BIOCENTURY
Innovations
FROM IDEA TO IND

JANUARY 12, 2017

TARGETS & MECHANISMS

GUT CONTROL

By Mark Zipkin, Staff Writer

As evidence mounts linking obesity to the microbiome, three independent studies have identified separate ways of harnessing gut microbiota to treat the condition. The spectrum of approaches, which involve a bacterial protein, a bacterial species and a gut signature, reflects the complexity and new thinking involved in harnessing the microbiome for therapeutics, and is likely a sign of the broad strategies companies will need to adopt to make headway in the rapidly emerging field.

The three papers were published late last year in different Nature journals, and have thus far translated into an early clinical trial and plans for a spinout, with two of the groups fast to file IP.

The third group declined to disclose the IP status for this study. However, a microbiome analysis platform developed by the same investigators was spun out to create RondinX, whose launch was announced last week.

While early translational work on the microbiome aimed at treating a handful of gastrointestinal (GI) disorders and infections, rapid scientific progress has opened a wide range of therapeutic and diagnostic applications, and spawned a steady stream of newcos and pharmas getting into the game.

For gut-related diseases, the list of indications and strategies is growing as research uncovers how GI microbes can exert effects on distant tissues by modulating immune function, metabolism and the gut-brain axis. For example, several companies are exploring microbiome-based therapies that either activate immune cells to fight cancer or suppress them to treat inflammation and autoimmunity. And at least two microbiome companies, neurology newco Axial Biotherapeutics Inc. and two-year-old 4D Pharma plc, have preclinical programs leveraging the gut-brain axis to treat autism.

Dirk Gevers, global head of Johnson & Johnson's Janssen Human Microbiome Institute (JHMI), told BioCentury he thinks metabolic disease is one of the principal areas where microbiome-based therapies will gain traction. His company sees the microbiome as a key tool for attacking disease before its onset, as part of its "disease interception" initiative.

At least 13 other companies have announced programs or collaborations focused on the microbiome in metabolic disease (see "Tapping the Microbiome for metabolic Disease").

The connection with Type II diabetes and obesity has been forged over the last decade through research linking the diseases to altered microbial signatures in the gut, and evidence that obesity can be induced in mice by transplantation of microbiota from humans with the disease. In addition, Novartis AG, joined with a consortium of academics — including Gevers in his former position — in mapping a link between Type I diabetes rates and microbiome composition in specific populations in Northern Europe and Russia.

However, while researchers have associated specific microbes either positively or negatively with obesity, working out the mechanisms by which the bacteria control energy extraction and storage, and discerning the best way to translate the discoveries, has proved challenging.

Now, three groups have presented findings they believe translate to tractable opportunities for generating therapeutics or diagnostics for obesity.

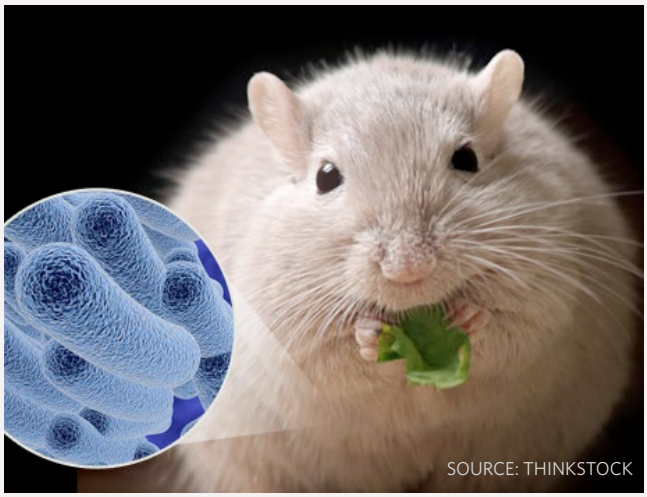
> The three papers were published late last year in different Nature journals, and have thus far translated into an early clinical trial and plans for a spinout.

RUNNING AMOK

The first approach, published in *Nature Medicine*, overcame translational hurdles to treating humans with *Akkermansia muciniphila*, a gut microbe that is protective against obesity, and identified a membrane protein responsible for the microbe's effects. The group, led by Patrice Cani and Willem de Vos, has already gathered some human safety data for the bacteria and is in the process of forming a newco based on the technology.

Cani is a professor and research associate at Universite Catholique de Louvain and de Vos is a professor at University of Helsinki and Wageningen University and Research Centre.

The study was a follow-up to a 2013 study by the duo in *Proceedings of the National Academy of Sciences* showing that


SOURCE: THINKSTOCK

A. muciniphila was less abundant in obese mice than in lean mice, and that boosting *A. muciniphila* levels with a growth-promoting prebiotic reversed metabolic symptoms associated with obesity and Type II diabetes.

In the new study, the groups not only identified the molecular mechanism underlying the bacteria's effects, but also found a way to improve on them.

Cani said two key problems had been preventing use of *A. muciniphila* therapeutically. The first was that the standard growth medium for the bacteria contained animal proteins that cannot be transferred into humans. The second was the bacteria's sensitivity to oxygen levels, which makes it difficult to formulate for oral use.

The collaborators overcame both hurdles by designing a new, synthetic growth medium for the species that is safe for humans, and by pasteurizing the bacteria. During the pasteurization process the researchers heated the bacteria just enough to stabilize it without destroying it, and discovered unexpectedly that the process itself actually improved the therapeutic potential.

"Because of the pasteurization, we were really surprised to find, the bacteria was more potent to completely block the diet-induced obesity and diabetes in rodents," said Cani.

The group pinpointed Amuc_1100, a protein in the outer membrane of *A. municiphila*, as the likely driver of the bacteria's effects because only intestinal cells expressing TLR2 were activated by *A. municiphila*, and Amuc_1100 was already known to mediate crosstalk with TLR2-expressing host cells.

TAPPING THE MICROBIOME FOR METABOLIC DISEASE

Select companies and collaborations targeting the intestinal microbiome to treat obesity and other metabolic conditions. *Source: BCIQ: BioCentury Online Intelligence, BioCentury Archives, company websites*

MICROBIOME COMPANIES AND INSTITUTIONS	DESCRIPTION	STATUS	DATE OF COLLABORATION
Brigham and Women's Hospital; OpenBiome	Collaboration to test fecal microbiota transplantation to treat obesity using oral capsules containing samples from the company's healthy donor stool bank	Phase I/II	April 2016
Massachusetts General Hospital; Seres Therapeutics Inc. (NASDAQ:MCRB)	Collaboration to identify strains of bacteria administered as oral capsules for obesity and metabolic syndrome	Phase I/II	August 2015
MicroBiome Therapeutics LLC	NM504, the company's β-glucan- and insulin-based prebiotic product, is an oral dietary supplement that modulates the microbiome to improve glucose regulation in diabetic patients	Pilot/Phase 0	N/A
C3J Therapeutics Inc.	Specifically Targeted Antimicrobial Peptides (STAMPs) to correct microbial dysbiosis in obesity.	Preclinical	N/A
Cedars-Sinai Medical Center, Synthetic Biomics, a subsidiary of **Synthetic Biologics Inc.** (NYSE-M:SYN)	Licensing deal in which the company received a license with options from the medical center to develop non-antibiotic oral drugs that selectively adjust the microflora in patients with obesity, Type II diabetes and irritable bowel syndrome (IBS).	Preclinical	December 2013
Enterome Bioscience S.A.	Microbiome-derived products for obesity, diabetes, IBS and other microbiome-related diseases	Preclinical	N/A
Genewiz Inc.; Hy Laboratories Ltd.	Partnership to develop diagnostics to characterize the gut microbiome for stratifying patients for clinical intervention	Preclinical	May 2015
Mayo Clinic; Second Genome Inc.	Collaboration to discover and translate microbiome diagnostics and therapeutics for obese patients with and without Type II diabetes	Preclinical	October 2014
MetaboGen AB	A platform to identify key microbial species and microbe-host interactions associated with obesity, diabetes and other metabolic diseases	Preclinical	N/A
Pfizer Inc. (NYSE:PFE); **Second Genome Inc.**	Collaboration to study the relationship between the human microbiome, obesity and metabolic disorders	Preclinical	May 2014
TargEDys	Oral compounds based on proteins produced by gut bacteria that regulate appetite and food intake	Preclinical	N/A

Cani told BioCentury that when mice on a high-fat diet were treated with Amuc_1100, the protein was able to replicate "almost all the beneficial effects of the bacteria."

