BIOCENTURY
# Innovations
FROM IDEA TO IND

NOVEMBER 30, 2017

*COVER STORY*

1 DOCTORS IN THE HOUSE

With a new twist on external innovation, GSK is bringing academics in-house for unconventional sabbaticals, giving them broad access to its internal goings-on.

TARGETS & MECHANISMS

6 ALL-PURPOSE HSCs

Why hematopoietic stem cells from UCSD spinout GenStem could compete with gene therapies for a host of indications, immune-related or not.

EMERGING COMPANY PROFILE

10 A VERSATILE SPONGE

Cellics has red blood cell-based nanosponges that act as broad-spectrum antitoxins for sepsis and other bacterial infections.

TRANSLATION IN BRIEF

11 TWO FACES OF FOXO1

Columbia and AstraZeneca have created FOXO1 inhibitors for Type II diabetes that can block glucose production without inducing weight gain.

Plus: Yeast studies suggest stimulating TORC1 aggregation could block the kinase more specifically than active site inhibitors

14 NEW TARGET ROUNDUP

A list of new therapeutic targets and biomarkers from company releases and the academic literature covered by BioCentury during November.

DISTILLERY

17 THERAPEUTICS

CD38-knockout T cells for melanoma and other cancers; inhibiting MKK6 to prevent obesity; combinations of *Plasmodium falciparum* antigens for malaria vaccine development; and more...

23 TECHNIQUES

SNPs on GDF1, MYH6 and FLT4 to predict the risk of subtypes of congenital heart disease; and more...

STRATEGY

# DOCTORS IN THE HOUSE

By Karen Tkach Tuzman, Senior Writer

While academic partnerships have become par for the course in pharma, GSK is going a step beyond the standard model of external alliances by bringing professors in-house with virtually unrestricted access to its activities. The initiative is the latest example of pharmas lowering their guard in order to both access cutting-edge science and foster the ecosystem's future innovators.

It's a necessary but worthwhile price to pay, according to Paul-Peter Tak, who created the program, dubbed Immunology Network, in 2015. Tak is Chief Immunology Officer and SVP of the R&D Pipeline at GlaxoSmithKline plc.

"Our philosophy is to be very open with the external world in terms of target identification and target validation. We compete in terms of molecules," Tak told BioCentury.

The core of the Immunology Network involves providing academic researchers with three-year sabbaticals inside GSK's R&D hub in Stevenage, where they are given a lab, personnel and access to the pharma's technology, compound libraries and internal meetings and data.

Tak noted the program is "not transforming them into GSK employees. They continue to be employees of the university, and we reimburse the university."

Moreover, the researchers can take their discoveries with them when they leave.

"If they discover something within our facilities that's completely based on their own research, then they actually own the IP. I think no other company has done it in this way," said Tak.

Louise Modis, the Immunology Network's scientific director, told BioCentury that the program's IP terms boil down to the principle that "they own the biology IP that they bring and that they do, and GSK protects molecules that are going into the clinic."

Thus far, the program has brought in seven investigators, expanded the indications of two internal programs, and founded an undisclosed newco in a white space area, which GSK is funding as a minority investor and has the option to buy.

Luke O'Neill, a program participant and a professor of inflammation research at Trinity College Dublin, gives GSK credit for creating

"Our philosophy is to be very open with the external world in terms of target identification and target validation. We compete in terms of molecules."

Paul-Peter Tak, GSK

something "brand new," and based on the program's success so far, thinks other companies should follow suit. "GSK was taking a risk, because nobody had done this before."

## TRANSPLANT MODEL

Tak joined GSK in 2011, and is one of the two primary leaders reporting to outgoing CSO and President of R&D Patrick Vallance, who on Jan. 1 will hand the reins over to Hal Barron, currently president of R&D at longevity company Calico LLC.

Vallance is leaving the pharma at the end of March to become the U.K. government's chief science adviser and head of the government's Office for Science. The Immunology Network program will continue under GSK's new leadership.

Having spent the bulk of his career as an academic researcher and physician, Tak created the Immunology Network to fill what he believed was a crucial gap in the pharma's extensive roster of external partnerships (see "Out of the Dark").

"There was one piece missing. That piece was actually bringing in senior academics into GSK," said Tak, who remains affiliated with University of Amsterdam, Ghent University and University of Cambridge. "We do this of course all the time to make them GSK employees. But here we did it differently, where they continue to do their academic research in a much more 'blue-sky thinking' way."

John Hamilton, a professor of medicine at University of Melbourne and the first investigator recruited into program, told BioCentury the program creates a microcosm inside the company that allows for unprescribed discoveries. "There's no pressure for people to come up with targets, because that's not how it really should work in academia. Some of the best results will probably come out of left field."

GSK has toyed with various structures for partnering with academia, such as its Discovery Partnerships with Academia (DPAc) program, and for incubating innovation from GSK scientists within in its Discovery Performance Units (DPUs).

Tak noted that unlike the DPAc program, which is "focused on very specific projects that could lead to a medicine," the Immunology Network is geared to capitalize on emerging areas that are further from the clinic. They can also fall outside the purview of the DPUs.

"When you talk about business development opportunities in fields that do not fit in the DPU's territory, then people are not interested, because they need to be focused," he said. "These very new opportunities are very high-risk, because there's less data. So I think the Immunology Network can complement that model with the creation of new companies."

While Tak's background as a rheumatologist played a role in the program's immunological focus, he said the field's recent successes, and relevance to a broad range of therapeutic areas such as autoimmunity, cancer and neuroinflammation, made it "a very good starting point to work in a new model."

## HOST ENVIRONMENT

The Immunology Network has four pillars, the center of which is the Immunology Catalyst Program, through which academics join GSK's campus. The Immunology Innovation Fund supports the Catalyst investigators, while the External Immunology Board contains academic experts who advise the company and its professors-in-residence.

The fourth pillar is a series of Immunology Network Summits that convene immunologists and vaccinologists from inside and outside the company.

Immunology Catalyst investigators are selected based on their expertise and projects in white space areas such as immunometabolism, crosstalk between pattern recognition receptors and complement signaling, and systems approaches to understanding autoimmune disorders (see "Immunologists-in-Residence").

"All the people that were recruited are working on frontier science," said O'Neill. "One motivation for GSK is to make sure they're on top of these emerging areas, and the Catalyst allows them to do that."

The Immunology Innovations Fund provides financing to turn the academics' translational work into commercial opportunities.

Tak runs proposals for new immunology investments by members of the External Immunology Board with relevant expertise to see "whether they can survive the challenge of academics who probably know more about that field than anyone else."

"When an idea bubbles up in the Immunology Catalyst that could lead ultimately to a drug — say you need a mouse experiment for £100,000, whatever it may be — if it's a great proposal, we will spend the money to bring it to the next inflection point," said Tak.

And if those experiments yield positive results, Tak said GSK is "completely free in our thinking" about how to take Immunology Catalyst projects further.

STRATEGY

## OUT OF THE DARK

In one of its most ambitious academic partnerships, GlaxoSmithKline plc and its collaborators in the ATOM consortium are feeding reams of shelved data into U.S. Department of Energy supercomputers, with the goal of using the resulting algorithms to go from target identification to a clinic-ready compound in 12 months.

John Baldoni, SVP of R&D at GSK, told BioCentury the consortium aims to tap the wealth of information hidden in the pharma's "dark data." "Companies have an obligation to share the data they're never going to use again," he said.

The Accelerating Therapeutics for Opportunities in Medicine (ATOM) consortium was launched last month by GSK, the DOE's Lawrence Livermore National Laboratory, NIH and the University of California San Francisco.

The project taps into a growing consensus that data locked away in pharma archives could provide valuable clues to either speed up drug development or serve as starting points for new projects.

The consortium will use the partners' chemical, biological and clinical data to create a series of computational models to guide drug discovery and development. The idea is that the models will capture underlying patterns governing small molecule properties such as toxicity, PK, blood-brain barrier penetration and effects on gene expression in disease models.

Baldoni said the first steps are to establish an organizational structure, computing infrastructure and data management policies.

"We're establishing architectures for digesting dissimilar data from different organizations," he said, including safety and tox data on hundreds of compounds, over 1,000 crystal structures, readouts from over 60 clinical trials, and thousands of rat and dog PK studies.

In the consortium's third year, the partners will test the models by attempting to create a personalized therapy for a single cancer patient, focused on a target specific to his or her disease.

ATOM is building laboratory space in San Francisco, where it plans to partner with companies with technologies that can "fill gaps in the algorithms," such as high throughput organoid screens and high-content single-cell imaging, said Baldoni.

He believes that because ATOM crunches its data into algorithms, other pharmas could join in without risking IP.

"What if it was set up such that they couldn't see the GSK compounds — they could only see algorithms derived from the compounds?" said Baldoni. "The only group that sees all the molecules is Livermore." The companies could then take the models and use them to create their own IP in-house, he said. "We don't want to generate any molecule IP in ATOM except for the one molecule we make to treat that one patient."

*— Karen Tkach Tuzman*

## IMMUNOLOGISTS-IN-RESIDENCE

So far, seven academic researchers have participated in **GlaxoSmithKline plc** (LSE:GSK; NYSE:GSK)'s Immunology Catalyst sabbatical program. Professor John Hamilton from the **University of Melbourne** participated in a seven-week pilot version of the program; the subsequent six participants may stay at GSK for sabbaticals lasting up to three years.

| DATE JOINED | NAME | PRIMARY ACADEMIC INSTITUTION | RESEARCH FOCUS |
|---|---|---|---|
| June 2015 | John Hamilton | **University of Melbourne** | Macrophage and granulocyte macrophage colony-stimulating factor (GM-CSF; CSF2) biology in inflammation and osteoarthritis |
| February 2016 | Luke O'Neill | **Trinity College Dublin** | Immunometabolism |
| April 2016 | Kathy Triantafilou | **Cardiff University** | Pattern recognition receptors and complement signaling |
| April 2016 | Seth Masters | **Walter and Eliza Hall Institute of Medical Research** | Autoinflammatory disorders |
| July 2016 | Timothy Radstake | **University Medical Center Utrecht** | Systems approach to understanding autoimmune disorders |
| July 2016 | Florent Ginhoux | **Agency for Science Technology and Research** (A*STAR) | Myeloid cell development |
| October 2016 | Clare Bryant | **University of Cambridge** | Pattern recognition receptors and innate immunity |

"It may lead to an additional investment from the Immunology Innovation Fund to bring it to the next inflection point," he said. "If it seems like a very exciting early idea that needs to be incubated further in the academic institute, maybe we'll support it with a grant. If it's more mature it could even lead to a DPU, the basic discovery entity within GSK. Or, we could co-create a biotech company based on new emerging science."

### OUTPUTS FROM INSIDE

Tak said the Immunology Network has given GSK "an incredible wealth of deliverables in the last two and half years," both in terms of commercial opportunities and relationship building.

According to Tak, both External Immunology Board and the Immunology Catalyst investigators have guided the pharma's business development decisions, and have pointed the pharma to new opportunities for its compounds.

