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KURMA CHAMELEON

By Lauren Martz, Senior Writer

French life science VC Kurma Partners S.A. is experimenting with a new investment model to accelerate the transfer of European academic research into the commercial setting with less risk than standard seed investments. The firm is balancing the new model with its traditional one, allowing it to continue investing in later-stage companies while also competing with the bigger players for highly innovative discoveries.

Kurma was formed in 2009. Its first fund, Kurma Biofund I, created newcos using a traditional route that invests money and other resources into translating an academic discovery.

In November 2016, it announced it is incorporating a new strategy into its latest fund, Kurma Biofund II, after rethinking the best way to access disruptive technologies while balancing the risk.

The idea is to syndicate with industry partners from the get-go, bringing them in at a pre-seed stage — prior to forming the company — to provide expertise that matches the newco's technology. Working alongside the academics to ripen the technology with low financial commitment de-risks the program.

Moreover, it should allow Kurma to compete for seed or series A stage assets with the bigger players.

According to managing partner Vanessa Malier, the new approach is unique among French life science investors and makes it possible for a small firm like Kurma to create new companies without tying up a large percentage of its capital in seed investments.

The firm's industry partners for these investments include Boehringer Ingelheim GmbH and Ionis Pharmaceuticals Inc.

Having an industry player on board "gives a lot of credibility to the newco and facilitates the recruitment of an experienced management team and the syndication with other VCs," said Malier.

The VC landscape in France is dominated by two major funds — Sofinnova Partners and Edmond de Rothschild — and smaller players like Kurma. In addition, BPIFrance, the investment arm of the French state, provides venture investments and grants and loans to new companies within the country.

Edmond de Rothschild partner Gilles Nobecourt said his firm is not heavily focused on early stage innovations, and he isn't aware of any

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other French funds that use a model similar to Kurma's. While most VCs, including his firm, provide access to networks of KOLs, forming relationships with industry partners so early in the process is rare, Nobecourt said.

Sofinnova's portfolio includes early stage investments, but skews to series A rather than seed. According to its website, the firm's investment strategy involves becoming the first institutional A round investor and leading its portfolio companies until exit. Sofinnova was not available to comment in time for publication.

THE FRENCH CONNECTION

Kurma Biofund I comprises €51 million ($53.7 million) of the firm's more than €250 million ($265 million) under management, and includes a portfolio of 11 companies, 5 of which were co-founded by the fund. Four of the new companies were sourced from academic institutions in Europe, and the fifth was created by a serial innovator.

At the pre-seed, tech transfer stage, Kurma contributed primarily non-financial resources to academic innovators.

Kurma Biofund II was launched in 2013 and dedicates at least 50% of its investment to rare disease projects. The fund, which closed in 2014 with €55 million but will manage over €100 million with co-investments from LPs, has formed four newcos: Step Pharma, Dynacure, Imcheck Therapeutics SAS and Pharvaris. It has also invested in six other companies.

"When we selected those four new projects, we decided not to go through seed investments but to use the first two years after we started working with academic groups to create the companies from scratch with an industry partner," said managing partner Rémi Droller.

According to Malier, the risk-sharing model came together after Kurma co-created Step Pharma with the U.K. CRO Sygnature Discovery Ltd. and the Imagine Institute - a research and health care institute focused on genetic disorders. Sygnature provides drug discovery support and created chemical compounds for preclinical testing before the company was formed.

The first step is to access innovation from the network of academic institutions and clinicians that Kurma has pulled together over the years and now represents a cornerstone of the firm's strategy.

Kurma has partnerships with Institut Pasteur, the University of Strasbourg's technology transfer office and regional technology transfer offices for Ile-de-France Innov and for Nord in France, and with Cancer Research Technology Ltd., the Flanders Institute for Biotechnology (VIB), Karolinska Development AB, Leiden University Research and Innovations Services (LURIS), and the Cydan orphan drug accelerator across Europe.

After identifying a technology, Kurma recruits an industry partner with relevant business and technical expertise, which provides in-kind contributions in exchange for shares of the newco. The VC contributes a small amount of capital.

"We usually do not invest more than €200,000-€300,000 before creation, but we dedicate a lot of internal resources for project management and business development, and for identifying the management team as soon as possible," said Malier.

The partners also take advantage of non-dilutive funding, in the form of grants and in-kind contributions from industry partners, as well as financing from maturation funds of the institution or its tech transfer office to support the project's "maturation phase" before creation.

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"We consider our structure as a dual model of an incubator project and a typical VC fund," Droller said.

Nobecourt noted there are plenty of financial resources available to start-ups in France, including location-based grants and tax incentives. Where Kurma's model can add value, and where there exists a funding gap in the country, he said, is after the initial idea is presented but before sufficient proof-of-concept results are available.

Malier agreed. Creating a company in an environment that brings together the academic researchers and industry expertise "significantly increases the chance of success, accelerates the development timeline and concentrates the financing on key phases of value creation between drug candidate selection and clinical proof of concept," she said.

Once the project is mature enough to create a viable company, Kurma increases its commitment with a more substantial seed or series A investment. "Thanks to the maturation period, we aim to be directly at the series A stage once the company is created. We may invest a small seed investment to facilitate the bridge towards the series A," said Droller. The seed usually ranges from €0.5-€1 million, and the series A from €5-€20

a player from industry to help attract larger amounts of external funding.

Kurma's target is to split its capital 40-60 between newcos and standard venture investments, with a goal of creating one to two new companies each year. While it makes investments all over Europe and occasionally in the U.S., Kurma is focusing the new platform in France. Three of the four newcos formed in the last three years are headquartered in France and spun out from French institutions.

Droller told BioCentury that Kurma wants to create an environment that presents academic entrepreneurs with all the elements they need. "We need to bring together one strong discovery, an investor and a management team. Basically, you can find all of that in a specialized area like Boston, but we don't have such a centralized environment in Europe and need someone to organize all the components," he said.

French academic science is one of the continent's top sources of translational opportunities and the country has seen a renaissance in its biotech sector, fueled partly by healthy access to early stage capital. According to data compiled from *BioCentury Innovations*' Distillery, which identifies preclinical

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>
> Rémi Droller, Kurma Partners

million depending on the company's needs to reach the next inflection point or exit, he said.

"All of our projects were started when only a target was identified, and all work was done in collaboration with industry to transform that target into a potential drug candidate," said Droller.

Kurma has focused on asset-centric projects with a clear exit after clinical proof of concept. However, Droller said the firm now will expand to platform technologies when it can bring in

research with translational potential from 40 top biomedical journals, France ranked third highest for translational science among European countries between 2008 and 2016.

STEP BY STEP
Step Pharma was founded in 2014 to develop a new class of immunosuppressive drugs, based on research from Alain Fischer at Hopital Necker-Enfants Malades' Imaging Institute.

The company is developing selective small molecule inhibitors of the enzyme CTPS1 to treat autoimmune diseases and

hematological malignancies, based on the discovery by Fischer that loss of function of the CPTS1 gene impairs lymphocyte proliferation. CEO Geoffroy De Ribains told BioCentury the company is testing its compounds in animal models to identify which autoimmune indications to pursue first.

In 2015, Kurma and Boehringer Ingelheim spun out Imcheck from the Institute Paoli-Calmettes in Marseille to develop new immuno-oncology antibodies.

Although Imcheck is not disclosing which checkpoint inhibitors it is pursuing, the biotech says the targets will generate innate and adaptive immune responses from both αβ and γδ T cells to treat hematological malignancies and solid tumors.