Cani's team plans first to test *A. muciniphila* as a therapeutic for Type II diabetes, hypercholesterolemia or metabolic syndrome, and has already moved into human safety trials using the synthetic medium it developed to culture the bacteria for oral delivery. "The results show that the bacteria has no deleterious impact on the kidney, the liver, or the blood formula," he said.

However, he thinks the bacterial protein might be a more suitable therapeutic agent in patients with inflammatory bowel disease (IBD) or an otherwise compromised gut barrier, for whom live bacterial therapies are not a safe option. The group is also planning to produce the protein and test its safety in humans.

NO GOING BACK

In the second study, published in *Nature*, Weizmann Institute of Science investigator Eran Elinav identified a microbiome signature in formerly obese mice that could predict how much weight lost during dieting would be regained later, and uncovered two flavonoid metabolites that can prevent the weight rebound.

Elinav's team modeled dieting and recurrent obesity in mice by switching between high-fat and normal fat diets to induce cycles of weight gain and loss. Although body fat, glucose tolerance, serum cholesterol, serum insulin levels and other metabolic measures all returned to pre-obesity levels following a period of weight loss, the team identified changes in the composition of gut microbiota that did not revert after weight loss, but instead persisted.

Next, the researchers showed the microbiome changes were linked to the recurrence of obesity in the model. The team compared the gut bacterial composition between mice that had gained and lost weight and mice that had gained weight and then received a broad-spectrum antibiotic during the weight loss phase to eliminate the obesity-based changes. When reintroduced to the high-fat diet, the mice that did not receive antibiotic regained more weight than mice that did.

Elinav's team then developed a machine-learning algorithm that could differentiate between the microbiomes of mice that had gained, then lost, weight from those that had never been obese, and then accurately predict the amount of weight individual mice would regain when once again exposed to a high-fat diet. The group found 189 different species that contributed to the predictive signature, suggesting the effect was not due to a small handful of commensal bacteria but to the overall composition of the gut microbiome.

According to Elinav, the algorithms could be used clinically to identify patients most at risk for regaining lost weight in order to treat them with a future therapeutic or tailor their diet to minimize the weight gain.

In addition, the team identified two approaches for preventing weight regain after dieting.

First, it showed that providing fecal transplants to the slimmed-down mice before putting them back on a high-fat diet decreased the amount of weight they regained.

Second, it identified two flavonoid molecules — apigenin and naringenin — whose levels significantly dropped in response to a high-fat diet and stayed low even after the weight had been lost. Oral replenishment of the flavonoids reduced weight gain after the reintroduction of a high-fat diet, without changing the microbiome, suggesting the compounds could counteract obesity-induced changes to the microbiome to prevent obesity recurrence (see Distillery, Endocrine/Metabolic: Obesity).

Microbiome analytics company RondinX, which is based on a computational platform developed by the same investigators, uses growth dynamics to better characterize links between the microbiome and disease states for drug discovery.

BIOCENTURY PRODUCT PROFILE	
INNOVATION STAGE	
Product	*Akkermansia muciniphila* or its protein Amuc_1100
Concept	Pasteurization-stabilized form of a commensal bacterial species that interacts with TLR2-expressing gut cells to treat obesity; or a bacteria-derived protein to treat the same in patients with compromised gut barrier
Disease	Obesity
Competition	Small molecule therapies; bariatric surgery
Differentiation	Fewer side effects due to lack of systemic exposure; non-invasive
Administration	Oral
Risks	Bacteria-induced peritonitis in patients with undiagnosed gut barrier problems; or immune response to protein
Development status	Phase I
Patents	Patented
Company; lead investigator	Universite Catholique de Louvain; Patrice Cani and Wageningen University and Research Centre; Willem de Vos

Breaking the barrier

The third paper focuses on a host protein that regulates how gut flora respond to a high-fat diet.

In *Nature Microbiology*, a group from Taiwan's National Health Research Institutes homed in on DUSP6, a phosphatase previously shown to confer resistance to obesity in mice, and pinned its effect on an altered response of the microbiome to a high-fat diet.

The team, led by assistant investigator Cheng-Yuan Kao, transferred fecal microbiotal transplants from DUSP6-knockout mice to germ-free recipient mice. When fed a high-fat diet, the germ-free mice that received the transplant gained less weight — without reducing food intake — than controls.

Kao told BioCentury DUSP6 promotes weight gain by down-regulating tight junction components and regulators, increasing gut permeability to nutrients. In human colonic epithelial cells, depleting DUSP6 increased transepithelial electrical resistance — a measure of the integrity of the cellular barrier — and DUSP6-knockout mice showed lower gut permeability to a fluorescent probe than wild-type mice.

However, Kao said his team isn't planning to develop DUSP6 inhibitors to treat obesity because the gene is a tumor suppressor in lung cancer. Instead, the researchers are looking for bacterial species in mice that can confer the same resistance to obesity as fecal transplants from DUSP6-knockout mice. After that, they will search for the same or similar species in the human microbiome to develop as therapeutic agents.

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>
> Patrice Cani, Universite Catholique de Louvain

His team is also on the hunt for metabolites secreted by the bacteria that can replicate the effects of the fecal transplants, and plans to file patents covering a probiotic cocktail it is developing replicating the downstream effects of DUSP6 inhibition. Kao said the cocktail would then be available for licensing.

COMPANIES AND INSTITUTIONS MENTIONED

4D Pharma plc (LSE:DDDD), Manchester, U.K.
Axial Biotherapeutics Inc., Boston, Mass.
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
National Health Research Institutes, Zhunan, Miaoli County, Taiwan
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
RondinX, Tel Aviv, Israel
Universite Catholique de Louvain, Louvain-la-Neuve, Belgium
University of Helsinki, Helsinki, Finland
Wageningen University and Research Centre, Wageningen, the Netherlands
Weizmann Institute of Science, Rehovot, Israel

TARGETS

Amuc_1100 - *Akkermansia muciniphila* protein 1100
DUSP6 (MKP3) - Dual specificity phosphatase 6
TLR2 - toll-like receptor 2

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Everard, A., et al. "Cross-talk between Akkermansia muciniphila and intestinal epithelium controls diet-induced obesity." *Proceedings of the National Academy of Science* **(2013)**