GSK sees an acquisition opportunity in the first newco founded by an Immunology Catalyst investigator, which the pharma is co-financing with VCs.

"We will be minority shareholders by design, we don't want to control it," said Tak. "When it matures, at least to a medicine, then we will be the first to say this is really interesting, we want to buy it at a competitive price."

The program has also helped GSK get insights on new indications for an undisclosed compound based on research that is not in the public domain.

"We in-licensed a medicine that was developed for one indication, whereas we knew based on knowledge in the Immunology Catalyst that has not been published that it should also work for a completely different indication," said Tak. "That's where we're going to develop it now."

In addition, Hamilton made the case that GSK should test its anti-GM-CSF mAb GSK3196165, which the company had in-licensed for rheumatoid arthritis, in osteoarthritis (OA) based on his research. The pharma and partner MorphoSys AG now have the mAb in Phase II testing for both OA and RA, and in Phase I testing for multiple sclerosis.

> "GSK was taking a risk, because nobody had done this before."
>
> Luke O'Neill, Trinity College Dublin

In January, Hamilton and Tak co-authored a *Nature Reviews Drug Discovery* article summarizing the therapeutic applications for GM-CSF and other colony-stimulating factors. "It has led to an expansion of indications," said Tak.

Tak said the cross-disciplinary Immunology Network Summits have already launched "concrete new projects" at GSK, including a collaboration looking at undisclosed factors "from the world

of immuno-inflammation" that keep activated T cells out of tumors, or promote immune suppression by stromal cells and macrophages.

Tak also counts the visiting investigators' growing understanding of pharma as a key gain.

"We're raising a new generation of leaders in academia. The idea is that they go back, and become very strong leaders who understand pharma," said Tak.

> "We're raising a new generation of leaders in academia. The idea is that they go back, and become very strong leaders who understand pharma."
>
> Paul-Peter Tak, GSK

He added that the academics change in the GSK environment, and not only because they start to think more about drug discovery. "They also get an understanding of what it takes take to become excellent in delivering projects, what quality really means in terms of industry standards, and what it means to develop people," Tak said.

For example, he thinks the investigators' experiences will improve future licensing negotiations with their home institutions, as the researchers will have more informed perspectives on the values of their preclinical assets and the investments required to develop them.

O'Neill said GSK researchers have also been learning from the Immunology Catalyst members, in some cases by temporarily joining an investigator's lab.

"It's a great opportunity because they step out of their traditional role," said O'Neill. "Then they go back to their original tasks, and hopefully have picked up new skills and approaches."

Hamilton thinks the sabbatical model is particularly well suited to fostering trust between academic and industry researchers. "When you get to know people and you build up relationships, then you can start talking freely," he said.

Modis noted the company had to commit significant human resources to build that trust. "We really invested in people here who are experts in operations, communications, immunology and drug discovery to build a relationship with them and to really make their transition to industry manageable. Just giving them money and space is not going to work."

"These are all things that sound like soft values, but they're very important," said Tak.

## COMPANIES AND INSTITUTIONS MENTIONED

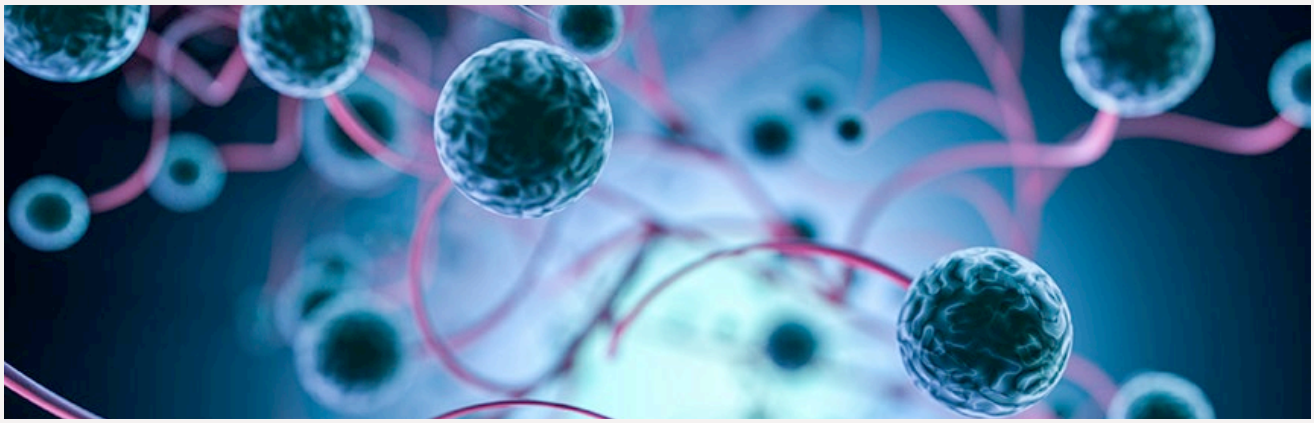
**Calico LLC**, South San Francisco, Calif.
**Ghent University**, Ghent, Belgium
**GlaxoSmithKline plc** (LSE:GSK; NYSE:GSK), London, U.K.
**MorphoSys AG** (Xetra:MOR; Pink:MPSYY), Martinsried, Germany
**National Institutes of Health** (NIH), Bethesda, Md.
**Trinity College Dublin**, Dublin, Ireland
**University of Amsterdam**, Amsterdam, the Netherlands
**University of California San Francisco**, San Francisco, Calif.
**University of Cambridge**, Cambridge, U.K.
**University of Melbourne**, Melbourne, Australia
**U.S. Department of Energy**, Washington, D.C.

## TARGETS

**GM**-CSF (CSF2) - Granulocyte macrophage colony-stimulating factor

## REFERENCES

**Hamilton, J., et al.** "Anti-colony-stimulating factor therapies for inflammatory and autoimmune diseases." *Nature Reviews Drug Discovery* **(2016)**



THINKSTOCK

TARGETS & MECHANISMS

# ALL-PURPOSE HSCs

By Selina Koch, Associate Editor

While most eyes are on hematopoietic stem cells for their ability to treat blood cancers, a UCSD group has built a body of work showing the immune cell precursors can treat diseases with no relation to the immune system, and has spun out GenStem Therapeutics Inc. to develop the technology.

The company was formed last year based on work from the lab of Stephanie Cherqui, an associate professor in the Department of Pediatrics at the University of California San Diego. Its funding is undisclosed.

In the last month, the researchers have signed a deal with gene and cell therapy company Avrobio Inc. to co-develop a program in cystinosis, and published a preclinical study in *Science Translational Medicine* showing the cells can be used to treat the neurological disorder Friedreich's ataxia.

Bone marrow transplants have long been used in oncology, sickle cell disease and a handful of other indications in which immune cells are cancerous or defective. The procedure replaces the diseased cells with hematopoietic stem cells (HSCs) from a disease-free donor that differentiate into mature cells with the relevant myeloid or lymphoid phenotypes.

Cherqui told BioCentury that although it was unclear whether or how HSCs could treat non-immune indications, the stem cells had been shown to secrete paracrine factors and vesicles carrying molecules that are "good for cells." She tested the idea on the lysosomal storage disorder cystinosis, a multisystem disease involving kidney and eye pathology that is caused by a mutation in the lysosomal cystine transporter gene CTNS.

> "HSCs are intelligent. They home to injured tissue and deliver protein where it is needed."
>
> Stephanie Cherqui, UCSD

In a series of studies conducted between 2009 and 2016, her group showed transplantation of HSCs expressing a normal copy of CTNS successfully treated symptoms in mice. The key feature, according to Cherqui, was the mechanism her team uncovered. Instead of secreting factors, the group demonstrated the cells used a previously described cellular structure — tunneling nanotubes — to rescue the genetic disorder.

HSCs are destined to give rise to immune and blood cells, and therefore don't regenerate kidney or eye tissue. Cherqui's team showed that instead, transplanted HSCs homed to damaged tissues and differentiated into macrophages that formed nanotube passageways to the diseased cells. The macrophages

then passed healthy lysosomes carrying wild-type CTNS protein from themselves through the nanotubes to treat the diseased cells (see "HSC Highways").

In *Sci. Transl. Med.,* Cherqui and colleagues showed the approach can be extended to a neurological disorder that involves dysfunctional mitochondria rather than lysosomes. In a mouse model of Friedreich's ataxia, a progressive movement disorder, HSC-derived immune cells transmitted their mitochondrial proteins to neurons both inside and outside the CNS and restored motor function.

Cherqui suspects HSCs can deliver a wide range of therapeutic RNAs, proteins and organelles, opening up a slew of translational opportunities for the cells. "I think this is a premise for many other disorders; the mechanism of action is very efficient."

## ATTACKING ATAXIA

Like cystinosis, Friedreich's ataxia is caused by loss-of-function mutations; in this case the defect is in the gene encoding the mitochondria-associated protein FXN.

The disease involves loss of neurons in the dorsal root ganglia (DRG) and cerebellum, with primary symptoms being muscle weakness and loss of coordination in the arms and legs. However, according to Cherqui, patients most commonly die from heart malfunction.

In the *Sci. Transl. Med.* study, her group showed transplantation of wild-type HSCs into a mouse model of Friedreich's ataxia restored activity levels, muscle coordination, and grip strength to levels indistinguishable from those in wild-type littermates.

Mechanistic studies showed the HSCs migrated into DRG, spinal cord, brain and heart tissue. Inside the CNS, the HSCs differentiated into microglial cells; outside the CNS they developed into macrophages, consistent with the group's observations in cystinosis.

When the HSCs were engineered to express GFP-labeled FXN or another mitochondrial protein, the labeled proteins ended up in neurons or heart cells directly contacted by the HSC-derived microglia or macrophages, respectively. About 50% of neurons in spinal cord sections contained the labeled proteins, an efficiency difficult to achieve with gene therapy, said Cherqui.

The transfer of multiple mitochondrial proteins raised the possibility that the cells transmitted whole mitochondria to neurons, similar to the lysosome transfer the group reported in the past.

However, the paper stopped short of answering that question, nor did it confirm the presence of tunneling nanotubes between the cells.

**BIOCENTURY PRODUCT PROFILE**

| INNOVATION STAGE | |
|---|---|
| Product | Autologous hematopoietic stem cells (HSCs) engineered to express a normal copy of FXN, the gene mutated in Friedreich's ataxia |
| Concept | Engineered HSCs will differentiate into microglia and macrophages that transmit wild-type FXN to neurons and heart cells impaired in the disease |
| Disease | Friedreich's ataxia |
| Competition | Supportive technologies for neurological deficits; ACE inhibitors for heart symptoms; clinical candidates that increase mitochondrial function or decrease inflammation |
| Differentiation | Disease modifying; directly addresses the cause of the disease by replacing lost protein |
| Administration | IV |
| Risks | Toxicity associated with partial myeloablation preconditioning regimen |
| Development status | Preclinical |
| Patents | Patent family covering use of engineered HSCs to treat movement disorders |
| Company; lead investigator | University of California San Diego; Stephanie Cherqui, GenStem Therapeutics Inc.; Jeffrey Ostrove |

"We see that it is transferred but we don't know if the protein or the whole mitochondria is transferred. And we don't know if it is transferred by nanotubes, exosomes, both or something else," said Cherqui. Her lab is currently working on those questions.