> "We consider our structure as a dual model of an incubator project and a typical VC fund."
>
> Rémi Droller, Kurma Partners

γδ T cells are an emerging area of importance in immuno-oncology for their ability to naturally detect and eliminate stressed cells, including cancer cells. In the last two years, two other startups, GammaDelta Therapeutics Ltd. and Gadeta B.V., were launched to develop γδ T cell therapies for cancer.

Kurma also co-founded rare disease company Dynacure last year based on research from Jocelyn Laporte and colleagues at the Institute of Genetics and Molecular and Cellular Biology in Illkirch. The company is targeting the dynamin subtype DNM2 to treat rare myopathies.

Because the company needs antisense technology to translate the findings, Kurma brought in Ionis as the industry partner last October. Ionis contributed antisense molecules to test in mouse models of rare centronuclear myopathies in the pre-company formation stage. The U.S. biotech is now collaborating to create clinical antisense candidates.

"We spent 12-18 months validating the target with oligos in animal models, and came to the conclusion that the data were good enough to co-create a company to develop the compound and push it into patients," said Droller. He added that Dynacure's management team will be named in the near future.

Kurma is not disclosing any details about the technology, indication or industry partner for its fourth newco from Kurma Biofund II, Netherlands-based Pharvaris.

COMPANIES AND INSTITUTIONS MENTIONED

Boehringer Ingelheim GmbH, Ingelheim, Germany
Cancer Research Technology Ltd., London, U.K.
Dynacure, Strasbourg, France
Flanders Institute for Biotechnology (VIB), Ghent, Belgium
Gadeta B.V., Utrecht, the Netherlands
GammaDelta Therapeutics Ltd., London, U.K.
Hopital Necker-Enfants Malades, Paris, France
Imagine Institute, Paris, France
Imcheck Therapeutics S.A.S., Marseille, France
Institute of Genetics and Molecular and Cellular Biology (IGBMC), Illkirch, France
Institut Paoli-Calmettes, Marseille, France
Institut Pasteur, Paris, France
Ionis Pharmaceuticals Inc. (NASDAQ:IONS), Carlsbad, Calif.
Karolinska Development AB (SSE:KDEV), Solna, Sweden
Kurma Partners S.A., Paris, France
Leiden University Research and Innovations Services, Leiden, the Netherlands
Pharvaris, Wassenaar, the Netherlands
Step Pharma, Paris, France
Sygnature Discovery Ltd., Nottingham, U.K.
University of Strasbourg, Strasbourg, France

TARGETS

CTPS1 - CTP synthase 1
DNM2 - Dynamin 2

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PIGGYBACK CAR RIDE

By Michael J. Haas, Associate Editor

The disappointing durability of CAR T cells in the clinic has been attributed to the cells' too-mature phenotype, and the immunogenicity and low stability of the chimeric antigen receptors (CARs) themselves. Poseida Therapeutics Inc. is using its virus-free gene delivery technology to load up T cells with modifications that address all three problems and provide long-lasting responses.

The company is pursuing allogeneic and autologous CAR T therapies, in addition to NK cell therapies.

According to President and COO Nishan de Silva, a core component of Poseida's technology is the piggyBac transposon system, a non-viral vector method of gene delivery that results in more stable, longer and higher expression of inserted genes than viral vectors allow. In addition, piggyBac can carry upwards of 300 kb cargo — about 20-30 times more than viral vectors — and that capacity lets Poseida engineer its CAR T cells with safety switches, plus two major modifications aimed at improving durability.

The first shifts the CAR T cells away from the predominantly mature effector phenotype that is needed to kill cancer cells but thought to lead to premature exhaustion, and towards a younger stem-cell memory phenotype. Those cells create a pool of cells that yield a steady crop of mature effectors over time. "With piggyBac, we can engineer about 70-80% of the CAR T cells to have this younger phenotype," compared with 15-20% for virus-based delivery systems, de Silva said.

The second modification involves centyrins, a class of human fibronectin type III domain-based molecules exclusively licensed for immuno-oncology applications from the Janssen Biotech unit of Johnson & Johnson. Poseida use centyrins to construct its CARs, which avoids several problems caused by the single-chain variable fragments (scFvs) used in most CARs.

"Antibody fragments used in current CAR T cells are rodent-derived, and so there may be an immune response to them" that wipes out the cells, de Silva said. Moreover, centyrins are more thermally stable than scFvs and "we see no tonic signaling in our CAR T cells indicative of T cell exhaustion."

Poseida's lead product, P-BCMA-101, is a CAR T cell therapy targeting B cell development protein BCMA. In a xenograft mouse model of aggressive multiple myeloma (MM), a single injection of the product eliminated tumors in all 37 mice and extended survival through day 57, whereas all 10 vehicle-treated mice died by day 29. Also in the treated animals, there were multiple instances of tumor relapse and re-elimination in response to the single injection, suggesting the cells had the desired durability.

Poseida plans to submit an IND for P-BCMA-101 to treat relapsed/refractory MM in 2Q17 and begin a Phase I/II trial by year-end.

Kite Pharma Inc., Novartis AG, bluebird bio Inc. and Celgene Corp. have CAR T cells targeting BCMA in preclinical or Phase I testing for MM.

POSEIDA THERAPEUTICS INC., San Diego, Calif.
Technology: CAR T cell therapies engineered for durability using the piggyBac non-viral gene delivery platform
Disease focus: Gene/cell therapy, Cancer
Clinical status: Preclinical
Founded: 2015 by Transposagen Biopharmaceuticals Inc.
University collaborators: None
Corporate partners: Johnson & Johnson
Number of employees: 34
Funds raised: $33 million
Investors: Malin Corp. plc, other undisclosed parties
CEO: Eric Ostertag
Patents: More than 30 issued covering piggyBac and proprietary CRISPR and TALEN gene editing platforms

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Poseida raised $33 million in a series A round in 2015, and is now looking to raise $40-$60 million in series B, to close this half, that will fund the trial and Poseida's earlier programs.

In addition to piggyBac, Poseida has gene editing technology it obtained when it was spun out of Transposagen Biopharmaceuticals Inc. Its CRISPR platform relies on a nuclease other than Cas9 and requires two components to bind the same point in the genome to allow gene editing. It also has a TALEN platform with "a unique architecture" that is different from that used by Cellectis S.A., de Silva said. ∎

COMPANIES AND INSTITUTIONS MENTIONED

bluebird bio Inc. (NASDAQ:BLUE), Cambridge, Mass.
Celgene Corp. (NASDAQ: CELG), Summit, N.J.
Cellectis S.A. (Euronext:ALCLS; NASDAQ:CLLS), Paris, France
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Kite Pharma Inc. (NASDAQ: KITE), Santa Monica, Calif.
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Poseida Therapeutics Inc., San Diego, Calif.
Transposagen Biopharmaceuticals Inc., Lexington, Ky.

TARGETS

Cas9 - CRISPR-associated protein 9
BCMA (TNFRSF17; CD269) - Tumor necrosis factor receptor superfamily member 17

REFERENCES

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PUBLIC FUNDING NOTEBOOK

IMI BRANCHES OUT

By Mark Zipkin, Staff Writer

The Innovative Medicines Initiative (IMI) is broadening its base in its latest call for proposals by bringing in funding partners from the non-profit sector. The new partners will add to the portfolio of projects backed through the EU's Horizon 2020 framework and the European Federation of Pharmaceutical Industries and Associations (EFPIA).

Under the second phase of IMI, "associate partner" non-profits are a core component of the strategy to expand the slate of stakeholders. Catherine Brett, external relations manager for IMI, told BioCentury that although non-profits were able to contribute funds under IMI 1, "that kind of contribution wasn't recognized in a formal way." Under IMI 2 they can now compete on an equal footing with the private sector for matching funds.

