via YAP1 overexpression could help promote liver regeneration. In mice, adeno-associated viral vector-mediated overexpression of <i>Yap1</i> in hepatocytes increased liver growth compared with no alteration and led to the formation of progenitor-like cells. <i>Ex vivo</i> , the <i>Yap1</i> -overexpressing livers formed more organoids in culture than livers with normal <i>Yap1</i> expression. In a mouse model of liver failure, intrasplenic injection of cells from <i>Yap1</i> -overexpressing organoids led to repopulation of the liver in three of four animals. Next steps include repeating the experiments in human cells and developing a method to transiently activate YAP1.	Unpatented; licensing status not applicable	Yimlamai, D. <i>et al. Cell</i> ; Published online July 5, 2014; doi:10.1016/j.cell.2014.03.060 Contact: Fernando D. Camargo, Boston Children's Hospital, Boston, Mass. e-mail: fernando.camargo@childrens.harvard.edu
SciBX 7(26); doi:10.1038/scibx.2014.780 Published online July 10, 2014			

This week in techniques (continued)

Approach	Summary	Licensing status	Publication and contact information
Markers			
Low ERBB receptor feedback inhibitor 1 (ERRFI1; MIG6) to microRNA-200 (miR-200) ratio predicts response of cancers with wild-type epidermal growth factor receptor (EGFR) to EGFR inhibition	<p><i>In vitro</i> and mouse studies suggest a low MIG6 to miR-200 ratio could help predict response of tumors to EGFR inhibitors. In multiple cancer cell lines expressing wild-type EGFR, resistance to the EGFR inhibitor Tarceva erlotinib was associated with transforming growth factor-β1 (TGFB1)-induced epithelial-to-mesenchymal transition and MIG6 expression. In mice with human wild-type EGFR lung and pancreatic tumor xenografts, a high ratio of MIG6 to miR-200 was associated with resistance to erlotinib. Next steps could include validating the marker in additional patient samples.</p> <p>Astellas Pharma Inc., Chugai Pharmaceutical Co. Ltd. and the Genentech Inc. unit of Roche market Tarceva erlotinib to treat various cancers including non-small cell lung cancer (NSCLC) and pancreatic cancer.</p> <p>SciBX 7(26); doi:10.1038/scibx.2014.781 Published online July 10, 2014</p>	Patent and licensing status unavailable	<p>Izumchenko, E. <i>et al. Cancer Res.</i>; published online May 15, 2014; doi:10.1158/0008-5472.CAN-14-0110 Contact: David Sidransky, The Johns Hopkins University, Baltimore, Md. e-mail: dsidrans@jhmi.edu</p>

Erratum: Analysis: Cover StoryBaas, T. *SciBX* 7(25); doi:10.1038/scibx.2014.725

Published online June 26, 2014

The Analysis item “Keys to the CAR” misquoted Isabelle Rivière in the ninth paragraph of the “Avoiding collateral damage” section. Rivière’s quote should be: “Some investigators are looking at transient CAR-expressing T cells as a tool for the preliminary validation of novel target antigens. Others are exploring safety switches and combinatorial targeting strategies to achieve selective tumor targeting. It would also be extremely useful to have means to modulate T cell numbers and persistence.”

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