But she noted the full mechanism does not need to be fleshed out to advance the program.

GenStem CEO Jeffrey Ostrove said the newco is gearing up for GLP tox and additional efficacy studies in Friedreich's ataxia. The therapy will comprise autologous HSCs engineered with a lentiviral vector to express a normal copy of FXN. He declined to provide a development timeline or to disclose whether GenStem plans to seek a partner.

## HSCS VS. AAVS

Ostrove believes autologous HSC therapies could overcome some of the biggest problems associated with adeno-associated viral (AAV)-mediated gene therapies, such as preexisting antibodies against the vector, limitations on dosing and the difficulties of delivering the therapies to target tissues.

"I think this work is going to open up novel treatments for multiple genetic diseases that, prior to this, really didn't have a pathway forward," he said.

Although gene therapies are designed to deliver therapeutic cargo directly to the cells that need it, rendering them capable of producing the therapeutic protein themselves, Cherqui argues HSCs have specific advantages.

"With *in vivo* gene therapy I doubt you would get such great engraftment everywhere and tissue targeting that is so efficient," she said. "Dose would be a limitation; it would require a lot of virus."

By contrast, she said, "HSCs are intelligent. They home to injured tissue and deliver protein where it is needed. In healthy mice these cells don't go anywhere; they stay in the bone marrow."

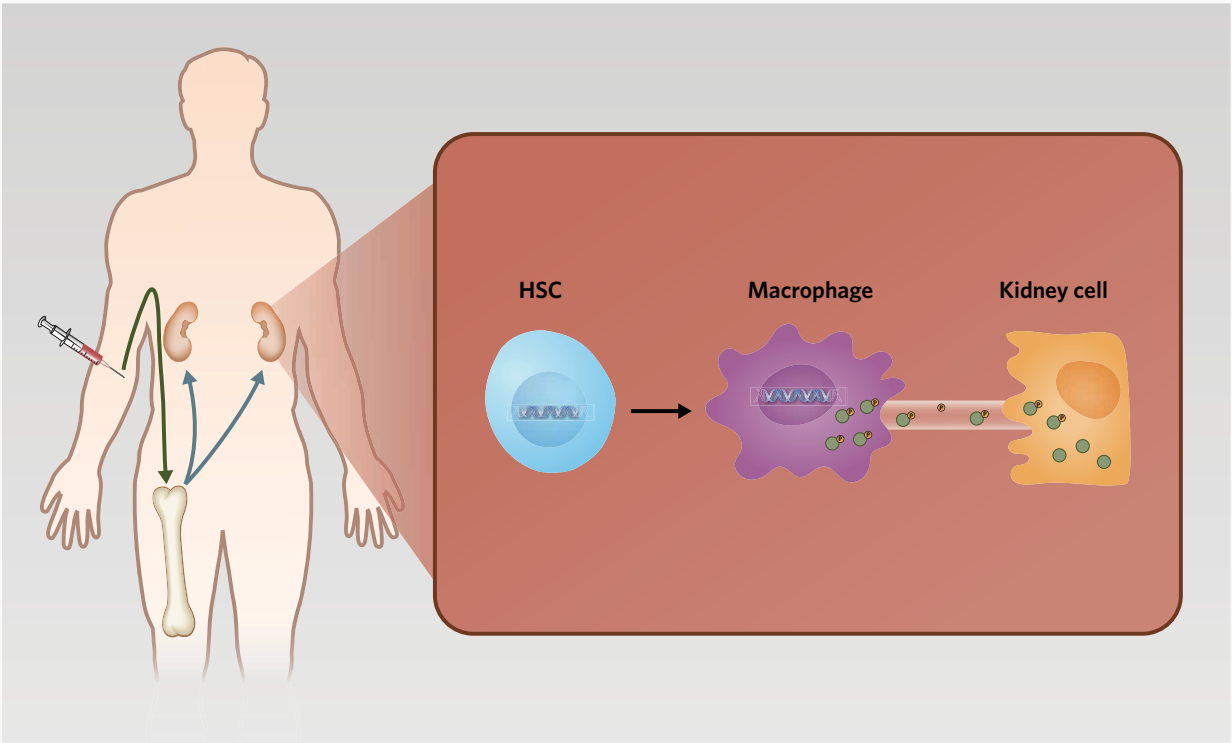
Moreover, she believes the approach will only require a single treatment. "The patient would have a source of healthy cells that

## HSC HIGHWAYS

A **University of California San Diego** team has shown hematopoietic stem cells (HSCs) can be used to treat diseases outside of the modality's standard indications of blood and bone marrow cancers. One such indication is cystinosis, a lysosomal storage disorder caused by mutations in cystinosin lysosomal cystine transporter (CTNS) that result in kidney pathology.

After IV injection, HSCs engineered to express wild-type CTNS **(blue DNA)** migrate and home to the bone marrow **(green arrow)**, where they engraft. Upon receiving disease-related signals, some of the HSCs migrate to sites of damage in the kidney **(blue arrow)**, where they differentiate into macrophages. The macrophages then form tunneling nanotubes **(pink)** that create passageways to the diseased kidney cells, which contain lysosomes devoid of CTNS. The macrophages pass CTNS-bearing lysosomes **(green circles)** to the kidney cells through the nanotubes, restoring normal kidney function.

In 1H18, UCSD plans to begin a Phase I/II trial of autologous HSCs engineered to express wild-type CTNS to treat cystinosis. Patients will receive a preconditioning regimen to partially ablate their bone marrow to make room for the transplanted HSCs.



are always there in the bone marrow. You wouldn't need to re-transplant."

Avrobio CEO Geoff MacKay added: "Maybe the most impressive feature of this approach is its durability," which he ascribed partly to the use of lentiviral vectors.

Whereas the effects of AAV gene therapies can fade over time, requiring re-treatment, lentiviral-delivered genes permanently integrate into the genome, he said. Although that creates a risk of insertional mutagenesis, hundreds of patients have been treated with lentiviral-modified HSCs "without insertional mutagenesis or serious adverse events," he said.

> "I think this work is going to open up novel treatments for multiple genetic diseases that, prior to this, really didn't have a pathway forward."
>
> Jeffrey Ostrove, GenStem

MacKay added that HSC engraftment will be easier on patients than standard regimens, because it uses preconditioning only to partially ablate the bone marrow. The goal is to create "just enough space for the cells to migrate in and find a home," he said. "This is not full myeloablation," as is used in oncology. "The regimen is far less toxic than that."

## LEADING WITH LYSOSOMES

Ostrove said UCSD will be the investigator on the upcoming cystinosis trial and noted the university has a clinic dedicated to the rare disease. "They have probably seen the most cystinosis patients in the world; that was very attractive," he said.

MacKay told BioCentury GenStem's cystinosis therapy will become Avrobio's fourth lysosomal storage disorder program and "fits perfectly" into its pipeline. "This is the exact same technology platform we are already using for our other lysosomal storage disorder programs," he said.

Like GenStem, Avrobio modifies HSCs *ex vivo* using lentiviral vectors. "Operationally, it fits like a glove: in manufacturing, CMC and even clinically, the designs of these trials are analogous," said MacKay.

MacKay said the approach has already been validated as a means of replacing lost enzymes in a handful of genetic disorders, including metachromatic and cerebral leukodystrophies and adenosine deaminase severe combined immunodeficiency (ADA-SCID). "This is not well understood, but there are now four or five really successful clinical trials of this approach with ten-plus years of data."

The only marketed autologous HSC therapy is GlaxoSmithKline plc's strimvelis, in which a retroviral vector is used to deliver ADA *ex vivo* to HSCs. The therapy is approved in Europe for ADA-SCID.

Avrobio's other lysosomal storage disease programs are in Fabry's, Gaucher's and Pompe's diseases. All are enzyme replacement therapies (ERTs) in which HSC-derived immune cells secrete the missing enzyme and target cells take it up.

However, cystinosis results from loss of a membrane transporter rather than an enzyme. And although GenStem's and Avrobio's technologies are "the same on the front end," MacKay said, "the one thing that is distinct is the mechanism on the back end, this concept of nanotubules."

He added: "Stephanie has been *the* pioneer in the world at developing this *ex vivo* approach for cystinosis," and noted Cherqui's program was unusual for an academic project in that "it was really clinic-ready."

Ostrove also said Cherqui's lab has gone the distance with preparing the findings for translation, including providing appropriate documentation and quality controls.

While UCSD is conducting the Phase I/II trial, MacKay said, Avrobio will perform the scale up, the CMC, and the preparations for the pivotal trial.

### COMPANIES AND INSTITUTIONS MENTIONED

**Avrobio Inc.**, Cambridge, Mass.
**GenStem Therapeutics Inc.**, San Diego, Calif.
**GlaxoSmithKline plc** (LSE:GSK; NYSE:GSK), London, U.K.
**University of California San Diego**, La Jolla, Calif.

### TARGETS

**ADA** - Adenosine deaminase
**CTNS** - Cystinosin lysosomal cystine transporter
**FXN** (FRDA) - Frataxin

### REFERENCES

**Li, V.** "Aiming for durability." *BioCentury* **(2017)**

**Naphade, S., et al.** "Lysosomal cross-correction by hematopoietic stem cell-derived macrophages via tunneling nanotubes." *Stem Cells* **(2015)**

**Rocca, C., et al.** "Transplantation of wild-type mouse hematopoietic stem and progenitor cells ameliorates deficits in a mouse model of Friedreich's ataxia." *Science Translational Medicine* **(2017)**

EMERGING COMPANY PROFILE

# A VERSATILE SPONGE

By Lauren Martz, Senior Writer

Treatment of sepsis and toxic shock requires eliminating bacterial toxins from the bloodstream, but it is often difficult to identify the causal pathogen and its products quickly enough to select a targeted therapy. Cellics Therapeutics Inc. is circumventing the problem with a strategy to mop up a wide range of sepsis-causing toxins, based on a nanosponge technology that mimics red blood cells.

"Most other treatments for sepsis, either mAbs or small molecules, are targeted to the specific structure of a toxin, so each compound can only target one type of toxin," said CEO Huiqing (Winnie) Zhu. "If you have multiple toxins in the bloodstream," the difference between persistent shock and sepsis resolution depends on removing all toxins, she added.

Cellics' technology involves coating a poly(lactic-co-glycolic acid) (PLGA) nanoparticle core with cell membranes isolated from human RBCs. "It leverages the natural interaction of bacterial toxins with cell membranes," said Zhu. The idea is that in circulation, the membrane-coated nanoparticles mimic RBCs by binding bacterial toxins, causing the toxins to be neutralized and then eliminated by normal proteolytic degradation.