The new call is the largest so far under IMI 2, and will include five disease-specific non-profits. The top disease areas to benefit from the change are diabetes and autism.

Diabetes charities JDRF and The Leona M. and Harry B. Helmsley Charitable Trust, who are already involved in IMI, will be joined by T1D Exchange in supporting research into the impact of hypoglycemia on diabetics.

In July 2014, JDRF and the Helmsley Charitable Trust contributed €2.8 million ($3.0 million) and €2.2 million ($2.3 million), respectively, toward the first IMI 2 call, which focused on diabetes detection.

Additionally, the Simons Foundation Autism Research Initiative (SFARI) and Autism Speaks Inc. will support a project to consolidate autism clinical research under a Europe-wide infrastructure to improve trials and validate biomarkers.

IMI also aims to build a pediatric clinical trials network for cancer and other diseases to improve drug development and simplify the process of running a trial.

Pierre Meulien, who completed his first year as executive director of IMI in September 2016, told BioCentury that the project had been incubating for years and the timing was finally right.

"It was not clear how a pediatric pan-European clinical trial network could be set up, but IMI was seen to be the perfect vehicle through which this could work — with benefits obviously for the private sector, because they could run their initial clinical assessments through it," said Meulien. He added that the public

> "We made the data available because we didn't think we had all the answers."
>
> Mark Frasier, MJFF

sector also benefits as the network is open to academic trials as well.

Other projects will focus on building a framework for better engaging patients, prostate cancer and pain, and broader topics such as biomanufacturing and tools for studying genes in the solute carrier family that have been implicated in diabetes, cancer and other diseases.

Half of the €348 million ($368 million) dedicated to the RFP will come from the European Commission and the other half from a combination of EFPIA companies and non-profits.

Going forward, Meulien thinks IMI would benefit from trans-Atlantic cooperation for clinical trials in autism spectrum disorders, towards building "a global capacity to really understand how we can work something out" in that disease, and also sees an opportunity to apply lessons learned from completed IMI-funded projects to new projects.

"We've been doing a lot of work trying to understand what has been the impact and the value, both to the public and private sectors — to understand what a good IMI project is — so that when we strategize going forward, we can learn from what we've done in the past," he said.

TAG TEAMS

A pair of December deals is connecting industry with researchers at Singapore's Agency for Science Technology and Research (A*STAR), both highlighting its Genome Institute of Singapore (GIS). The new agreements brought the total number of public-private partnerships (PPPs) for A*STAR to six for 2016, and underscore the agency's eagerness to work with industry to further its research goals.

That puts A*STAR in the same ballpark for PPPs as NIH, which announced 13 deals with industry in 2016.

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Pierre Meulien, Innovative Medicines Initiative

The first A*STAR deal, announced Dec. 8, will establish a whole-genome sequencing center at GIS. The Singapore-based for-profit organization NovogeneAIT — a joint venture between Beijing Novogene Bioinformatics Technology Co. Ltd. and AITbiotech Pte. Ltd. — will use the center to develop new applications of next-generation sequencing, such as cancer diagnosis and patient stratification, while a range of GIS researchers will have access to the facility.

In the second deal, announced Dec. 13, cancer immunotherapy play Atreca Inc. will jointly fund a lab with A*STAR at GIS to improve and develop technologies that can supplement Atreca's microfluidic technology for single-cell, sequence-based analysis of antibodies produced in the human immune response.

The partnership will improve Atreca's ability to identify genes relating to immune response to pathogens or cancer, including those in B cells, T cells and immunoglobulin superfamily members such as T cell receptors and antibodies.

The approach marks the first time Atreca is supporting a joint lab, a new avenue made possible in part through one of the researchers, Yann Chong Tan, whose findings were key to developing the core technology behind the company. Tan, who is director of the Atreca-GIS Joint Laboratory for Immuno-Oncology, is co-founder and chief technologist at Atreca.

MJFF PICKS PREDICTORS

The Parkinson's Progression Markers Initiative (PPMI) Data Challenge, an open data competition launched by The Michael J. Fox Foundation for Parkinson's Research to stratify patients and find baseline predictors of progression, announced two $25,000 prize winners in November. The winners — Duygu Tosun-Turgut and Fei Wang — analyzed PPMI data to develop algorithms for predicting the speed of Parkinson's disease progression and identifying patient subgroups based on symptoms, respectively.

Tosun-Turgut is assistant professor of radiology and biomedical imaging at University of California San Francisco, and co-director of the Center for Imaging of Neurodegenerative Diseases at San Francisco Veterans Affairs Health Care System. Wang is assistant professor of health care policy and research at Weill Cornell Medical College.

The challenge was set up to ask broad questions, such as "what are the subtypes of PD?" and "what are the baseline predictors of progression?" Mark Frasier, SVP of research programs at MJFF, said the questions were kept broad intentionally, to draw out definitions from the community. "Researchers can define progression very differently, so we wanted to really generate some new ideas and new, creative ways of thinking and responding to these broad questions."

The award, co-sponsored by MJFF and the GE Healthcare unit of General Electric Co., was designed to tap into talent from other disciplines to help solve the problem of how to use clinical data — including brain imaging scans and biospecimens — to improve clinical trial designs. "We made the data available because we didn't think we had all the answers," said Frasier.

Frasier said the steering committee felt the ongoing longitudinal study was at a "tipping point" in terms of having "a large data set right ripe for computational multidimensional, multimodal analyses."

He added that the strategy was "to engage a different research audience that may not be familiar with Parkinson's disease, but would have the analytical and computational experience to really interrogate these large multidimensional data sets."

Commonly, PD researchers consider a single clinical predictor of disease progression, but the robustness of the PPMI dataset allows for multiple factors to be considered and measured. Tosun-Turgut found that a combination of MRI brain scans and a common clinical motor score at baseline could accurately predict progression speed.

"There had been many different MRI studies just characterizing what happens in the brain of people with Parkinson's disease, but never a combination that looked at this baseline predicting a clinical outcome. So I think that was surprising and very exciting," said Frasier.

Wang developed separate classifications based on combinations of observable clinical symptoms such as specific types of motor and cognitive dysfunction. Using these subtypes could aid in the design of clinical trials aimed at treating one PD symptom.

Frasier said one of the most exciting scenarios would be to see clinical trials integrating some of the outcome measures, or using the predictors for patient stratification or patient selection.

Selected publicly funded initiatives from 4Q16 are included in the Public Funding Highlights table (see "Public Funding Highlights"). ▨

COMPANIES AND INSTITUTIONS MENTIONED

Agency for Science Technology and Research (A*STAR), Singapore

AITbiotech Pte. Ltd., Singapore

Atreca Inc., Redwood City, Calif.

Autism Speaks Inc., New York, N.Y.

Beijing Novogene Bioinformatics Technology Co. Ltd., Beijing, China

European Federation of Pharmaceutical Industries and Associations (EFPIA), Brussels, Belgium

General Electric Co. (NYSE:GE), Fairfield, Conn.

Innovative Medicines Initiative (IMI), Brussels, Belgium

JDRF, New York, N.Y.

The Leona M. and Harry B. Helmsley Charitable Trust, New York, N.Y.

The Michael J. Fox Foundation for Parkinson's Research (MJFF), New York, N.Y.

San Francisco Veterans Affairs Health Care System, San Francisco, Calif.

Simons Foundation Autism Research Initiative (SFARI), New York, N.Y.

T1D Exchange, Boston, Mass.

University of California San Francisco, San Francisco, Calif.