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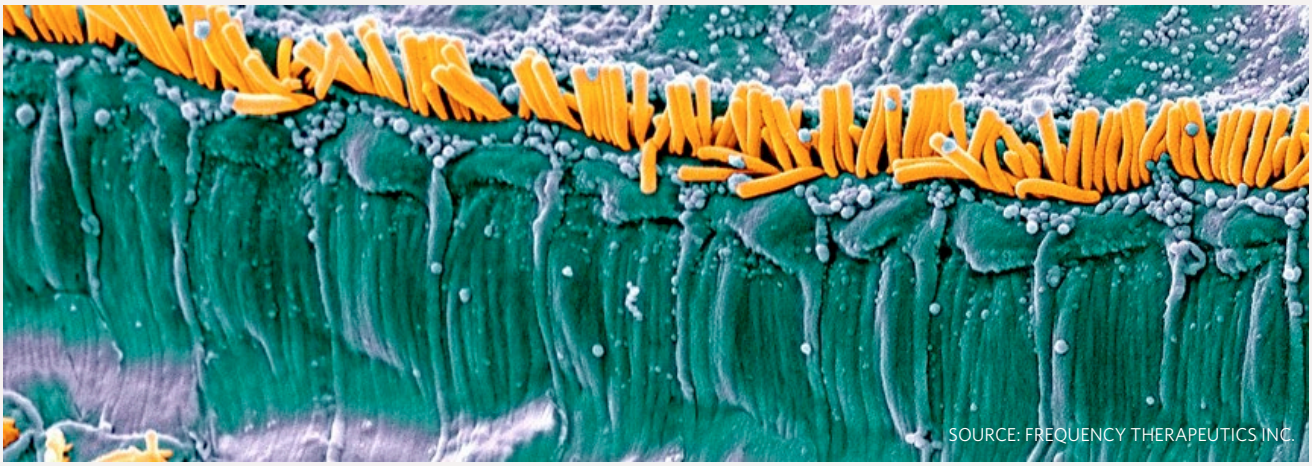
Ruan, J.-W., et al. "Dual-specificity phosphatase 6 deficiency regulates gut microbiome and transcriptome response against diet-induced obesity in mice." *Nature Microbiology* **(2016)**

Thaiss, C., et al. "Persistent microbiome alterations modulate the rate of post-dieting weight regain." *Nature* **(2016)**


SOURCE: FREQUENCY THERAPEUTICS INC.

PRODUCT R&D

NOW HEAR THIS

By Lauren Martz, Senior Writer

Most regenerative medicine companies are using stem cell therapies to replace and regrow damaged tissues, but development of stem cell therapies is complicated by manufacturing and regulatory challenges. Frequency Therapeutics Inc. is creating a next generation approach to regenerative medicine that uses small molecules to reactivate a patient's dormant progenitor cells *in vivo*.

The newco emerged from stealth mode last week with the announcement of its new board of directors, which is headed by Chairman Marc Cohen, co-founder of Cobro Ventures, and includes serial entrepreneur and co-founder Robert Langer, David H. Koch Institute Professor at the Massachusetts Institute of Technology. The company has an undisclosed amount of financing from Cobro, and a group of angel and super angel investors.

Langer launched the company with Harvard University professor Jeffrey Karp in 2015, to develop a regenerative treatment for chronic noise-induced hearing loss using progenitor cell activation (PCA) technology created by the duo. Also on the list of co-founders are President and CEO David Lucchino and CSO Chris Loose, who previously teamed up with Langer to create Semprus Biosciences Corp., a medical device company acquired by Teleflex Inc. in 2012.

Lucchino told BioCentury Frequency's goal is to create "a regenerative medicine platform that is next-generation in nature," by modulating stem cells already in place in the body, rather than extracting and re-implanting them.

"There have certainly been some meaningful advances in stem cell therapy, but it's still an arduous process that involves removing the cells, managing them externally and putting them back," he said.

The company's PCA platform works by employing a combination of small molecules that first trigger proliferation of a subset of dormant progenitor cells and then cause them to differentiate and replace damaged tissue.

According to Loose, the next-generation method circumvents the problem of delivery, which remains one of the biggest challenges associated with using stem cells. "Delivering the cells to get them exactly where you want them, and only where you want them, to work how you want them to work, is one of the hardest challenges. We're using what's already in place and already programmed to create the right type of cells."

CUTTING THROUGH THE NOISE

Frequency's platform originated from the discovery that certain epithelial cells lining the gut — LGR5-positive progenitors —

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>
> Chris Loose, Frequency Therapeutics

have regenerative potential, and that similar cells are found in other parts of the body including the ear, pancreas, skin and eyes. The only difference is that the cells in the intestines retain their regenerative potential, whereas the other cells become dormant after early development.

In 2014, Langer, Karp and colleagues discovered a way to expand and then differentiate the intestinal progenitors. In a *Nature Methods* paper they demonstrated that combining a GSK3B inhibitor with an HDAC inhibitor expanded the cells in culture and maintained them in a multipotent state, while adding a Wnt pathway inhibitor and a Notch pathway inhibitor drove them to differentiate.

Although the LGR5-positive cells of the inner ear lack the spontaneous regeneration potential of the gut-resident cells, Frequency's co-founders hypothesized that a similar combination of small molecules could bring dormant progenitors in the ear back to a pluripotent state.

The company settled on chronic noise-induced hearing loss as the first indication for its platform because there are no treatments, and the group reasoned it might be possible to re-activate LGR5-positive cells in the inner ear.

Noise-induced hearing loss is thought to be caused by reactive oxygen species (ROS)-induced damage to the hair cells in the inner ear, which are responsible for converting sound waves to nerve impulses.

Lucchino told BioCentury that there is "absolutely no therapy" for noise-induced hearing loss, and "hearing aids can make it louder, but not clearer," which doesn't provide anything similar to normal hearing.

Several companies have been exploring regenerative medicine and gene therapy to restore hearing.

GenVec Inc. has CGF116, a gene therapy that delivers the ATOH1 gene to the ear to induce differentiation of sensory cells, in Phase I/II testing for noise-induced hearing loss. Living Cell Technologies Ltd. has shown that its choroid plexus cell therapy NTCELL, which secretes neuroprotective factors, can treat hearing loss in animal models.

Loose told BioCentury Frequency's platform differentiates itself from other techniques in development for hearing loss, and other regenerative medicine platforms in general, because it is the first to re-ignite progenitors *in vivo*.

"We're unique in our ability to activate the cells in such a way that they can go into asymmetric cell division, behave as progenitors and replace themselves to form new tissues," he said.

Loose also noted that lessons from other species provide further support for using the inner ear progenitors as a target for the PCA platform, because inner ear hair cells are able to regenerate in non-mammalian animals such as birds and reptiles.

"When humans are born, they have 15,000 hairs in the cochlea that move with sound but are damaged when they move too much. Although mammals can't restore the damaged hair cells, other species can," said Loose.

He declined to disclose whether Frequency has animal data on use of its platform in hearing loss, or the targets of the small molecules it's developing to trigger regeneration.

The company expects to have a hearing loss therapy in the clinic within 18 months, which will be administered using intratympanic injection — a method that involves injecting the small molecule cocktail in a slow-release gel directly into the

BIOCENTURY PRODUCT PROFILE	
INNOVATION STAGE	
Product	Progenitor cell activation (PCA) molecules
Concept	Regeneration of inner ear hair cells using a small molecule combination that causes proliferation, then differentiation, of dormant progenitor cells *in vivo*
Disease	Chronic noise-induced hearing loss
Competition	Stem cell therapies; gene therapies; otoprotective agents
Differentiation	Simple manufacturing and delivery; targets progenitor cells already programmed to become the desired tissue type; regenerates damaged tissue rather than preventing damage
Administration	Intratympanic injection
Risks	Injection complications, including persistent perforation; potential for hair cell regeneration at levels not sufficient to improve hearing
Development status	Preclinical
Patents	Patent applications filed covering the PCA technology and its application to hearing loss and other indications
Company; lead investigator	Frequency Therapeutics Inc.; Robert Langer, Massachusetts Institute of Technology; Jeff Karp, Harvard University

middle ear. The technique is already approved to deliver steroids to the ear.

REGENERATING VALUE

At the moment, Frequency is "laser-focused" on developing a treatment for hearing loss, said Loose, but it plans to apply the platform to other tissues and indications after validating it in the first indication.

Other potential applications include skin conditions, eye diseases, gastrointestinal diseases and diabetes, which all affect tissues containing LGR5-positive progenitor cells.

Additionally, Loose believes that the same concept could extend to regeneration of tissues containing other types of stem cells. "We're in the process of understanding what the pathways are that control how progenitor cells wake up and form new cells of interest in the tissues we're targeting," he said. "Many progenitors have different regeneration signals and will respond to different modulators."