According to Zhu, the nanosponge acts as a decoy to absorb pore-forming toxin virulence factors such as α- and γ-toxins, and about 80 different families of toxins that target RBCs.

University of California San Diego exclusively out-licensed IP covering broad applications of the nanosponge platform, which includes nanoparticles coated with membranes from RBCs, leukocytes, platelets and other blood and immune cells, to biotech incubator Arytha Biosciences LLC. Arytha spun out Cellics in 2014 to develop the RBC-coated nanosponges.

Cellics is focusing on three indications — sepsis, pneumonia, and skin and soft tissue infections — caused by *Staphylococcus aureus* and *Streptococcus pyogenes*, because those pathogens secrete toxins that target RBCs.

Pneumonia patients have a high risk of developing sepsis because bacterial toxins can enter the bloodstream from the highly vascularized lung, and Cellics' nanosponges would bind those toxins, Zhu said. "For skin infections, our goal is to develop a topical formulation of the nanosponges, which can be applied to the infection site as a means of locally absorbing and neutralizing toxins."

In a 2015 *Advanced Materials* paper, Liangfang Zhang and colleagues showed subcutaneous implantation of hydrogels containing RBC-coated nanosponges reduced the development of methicillin-resistant *S. aureus* (MRSA) skin lesions in a mouse model of infection.

Several companies are developing mAbs against specific *S. aureus* toxin antigens for pneumonia, although none has a wide-ranging anti-toxin strategy. Another newco, Critical Pressure Ltd., was launched earlier this month to treat sepsis. The company has the DDAH1 inhibitor CPL001, in preclinical development to prevent the hypotension that characterizes septic shock.

CELLICS THERAPEUTICS INC., San Diego, Calif.
**Technology:** Nanoparticles coated with human red blood cell membranes that absorb multiple bacterial toxins
**Disease focus:** Infectious
**Clinical status:** Preclinical
**Founded:** 2014 by Liangfang Zhang
**University collaborators:** None
**Corporate partners:** None
**Number of employees:** 8
**Funds raised:** Undisclosed
**Investors:** Undisclosed
**CEO:** Huiqing (Winnie) Zhu
**Patents:** Three issued covering undisclosed aspects of nanosponge technology

Cellics is using undisclosed series A funds to develop a manufacturing process and analytical testing assays for its nanosponges, and is conducting animal studies, including a PK study of its human RBC nanosponge, ALN-001, and efficacy studies in rodent models of Gram-positive infections. The company plans to submit INDs for sepsis and one of the other two indications in mid-2018, and for the third in 2019.

Cellics is raising funds in a series B round expected to close early next year to support the IND submissions and Phase I testing, and is open to partnering or licensing its technology. In addition to in-licensing three issued patents from Arytha, Cellics has filed about 27 patent applications of its own.

Arytha has not spun out additional newcos to develop other components of the nanosponge platform.

## COMPANIES AND INSTITUTIONS MENTIONED

**Arytha Biosciences LLC**, San Diego, Calif.
**Cellics Therapeutics Inc.**, San Diego, Calif.
**Critical Pressure Ltd.**, Cambridge, U.K.
**University of California San Diego**, La Jolla, Calif.

## TARGETS

**aHL** - S. aureus α-hemolysin
**DDAH1** - Dimethylarginine dimethylaminohydrolase1

## REFERENCES

**Wang, F., et al.** "Hydrogel retaining toxin-absorbing nanosponges for local treatment of methicillin-resistant *Staphylococcus aureus* infection." *Advanced Materials* **(2015)**

TRANSLATION IN BRIEF

# TWO FACES OF FOXO1

By Mark Zipkin, Staff Writer

Columbia University and AstraZeneca plc (LSE:AZN; NYSE:AZN) have identified the first FOXO1 inhibitors that can selectively block the transcription factor's glucose-stimulating activity without inducing lipogenesis. Optimization of the compounds could yield a therapy for Type II diabetes that avoids the weight gain and cardiovascular effects of marketed drugs.

Insulin sensitizers such as the generic drug metformin help keep blood glucose levels in check, but because of insulin's dual role in the liver they also trigger lipogenesis. Both those effects result from insulin's inhibition of forkhead box O1 (FOXO1).

The transcription factor boosts glucose production by triggering expression of glucose-6-phosphatase catalytic subunit-related protein (G6PC; G6Pase) and inhibits glucose utilization and lipogenesis by blocking glucokinase (GCK; GK).

While the mechanism by which FOXO1 regulates G6PC has been known for some time, how it inhibits GCK was a mystery. That has made it difficult to selectively target one and not the other, leading many researchers to conclude that FOXO1 is not a good drug target.

In an October study in *Cell*, a Columbia team led by Domenico Accili solved the mechanism of FOXO1's inhibition of GCK. Accili is director of the Columbia University Diabetes and Endocrinology Research Center.

His group showed that, unlike G6PC, FOXO1 does not directly bind the GCK's promoter but acts through the co-repressor SIN3 homolog A transcription regulator (SIN3A). Liver-specific knockout of SIN3A from mice lowered glycemia without causing steatosis.

The Columbia team joined forces with scientists at AZ's Innovative Medicines and Early Development (IMED) Biotech Unit to develop a HEK cell screen for FOXO1 inhibitors that would spare FOXO1-SIN3A complexes, and thus inhibit glucogenesis without inducing lipogenesis.

Screening of a million-compound library identified 15 small molecules that were specific for FOXO1 over other FOXO family members and were not cytotoxic. Of those, three lead candidates inhibited FOXO1 only when it was not bound to SIN3A. Assays in primary mouse hepatocytes showed that one of the three had the activity the researchers sought.

"The key discovery is that these compounds can lower glucose-making but not turn on lipid-making," Accili told BioCentury.

However, he said there's still a long road to translating the leads into clinical candidates. "Their pharmacokinetic properties are not such that they can go *in vivo* with a great likelihood of success — they're too short-lived."

"The key discovery is that these compounds can lower glucose-making but not turn on lipid-making."

Domenico Accili, Columbia

According to Accili, AZ is no longer working on the project. However, Accili's group is pushing the project forward, collaborating with chemists to develop optimized versions of the leads.

The pharma did not respond to requests for comment in time for publication, and the IP status of the *Cell* findings is undisclosed.

According to BioCentury's BCIQ database, no companies currently are developing compounds that target the FOXO pathway for Type II diabetes.

At least three companies have new insulin sensitizers in the clinic — all in Phase II testing — that they think will not induce weight gain. Metabolic Solutions Development Co. has two modulators of mitochondrial target of thiazolidinediones (mTOT): MSDC-0160 and the next-generation compound MSDC-0602. Verva Pharmaceuticals Ltd.'s methazolamide is a non-thiazolidinedione, non-peroxisome proliferation activated receptor (PPAR)-modulating insulin sensitizer. Wellstat Therapeutics Corp. has PN2034, an oral insulin sensitizer. *Langlet, F., et al. "Selective inhibition of FOXO1 activator/repressor balance modulates hepatic glucose handling." Cell (2017)*

# TOROIDS DISABLE TORC

By Michael Leviten, Senior Writer

A *Nature* study from a University of Geneva team has shown that the yeast homolog of mTORC1 forms large aggregates that block the complex's catalytic site, highlighting an approach for specific inhibition of the complex that small molecule blockers have failed to accomplish.

Mammalian target of rapamycin (mTOR; FRAP; RAFT1), a kinase that regulates cell growth and metabolism, is conserved between yeast and humans. Yeast have two TOR proteins, while humans have one mTOR that is part of two distinct complexes: mammalian target of rapamycin complex 1 (mTORC1) and mTORC2.

mTOR is widely targeted by compounds on the market and in development for cancer, diabetes, obesity and cardiovascular disease. But targeting each complex selectively has been a major challenge, and most inhibitors act on the common mTOR.

The Geneva team, led by Professor of Molecular Biology Robbie Loewith, showed in yeast culture that glucose withdrawal stimulates a change in TORC1, which shifts from a fairly uniform distribution of TORC1 dimers on vacuole membrane surfaces to a single helical oligomer filament the team dubbed "TORC1 organized in inhibited domain (TOROID)".

The initial TOROID foci, containing about 25 dimers, formed within two and a half minutes of glucose withdrawal and expanded within a few more minutes to structures with roughly 100 dimers — large enough to be visible by electron microscopy (EM) and stochastic optical reconstruction microscopy (STORM).

"The protomer that forms the TOROID helix is the size of a 40S ribosome. The helix itself is even more enormous, you could easily fit tubulin down the center of it," he told BioCentury.

"The protomer that forms the TOROID helix is the size of a 40S ribosome. The helix itself is even more enormous, you could easily fit tubulin down the center of it."

Robbie Loewith, University of Geneva


The kinetics of TOROID formation were accompanied by a decline in the kinetics of yeast mTOR1 activity, which the team determined from the phosphorylation state of a yeast mTOR1 substrate. A yeast strain engineered with a mutant version of mTOR that couldn't form TOROIDs maintained activity after glucose withdrawal, suggesting the oligomer inhibited the kinase's activity. *In silico* structural models showed that TOROIDs occluded the mTOR active site, supporting the findings of the cellular experiments.

Loewith noted his team hasn't observed TOROID formation in mammalian cells, possibly because the oligomers haven't yet been tested in the appropriate cells, or because they might be much smaller in mammalian cells than in yeast, and consequently harder to see by microscopy.

Loewith believes that TOROIDs open the door to the possibility that small molecules could induce the formation of the aggregates and specifically inhibit mTORC1 or mTORC2.

By contrast, he said, it's virtually impossible to specifically inhibit mTORC1 and mTORC2 with small molecules that target the kinase's active site, because the ATP binding sites are so highly conserved.

Besides the implications the findings hold for inhibiting mTOR itself, Loewith believes TOROIDs are just the "tip of the iceberg" of aggregation-based regulatory mechanisms. "There was a recent *Nature* paper where an oligomer could form filaments with a few mutations," he said. "So lots of proteins are on the cusp of doing this and could be modified to do this by upstream signals. This may be an energetically favorable form to store inactive proteins in and it's highly reversible." *Garcia-Seisdedos, H., et al. "Proteins evolve on the edge of supramolecular self-assembly." Nature (2017); Prouteau, M., et al. "TORC1 organized in inhibited domains (TOROIDs) regulate TORC1 activity." Nature (2017)*

## CORRECTION

Suzhou Alphamab Co. Ltd., Suzhou, China

3DMed, Shanghai, China

Business category: Cancer

Suzhou Alphamab Co. Ltd. is developing its lead product, KN035, with partner 3DMed. The Sept. 21 issue of *BioCentury Innovations* misstated the partner company's name.