Weill Cornell Medical College, New York, N.Y.

PUBLIC FUNDING HIGHLIGHTS

Selected developments and initiatives in 4Q16 from major sources of public funding including **National Institutes of Health** (NIH), the U.K.'s **Medical Research Council** (MRC), the **Innovative Medicines Initiative** (IMI), the **Canadian Institutes of Health Research** (CIHR), the **Agency for Science Technology and Research** (A*STAR) and the **Japan Agency for Medical Research and Development** (AMED).

DATE	AGENCY	SUMMARY	TYPE
Dec. 20	CIHR	Alain Beaudet, president of CIHR, will retire effective March 30. Beaudet has been president since July 2008, and no replacement has yet been appointed.	Management
Dec. 16	MRC	David Lomas, vice provost of health at **University College London**, has been named deputy chief executive of MRC effective Jan. 1. Lomas will continue at UCL through his term, which expires in March 2018.	Management
Dec. 16	A*STAR	A*STAR's Singapore Bioimaging Consortium, a research institute focused on using imaging tools to investigate human health, will collaborate with France's XLIM to develop a sensitive new biosensing platform built on surface-enhanced Raman scattering (SERS) to study biomarkers in body fluids. The platform will produce vibrational "fingerprint" spectra using photonic crystal fiber (PCF) technologies. XLIM is a multidisciplinary institution within the **Centre National de la Recherche Scientifique** (CNRS).	Deals
Dec. 15	MRC	The Global Challenges Research Fund, a £1.5 billion ($1.81 billion) global health program involving five of the seven members of **Research Councils UK** (RCUK), announced its first grant awards through MRC. The fund dedicated £20 million ($24.1 million) to multidisciplinary research on non-communicable diseases and infection in low- and middle-income countries.	Grants
Dec. 14	MRC	The **Dementia Research Institute** named Bart De Strooper its new director. De Strooper is leader of the neurodegenerative diseases research lab at **Catholic University Leuven** and scientific director at Flanders Institute for Biotechnology (VIB). The Dementia Research Institute, a £250 million ($300.9 million) collaboration between MRC, **Alzheimer's Society** and **Alzheimer's Research UK**, was announced last year and is expected to launch by 2020 (see "Transparency from Outside." BioCentury Innovations (April 7, 2016)).	Management
Dec. 9	NIH	James Gilman was named the first CEO of the **NIH Clinical Center**, the largest clinical hospital in the U.S. The center had previously been run by Director John Gallin, who became NIH's associate director for clinical research and CSO.	Management

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DATE	AGENCY	SUMMARY	TYPE
Dec. 8	NIH	Researchers at the **Albert Einstein College of Medicine of Yeshiva University** received an NIH grant to build the **New York Regional Center for Diabetes Translation Research**. The $2.9 million grant will support faculty from Einstein, **New York Academy of Medicine**, the **Icahn School of Medicine at Mount Sinai** and researchers from 16 other institutions conducting collaborative research into treatments for pre-diabetes, diabetes and disease complications.	Grants
Dec. 8	**Foundation for the National Institutes of Health** (FNIH)	The FNIH released the document, Framework for Defining Evidentiary Criteria for Biomarker Qualification, to help define regulatory criteria for biomarker developers. The framework — produced in collaboration with the **U.S. Food and Drug Administration** (FDA), NIH, **Critical Path Institute** and **Pharmaceutical Research and Manufacturers of America** (PhRMA) — sets the level of evidence for qualifying new biomarkers.	Strategy
Dec. 6	**National Health Service** (NHS)	The Medtech Accelerator was launched to promote innovation and spin out new companies from within NHS. The funding mechanism will have £1.5 million ($1.81 million) to use toward developing medical technology, diagnostics and software.	Deals
Nov. 25	CIHR	CIHR's foundation grants section reported a smaller number of applicants than expected from new and early career investigators, leading CIHR to pool the applications with more experienced investigators. CIHR will still guarantee 15% of grantees will be early career investigators. Foundation grants are career-building grants that last five or seven years.	Grants
Nov. 9	MRC	**King's College London** will house a new £3 million ($3.6 million) MRC center, the Centre for Neurodevelopmental Disorders. Researchers at the center will focus on identifying biological mechanisms of disease development in epilepsy, autism and schizophrenia.	Deals
Nov. 8	RCUK	A research partnership between India and U.K. was announced during the India-U.K. Tech Summit. The £80 million ($96 million) program, backed by the Newton Fund, will include a £13 million ($15.6 million) research program between RCUK and the Department of Biotechnology within India's **Ministry of Science & Technology** to fight antimicrobial resistance.	Deals
Nov. 4	NIH	In a recent Open Mike blog, Michael Lauer, NIH's deputy director for extramural research, compared high risk/high reward R21 grants with traditional and longer-term R01 grants. While the popularity of R21's has grown — R01 applications were six times as common in as R21 applications in 2001, but were only twice as common by 2015 — only 15% of successful R21's lead to an R01 application, and only one in three are funded.	Grants
Oct. 25	MRC	MRC named Declan Mulkeen as its new chief of strategy, replacing the outgoing Jim Smith. Mulkeen had been MRC's CSO since 2008. MRC will recruit a new CSO.	Management
Oct. 24	NIH	**National, Heart, Lung, and Blood Institute** (NHLBI) researchers released 8,600 whole genomes through its Trans-Omics for Precision Medicine Program (TOPMed). The genomes were from clinical trials in heart, lung, blood or sleep disorders, and were sequenced in conjunction with the **National Human Genome Research Institute** (NHGRI).	Strategy
Oct. 13	NIH	The **National Institute of Neurological Disorders and Stroke** (NINDS)-led Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative announced a new round of grants totaling $70 million. The grants will help develop new technologies that will improve understanding of brain circuitry. The program funded over $150 million in grants in 2016.	Grants
Oct. 6	NIH	NIH awarded $20 million through its Common Fund for Stimulating Peripheral Activity to Relieve Conditions (SPARC) program. SPARC researchers will work as a consortium to improve understanding of the peripheral nervous system and how it controls organ function, to develop techniques for better treatment of diseases like rheumatoid arthritis and heart failure.	Grants
Oct. 5	MRC	With the goal of helping researchers access funding in the U.K., MRC teamed with Alzheimer's Research UK, Alzheimer's Society, the **British Heart Foundation**, **Cancer Research UK** (CRUK), the **National Centre for the Replacement Refinement and Reduction of Animals in Research**, the **National Institute for Health Research** and **Wellcome Trust** to build an interactive map of funding mechanisms. The career framework laid out by the map allows researchers to compare different career stage awards, their requirements and funding details.	Strategy
Oct. 4	NIH	NIH announced 88 recipients of its annual High-Risk, High-Reward Research program, supported through NIH's Common Fund. Researchers received a total of $127 million that was earmarked for early career scientists, to encourage collaborative and transformative research in immunotherapy, infectious disease, and several other areas.	Grants
Oct. 13	**Government of U.K.**	Chancellor of the Exchequer Philip Hammond announced a £220 million ($265 million) boost to the U.K. life sciences sector in the wake of the country's vote to withdraw from the European Union. The funding includes £100 million ($120 million) for The Biomedical Catalyst (BMC) translational de-risking program and £120 million ($144 million) in tech transfer incentives for British universities. Hammond also plans to expand the Challenger Business Programmes into the life sciences sector.	Deals

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KEEP A COOL HEAD

Neuro Pharmalogics Inc. plans to treat orphan neurological diseases by borrowing the mechanisms by which insect brains survive oxygen deprivation and heat shock. With IP from Florida Atlantic University in hand, the company is focusing on hemiplegic migraines, and thinks the strategy could extend to other neurological diseases including febrile seizures and traumatic brain injury (TBI).