Frequency doesn't have plans to partner or license the platform, although that could change in the future, said Lucchino. "This is a real opportunity to move this technology efficiently through the pipeline into patients while retaining what I call 'ball control" for it. We're looking to build a company where we can bring therapeutics to the market."

Frequency has a license from MIT and Partners HealthCare Systems Inc. to a portfolio of patent applications covering the PCA platform, its application to hearing loss and other applications. The company is not disclosing details about its financing or investors.

COMPANIES AND INSTITUTIONS MENTIONED

Frequency Therapeutics Inc., Cambridge, Mass.
GenVec Inc. (NASDAQ:GNVC), Gaithersburg, Md.
Harvard University, Cambridge, Mass.
Living Cell Technologies Ltd.(ASX:LCT; OTCQX:LVCLY), Sydney, Australia
Massachusetts Institute of Technology, Cambridge, Mass.
Partners HealthCare Systems Inc., Boston, Mass.
Teleflex Inc. (NYSE:TFX), Limerick, Pa.

TARGETS

ATOH1 (HATH1) - Atonal homolog 1
GSK3β - Glycogen synthase kinase 3β
HDAC - Histone deacetylase
LGR5 (GPR49) - Leucine-rich repeat-containing G protein-coupled receptor 5

REFERENCES

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EMERGING COMPANY PROFILE

LOOKING BEYOND VEGF

By Michael Leviten, Senior Writer

SemaThera Inc. launched this week to develop a recombinant SEMA3A trap to treat vascular pathologies in the large fraction of diabetic macular edema (DME) patients who don't respond to marketed anti-VEGF therapies.

Semaphorins are a family of secreted and transmembrane proteins that bind a heterocomplex of a plexin protein, a neuropilin, and a cell adhesion molecule.

Co-founder and CSO Przemyslaw "Mike" Sapieha told BioCentury, "We've been working for three years developing these trap-like molecules that are built on neuropilin scaffolding and we've rationally designed some to be very strong semaphorin binders." Sapieha is also an associate professor of ophthalmology at the University of Montreal.

The company has a series of potential clinical leads that, in addition to binding SEMA3A, bind VEGF proteins with varying affinity. That creates the potential to neutralize both SEMA3A and VEGF, giving the molecules an advantage over the marketed VEGF inhibitors which, according to Sapieha, don't bind SEMA3A.

CEO Maxime Ranger told BioCentury that treating patients with anti-SEMA3A might prevent the progression or even reverse the DME vasculopathy in situations where anti-VEGFs show no efficacy. "We target the 40% of poor or non-responders to anti-VEGF therapies."

In 2013, Sapieha published data showing elevations in SEMA3A levels occurred earlier than elevations in VEGF in the vitreous fluid of mice with ocular edema, and shRNA knockdown of SEMA3A or knockdown of the neuropilin NRP1 in the retinal vasculature reduced edema-associated vascular leakiness.

Last October, his team published a study in *Science Translational Medicine* that showed senescence plays a pathogenic role, and SEMA3A drives the spread of this senescence, in a mouse model of diabetic retinopathy (DR).

In culture, recombinant SEMA3A induced senescence and stunted the growth of human retinal microvascular endothelial cells. Conversely, suppressing SEMA3A via intravitreal injection of shRNA reduced senescence in the developing retina.

Using a mouse model of DR, the team connected senescence in retinal neurons with up-regulation of SEMA3A expression, and showed pharmacological inhibition of senescence or SEMA3A expression ameliorated the pathogenic angiogenesis. In addition, the team presented evidence suggesting blocking SEMA3A might modify disease onset before VEGF inhibitors can act.

Ranger said the company will select a lead candidate by 3Q17, with GMP manufacturing and GLP toxicology studies slated to begin by year-end and an IND submission planned for early 2019.

The anti-VEGF therapies Eylea aflibercept opthalmic solution (VEGF Trap Eye) and Lucentis ranibizumab are marketed by Regeneron Pharmaceuticals Inc. and Roche's Genentech Inc. unit respectively, both for DME and DR. Molecular Partners AG has a VEGF inhibitor in Phase III for DME.

SemaThera was spawned by a deal between AmorChem L.P., a Montreal-based venture firm that specializes in commercializing research at universities and research centers in the Quebec province, and Univalor, the tech transfer arm of Hôpital Maisonneuve-Rosemont.

Ranger said SemaThera has exclusive rights to two patent applications from Hôpital Maisonneuve-Rosemont covering the composition and use of SEMA3A inhibitors in ocular vasculopathies including DME, DR, and wet advanced macular degeneration (AMD).

SEMATHERA INC., Montreal, Quebec
Technology: Recombinant SEMA3A trap for diabetic retinopathy
Disease focus: Ophthalmic
Clinical status: Preclinical
Founded: 2016 by John Clement and Przemyslaw "Mike" Sapieha
University collaborators: Hôpital Maisonneuve-Rosemont, University of Montreal
Corporate partners: None
Number of employees: 3
Funds raised: C$1 million ($0.75 million)
Investors: AmorChem Venture Fund I
CEO: Maxime Ranger
Patents: None issued

COMPANIES AND INSTITUTIONS MENTIONED

Genentech Inc., South San Francisco, Calif.
Hôpital Maisonneuve-Rosemont, Montreal, Quebec
Molecular Partners AG (SIX:MOLN), Schlieren, Switzerland
Regeneron Pharmaceuticals Inc. (NASDAQ:REGN), Tarrytown, N.Y.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
SemaThera Inc., Montreal, Quebec
University of Montreal, Montreal, Quebec

TARGETS

NRP1 - Neuropilin 1
SEMA3A - Semaphorin 3A
VEGF - Vascular endothelial growth factor

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TRANSLATION IN BRIEF

GIVE ME A BREAK

In 2013, two groups introduced the paradoxical and, at the time, controversial hypothesis that blocking antiviral cytokine signals can help clear chronic infections by reinvigorating T cells exhausted from non-stop inflammation. One of those groups has now bolstered that theory by showing its relevance to HIV, and is looking for ways to retain the antiviral effects while dialing out the mechanism that leads to exhaustion.

Moreover, a second study, published in the same issue of *The Journal of Clinical Investigation* last month, arrived at the same conclusion in a mouse model of HIV infection controlled by antiretrovirals (ARVs).

At the center of the idea are type I interferons, cytokines that play a critical role in suppressing viral replication during the acute phase of infection. But the 2013 studies, published in *Science*, showed in mouse models of chronic lymphocytic choriomeningitis (LCMV) infection that prolonged type I interferon signaling can cause damage, as it exhausts T cells, making them less effective at fighting infection (see "Interfering with Interferon." *SciBX: Science-Business eXchange* (April 25, 2013)).

"When we published those papers they were, to put it mildly, very counterintuitive," said David Brooks, an associate professor of immunology at University of Toronto and a co-author of one of the recent studies. "These new papers are the first in HIV, but the field had been prepped to accept the idea. Going forward, these studies will make that even more of a reality."

The two HIV studies showed mAbs blocking the receptor for type I interferon, which is composed of the subunits interferon α/β receptor 1 (IFNAR1) and interferon α/β receptor 2 (IFNAR2; IFN-R), decreased T cell exhaustion and viral loads in a humanized mouse model of HIV infection. In addition, combining the mAbs with a cocktail of marketed antiretrovirals had more potent effects on HIV clearance than either treatment alone (see Distillery, Infectious Disease: HIV/AIDS).

However, Brooks said that while the two studies were "very complementary," they weren't identical.

His team studied the effects of IFNAR2 blockade on endogenous immune responses or ARV treatment in HIV-1-infected mice. By contrast, the other team, from the University of North Carolina at Chapel Hill and the Chinese Academy of Sciences (CAS), showed blocking IFNAR1 before withdrawing ARV therapy from HIV-1 infected mice delayed viral rebound.

But Brooks isn't suggesting the results overturn what's known about the positive antiviral role of type I interferons in chronic infection. Instead, he proposes inhibiting the pathways transiently to "reset" the immune system to a non-exhausted state.