# NEW THERAPEUTIC TARGETS AND BIOMARKERS: NOVEMBER 2017

Select top therapeutic targets and biomarkers covered by BioCentury or added to the BCIQ database during November 2017. Therapeutic targets are defined as any protein, gene or other molecule that is the focus of a clinical or preclinical program, or that has been selected from the academic literature for coverage in the Distillery section of *BioCentury Innovations*, based on demonstration of translational potential in relevant preclinical assays. Biomarkers are defined as any protein, gene or other molecule that can be used as an indicator or predictor of pathogenic processes or pharmacologic responses. Entries include only human molecules or markers, or pathogenic molecules that can be targeted to treat human diseases. The list excludes targets or biomarkers for existing therapeutics and well-established targets from the literature. Institutions mentioned represent the affiliations of the corresponding authors on the relevant study covered in the Distillery. Full details from BioCentury's coverage of each target can be obtained from the link in the Notes column. *Source: BCIQ: BioCentury Online Intelligence; BioCentury Archives*

| INDICATION | TARGET | DESCRIPTION | COMPANY OR INSTITUTION | NOTES |
|---|---|---|---|---|
| **Therapeutic targets** | | | | |
| Autoimmune disease | | | | |
| Inflammatory bowel disease (IBD) | *Bacteroides* integrase | Cell culture and mouse studies suggest stimulating T cells with a nine-mer G6PC2 peptide or its *Bacteroides* integrase-derived homolog could help treat IBD. | **University of Bern**; **University of Calgary** | Distillery Therapeutics |
| Autoimmune disease; musculoskeletal; neurology; renal | | | | |
| Multiple sclerosis (MS); tissue damage; ataxia; renal | Ubiquitin conjugating enzyme E2 M (UBE2M) | *In vitro* and cell culture studies identified a UBE2M-derived peptide inhibitor of the UBE2M-defective in cullin neddylation 1 domain containing 1 (DCUND1) interaction that could help treat nuclear factor (erythroid-derived 2)-like 2 (NFE2L2; NRF2)-deficient diseases such as MS, tissue damage, Friedreich's ataxia and Alport syndrome. | **University of Michigan** | Distillery Therapeutics |
| Cancer | | | | |
| Brain cancer; sarcoma | Mannose receptor C type 2 (MRC2) | Preclinical studies suggest antibody-drug conjugates (ADCs) targeting MRC2 could help treat sarcoma and glioblastoma. | **ADCendo ApS** | Company News<br>Deals |
| Breast cancer | F-box protein 32 (FBXO32) | Patient sample and mouse studies suggest inhibiting FBXO32 could help prevent breast cancer metastasis. | **Johannes Gutenberg University** | Preclinical News |
| Cancer | Ubiquitin specific peptidase 25 (USP25) | Preclinical studies suggest dual USP25/USP21 inhibitors could help treat cancer. | **Mission Therapeutics Ltd.** | Targets & Mechanisms |
| Colorectal cancer | NAD kinase (NADK)<br>Succinate-CoA ligase ADP-forming β subunit (SUCLA2) | Mouse studies suggest inhibiting the metabolic enzymes NADK or SUCLA2 could help treat K-Ras (KRAS)-mutant colorectal cancer. | **University of California San Diego** | Distillery Therapeutics |
| Liver cancer | BicC family RNA binding protein 1 (BICC1)<br>FYN binding protein 1 (FYB1)<br>p53 upregulated regulator of p53 levels (PURPL; LINC01021) | Cell culture studies suggest inhibiting BICC1, FYB1, PURPL or phosphodiesterase 3A (PDE3A) could help treat liver cancer. | **Shanghai Jiao Tong University School of Medicine**; **Tongji University** | Distillery Therapeutics |
| Dermatology | | | | |
| Blistering disorder | Laminin β 3 (LAMB3) | Patient sample and cell culture studies suggest transplant of keratinocytes engineered to express LAMB3 could help treat junctional epidermolysis bullosa (EB). | **Ruhr University Bochum**; **University of Modena and Reggio Emilia** | Preclinical News |

| INDICATION | TARGET | DESCRIPTION | COMPANY OR INSTITUTION | NOTES |
|---|---|---|---|---|
| | | Endocrine / Metabolic | | |
| Hypercholesterolemia | Nuclear factor erythroid 2 like 1 (NFE2L1; NRF1) | Mouse studies suggest overexpressing NFE2L1 could help treat high cholesterol. | **Harvard T. H. Chan School of Public Health** | Preclinical News |
| | | Infectious disease | | |
| Dengue fever; West Nile virus; Zika virus | Reticulon 3 (RTN3) | Cell culture studies suggest inhibiting the host factor RTN3 could help treat dengue fever, West Nile and Zika infections. | **University of Melbourne** | Distillery Therapeutics |
| Hepatitis B virus (HBV) | CRISPR-associated protein X (Cas X) | Preclinical studies suggest EBT106, an HBV-targeting Cas X/guide RNA (gRNA) duplex biologic, could help treat HBV infections. | **Excision BioTherapeutics Inc.** | Deals |
| Herpes simplex virus (HSV) | CRISPR-associated protein Y (Cas Y) | Preclinical studies suggest EBT105, an HSV-targeting Cas Y/gRNA triplex biologic, could help treat HSV infections. | | |
| Herpes simplex virus (HSV); viral infection | Long non-coding RNA ACOD1 (lncRNA-ACOD1) | Cell culture and mouse studies suggest inhibiting lncRNA-ACOD1 could help treat vesicular stomatitis virus (VSV), HSV type 1 (HSV-1) and vaccinia virus infections. | **Second Military Medical University** | Distillery Therapeutics |
| Malaria | *Plasmodium falciparum* cysteine-rich protective antigen (*P. falciparum* CyRPA) | Cell culture and human sample studies suggest the *P. falciparum* antigens SERA9, MSP5, eba-181, CyRPA and RAMA could be used to develop a malaria vaccine. | **Wellcome Trust Sanger Institute** | Distillery Therapeutics |
| | *Plasmodium falciparum* erythrocyte binding antigen-181 (*P. falciparum* eba-181) | | | |
| | *Plasmodium falciparum* merezoite surface protein 5 (*P. falciparum* MSP5) | | | |
| | *Plasmodium falciparum* rifin-like protein (*P. falciparum* RAMA) | | | |
| | *Plasmodium falciparum* serum repeat antigen 9 (*P. falciparum* SERA9) | | | |
| Staphylococcus | *Staphylococcus aureus* lipoyl synthase (*S. aureus* lipA) | Cell culture and mouse studies suggest inhibiting *S. aureus* lipA could help treat *S. aureus* infection. | **Loyola University Chicago** | Distillery Therapeutics |
| | | Inflammation | | |
| Inflammation | Cezanne-1 (CEZANNE; OTUD7B) | Preclinical studies suggest inhibiting Cezanne-1 could help treat inflammation. | **Mission Therapeutics Ltd.** | Targets & Mechanisms |
| | | Neurology | | |
| Frontotemporal dementia | Cyclin dependent kinase 5 regulatory subunit 1 (CDK5R1) | Cell culture and mouse studies suggest inhibiting proteolytic processing of CDK5R1 into its truncated form could help treat frontotemporal dementia (FTD). | **Massachusetts Institute of Technology** | Distillery Therapeutics |
| Neurology | Pleckstrin homology and RhoGEF domain containing G5 (PLEKHG5) | Mouse studies suggest activating RAB26 could help treat motor neuron diseases involving PLEKHG5 mutations, such as distal spinal muscular atrophy type IV, Charcot-Marie-Tooth disease and amyotrophic lateral sclerosis (ALS). | **University of Bielefeld**; **University Hospital Würzburg** | Distillery Therapeutics |
| | RAB26 member RAS oncogene family (RAB26) | | | |

| INDICATION | TARGET | DESCRIPTION | COMPANY OR INSTITUTION | NOTES |
|---|---|---|---|---|
| **Biomarkers** | | | | |
| Cancer | | | | |
| Colorectal cancer | Epithelial splicing regulatory protein 1 (ESRP1)<br>G protein-coupled receptor 137 (GPR137) | Tumor levels of two splice variants of GPR137 mRNA and its splicing regulator ESRP1 could help predict outcomes in colorectal cancer. | **University of Bern** | Distillery Techniques |
| Cardiovascular disease | | | | |
| Cardiovascular | Growth differentiation factor 1 (GDF1) | SNPs on GDF1 could help predict the risk of subtypes of congenital heart disease. | **Harvard Medical School**; **Icahn School of Medicine at Mount Sinai**; **Yale University School of Medicine** | Distillery Techniques |
| Hematology | | | | |
| Neutropenia | Signal recognition particle 54 (SRP54) | Mutations in SRP54 could help diagnose congenital neutropenia. | **Institut Gustave Roussy** | Preclinical News |

# 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

### AUTOIMMUNE DISEASE; MUSCULOSKELETAL; NEUROLOGY; RENAL

#### INDICATION: Multiple sclerosis (MS); tissue damage; ataxia; renal

*In vitro* and cell culture studies identified a UBE2M-derived peptide inhibitor of the DCUND1-UBE2M interaction that could help treat NFE2L2-deficient diseases such MS, tissue damage, Friedreich's ataxia and Alport syndrome. Structure-based design, chemical synthesis, *in vitro* testing and cell-based binding assays of analogs of a UBE2M-derived peptide yielded a compound that bound DCUND1 with a $K_i$ of 12 nM and decreased the DCUND1-UBE2M interaction compared with an inactive control. In six human epithelial cell lines, the compound decreased levels of an E3 ubiquitin ligase complex activated by the DCUND1-UBE2M interaction and increased levels of NFE2L2, a target down-regulated by the complex. Next steps include testing the compound in models of MS, connective tissue disease associated with pulmonary arterial hypertension (PAH), Friedreich's ataxia and Alport syndrome.

Almirall S.A. markets skilarence (LAS41008), an oral dimethyl fumarate targeting NFE2L2, for psoriasis.

Biogen Inc., Forward Pharma A/S and UCB S.A. market the NFE2L2 activator Tecfidera dimethyl fumarate for MS.

CinnaGen Pharmaceutical Group markets CinnoTec, biosimilar dimethyl fumarate, for MS.

At least seven other companies have NFE2L2 activators in Phase I through Phase III testing for MS, psoriasis, Friedreich's ataxia, Alport syndrome and other indications.

**TARGET/MARKER/PATHWAY:** Ubiquitin conjugating enzyme E2 M (UBE2M); defective in cullin neddylation 1 domain containing 1 (DCUND1); nuclear factor (erythroid-derived 2)-like 2 (NFE2L2; NRF2)

**LICENSING STATUS:** Patent application filed; available for licensing or partnering

**PUBLICATION DETAILS:** Zhou, H. et al. *Nat. Commun.*; published online Oct. 27, 2017

**doi:**10.1038/s41467-017-01243-7

**CONTACT:** Shaomeng Wang, University of Michigan, Ann Arbor, Mich.

**email:** shaomeng@umich.edu

### CANCER

#### INDICATION: Brain cancer

Patient sample, cell culture and mouse studies suggest inhibiting TRIM24 could help treat EGFR-driven glioblastoma multiforme (GBM). In tumor samples from patients, levels of TRIM24 were higher than in brain tissue samples from unaffected subjects, and in patients, high tumor levels of both EGFR and TRIM24 were associated with poor survival. In two human GBM cell lines overexpressing EGFR, shRNA targeting TRIM24 decreased proliferation, colony formation and migration compared with non-specific control shRNA. In two EGFR-expressing human glioblastoma stem cell lines, the shRNA decreased proliferation and neurosphere formation. In a xenograft mouse model of EGFR-overexpressing GBM, shRNA targeting TRIM24 decreased tumor growth. Next steps include identifying and testing TRIM24 inhibitors in models of GBM.