The company is housed in FAU's Tech Runway incubator, and is seeking funding to take it through Phase I.

CSO Ken Dawson-Scully, who is also an associate professor of biological sciences at FAU, told BioCentury that insects prevent their brains from shutting down during hours of oxygen deprivation or large fluctuations in body temperature by dialing down neuronal potassium release, which is controlled by the protein kinase cGMP-dependent type 1 (PRKG1; PKG1) pathway.

"What we figured out is that the process insects use to shut down their brains is the same as the one that drives spreading depolarization waves," which are associated with migraine and head trauma, he said. "We're looking to prevent this spreading depolarization, or stop it cold."

In November, the company licensed patents from FAU covering the use of PRKG1 pathway inhibitors in neurological diseases related to cortical spreading depolarization, oxygen deprivation or heat shock, such as migraine, stroke or febrile seizures, respectively. "Given the breadth of these patents, we think there will be opportunities for a number of programs," said CEO David Muth.

The company is starting with hemiplegic migraines, an orphan disease that involves muscle paralysis or weakness, where it believes targeting the PRKG1 pathway could address the neurobiology driving the pathology instead of just treating the symptoms.

"Historically, people have focused more on treating the inflammation and pain in migraine," Muth said. "Our hypothesis is that we can intervene earlier in these upstream spreading depolarization cascades."

Its first compound is NP-101, an inhibitor of protein phosphatase 2 (PPP2CA; PP2A) that acts downstream of PRKG1 to control potassium efflux. Muth thinks inhibiting PPP2CA will have fewer off-target effects than targeting proteins upstream on the pathway.

Dawson-Scully told BioCentury the compound has already proven safety in the clinic, because the National Cancer Institute (NCI) studied it in Phase I oncology trials in doses about 1,000-10,000 times higher than Neuro Pharmalogics is planning to use, before abandoning it in favor of more potent antitumor agents.

Lixte Biotechnology Holdings Inc. (OTCQB:LIXT), Dual Therapeutics LLC and PEP-Therapy S.A.S. are each developing PPP2CA inhibitors for cancer indications.

Neuro Pharmalogics' next steps include proof-of-concept studies for NP-101 in mammalian models of cortical spreading depolarization.

—-*Karen Tkach*

> "What we figured out is that the process insects use to shut down their brains is the same as the one that drives spreading depolarization waves."
>
> Ken Dawson-Scully, Neuro Pharmalogics

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JET-LAGGED LIVER

A Baylor team has discovered how abnormal circadian rhythms lead to non-alcoholic fatty liver disease (NAFLD) and hepatocellular carcinoma (HCC), and reported on a target whose inhibition may be able to block the progression from the former to the latter.

Chronic disruption of circadian rhythms — for example, in people who frequently travel to different time zones or work night shifts — has long been associated with increased rates of obesity, metabolic disorders, NAFLD and cancer, but the underlying mechanisms were not known.

Last month, in *Cancer Cell*, a team led by Loning Fu and David Moore at Baylor College of Medicine showed that disruption of circadian signaling alone, without any disease-predisposing mutations, was sufficient to cause NAFLD in otherwise healthy, wild-type mice. About 10% of the mice went on to develop HCC.

"When the circadian clock is shifting in the brain, that leads to neuroendocrine dysfunction, which is sufficient to abolish liver homeostasis and liver function," said Fu.

Fu is an associate professor of pediatrics at Baylor; Moore is a professor of molecular and cellular biology.

The duo's team created a mouse model of circadian disruption, in which the animals' established 12-hour light and dark periods were switched. These mice showed increases in liver biomarkers indicative of metabolic syndrome, developed NAFLD and HCC at young ages, and died early compared with mice with normal light and dark cycles.

Using metabolomics and RNA expression profiling, the group found that circadian disruption affected "several hundred pathways in the mice, which led to a coupled increase in fat storage and synthesis in the liver, as well as increased synthesis and accumulation of bile acids," said Fu.

Specifically, the mice showed dysregulation of nuclear receptor-controlled bile acid, cholesterol and foreign chemical metabolic pathways, and increased activation of constitutive androstane receptor (NR1I3; CAR).

Since elevated bile acids had already been shown to promote HCC by activating NR1I3, the team examined whether knockout of NR1I3 could interrupt the link between chronic circadian disruption and HCC.

While knocking out the receptor didn't prevent development of NAFLD or cholestasis in the mice, it did decrease hepatomegaly, liver inflammation, fibrosis and hepatocyte proliferation. Moreover, none of the NR1I3 knockout mice developed HCC.

"Although NR1I3 knockout mice spontaneously develop fatty liver, they don't have downstream inflammatory gene or oncogene activation," said Fu. "So if we inhibit NR1I3, it should significantly decrease the risk of metabolic disorder-induced HCC."

Moore told BioCentury the team is planning to test whether pharmacological inhibition of NR1I3 with an inverse agonist will also prevent HCC in the mice.

In addition, the researchers are looking at human sleep habits as part of a project called the Texas Hepatocellular Carcinoma Consortium, a prospective study aimed

"If we inhibit NR1I3, it should significantly decrease the risk of metabolic disorder-induced HCC."

Loning Fu, Baylor College of Medicine

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Loning Fu, Baylor College of Medicine

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at identifying risk factors for HCC. "We have a project that has a component that is meant to further test the link between circadian disruption in human populations and liver cancer," he said.

Moore said the work is unpatented, and the team has no plans to commercialize the findings at this time. *Kettner, N., et al. "Circadian homeostasis of liver metabolism suppresses hepatocarcinogenesis." Cancer Cell (2016)*

— *Mary Romeo*

POCKETS AGAINST PAIN

Amgen Inc. (NASDAQ:AMGN) is aiming to tackle neuropathic pain by boosting glycine receptor α 3 (GLRA3) activity in the CNS. In a December study, the company presented preclinical data and crystal structures for its GLRA3 positive allosteric modulators (PAMs) that pointed to a new druggable pocket in the target.

Upon glycine binding, GLRA3 triggers chloride ion currents, which mediate inhibitory neurotransmission that dampens pain signals. Jacinthe Gingras, a senior scientist in neuroscience at Amgen and author on the study, told BioCentury that glycine receptors have been recognized as potential pain targets for over a decade, but have been passed over by drug developers so far in favor of lower-hanging fruit that doesn't have to cross the blood-brain barrier.

"Due to the large number of targets that could be engaged in the periphery to modulate pain, pain drug discovery efforts have not focused on central nervous system targets, which require that efficacious compounds cross the blood-brain barrier to access the spinal cord and brain," she said.

In mice with nerve injury, the compound produced pain resistance comparable to that of neuropathic pain drug Lyrica.

In the study, published in *Nature Structural & Molecular Biology*, the Amgen team showed a tricyclic sulfonamide-based compound, AM-1488, lowered the amount of glycine needed to evoke currents through GLRA3 in human cell cultures and mouse brain slices. In mice with nerve injury, the compound produced pain resistance comparable to that of neuropathic pain drug Lyrica pregabalin (see Distillery, Neurology: Pain).

Lyrica is a GABA receptor agonist marketed by Pfizer Inc. (NYSE: PFE) and Eisai Co. Ltd. (Tokyo:4523) for pain; Pfizer also markets the drug for other CNS indications.

Gingras said GLRA3-targeting agents could help patients who are not effectively treated by marketed therapies. "Given that it is such a complex disease, with the standard of care showing limited population-wide relief, we feel it is important to investigate several different portions of the pain pathway and associated targets."