He said the "pie in the sky" goal is to selectively target a regulator downstream of type I interferons, to interrupt the pathway that leads to T cell exhaustion. That kind of intervention could have applications across many fields, including cancer, he said.

"Blocking it altogether is one way of doing it, and that's fine if that's what we have now," said Brooks. "But if we can whittle the interferon signaling system apart, we may

> "If we can whittle the interferon signaling system apart, we may be able to do this in a much more directed and effective way."
>
> David Brooks, University of Toronto

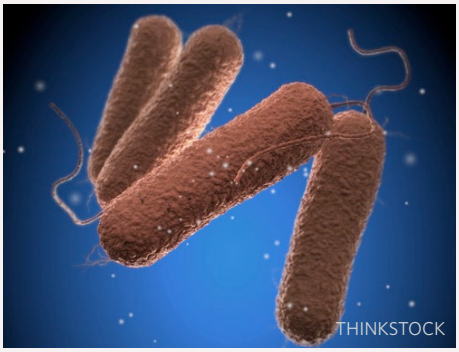
be able to do this in a much more directed and effective way. One of the major goals in our lab is to try and dissect what drives the positive and negative aspects of type I interferon signaling, and see if those can be uncoupled."

Brooks and his co-authors at University of California Los Angeles plan to file patents covering ongoing aspects of the work, which are available for partnering. The UNC and CAS team did not respond to requests to comment. *Cheng, L., et al. "Blocking type I interferon signaling enhances T cell recovery and reduces HIV-1 reservoirs." The Journal of Clinical Investigation (2016); Zhen, A., et al. "Targeting type I interferon-mediated activation restores immune function in chronic HIV infections." The Journal of Clinical Investigation (2016).*

—Karen Tkach

IRON AGE ARMS RACE

Two research groups have turned bacteria's own survival mechanisms against them with therapeutic vaccines based on siderophores — iron-scavenging molecules the pathogens secrete that are not ordinarily immunogenic. The preclinical studies showed conjugating siderophores to immunogenic carrier proteins could treat urinary tract infection (UTI) and salmonella, but the idea could have widespread utility because of the large number of bacteria that depend on iron.



The results were published in November in two independent studies in *Proceedings of the National Academy of Sciences*, one from the University of Michigan and the other from a collaboration between researchers at the Massachusetts Institute of Technology and the University of California Irvine (see Distillery, Jan. 5, 2017).

During infection, both the host and bacteria deploy strategies aimed at overcoming the defenses of the other: The host sequesters iron critical to bacterial growth, but bacteria get around this by secreting siderophores to recruit iron. The host counters by secreting lipocalin (NGAL; LCN2) to bind and inactivate the siderophores, but some bacteria secrete "stealth" siderophores that are too large for NGAL to bind, giving the pathogens the upper hand.

"This is an arms race between us – the host – and microbes for iron" that could be exploited to treat bacterial infection, said Manuela Raffatellu, an associate professor of microbiology and molecular genetics at UC Irvine who led the collaboration.

The two studies exploited these stealth siderophores in different ways to stimulate an immune response and target infection.

The UMich team conjugated bovine serum albumin (BSA) to two stealth siderophores produced by uropathogenic *E. coli* (UPEC) — yersiniabactin and aerobactin. In a mouse model of UPEC-induced UTI, the conjugates decreased bacteria burden in the kidneys and urine, and decreased inflammation in the bladder and kidneys compared with unconjugated BSA.

The conjugates had no effect in a UTI mouse model challenged with mutant UPEC strains unable to synthesize the two siderophores, demonstrating that the immune response specifically targeted the two scavenger molecules to treat UPEC infection.

The MIT-UC Irvine group took a similar approach against salmonella, but based its conjugate on enterobactin, a non-stealth siderophore produced by *Salmonella* species.

> "This is an arms race between us – the host – and microbes for iron."
>
> Manuela Raffatellu, UC Irvine

While small enough for NGAL to bind, enterobactin has a glycosylated analog, salmochelin, that NGAL cannot bind. The group hypothesized that a conjugate based on the smaller molecule would generate an immune response against both, and created an enterobactin-cholera toxin B conjugate that elicited antibodies specific for the two siderophores in mice.

In a mouse model of salmonella-induced colitis, the conjugate decreased *Salmonella enterica* colonization in the colon, bacterial burden in the spleen and weight loss compared with the unconjugated cholera toxin.

The group also examined the composition of the animals' gut microbiome and found that while salmonella decreased the overall diversity of the microbiome, immunization with the conjugate increased levels of beneficial *Lactobacilli* species.

Lactobacilli "are beneficial microbes that are also well suited to growing during inflammation, and they were able to expand in an environment where salmonella was suppressed," Raffatellu told BioCentury. "That was an unexpected but very cool finding."

She added that the siderophore-based vaccination strategy could be broadly applicable to other bacterial infections "because there are many other organisms that need iron." She thinks the strategy could also work well in HIV and other immunocompromised patients, in whom NGAL levels are low.

Raffatellu's group is optimizing the synthesis of its siderophore conjugates, but the eventual goal is to immunize mice with siderophore-based vaccines to produce antibodies that could be isolated, purified and used as therapeutic agents for infection. "We've shown a correlation: the more antibody we had, the better protection we had. But to truly show that it is dependent on the antibodies, we need to purify those antibodies and test them."

MIT has patented the siderophore conjugate used in the MIT-UC Irvine study and the IP is available for licensing. The UMich team did not respond to requests for comment. *Mike, L. et al. "Siderophore vaccine conjugates protect against uropathogenic Escherichia coli urinary tract infection." Proceedings of the National Academy of Sciences (2016); Sassone-Corsi, M. et al. "Siderophore-based immunization strategy to inhibit growth of enteric pathogens." Proceedings of the National Academy of Sciences (2016)*

— Mary Romeo

DISTILLERY

THE DISTILLERY brings you this week's most essential scientific findings in therapeutics, distilled by *BioCentury Innovations* 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.

THERAPEUTICS

CANCER

INDICATION: Brain cancer

Patient sample, cell culture and mouse studies suggest inhibiting the long non-coding RNA (lncRNA) TUG1 could help treat glioblastoma multiforme (GBM). In tissue samples from patients, levels of TUG1 were higher in tumor tissue than in normal brain tissue. In human glioblastoma stem cell lines, siRNA targeting TUG1 decreased proliferation and levels of two markers of stemness compared with non-specific siRNA. In an orthotopic xenograft mouse model of GBM, an antisense oligonucleotide (ASO) targeting TUG1 conjugated to polymeric micelles decreased tumor growth and levels of the two stemness markers compared with unconjugated micelles. Next steps include developing a delivery method for the TUG1 ASO and identifying additional TUG1 inhibitors.

TARGET/MARKER/PATHWAY: Taurine upregulated gene 1 (TUG1)
LICENSING STATUS: Patent application filed; available for licensing or partnering
PUBLICATION DETAILS: Katsushima, K. et al. *Nat. Commun.*; published online Dec. 6, 2016
doi:10.1038/ncomms13616
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INDICATION: Breast cancer

Patient sample and mouse studies suggest inhibiting GPR132 could help treat metastatic breast cancer. In breast cancer patients, high levels of GPR132 in primary tumors correlated with poor metastasis-free and relapse-free survival. In a mouse model of metastatic breast cancer, knockout of GPR132 decreased lung metastasis compared with normal GPR132 expression. Next steps include identifying and testing GPR132 inhibitors in additional models of breast cancer.