**TARGET/MARKER/PATHWAY:** Epidermal growth factor receptor (EGFR; ErbB1; HER1); tripartite motif containing 24 (TRIM24; TIF1)

**LICENSING STATUS:** Patent application filed; available for licensing or partnering

**PUBLICATION DETAILS:** Lv, D. et al. *Nat. Commun.*; published online Nov. 13, 2017

**doi:**10.1038/s41467-017-01731-w

**CONTACT:** Haizhong Feng, Shanghai Jiao Tong University, Shanghai, China

**email:** Fenghaizhong@sjtu.edu.cn

# THERAPEUTICS

## CANCER

### INDICATION: Colorectal cancer

Patient sample and mouse studies suggest inhibiting the growth of *Fusobacterium* species could help treat colorectal cancer harboring intratumoral *Fusobacterium*. In colorectal cancer patients, high tumor loads of *F. nucleatum* and other *Fusobacterium* species were associated with poor overall survival. In a patient-derived xenograft (PDX) mouse model of colorectal cancer harboring intratumoral *Fusobacterium*, the *Fusobacterium*-killing generic antibiotic metronidazole decreased tumor growth and tumor cell proliferation compared with vehicle or the generic antibiotic erythromycin, which does not inhibit *Fusobacterium* growth. Next steps include identifying and testing *Fusobacterium*-specific antibacterial agents alone or in combination with undisclosed chemotherapies in animal models of colorectal cancer harboring intratumoral *Fusobacterium*.

**TARGET/MARKER/PATHWAY:** An undetermined target

**LICENSING STATUS:** Patent application filed; available for licensing or partnering

**PUBLICATION DETAILS:** Bullman, S. et al. *Science*; published online Nov. 23, 2017

**doi:**10.1126/science.aal5240

**CONTACT:** Matthew Meyerson, Dana-Farber Cancer Institute, Harvard medical School, Boston, Mass.

**email:** matthew_meyerson@dfci.harvard.edu

### INDICATION: Colorectal cancer

Mouse studies suggest inhibiting the metabolic enzymes ketohexokinase, NADK or SUCLA2 could help treat KRAS-mutant colorectal cancer. In a xenograft mouse model of KRAS-mutant colorectal cancer, screening of a CRISPR guide RNA (gRNA) library identified ketohexokinase, NADK and SUCLA2 as genes whose knockout decreased tumor burden compared with normal expression. Knockout of the three genes in xenograft mouse models of colorectal cancer also decreased tumor burden more potently in mice with KRAS-mutant tumors than with KRAS wild-type tumors. In the KRAS-mutant model, ketohexokinase or NADK inhibitor tool compounds decreased tumor burden compared with vehicle, whereas in the KRAS wild-type model, the inhibitors had no effect. Next steps could include testing inhibition of ketohexokinase, NADK or SUCLA2 in patient-derived xenograft (PDX) models of KRAS-mutant colorectal cancer.

Pfizer Inc. has PF-06835919, a ketohexokinase inhibitor, in Phase I testing for non-alcoholic steatohepatitis (NASH).

**TARGET/MARKER/PATHWAY:** Ketohexokinase (fructokinase; KHK); K-Ras (KRAS); NAD kinase (NADK); succinate-CoA ligase ADP-forming β subunit (SUCLA2)

**LICENSING STATUS:** Patent and licensing status unavailable

**PUBLICATION DETAILS:** Yau, E. et al. *Cancer Res.*; published online Sept. 27, 2017

**doi:**10.1158/0008-5472.CAN-17-2043

**CONTACT:** Tariq M. Rana, University of California San Diego, La Jolla, Calif.

**email:** trana@ucsd.edu

### INDICATION: Liver cancer

Cell culture studies suggest inhibiting PDE3A, FYB1, BICC1 or PURPL could help treat liver cancer. In two human liver cancer cell lines, shRNA targeting PDE3A, FYB1, BICC1 or PURPL decreased viability and colony formation and increased apoptosis compared with non-specific shRNA. Next steps could include identifying and testing inhibitors of the four targets in models of liver cancer.

**TARGET/MARKER/PATHWAY:** Phosphodiesterase 3A, bGMP-inhibited (PDE3A); FYN binding protein 1 (FYB1); BicC family RNA binding protein 1 (BICC1); p53 upregulated regulator of p53 levels (PURPL; LINC01021)

**LICENSING STATUS:** Patent and licensing status unavailable

**PUBLICATION DETAILS:** Zhang, X. et al. *Cell Rep.*; published online Oct. 31, 2017

**doi:**10.1016/j.celrep.2017.10.017

**CONTACT:** Qiuhui Pan, Shanghai Jiao Tong University School of Medicine, Shanghai, China

**email:** panqiuhui@263.net

**CONTACT:** Jiayi Wang, Tongji University, Shanghai, China

**email:** karajan2@163.com

# THERAPEUTICS

## CANCER

### INDICATION: Lung cancer

Cell culture and mouse studies suggest the GLS inhibitor CB-839 could help treat KRAS-mutant lung cancers that also harbor KEAP1 mutations. In a mouse model of KRAS- and KEAP1-mutant lung cancer, the GLS inhibitor CB-839 decreased tumor burden compared with vehicle, whereas in a mouse model of KRAS-mutant, KEAP1 wild-type lung cancer, CB-839 had no effect on tumor burden. In patient-derived xenograft (PDX) mouse models of lung cancer harboring KRAS and KEAP1 mutations, but not in PDX models of KRAS-mutant, KEAP1 wild-type lung cancer, CB-839 decreased tumor burden. Next steps could include investigating whether KRAS and KEAP1 mutation status predicts responses to CB-839 in clinical trials.

Calithera Biosciences Inc. has CB-839 in Phase II testing for breast cancer and renal cancer; Phase I/II testing for other solid tumors, including KRAS-mutant non-small cell lung cancer (NSCLC); and Phase I testing for hematologic malignancies, leukemia and multiple myeloma (MM).

**TARGET/MARKER/PATHWAY:** Glutaminase (GLS); K-Ras (KRAS); kelch-like ECH-associated protein 1 (KEAP1)

**LICENSING STATUS:** Patent and licensing status unavailable

**PUBLICATION DETAILS:** Romero, R. et al. *Nat. Med.*; published online Oct. 2, 2017

**doi:**10.1038/nm.4407

**CONTACT:** Tyler Jacks, Massachusetts Institute of Technology, Cambridge, Mass.

**email:** tjacks@mit.edu

**CONTACT:** Thales Papagiannakopoulos, New York University School of Medicine, New York, N.Y.

**email:** Thales.Papagiannakopoulos@nyumc.org

### INDICATION: Melanoma

Patient sample and mouse studies suggest inhibiting CCR5 or its interactions with CCL3, CCL4 and RANTES could help treat melanoma. In patient tissue samples, the number of CCR5-positive myeloid-derived suppressor cells (MDSC) and levels of the CCR5 ligands CCL3, CCL4 and RANTES were higher in tumor samples than in peripheral blood or serum. In a mouse model of melanoma, CCR5 knockout decreased tumor growth compared with normal CCR5 expression. In another mouse model of melanoma, a fusion protein consisting of a mouse CCR5 extracellular domain that inhibits CCR5-ligand interactions and the Fc region of mouse immunoglobulin light chain (IgLC) increased survival compared with a non-specific IgG. Next steps could include identifying and testing inhibitors of other CCR5 inhibitors in melanoma models.

Pfizer Inc. and GlaxoSmithKline plc market Selzentry maraviroc, a CCR5 antagonist, to treat HIV / AIDS.

CytoDyn Inc. has PRO 140, a humanized IgG4 mAb against CCR5, in Phase III testing to treat HIV / AIDS and graft-versus-host disease (GvHD).

**TARGET/MARKER/PATHWAY:** CC chemokine receptor 5 (CCR5; CD195); macrophage inflammatory protein-1 α (CCL3; MIP1A); macrophage inflammatory protein-1 β (CCL4; MIP1B); chemokine CC motif ligand 5 (RANTES; CCL5)

**LICENSING STATUS:** Patent and licensing status unavailable

**PUBLICATION DETAILS:** Blattner, C. et al. *Cancer Res.*; published online Oct. 31, 2017

**doi:**10.1158/0008-5472.CAN-17-0348

**CONTACT:** Viktor Umansky, German Cancer Research Center (DKFZ) and University Medical Center Mannheim, Heidelberg, Germany

**email:** v.umansky@dkfz.de

# THERAPEUTICS

## CANCER

### INDICATION: Melanoma

Cell culture and mouse studies suggest CD38-knockout T cells could help treat melanoma and other cancers. In a mouse model of melanoma, adoptive transfer of hybrid T helper type 1 (Th1)/Th17 cells that co-expressed high levels of interferon γ (IFNγ) and IL-17 decreased tumor growth compared with unmodified Th1 or Th17 cells. Also in the model, low expression of CD38 on the hybrid T cells was associated with antitumor activity, and adoptive transfer of naïve T cells from CD38-knockout mice decreased tumor growth compared with adoptive transfer of wild-type naïve T cells. Next steps could include testing adoptive transfer of CD38-knockout cells in models of other cancers.

**TARGET/MARKER/PATHWAY:** CD38
**LICENSING STATUS:** Patent application filed; available for licensing or partnering
**PUBLICATION DETAILS:** Chatterjee, S. et al. *Cell Metab.*; published online Nov. 9, 2017
**doi:**10.1016/j.cmet.2017.10.006
**CONTACT:** Shikhar Mehrotra, Medical University of South Carolina, Charleston, S.C.
**email:** mehrotr@musc.edu

## ENDOCRINE / METABOLIC

### INDICATION: Obesity

Patient sample and mouse studies suggest inhibiting MKK6 could help prevent obesity. In obese patients, MKK6 expression was higher in white adipose tissue (WAT) than in WAT from non-obese individuals. In obese mice fed a high-fat diet, MKK6 knockout decreased body weight and increased glucose tolerance and insulin sensitivity. Next steps could include developing and testing an MKK6 inhibitor.