Her team solved the crystal structure of GLRA3 bound to both glycine and AM-3607— an analog of AM-1488 — at 2.6-angstrom (Å) resolution, and found the compound bound a previously unreported allosteric site in the receptor's extracellular domain. Based on this structure, the team hypothesized the compounds promoted GLRA3 activity by stabilizing its glycine binding site. Biochemical experiments confirmed AM-3607 increased GLRA3 affinity for glycine about 200-fold compared with no treatment.

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Gingras thinks that by "illuminating druggable pockets," the structure "will facilitate both forward and reverse engineering" of improved compounds targeting GLRA3 or similar targets in the cysteine-loop family of ligand-gated ion channels.

Amgen did not disclose the IP status or next steps for its GLRA3 PAMs.

Pfizer is also investigating GLRA3 PAMs for pain. Last June, the pharma's Neusentis unit published a *Journal of Biomolecular Screening* study describing *in vitro* screening and identification of a tool GLRA3 PAM, which it said could be a starting point for analgesic development. *Huang, X., et al. "Crystal structures of human glycine receptor α3 bound to a novel class of analgesic potentiators." Nature Structural & Molecular Biology (2016); Stead, C., et al. "Identification of positive allosteric modulators of glycine receptors from a high-throughput screen using a fluorescent membrane potential assay." Journal of Biomolecular Screening (2016)*

— *Karen Tkach*

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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

INDICATION: Inflammatory bowel disease (IBD); Crohn's disease

Patient sample and mouse studies suggest inhibiting *E. coli* qseC could help treat Crohn's disease and ulcerative colitis (UC). In an *E. coli* strain isolated from a patient with Crohn's disease, knockout of qseC decreased numbers of bacterial flagella — a marker of endothelial adhesion and invasion ability associated with Crohn's disease — compared with normal qseC expression. In two mouse models of UC, a qseC inhibitor tool compound decreased a histological score of disease severity compared with no treatment. Next steps could include identifying and testing *E. coli* qseC inhibitors in models of Crohn's disease and UC.

TARGET/MARKER/PATHWAY: *E. coli* sensor protein QseC (qseC)

LICENSING STATUS: Patent and licensing status unavailable

PUBLICATION DETAILS: Rooks, M. et al. *Proc. Natl. Acad. Sci. USA*; published online Dec. 15, 2016

doi:10.1073/pnas.1612836114

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INDICATION: Lupus

Cell culture and mouse studies suggest inhibiting TNFRSF21 could help treat lupus. In spleens from a mouse model of lupus, the number of TNFRSF21-positive follicular helper T (Tfh) cells was higher than in normal mouse spleens. In Tfh cells from the model, an anti-TNFRSF21 mAb decreased IL-21 production — a measure cellular activation — compared with a rat control IgG. In the lupus model, the mAb decreased proteinuria, the number of TNFRSF21-positive T cells in the spleen and serum levels of auto-antibodies against double-stranded DNA and increased survival. Next steps include screening for additional TNFRSF21 inhibitors.

TARGET/MARKER/PATHWAY: Tumor necrosis factor receptor superfamily member 21 (TNFRSF21; DR6)

LICENSING STATUS: Patent application filed; licensing status undisclosed

PUBLICATION DETAILS: Fujikura, D. et al. *Nat. Commun.*; published online Jan. 3, 2017

doi: 10.1038/ncomms13957

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THERAPEUTICS

CANCER

INDICATION: Acute myelogenous leukemia (AML)

Patient sample, cell culture and mouse studies suggest combining cytarabine with SAMHD1 inhibition could help treat AML. In patients, levels of SAMHD1 in myeloblasts correlated with poor overall survival. In primary human AML myeloblasts treated with the generic chemotherapy cytarabine, SAMHD1 knockout or co-treatment with a lentiviral vector encoding a SAMHD1-inhibiting non-human primate protein decreased viability compared with normal SAMHD1 expression or empty vector. In a xenograft mouse model of AML, cytarabine plus tumor-specific SAMHD1 knockout decreased tumor growth and increased survival compared with cytarabine plus normal SAMHD1 expression. In an orthotopic xenograft mouse model of AML, cytarabine plus tumor-specific knockout of SAMHD1 decreased clinical measures of systemic AML and increased survival. Next steps could include identifying SAMHD1 inhibitors.

TARGET/MARKER/PATHWAY: SAM and HD domain containing deoxynucleoside triphosphate triphosphohydrolase 1 (SAMHD1)

LICENSING STATUS: Patent and licensing status undisclosed

PUBLICATION DETAILS: Herold, N. et al. *Nat. Med.*; published online Jan. 9, 2017

doi:10.1038/nm.4265

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INDICATION: Breast cancer

Patient sample, cell culture and mouse studies suggest inhibiting GALNT14 could help treat breast cancer that metastasizes to the lung. In patients, low primary tumor levels of GALNT14 were associated with lung and distal metastasis-free survival. In two lung-metastatic human breast cancer cell lines, GALNT14 knockdown decreased sphere formation compared with normal GALNT14 expression. In an orthotopic xenograft mouse model of lung-metastatic breast cancer, tumor-specific GALNT14 knockdown decreased primary tumor growth. In two other xenograft mouse models of lung-metastatic breast cancer, tumor-specific GALNT14 knockdown decreased the total volume of metastases in the lung. Next steps could include identifying and testing GALNT14 inhibitors.

TARGET/MARKER/PATHWAY: Polypeptide N-acetylgalactosaminyltransferase 14 (GALNT14; GalNAc-T14)

LICENSING STATUS: Patent and licensing status unavailable

PUBLICATION DETAILS: Song, K.-H. et al. *Nat. Commun.*; published online Dec. 16, 2016

doi:10.1038/ncomms13796

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INDICATION: Breast cancer; colorectal cancer; lung cancer

Mouse studies suggest inhibiting IL-4 or its signaling agonist CNS2 could help treat breast, colorectal and lung cancers. In mouse models of the three cancers, homozygous knockout of CNS2 decreased tumor levels of IL-4 and tumor growth compared with heterozygous or normal expression of CNS2. Next steps could include identifying and testing direct IL-4 inhibitors in the models.

TARGET/MARKER/PATHWAY: Interleukin-4 (IL-4; BSF1); conserved non-coding sequence 2 (CNS2)

LICENSING STATUS: Patent and licensing status unavailable

PUBLICATION DETAILS: Shirota, H. et al. *Cancer Immunol. Res.*; published online Dec. 5, 2016

doi:10.1158/2326-6066.CIR-16-0113

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THERAPEUTICS

CANCER

INDICATION: Cervical cancer

Cell culture studies identified a complex of ferrous iron and a phenanthroline analog that could help treat cervical cancer. Chemical synthesis and *in vitro* testing of the ferrous iron complex with phenanthroline analogs yielded a complex that inhibited growth of a human cervical cancer cell line and a human normal liver cell line with IC_{50} values of 0.75 and 23.71 μM, respectively. In the cancer cell line, the complex increased apoptosis compared with vehicle. Next steps could include testing the complex in animal models of cervical cancer.