TARGET/MARKER/PATHWAY: G protein-coupled receptor 132 (GPR132)
LICENSING STATUS: Patent application filed; available for licensing
PUBLICATION DETAILS: Chen, P. et al. *Proc. Natl. Acad. Sci. USA*; published online Jan. 3, 2017
doi:10.1073/pnas.1614035114
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INDICATION: Breast cancer

In vitro, cell culture and mouse studies identified two allosteric PHGDH inhibitors that could help treat breast cancer. *In silico* screening of a virtual compound library against PHGDH followed by testing of hits in enzyme activity assays identified a methylidenebenzohydrazide analog and a methylfuranylbenzoic acid analog that bound an allosteric site on PHGDH and inhibited the enzyme with IC_{50} values of 34.8 µM and 35.7 µM, respectively. In two human breast cancer cell lines, the compounds inhibited growth with EC_{50} values of 6.9-10.8 µM. In two orthotopic xenograft mouse models of breast cancer, the compounds decreased tumor growth compared with vehicle. Next steps include optimizing and testing the compounds in additional animal models.

TARGET/MARKER/PATHWAY: Phosphoglycerate dehydrogenase (PHGDH)
LICENSING STATUS: Patent application filed; available for licensing and partnering
PUBLICATION DETAILS: Wang, Q. et al. *Cell Chem. Biol.*; published online Dec. 29, 2016
doi:10.1016/j.chembiol.2016.11.013
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THERAPEUTICS

CANCER

INDICATION: Cancer

Cell culture studies identified an oxadiazole-based tubulin inhibitor that could help treat cancer. Chemical synthesis and *in vitro* testing in tubulin network formation assays and cell lines of oxadiazole analogs yielded a compound that disrupted microtubule organization and was cytotoxic in human breast cancer, cervical cancer, glioblastoma multiforme (GBM), neuroblastoma, non-small cell lung cancer (NSCLC), prostate cancer, rhabdomyosarcoma and four other human cancer cell lines with IC_{50} values of 50-670 nM and was cytotoxic in multiple normal human cell lines with IC_{50} values of 1.6-1.9 μM. In the cervical adenocarcinoma cell line, the compound decreased colony-forming ability compared with vehicle. Next steps could include optimizing the compound's potency and testing it in animal models of cancer.

TARGET/MARKER/PATHWAY: Tubulin
LICENSING STATUS: Patent and licensing status unavailable
PUBLICATION DETAILS: Nieddu, V. et al. *J. Med. Chem.*; published online Nov. 1, 2016
doi:10.1021/acs.jmedchem.6b00468
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INDICATION: Liver cancer

Mouse studies suggest inhibiting NR1I3 could help prevent circadian disruption-induced hepatocellular carcinoma (HCC). The mouse model of chronic circadian disruption involved switching light and dark cycles in a 24-hour period to increase the incidence of spontaneous non-alcoholic fatty liver disease (NAFLD) and hepatocellular carcinoma (HCC) compared with mice kept under normal light and dark cycles. In the model, NR1I3 knockout decreased hepatomegaly, liver inflammation and fibrosis, hepatocyte proliferation and the incidence of HCC compared with normal NR1I3 expression. Next steps include testing NR1I3 inhibitors in the model.

TARGET/MARKER/PATHWAY: Constitutive androstane receptor (NR1I3; CAR)
LICENSING STATUS: Patented; unavailable for licensing
PUBLICATION DETAILS: Kettner, N. et al. *Cancer Cell*; published online Nov. 23, 2016
doi:10.1016/j.ccell.2016.10.007
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INDICATION: Liver cancer

Patient sample, cell culture and mouse studies suggest inhibiting SMARCA2 or its downstream effector YAP1 could help treat hepatocellular carcinoma (HCC). In patient samples, levels of SMARCA2 and YAP1 were higher in tumors than in surrounding normal tissue, and tumor levels of the two proteins were associated with disease progression. In two human HCC lines and primary tumor cells from six HCC patients, SMARCA2 knockdown or knockout decreased tumorsphere formation compared with normal SMARCA2 expression. In the patients' cells, YAP1 knockout decreased tumorsphere formation compared with normal YAP1 expression, and in four patients' cells the YAP1 inhibitor Visudyne verteporfin decreased tumorsphere formation compared with vehicle. In a xenograft mouse model of HCC, tumor-specific knockdown of SMARCA2 or YAP1 decreased tumor growth compared with normal SMARCA2 and YAP1 expression. Next steps could include identifying and testing SMARCA2 or YAP1 inhibitors in HCC models.

Valeant Pharmaceuticals International Inc. and Novartis AG market Visudyne to treat choroidal neovascularization (CNV)

TARGET/MARKER/PATHWAY: Yes-associated protein 1 (YAP1; YAP); SWI/SNF related matrix associated actin dependent regulator of chromatin subfamily a member 2 (SMARCA2; BRM)
LICENSING STATUS: Patent and licensing status unavailable
PUBLICATION DETAILS: Zhu, P. et al. *Nat. Commun.*; published online Dec. 1, 2016
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THERAPEUTICS

CANCER

INDICATION: Pancreatic cancer

Cell culture and mouse studies suggest dual inhibition of the HGF/SF/c-MET/Src and SHH/IGF-1/IGF1R pathways could help treat pancreatic ductal adenocarcinoma (PDAC). In human PDAC cell lines, the Src inhibitor Sprycel dasatinib or an IGF1R inhibitor tool compound decreased cell surface levels of annexin A2 (ANXA2), which is required for PDAC invasiveness. In co-culture of a human PDAC cell line and human cancer-associated fibroblasts, fibroblast knockdown of HGF/SF or IGF-1 decreased cancer cell invasiveness compared with normal expression of the two genes. Also in the co-culture, the c-MET inhibitor capmatinib plus an SHH/IGF-1 inhibitor tool compound decreased ANXA2 levels in cancer cells compared with either agent alone. In spontaneous and orthotopic xenograft mouse models of PDAC, the inhibitor combination decreased cancer cell levels of ANXA2 compared with either agent alone, and in the orthotopic xenograft model, the combination decreased primary tumor growth and the number of metastases compared with vehicle. Next steps could include combining and testing other inhibitors of the two pathways in PDAC models.

Incyte Corp. and Novartis AG have capmatinib (INC280) in Phase II testing for liver cancer, non-small cell lung cancer (NSCLC) and solid tumors.

Bristol-Myers Squibb Co. and Otsuka Pharmaceutical Co. Ltd. market Sprycel for acute lymphoblastic leukemia (ALL) and chronic myelogenous leukemia (CML) and have the compound in Phase II testing for pancreatic and breast cancers and Phase I testing for leukemia.

TARGET/MARKER/PATHWAY: Hepatocyte growth factor/scatter factor (HGF/SF); c-Met receptor tyrosine kinase (c-MET; MET; HGFR; c-Met proto-oncogene); Src; insulin-like growth factor-1 (IGF-1); sonic hedgehog homolog (SHH); IGF-1 receptor (IGF1R; CD221)

LICENSING STATUS: Patent and licensing status unavailable

PUBLICATION DETAILS: Rucki, A. et al. *Cancer Res.*; published online Nov. 7, 2016

doi:10.1158/0008-5472.CAN-16-1383

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CARDIOVASCULAR

INDICATION: Heart failure

Patient sample and mouse studies suggest inhibiting LOXL2 could help treat heart failure. LOXL2 levels were higher in serum samples from heart failure patients and cardiac tissue samples from cardiomyopathy patients than in serum and cardiac tissue samples from healthy volunteers, respectively. In a mouse model of transaortic constriction-induced heart failure, LOXL2 knockout or an anti-LOXL2 mAb decreased cardiac fibrosis and increased cardiac function compared with normal LOXL2 expression or a control IgG. Next steps could include testing LOXL2 inhibitors in additional models of heart failure.

Pharmaxis Ltd. has the LOXL2 inhibitor PXS-5033A in preclinical testing for liver failure.