**TARGET/MARKER/PATHWAY:** Mitogen-activated protein kinase kinase 6 (MKK6)
**LICENSING STATUS:** Patent and licensing status unavailable
**PUBLICATION DETAILS:** Matesanz, N. et al. *Nat. Commun.*; published online Oct. 11, 2017
**doi:**10.1038/s41467-017-00948-z
**CONTACT:** Guadalupe Sabio, Spanish National Center for Cardiovascular Research (CNIC), Madrid, Spain
**email:** gsabio@cnic.es

## GASTROINTESTINAL; CANCER

### INDICATION: Colitis; colorectal cancer

Mouse studies suggest iron chelation or superoxide reduction could help treat colitis or colitis-induced colorectal cancer. In a mouse model of acute colitis, the iron-chelating agent Ferriprox deferiprone increased body weight and colon length and decreased histological changes and pathological scores compared with no treatment. In a mouse model of chronic colitis, Ferriprox decreased pathological scores. In a mouse model of colitis-induced colon cancer, Ferriprox or the superoxide scavenger tempol decreased tumor number, tumor burden and tumor cell proliferation. Next steps could include testing Ferriprox and tempol in additional models of colitis and colitis-induced colon cancer.

Apotex Inc. markets Ferriprox to treat iron overload and thalassemia.

Cary Pharmaceuticals Inc. has tempol (4-hydroxy-2,2,6,6-tetramethyl-1-piperidine-1-oxyl), a small molecule that reduces oxidative stress by mimicking the function of superoxide dismutase (SOD), in preclinical testing to treat chronic hypertension.

**TARGET/MARKER/PATHWAY:** Fe ion
**LICENSING STATUS:** Patent and licensing status unavailable
**PUBLICATION DETAILS:** Xue, X. et al. *Proc. Natl. Acad. Sci. USA*; published online Oct. 23, 2017
**doi:**10.1073/pnas.1712946114
**CONTACT:** Xiang Xue, University of Michigan, Ann Arbor, Mich.
**email:** xxue@umich.edu
**CONTACT:** Yatrik M. Shah, same affiliation as above
**email:** shahy@umich.edu

# THERAPEUTICS

## INFECTIOUS DISEASE

### INDICATION: Dengue fever; West Nile virus; Zika virus

Cell culture studies suggest inhibiting the host factor RTN3 could help treat dengue fever, West Nile and Zika infections. In HeLa cells infected with dengue, West Nile virus or Zika virus, siRNA targeting RTN3 decreased viral protein abundance and viral titers compared with non-specific siRNA. In HEK cells infected with each pathogen, the siRNA decreased host membrane remodeling associated with viral replication. Next steps could including identifying and testing RTN3 inhibitors in models of dengue fever, West Nile and Zika.

**TARGET/MARKER/PATHWAY:** Reticulon 3 (RTN3)

**LICENSING STATUS:** Patent and licensing status unavailable

**PUBLICATION DETAILS:** Aktepe, T. et al. *Cell Rep.*; published online Nov. 7, 2017

**doi:**10.1016/j.celrep.2017.10.055

**CONTACT:** Jason M. Mackenzie, University of Melbourne at the Peter Doherty Institute for Infection and Immunity, Melbourne, Australia

**email:** jason.mackenzie@unimelb.edu.au

### INDICATION: Malaria

Cell culture and human sample studies identified combinations of *Plasmodium falciparum* antigens that could be used to develop a malaria vaccine. In a human erythrocyte-based assay of *P. falciparum* growth, polyclonal rabbit IgGs against five parasitic antigens — *P. falciparum* SERA9, MSP5, eba-181, CyRPA and RAMA — inhibited growth of two parasitic strains with potencies comparable to an antibody against the candidate antigen, *P. falciparum* Rh5 ($IC_{50}$ values = 0.25-1.5 mg/mL). Also in the assay, combinations of antibodies against RAMA/Rh5 and RAMA/CyRPA — antigen pairs that are highly expressed at differing stages of parasitic infection — synergistically decreased parasite growth compared with any of the antibodies alone. In serum samples from individuals previously exposed to *P. falciparum*, the presence of one of five combinations of human versions of the antibodies — eba-181/Rh5, MSP5/Rh5, RAMA/Rh5, MSP5/RAMA and eba-181/MSP5/RAMA — decreased the incidence of *P. falciparum* infection upon subsequent exposure compared with the presence of any antibody alone. Next steps could include developing a malaria vaccine based on the identified combinations of antigens.

**DESCRIPTION:** Plasmodium falciparum serum repeat antigen 9 (P. *falciparum* SERA9); *P. falciparum* merezoite surface protein 5 (*P. falciparum* MSP5); *P. falciparum* erythrocyte binding antigen-181 (*P. falciparum* eba-181); *P. falciparum* cysteine-rich protective antigen (*P. falciparum* CyRPA); *P. falciparum* rifin-like protein (*P. falciparum* RAMA); *P. falciparum* reticulocyte-binding protein homolog 5 (*P. falciparum* Rh5)

**LICENSING STATUS:** Patent and licensing status unavailable

**PUBLICATION DETAILS:** Bustamante, L. et al. *Proc. Natl. Acad. Sci. USA;* published online Oct. 23, 2017

**doi:**10.1073/pnas.1702944114

**CONTACT:** Julian C. Rayner, Wellcome Trust Sanger Institute, Cambridge, U.K.

**email:** julian.rayner@sanger.ac.uk

### INDICATION: Viral infection

Macaque studies suggest nanoparticles loaded with siRNA targeting Marburg virus nucleoprotein could help treat Ravn viral infections. In macaque models of late-stage Ravn viral infection, cationic liposomal nanoparticles loaded with siRNA targeting the Marburg virus nucleoprotein increased survival and decreased clinical disease scores, liver damage, renal damage and levels of viral RNA in the serum and multiple tissues compared with no treatment. Next steps by Arbutus Biopharma Corp. include testing the siRNA-loaded nanoparticles in combination with undisclosed antibody-based therapies in models of Ravn viral infection.

**TARGET/MARKER/PATHWAY:** Marburg virus nucleoprotein

**LICENSING STATUS:** Patented; licensed to Arbutus Biopharma Corp.

**PUBLICATION DETAILS:** Thi, E. et al. *J. Clin. Invest.*; published online Nov. 6, 2017

**doi:**10.1172/JCI96185

**CONTACT:** Thomas Geisbert, University of Texas Medical Branch, Galveston, Texas

**email:** twgeisbe@utmb.edu

# THERAPEUTICS

## INFECTIOUS DISEASE

### INDICATION: Viral infection; herpes simplex virus (HSV)

Cell culture and mouse studies suggest inhibiting lcnRNA-ACOD1, a long non-coding RNA (lncRNA) near ACOD1, could help treat vesicular stomatitis virus (VSV), HSV type 1 (HSV-1) and vaccinia virus infections. In primary mouse peritoneal macrophages infected with VSV, HSV-1 or vaccinia virus, siRNA targeting lncRNA-ACOD1 decreased viral titers compared with a non-specific siRNA. In a mouse macrophage cell line infected with VSV, knockout of the lncRNA decreased viral replication compared with normal lnc-ACOD1 expression. In a mouse model of VSV infection, knockout of the lncRNA decreased viral replication in the spleen, liver and lung and increased survival. Next steps could include identifying and testing lncRNA-ACOD1 inhibitors in models of HSV-1 and vaccinia virus infections.

**TARGET/MARKER/PATHWAY:** Long non-coding RNA ACOD1 (lncRNA-ACOD1); aconitate decarboxylase 1 (ACOD1)

**LICENSING STATUS:** Patent and licensing status unavailable

**PUBLICATION DETAILS:** Wang, P. et al. *Science*; published online Oct. 26, 2017

**doi:**10.1126/science.aao0409

**CONTACT:** Xuetao Cao, Second Military Medical University, Shanghai, China

**email:** caoxt@immunol.org

## NEUROLOGY

### INDICATION: Nerve damage

Mouse studies suggest inhibiting SARM1 could help treat severe axonopathy. In a mouse model of the indication, SARM1 knockout increased gastrocnemius muscle weight and locomotor performance and decreased neuromuscular denervation compared with normal expression. Next steps could include identifying and testing SARM1 inhibitors in the model.

**TARGET/MARKER/PATHWAY:** Sterile α and TIR motif containing 1 (SARM1)

**LICENSING STATUS:** Patent and licensing status unavailable

**PUBLICATION DETAILS:** Gilley, J. et al. *Cell Rep.*; published online Oct. 3, 2017

**doi:**10.1016/j.celrep.2017.09.027

**Contact:** Jonathan Gilley, University of Cambridge, Cambridge, U.K.

**email:** jg792@cam.ac.uk

## RENAL

### INDICATION: Renal damage

Mouse studies suggest 14,15-epoxyeicosatrienoic acid (EET) or inhibition of its catabolic enzyme EPHX2 could help treat acute kidney injury (AKI). In a mouse model of AKI, 14,15-EET decreased kidney injury and increased survival compared with no treatment. Also in the model, the EET plus a tool compound that inhibits EPHX2 decreased kidney injury and plasma levels of inflammatory cytokines and increased survival compared with the EET alone. Next steps in collaboration with EicOsis LLC include planning for Phase I testing of undisclosed EPHX2 inhibitors in renal disease.

**TARGET/MARKER/PATHWAY:** Epoxide hydrolase 2 (EPHX2; CEH)

**LICENSING STATUS:** Patented; licensed to EicOsis LLC; available for partnering

**PUBLICATION DETAILS:** Deng, B.-Q. et al. *Proc. Natl. Acad. Sci. USA*; published online Nov. 6, 2017

**doi:**10.1073/pnas.1705615114

**CONTACT:** Bruce D. Hammock, University of California, Davis, Calif.

**email:** bdhammock@ucdavis.edu

**CONTACT:** Jun-Yan Liu, Tongji University School of Medicine, Shanghai, China

**email:** jyliu@tongji.edu.cn

# TECHNIQUES

## BIOMARKERS

### TECHNOLOGY: Gene profiling

Protein-truncating variants of RFX6 DNA could help predict risk of maturity-onset diabetes of the young (MODY). In 38 MODY patients, the frequencies of two RFX6 protein-truncating DNA variants were higher than in 33,346 control subjects. In 80 Finnish MODY patients, the frequency of a third RFX6 DNA variant was higher than in 7,040 Finnish control subjects. Next steps could include determining the functional consequences of the RFX6 variants in MODY.

**DESCRIPTION:** Protein-truncating variants of regulatory factor X 6 (RFX6) to predict the risk of maturity-onset diabetes of the young (MODY)

**LICENSING STATUS:** Patent and licensing status unavailable

**PUBLICATION DETAILS:** Patel, K. et al. *Nat. Commun.*; published online Oct. 12, 2017

**doi:**10.1038/s41467-017-00895-9

**CONTACT:** Miriam Cnop, Free University of Brussels, Brussels, Belgium

**email:** mcnop@ulb.ac.be

**CONTACT:** Michael N. Weedon, University of Exeter Medical School, Exeter, U.K.

**email:** M.N.Weedon@exeter.ac.uk

### TECHNOLOGY: SNPs

SNPs on GDF1, MYH6 and FLT4 could help predict the risk of subtypes of congenital heart disease. Whole-exome sequencing of 2,871 congenital heart disease patients identified associations between severe disease in the Ashkenazi Jewish population and the T1091C mutation on GDF1; between Shone's syndrome and SNPs on MYH6; and between Tetralogy of Fallot and SNPs on FLT4. Next steps could include determining the functional consequences of the SNPs in each disease subtype.