TARGET/MARKER/PATHWAY: An undetermined target

LICENSING STATUS: Patent and licensing status unavailable

PUBLICATION DETAILS: Xie, L. et al. *J. Med. Chem.*; published online Dec. 7, 2016

doi:10.1021/acs.jmedchem.6b00917

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INDICATION: Colorectal cancer

Patient sample, cell culture and mouse studies suggest inhibiting the long non-coding RNA SNHG5 or its target SPATS2 could help treat colorectal cancer. In patients, levels of SNHG5 and SPATS2 were higher in tumor samples than in adjacent normal tissue, and the tumor levels of SNHG5 correlated with disease progression. In three human colorectal cancer cell lines, knockdown of SNHG5 or SPATS2 increased apoptosis compared with normal SNHG5 and SPATS2 expression. In a xenograft mouse model of colorectal cancer, tumor-specific knockdown of SNHG5 decreased tumor growth compared with normal SNHG5 expression. Next steps could include testing inhibition of SNHG5 or SPATS2 in additional models of colorectal cancer.

TARGET/MARKER/PATHWAY: Small nucleolar RNA host gene 5 (SNHG5); spermatogenesis associated serine rich 2 (SPATS2)

LICENSING STATUS: Patent and licensing status unavailable

PUBLICATION DETAILS: Damas, N. et al. *Nat. Commun.*; published online Dec. 22, 2016

doi:10.1038/ncomms13875

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INDICATION: Leukemia

Cell culture and mouse studies suggest inhibiting IRAK4 could help treat mixed-lineage leukemia (MLL). In HEK cells, shRNA targeting IRAK4 or an IRAK4 inhibitor tool compound increased the stability of wild-type MLL1, but not an oncogenic mutant form, compared with normal IRAK4 expression or vehicle. In MLL cells from patients, another IRAK4 inhibitor tool compound decreased proliferation compared with vehicle. In a xenograft mouse model of MLL, the IRAK4 inhibitors decreased the number of leukemic cells in the blood and increased survival. Next steps include testing the effects of additional MLL1-stabilizing compounds in MLL models.

Bristol-Myers Squibb Co. has an IRAK4 inhibitor in Phase I testing for systemic lupus erythematosus (SLE).

Pfizer Inc. has the IRAK4 inhibitor PF-06650833 in Phase I testing for SLE.

Nimbus Therapeutics LLC has three IRAK4 inhibitors — ND-2110, ND-2158 and ND-346 — in preclinical testing for various autoimmune and cancer indications.

TARGET/MARKER/PATHWAY: Interleukin-1 receptor-associated kinase 4 (IRAK4); myeloid-lymphoid or mixed-lineage leukemia protein (MLL1; MLL; HRX; KMT2A)

LICENSING STATUS: Unpatented; licensing status not applicable

PUBLICATION DETAILS: Liang, K. et al. *Cell*; published online Jan. 5, 2017

doi:10.1016/j.cell.2016.12.011

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CANCER

INDICATION: Lung cancer

Patient sample, cell culture and mouse studies suggest promoting DAXX expression could help treat lung cancer. In patients with non-small cell lung cancer (NSCLC) tumors that overexpressed the metastasis-promoting SNAI2 gene, low levels of DAXX expression correlated with poor overall survival. In human lung cancer cell lines engineered to overexpress SNAI2, DAXX overexpression decreased cell migration and invasiveness compared with normal DAXX expression. In a xenograft mouse model of SNAI2-overexpressing lung cancer, mice, tumor overexpression of DAXX decreased the number of lung metastases. Next steps could include identifying a therapeutic that upregulates DAXX.

TARGET/MARKER/PATHWAY: Death-domain associated protein (DAXX); snail family transcriptional repressor 2 (SNAI2; SLUG)

LICENSING STATUS: Patent and licensing status unavailable

PUBLICATION DETAILS: Lin, C.-W. et al. *Nat. Commun.*; published online Dec. 22, 2016

doi:10.1038/ncomms13867

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CARDIOVASCULAR

INDICATION: Cardiomyopathy

Mouse and cell culture studies suggest inhibiting LY96 could help treat saturated fatty acid-associated cardiomyopathy. In a mouse cardiomyoblast-based assay of apoptosis induced by palmitic acid, siRNA targeting LY96 or an LY96 inhibitor tool compound decreased cell death and pro-inflammatory cytokine levels compared with normal LY96 expression or vehicle. In a mouse model of palmitic acid-induced cardiomyopathy, knockout of LY96 decreased myocardial injury and pro-inflammatory cytokine levels in serum and cardiac tissue compared with normal LY96 expression. Next steps could include testing LY96 inhibition in other cardiomyopathy models.

TARGET/MARKER/PATHWAY: Lymphocyte antigen 96 (LY96; MD2)

LICENSING STATUS: Patent and licensing status unavailable

PUBLICATION DETAILS: Wang, Y. et al. *Nat. Commun.*; published online Jan. 3, 2017

doi:10.1038/ncomms13997

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INFECTIOUS DISEASE

INDICATION: HIV/AIDS

Cell culture studies suggest CRISPR-Cas9 editing of two or three HIV genes could help prevent reactivation of latent HIV in patients. In an HIV-1-infected human cell line expressing Cas9, lentiviral vector-encoded guide RNAs targeting the combination of HIV gag polyprotein and HIV env, or the combination of HIV gag, HIV tat and HIV reverse transcriptase, delayed the formation of syncytia — a marker of breakthrough viral replication — compared with any of the vector-encoded guide RNAs alone. Also in the infected, Cas9-expressing cell line, the guide RNAs targeting HIV gag, tat and reverse transcriptase delayed HIV-1 gene expression compared with any of the guide RNAs alone. Next steps include testing the efficacy of multi-gene editing against additional HIV-1 subtypes and in animal models of HIV infection.

TARGET/MARKER/PATHWAY: CRISPR-associated protein 9 (Cas9); HIV tat protein (HIV tat); HIV reverse transcriptase; HIV gag polyprotein; HIV env

LICENSING STATUS: Unpatented; licensing and partnering status undisclosed

PUBLICATION DETAILS: Wang, G. et al. *Cell Rep.*; published online Dec. 13, 2016

doi:10.1016/j.celrep.2016.11.057

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INFECTIOUS DISEASE

INDICATION: Malaria

Mosquito and mouse studies suggest inhibiting *Plasmodium* ORP1 or ORP2 could help treat malaria. In a three-species model of parasite transmission comprising *P. berghei*, infected mosquitoes and mice infected by mosquito bites, parasitic knockout of ORP1 or ORP2 decreased mosquito transmission of *P. berghei* to mice compared with normal ORP1 and ORP2 expression. In a mouse model of *P. berghei* sporozoite infection, parasitic knockout of ORP1 or ORP2 decreased the number of infected animals. Next steps could include identifying and testing inhibitors of *Plasmodium* ORP1 or ORP2.

TARGET/MARKER/PATHWAY: Plasmodium oocyst rupture protein 1 (ORP1); Plasmodium ORP2
LICENSING STATUS: Patent and licensing status unavailable
PUBLICATION DETAILS: Currà, C. et al. *Nat. Commun.*; published online Dec. 16, 2016
doi:10.1038/ncomms13846
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INDICATION: Sepsis

Mouse studies suggest orexin could help treat septic shock. In a mouse model of lipopolysaccharide (LPS)-induced toxic shock, subcutaneous or intracerebroventricular injection of human orexin decreased levels of pro-inflammatory cytokines in serum and brain tissue and increased body temperature and survival compared with vehicle. Next steps include testing orexin in non-primate models of septic shock.

TARGET/MARKER/PATHWAY: Orexin (Hypocretin; HCRT)
LICENSING STATUS: Patent application filed; available for partnering or licensing
PUBLICATION DETAILS: Ogawa, Y. et al. *eLife*; published online Dec. 30, 2016
doi:10.7554/eLife.21055
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INDICATION: Viral infection

Cell culture and mouse studies suggest inhibiting PLA2G16 could help treat picornaviral infections. In HeLa cells infected with coxsackievirus, enterovirus, human rhinovirus or other picornaviruses, PLA2G16 knockout decreased infectivity by picornaviruses compared with normal PLA2G16 expression. In a mouse model of coxsackievirus infection, PLA2G16 knockout increased survival. Next steps by Haplogen GmbH and Evotec AG include developing PLA2G16 inhibitors.