TARGET/MARKER/PATHWAY: Lysyl oxidase-like 2 (LOXL2)

LICENSING STATUS: Patent and licensing status unavailable

PUBLICATION DETAILS: Yang, J. et al. *Nat. Commun.*; published online Dec. 14, 2016

doi:10.1038/ncomms13710

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THERAPEUTICS

DERMATOLOGY

INDICATION: Scars / wrinkles

Mouse and patient sample studies suggest BMP2 or BMP4 could help prevent or treat scars. Under culture conditions that promote adipocyte differentiation, dermal cells of wild-type mice taken from wounds containing hair-follicles — which express BM2 and BMP4 — differentiated into the mature adipocytes known to promote tissue regeneration instead of scarring, whereas dermal cells of wild-type mice taken from hairless wounds or dermal wound cells from mice that overexpressed the BMP2/BMP4 antagonist noggin (NOG) did not differentiate into adipocytes. In myofibroblasts from mouse wounds, BMP2 or BMP4 increased reprogramming into adipocytes compared with no treatment. In keloid scar cells from patients, BMP4 increased levels of adipocyte markers. Next steps could include testing topical BMP2 or BMP4 in hairless mouse wounds.

SMC Biotechnology Inc. has SMC-103, a glycosaminoglycan that enhances the effects of BMP2, in preclinical testing for bone repair.

TARGET/MARKER/PATHWAY: Bone morphogenetic protein 2 (BMP2); BMP4

LICENSING STATUS: Patent application filed; licensing status unavailable

PUBLICATION DETAILS: Plikus, M. et al. *Science*; published online Jan. 5, 2017

doi:10.1126/science.aai8792

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ENDOCRINE / METABOLIC

INDICATION: Obesity

Mouse studies suggest fecal microbiota transplants or the flavonoids apigenin and naringenin could help treat recurrence of obesity after dieting. The mouse model of recurrent obesity involved a cycle of high-fat diet to induce weight gain, normal diet to induce weight loss, reintroduction of the high-fat diet to induce secondary weight gain, then normal diet again. In the model, fecal transplants from mice fed a normal diet decreased secondary weight gain, body fat and glucose intolerance and increased lean body mass compared with fecal transplants from mice fed the cycling diet. Also in the model, oral administration of apigenin or naringenin decreased secondary weight gain and increased energy expenditure compared with vehicle. Next steps include studying the mechanisms of weight regain in humans (see Cover Story).

TARGET/MARKER/PATHWAY: An undetermined target

LICENSING STATUS: Patent and licensing status undisclosed

PUBLICATION DETAILS: Thaiss, C. et al. *Nature*; published Nov. 24, 2016

doi:10.1038/nature20796

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THERAPEUTICS

INFECTIOUS DISEASE

INDICATION: Hepatitis C virus (HCV)

Cell culture studies identified cajanine and its analogs as CSGALNACT1 inhibitors that could treat HCV infection. A human hepatoma cell line-based mRNA assay identified cajanine as an inhibitor of CSGALNACT1. Chemical synthesis and testing in a human hepatoma-based HCV replication assay yielded cajanine and multiple analogs that inhibited replication of wild-type HCV replication with IC_{50} values of 0.33-3.17 μM. Also in the assay, cajanine plus Daklinza daclatasvir, Olysio simeprevir or Sovaldi sofosbuvir synergistically decreased viral replication compared with any of the agents alone. Next steps could include testing cajanine and its analogs in a humanized mouse model of HCV infection.

Bristol-Myers Squibb Co. markets the HCV NS5A protein inhibitor Daklinza for HCV.

Medivir AB and Johnson & Johnson market the HCV NS3/4A protease complex inhibitor Olysio for HCV.

Gilead Sciences Inc. and Mylan N.V. market the HCV NS5B polymerase inhibitor Sovaldi for HCV.

TARGET/MARKER/PATHWAY: Chondroitin sulfate N-acetylgalactosaminyltransferase 1 (CSGALNACT1)
LICENSING STATUS: Patent and licensing status unavailable
PUBLICATION DETAILS: Ji, X. et al. *J. Med. Chem.;* published online Oct. 26, 2016
doi:10.1021/acs.jmedchem.6b01301
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INDICATION: HIV/AIDS

Mouse studies suggest inhibiting IFNAR2 or IFNAR1 could help treat HIV1 infection. In a humanized mouse model of chronic HIV infection, an anti-IFNAR2 mAb decreased plasma viral load and levels of exhaustion markers such as PD-1 on circulating $CD8^+$ T cells compared with a control mAb. Also in the model, the anti-IFNAR2 mAb plus a cocktail of the antiretrovirals (ARVs) Isentress raltegravir, emtricitabine and tenofovir decreased plasma and latent splenic viral loads compared with the cocktail plus a control mAb. In the same model, an anti-IFNAR1 mAb plus the ARV cocktail decreased levels of splenic T cell exhaustion markers such as PD-1. Also in the model, the anti-IFNAR1 mAb plus the ARV cocktail decreased latent viral loads in the spleen and bone marrow compared with either the mAb or cocktail alone, and upon cessation of ARV therapy, the mAb increased the time to plasma viremia rebound compared with a control mAb. Next steps include identifying regulators of T cell exhaustion downstream of IFNAR2 and IFNAR1 that could promote antiviral T cell activity without inhibiting the receptors' antiviral functions (see "Give Me a Break").

Merck & Co. Inc. markets Isentress, an HIV integrase inhibitor, to treat HIV infection.

The generic nucleoside analog emtricitabine is marketed to treat HIV infection.

The generic nucleotide analog tenofovir is marketed to treat HIV infection.

TARGET/MARKER/PATHWAY: Interferon α/β receptor 1 (IFNAR1); IFNAR2 (IFN-R)
LICENSING STATUS: Unpatented; available for partnering
PUBLICATION DETAILS: Zhen, A. et al. *J. Clin. Invest.;* published online Dec. 12, 2016
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LICENSING STATUS: Patent and licensing status unavailable
PUBLICATION DETAILS: Cheng, L. et al. *J. Clin. Invest.;* published online Dec. 12, 2016
doi:10.1172/JCI90745
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THERAPEUTICS

NEUROLOGY

INDICATION: Epilepsy

Cell culture and rat studies identified a benzodiazepine-based triple-inhibitor of CACNA1G, CACNA1H and CACNA1I that could help treat epilepsy. Chemical synthesis and testing in HEK cells expressing the three calcium channels identified a pyridodiazepine that inhibited calcium flux mediated by each channel with IC_{50} values of 138, 102 and 11 nM, respectively. In a rat model of epilepsy, the compound decreased the number and duration of seizures compared with vehicle. Next steps by Actelion Ltd. could include optimizing and testing the compound in additional epilepsy models.

TARGET/MARKER/PATHWAY: Calcium channel voltage-dependent T type α 1G subunit (CACNA1G; Cav3.1); CACNA1H (Cav3.2); CACNA1I (Cav3.3)

LICENSING STATUS: Patent and licensing status unavailable

PUBLICATION DETAILS: Siegrist, R. et al. *J. Med. Chem.*; published online Nov. 23, 2016

doi:10.1021/acs.jmedchem.6b01356

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INDICATION: Huntington's disease (HD)

Cell culture studies suggest inhibiting the bromodomains of CREBBP and EP300 could help treat HD. In a human osteosarcoma cell line expressing a disease-associated mutant HTT, three tool compounds that inhibit the bromodomains of CREBBP and EP300 decreased mutant HTT aggregation compared with no treatment. Next steps include optimizing the compound.