**DESCRIPTION:** SNPs on growth differentiation factor 1 (GDF1), myosin heavy chain 6 cardiac muscle α (MYH6) and vascular endothelial growth factor receptor 3 (FLT4; VEGFR-3) as risk markers for congenital heart disease

**LICENSING STATUS:** Patent and licensing status unavailable

**PUBLICATION DETAILS:** Jin, S. et al. *Nat. Genet.*; published online Oct. 9, 2017

**doi:**10.1038/ng.3970

**CONTACT:** Jonathan Seidman, Harvard Medical School, Boston, Mass.

**email:** seidman@genetics.med.harvard.edu

**CONTACT:** Christine Seidman, same affiliation as above

**email:** cseidman@genetics.med.harvard.edu

**CONTACT:** Bruce Gelb, Icahn School of Medicine at Mount Sinai, New York, N.Y.

**email:** bruce.gelb@mssm.edu

**CONTACT:** Richard Lifton, Yale University School of Medicine, New Haven, Conn.

**email:** richard.lifton@rockefeller.edu

**CONTACT:** Martina Brueckner, same affiliation as above

**email:** martina.brueckner@yale.edu

# TECHNIQUES

## DISEASE MODELS

### TECHNOLOGY: Transgenics and knockouts

Mice with humanized immune systems could be used to screen immunotherapies for cancer. The model involved modifying NK cell-deficient mice by knocking in genes encoding human IL-15 and signal regulatory protein α (SIRPA; CD172a; SHPS-1) to induce development of humanized NK cells, intraepithelial lymphocytes and two subsets of innate lymphoid cells (ILCs), all of which mediate the effects of cancer immunotherapies in patients. In a mouse xenograft model of Burkitt's lymphoma generated with the humanized mice, the anti-CD20 antibody rituximab induced antibody-dependent cellular cytotoxicity (ADCC) mediated by NK cells and inhibited tumor growth, recapitulating the therapeutic responses observed in patients, whereas in a conventional mouse model of Burkitt's lymphoma, rituximab had no effect on tumor growth. Next steps could include using the humanized mice to generate models of other cancers and test immunotherapies.

Rituxan rituximab and biosimilar rituximab are marketed for non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), B cell lymphoma and lymphoma, and a range of autoimmune and inflammatory diseases.

**DESCRIPTION:** Mice with humanized immune systems for screening of cancer immunotherapies

**LICENSING STATUS:** Patent and licensing status unavailable

**PUBLICATION DETAILS:** Herndler-Brandstetter, D. et al. *Proc. Natl. Acad. Sci. USA*; published online Oct. 25, 2017

**doi:**10.1073/pnas.1705301114

**CONTACT:** Richard Flavell, Yale University School Of Medicine, New Haven, Conn.

**email:** richard.flavell@yale.edu

## DRUG DELIVERY

### TECHNOLOGY: Nanoparticles

Intranasally administered albumin-based nanoparticles could deliver therapies to the brain to help treat Alzheimer's disease and other CNS diseases, bypassing the need to cross the blood-brain barrier (BBB). In CHO cells expressing mouse amyloid precursor protein (APP), human serum albumin-based nanoparticles loaded with an NSAID tool compound decreased mitochondrial respiration dysfunction — a potential marker of AD — compared with the free NSAID. In mice, intranasal delivery of the NSAID-loaded nanoparticles increased the area under the curve (AUC) for the brain and plasma concentration-time curves compared with intranasal or oral delivery of free NSAID. Next steps could include testing the nanoparticles loaded with other therapies in additional models of CNS disease.

**DESCRIPTION:** Albumin-based nanoparticles for brain delivery of therapies for CNS diseases

**LICENSING STATUS:** Patent and licensing status unavailable

**PUBLICATION DETAILS:** Wong, L. and Ho, P. *J. Pharm. Pharmacol.*; published online Oct. 16, 2017

**doi:**10.1111/jphp.12836

**CONTACT:** Paul C. Ho, National University of Singapore, Singapore

**email:** phahocl@nus.edu.sg

## SCIENTIFIC ADVISORY BOARD

## EDITORIAL & RESEARCH

NEWSROOM:
pressreleases@biocentury.com

SAN CARLOS, CA:
+1 650-595-5333; Fax: +1 650-595-5589

CHICAGO:
+1 312-755-0798; Fax: +1 650-595-5589

WASHINGTON, DC:
+1 202-462-9582; Fax: +1 202-667-2922

UNITED KINGDOM:
+44 (0)1865-512184; Fax: +1 650-595-5589

**Editor:** C. Simone Fishburn, Ph.D.

**Associate Editors:** Michael J. Haas; Selina Koch, Ph.D.; Meredith Durkin Wolfe (Data & Analytics)

**Senior Writers:** Michael Leviten, Ph.D.; Lauren Martz; Karen Tkach Tuzman, Ph.D.

**Staff Writers:** Hongjiang Li, Ph.D.; Winnie Pong, Ph.D.; Mary Romeo; Mark Zipkin

**Copy Editor:** Stephanie Goldman

Use of Images: Certain Images used in BioCentury Inc.'s Publications, Video Content, Websites, Services, Notices and/or Marketing Materials are licensed from Getty Images (US), Inc. Any such image of a person or object so displayed is being used for illustrative purposes only and any such person or object depicted, if any, is merely a model. For more information see "Use of Images" found under the "Legal" section on the footer of the homepage at www.biocentury.com.



## CORPORATE, SUBSCRIPTIONS & PRIVACY

BioCentury's mission is to provide value-added business information & analysis for life science companies, investors, academia and government on the strategic issues essential to the formation, development and sustainability of life science ventures.

BioCentury Inc.
BioCentury International Inc.

MAIN OFFICES
PO Box 1246
San Carlos CA 94070-1246
+1 650-595-5333; Fax: +1 650-595-5589

CORPORATE

**Chairman:** Karen Bernstein, Ph.D.

**President & CEO:** David Flores

**Vice President/Commercial Operations:** Thomas Carey

**Vice President/Administration & CFO:** Bennet Weintraub

**Publisher:** Eric Pierce

**Executive Editor and Director, New Ventures:** Joshua L. Berlin

**Senior Director/Commercial Operations:** Tim Tulloch

**Director/Digital Content:** Shabnam Sigman

**Director/Marketing & Promotional Services:** Greg Monteforte

**Director/Administration & Human Resources:** Susan Morgan

**Director/Publishing:** Jenny Nichols

SUBSCRIBER SERVICES

**Subscriber Services**: subscribe@biocentury.com

**Account Managers:** Orlando Abello; Celeste Cabral; Matt Krebs; Michelle Ortega; Ron Rabinowitz

BUSINESS SERVICES

**Accounting & Billing:** finance@biocentury.com

**Conferences:** conferences@biocentury.com

**Data Solutions Support:** support@biocentury.com

**Privacy Policy:** privacy@biocentury.com

**Reprints/Permissions:** businessservices@biocentury.com

PRIVACY & ADVERTISING
In accordance with its Privacy Policy, BioCentury does NOT sell its customer information or usage data to third parties.
BioCentury does NOT sell advertising in the BioCentury, BioCentury Innovations or BioCentury Week in Review. BioCentury is pleased to acknowledge its conference partners and sponsors through unpaid promotional announcements in its publications. BioCentury MAY accept paid promotional messages from sponsors, which are displayed only on BioCentury's websites.

BIOCENTURY

# CHINA HEALTHCARE SUMMIT 2017

*The Bridge to Innovation*

**Nov. 14-15, 2017**
**Shanghai, China**

## *2017 BayHelix China Healthcare Awards*

The BayHelix awards celebrate outstanding individuals and companies for their contribution to China's healthcare ecosystem. This year's awards were presented at the 2017 ***BioCentury China Healthcare Summit***.

## CONGRATULATIONS TO THE WINNERS

### R&D Achievement of the year

**ASCENTAGE PHARMA GROUP CORP. LTD.**

*Recognizing a scientific discovery in China with direct impact to drug and/or medtech R&D or a significant achievement in pharmaceutical and/or medtech development milestones.*

### Deal of the year

**BEIGENE LTD./ CELGENE CORP.**

*Global strategic immuno-oncology collaboration between BeiGene and Celgene: Celgene to advance BeiGene's PD-1 inhibitor program BGB-A317 for solid tumor cancers, and BeiGene to assume responsibility of Celgene's commercial operations and its oncology commercial portfolio in China to become a fully integrated biotech company.*

### Commercial Achievement of the year

**WUXI BIOLOGICS INC.**

*A powerful globally-leading end-to-end biologics discovery, development and manufacturing platform that is transforming the biologics industry by enabling anyone and any company to excel in biologics.*

### Company of the year

**ZAI LAB LTD.**

*Successful NASDAQ IPO after 3 years of company inception and a broad and sustainable pipeline.*

### Person of the year

**HAO HONG, PH.D.**

Chairman & CEO, Asymchem Laboratories Inc.

*Built Asymchem in the last twenty years into one of the leading CDMO companies in the world and one of the global front-runners in green pharmaceutical manufacturing technologies, with proprietary green chemistry such as flow chemistry and biocatalysis.*

BIOCENTURY

*The 25th Annual*

# *Future Leaders in the Biotech Industry*

*A Collaborative Gathering for the Corporate & Investment Communities*
*Featuring Rising Private Plays and Momentum-Building Companies*

*March 23, 2018 • New York City*

## CALL FOR PRESENTING COMPANIES

The *Future Leaders* class of 2018 will include up to 48 public and private companies independently selected by BioCentury based on objective selection criteria, including investor validation, unpartnered assets, upcoming value-creating milestones and innovative science.

### Apply to be a Presenting Company

*Email conferences@biocentury.com*

### SAVE THE DATE

March 23, 2018
Millennium Broadway Hotel & Conference Center
New York City

### Sponsorship Opportunities

*Contact Eric Pierce at ericpierce@biocentury.com for sponsorship opportunities.*

# BIO€QUITY EUROPE 2018

BIOCENTURY

EBD GROUP

Bio Biotechnology Industry Organization

May 14-16, 2018
*Ghent, Belgium*

## CALL FOR PRESENTING COMPANIES

Reserve Your Seat Today

Now celebrating its 19th meeting, *Bio€quity Europe* is the premier industry event for financial and licensing dealmakers looking for investor-validated life science companies positioning themselves to attract capital, and for pharmaceutical licensing professionals to assess top biotech prospects.

*Bio€quity Europe* has showcased more than 800 leading European companies to thousands of investment and pharma business development professionals. Delegates from over 24 nations attended last year.

## SAVE THE DATE

### Monday, May 14th - Wednesday, May 16th

***Ghent, Belgium***

**APPLY TO BE A PRESENTING COMPANY**

Email
conferences@biocentury.com

**SPONSORSHIP OPPORTUNITIES**

Contact Eric Pierce at
ericpierce@biocentury.com