TARGET/MARKER/PATHWAY: CREB binding protein (CREBBP; CBP); E1A binding protein p300 (EP300; p300); huntingtin (HTT)

LICENSING STATUS: Patent application filed; available for partnering

PUBLICATION DETAILS: Olzscha, H. et al. *Cell Chem. Biol.*; published online Dec. 15, 2016

doi:10.1016/j.chembiol.2016.11.009

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INDICATION: Pain

Mouse studies identified a STOML3 inhibitor that could help treat neuropathic pain associated with nerve injury and diabetes. Screening of a small molecule library for inhibitors of mouse and human STOML3 dimerization followed by testing of hits in a mouse neuroblastoma cell-based assay identified a nitroimidazoloxybenzofuran analog that inhibited mechanically stimulated PIEZO1 current amplitude — a measure of STOML3-regulated pain signaling — with an IC_{50} of 10 nM. In mouse models of traumatic nerve injury and diabetic peripheral neuropathy, the compound decreased mechanical allodynia compared with vehicle. Next steps in collaboration with Lead Discovery Center GmbH include optimizing the compound.

TARGET/MARKER/PATHWAY: Piezo-type mechanosensitive ion channel component 1 (PIEZO1); stomatin like 3 (STOML3)

LICENSING STATUS: Patent application filed; available for licensing and partnering

PUBLICATION DETAILS: Wetzel, C. et al. *Nat. Neurosci.*; published online Dec. 12, 2016

doi:10.1038/nn.4454

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THERAPEUTICS

NEUROLOGY

INDICATION: Stroke

Mouse studies suggest inhibiting signaling between RTN4R, RTN4RL2 and their ligands could help treat white matter stroke. In a mouse model of the disease, white matter levels of three negative regulators of Nogo signaling were lower and the number of oligodendrocyte progenitor cells (OPCs) differentiating into astrocytes were higher than in normal mice. In a young adult mouse model of white matter stroke, a chimeric RTN4R-RTN4RL2-Fc fusion protein that inhibits the Nogo signaling ligands MAG, OMG and RTN4 increased differentiation of OPCs into oligodendrocytes compared with a control IgG-Fc fusion protein. In an aged mouse model of white matter stroke, the ligand inhibitor increased forelimb motor control. Next steps include identifying additional signaling pathways that affect the differentiation of OPCs in white matter stroke.

GlaxoSmithKline plc has GSK249320, a mAb against MAG, in Phase II testing for cerebral stroke.

Novartis AG has ATI355, a mAb against RTN4, in Phase I testing for spinal cord injury (SCI).

TARGET/MARKER/PATHWAY: Reticulon 4 receptor (RTN4R; NGR); reticulon 4 receptor-like 2 (RTN4RL2; NgR2); myelin associated glycoprotein (MAG); oligodendrocyte myelin glycoprotein (OMG; OMGP); reticulon 4 (RTN4; NOGO-A; NOGO; NOGO-B)

LICENSING STATUS: Unpatented; unavailable for licensing

PUBLICATION DETAILS: Sozmen, E. et al. *Proc. Natl. Acad. Sci. USA*; published online Dec. 12, 2016

doi:10.1073/pnas.1615322113

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OPHTHALMIC DISEASE

INDICATION: Ophthalmic; optic neuropathy

Mouse studies suggest inhibiting estrogen-ESR2 signaling could help treat visual dysfunction and optic nerve damage associated with optic pathway glioma neurofibromatosis type 1 in female patients. In a female mouse model of neurofibromatosis type 1, an ESR2 antagonist tool compound, a tool compound that inhibits ovarian production of estrogen, or surgical ovariectomy decreased retinal ganglion cell (RGC) apoptosis and increased the number of RGCs and thickness of the retinal nerve fiber layer compared with vehicle or no treatment. Also in the model, the ESR2 antagonist or surgical ovariectomy decreased levels of a marker of axonal injury in the optic nerve compared with vehicle or no treatment. Next steps include identifying and testing additional inhibitors of estrogen-ESR2 signaling in models of neurofibromatosis type 1.

TARGET/MARKER/PATHWAY: Estrogen receptor 2 (ESR2)

LICENSING STATUS: Unpatented; available for licensing

PUBLICATION DETAILS: Toonen, J. et al. *J. Exp. Med.*; published online Dec. 6, 2016

doi:10.1084/jem.20160447

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THERAPEUTICS

OTHER

INDICATION: Poisoning

Human blood and mouse studies suggest an engineered variant of NGB could help treat carbon monoxide (CO) poisoning. In CO-treated human red blood cells, an NGB variant engineered to have enhanced affinity for CO increased the dissociation of CO from hemoglobin compared with vehicle. In a mouse model of non-lethal CO poisoning, the NGB variant decreased levels of CO-bound hemoglobin in RBCs and increased blood pressure compared with vehicle. In a mouse model of lethal CO poisoning, the NGB variant decreased levels of CO-bound hemoglobin in RBCs and blood levels of the CO-poisoning marker lactate, and increased heart rate, blood pressure and survival. Next steps include optimizing and testing the safety, efficacy and PK of the engineered NGB in additional models.

TARGET/MARKER/PATHWAY: Neuroglobin (NGB)
LICENSING STATUS: Patented; available for partnering
PUBLICATION DETAILS: Azarov, I. et al. *Sci. Transl. Med.*; published online Dec. 7, 2016
doi:10.1126/scitranslmed.aah6571
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TRANSPLANT

INDICATION: Graft rejection; heart transplant rejection

Mouse studies identified a dipeptide inhibitor of PSMB8 that could help prevent skin and heart transplant rejection. Chemical synthesis and testing in *in vitro* activity assays of dipeptides yielded a compound that inhibited human and mouse PSMB8 with IC_{50} values of 4.5 and 9 nM, respectively. In a mouse model of allogeneic skin transplant, the compound decreased spleen numbers of $CD4^+$ and $CD8^+$ effector T cells — markers of immune response — and increased levels of T cell exhaustion markers — a marker of immune tolerance — compared with vehicle. In a mouse model of allogeneic heart transplant, the compound alone or in combination with an anti-CTLA4 antibody decreased acute rejection markers in the allograft and increased allograft survival compared with vehicle or the anti-CTLA4 antibody alone, respectively. Also in the model, the combination therapy decreased levels of effector T cell exhaustion markers in the allograft and draining lymph nodes compared with the anti-CTLA4 antibody alone. Next steps include optimizing and testing the dipeptide inhibitor in additional models of skin and heart transplant.

TARGET/MARKER/PATHWAY: β 8 subunit of the proteasome (PSMB8; LMP7); cytotoxic T-lymphocyte associated protein 4 (CTLA4; CD152)
LICENSING STATUS: Patent application filed; licensing status undisclosed
PUBLICATION DETAILS: Sula Karreci , E. et al. *Proc. Natl. Acad. Sci. USA*; published online Dec. 12, 2016
doi:10.1073/pnas.1618548114
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TECHNIQUES

DRUG PLATFORMS

TECHNOLOGY: Structural analyses

Crystallographic studies of CCR9 and CCR2 bound to antagonists could aid the design of allosteric inhibitors of chemokine receptors. Structural analysis of a 315-residue region of a mutant, thermostabilized version of CCR9 complexed with the allosteric CCR9 antagonist Traficet-EN vercirnon and a 329-residue region of CCR2 fused to T4 lysozyme and complexed with orthosteric and allosteric antagonist tool compounds revealed the allosteric antagonists bound to an intracellular allosteric pocket enclosed by helices I to III and VI to VIII in their respective receptors. Mutagenesis studies of the CCR9 allosteric site identified five residues involved in the binding interaction and sequencing showed the binding site was conserved across multiple chemokine receptors. In *in vitro* CCR2 binding assays, the orthosteric antagonist enhanced binding of the allosteric antagonist and structural analyses showed the orthosteric and allosteric antagonists bound the receptor via cooperative interactions with helix VII. Next steps include the identification and testing of allosteric inhibitors of other G protein-coupled chemokine receptors.

ChemoCentryx Inc. has Traficet-EN (vercirnon; GSK1605786) in Phase III testing to treat Crohn's disease.

DESCRIPTION: Co-crystal structures of antagonist-bound CC chemokine receptor 9 (CCR9) and CCR2 to aid design of allosteric inhibitors of chemokine receptors

LICENSING STATUS: Patent and licensing status undisclosed; available for partnering

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