TARGET/MARKER/PATHWAY: Phospholipase A2 group XVI (PLA2G16)
LICENSING STATUS: Patented; licensed to Haplogen GmbH; available for partnering
PUBLICATION DETAILS: Staring, J. et al. *Nature*; published online Jan. 11, 2017
doi:10.1038/nature21032
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NEUROLOGY

INDICATION: Cognitive dysfunction

In vitro and rat studies suggest agonizing the GRIN2A signaling pathway could help treat age-related cognitive dysfunction. In brain slices from a rat model of the disease, a tool compound that agonizes the GRIN2A pathway increased NMDA receptor-mediated synaptic transmission — a marker of working memory — in pyramidal neurons compared with no treatment. In the model rats, intra-medial prefrontal cortex injection of the GRIN2A pathway agonist increased working memory compared with vehicle. Next steps could include identifying and testing direct GRIN2A agonists in models of cognitive dysfunction.

TARGET/MARKER/PATHWAY: NMDA receptor NR2A subtype (GRIN2A; NR2A); NMDA receptor
LICENSING STATUS: Patent and licensing status unavailable
PUBLICATION DETAILS: McQuail, J. et al. *J. Neurosci.*; published online Dec. 14, 2016
doi:10.1523/JNEUROSCI.2332-16.2016
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INDICATION: Neurology

Mouse studies suggest inhibiting NAT8L could help treat Canavan disease. In a mouse model of the disease, knockout of NAT8L decreased vacuolation of the cerebellum, swelling of Purkinje cell axons and apoptosis in the cerebellar internal granule cell layer — which are all markers of Canavan disease — and increased motor function, thickness of the somatosensory cortex and the area occupied by neurons in the cerebellar internal granule cell layer, compared with normal NAT8L expression. Next steps include identifying and testing NAT8L inhibitors.

TARGET/MARKER/PATHWAY: N-acetyltransferase 8 like (NAT8L)
LICENSING STATUS: Unpatented; available for partnering
PUBLICATION DETAILS: Sohn, J. et al. *J. Neurosci.*; published online Jan. 11, 2017
doi:10.1523/JNEUROSCI.2013-16.2017
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INDICATION: Pain

Cell culture and mouse studies identified a positive allosteric modulator (PAM) of GLRA3 that could help treat neuropathic pain. High throughput screening and chemical synthesis to optimize hits yielded a tricyclic sulfonamide-based GLRA3 PAM that increased analgesia-related glycine-induced synaptic currents in mouse spinal cord slices compared with no treatment. In a mouse model of injury-induced neuropathic pain, the compound decreased mechanical allodynia with potency comparable to Lyrica pregabalin. Next steps by Amgen Inc. could include testing the compound in other models of neuropathic pain (see "Pockets Against Pain").

Pfizer Inc. and Eisai Co. Ltd. market the GABA receptor agonist Lyrica for pain. Pfizer also markets the drug for neuropathy, fibromyalgia syndrome, bipolar disorder, epilepsy and partial onset seizures and has it approved for anxiety, in Phase IV testing for obsessive compulsive disorder (OCD) and in Phase II testing for irritable bowel syndrome (IBS).

TARGET/MARKER/PATHWAY: Glycine receptor α 3 (GLRA3)
LICENSING STATUS: Patent and licensing status undisclosed
PUBLICATION DETAILS: Huang, X. et al. *Nat. Struct. Mol. Biol.*; published online Dec. 19, 2016
doi:10.1038/nsmb.3329
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Innovations
BIOCENTURY

FROM IDEA TO IND

EMERGING COMPANY PROFILE

FINANCE

TRANSLATION IN BRIEF

DISTILLERY

THERAPEUTICS

NEUROLOGY

INDICATION: Spinal muscular atrophy (SMA)

Human sample, cell culture and mouse studies suggest combining inhibition of the long noncoding RNA (lncRNA) SMN-AS1 and promoting full-length SMN2 expression could help treat SMA. In prenatal and postnatal human spinal cord samples, high levels of SMN-AS1 correlated with low levels of SMN — a marker that is decreased in SMA. In cortical neurons from a transgenic mouse model of SMA expressing human SMN2 and SMN-AS1, antisense oligonucleotides (ASOs) targeting SMN-AS1 increased SMN levels compared with scrambled oligos. In the mouse model, subcutaneous injection of a combination of ASOs targeting human SMN-AS1 and a splice-switching oligo that included exon 7 of the SMN2 transcript increased SMN2 levels in the brain and spinal cord and survival compared with either oligo alone. Next steps include optimizing the ASO targeting SMN-AS1.

TARGET/MARKER/PATHWAY: Survival of motor neuron 1 telomeric (SMN1); SMN2; survival motor neuron transcript intron 1 antisense RNA (SMN-AS1)

LICENSING STATUS: Patent application filed; licensing status undisclosed

PUBLICATION DETAILS: d'Ydewalle, C. et al. *Neuron*; published online Dec. 22, 2016

doi:10.1016/j.neuron.2016.11.033

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TECHNIQUES

BIOMARKERS

TECHNOLOGY: Plasma markers

Serum ANG2 levels could help predict responses to anti-CTLA4 or anti-PD-1 mAbs in melanoma patients. In 134 melanoma patients treated with the anti-CTLA4 mAb Yervoy ipilimumab, Yervoy plus a biosimilar of the anti-VEGF mAb bevacizumab, the anti-PD-1 mAb Keytruda pembrolizumab or the anti-PD-1 mAb Opdivo nivolumab, high pretreatment levels of ANG2 in serum were associated with low overall survival post-treatment. Also in the patients, post-treatment serum ANG2 levels that were at least 1.25-fold pretreatment baselines were associated with low overall survival. Next steps could include validating the results in larger patient cohorts.

Bristol-Myers Squibb Co. and Ono Pharmaceutical Co. Ltd. market Yervoy and Opdivo to treat multiple cancers.

Merck & Co. Inc., MRC Technology and Taiho Pharmaceutical Co. Ltd. market Keytruda to treat multiple cancers.

The Genentech Inc. unit of Roche and Chugai Pharmaceutical Co. Ltd. market Avastin bevacizumab to treat multiple cancers.

DESCRIPTION: Serum levels of angiopoietin 2 (ANG2; ANGPT2) to predict response to anti-cytotoxic T-lymphocyte associated protein 4 (CTLA4; CD152) or anti-PD-1 mAbs in melanoma patients

LICENSING STATUS: Patent application filed; available for licensing

PUBLICATION DETAILS: Wu, X. et al. *Cancer Immunol. Res.*; published online Dec. 21, 2016

doi:10.1158/2326-6066.CIR-16-0206

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TECHNOLOGY: SNPs

SNPs on four genes could help predict the risk of primary sclerosing cholangitis. Genome-wide association studies in a total of 4,796 primary sclerosing cholangitis patients and 19,955 healthy volunteers identified independent associations between the disease and SNPs on four genes: FOXP1 (rs80060485), CCDC88B (rs663743), CLEC16A (rs725613) and UBASH3A (rs1893592) . Next steps could include determining the functional significance of the SNPs in primary sclerosing cholangitis.

DESCRIPTION: SNPs on four genes as risk markers for primary sclerosing cholangitis

LICENSING STATUS: Unpatented; unavailable for licensing

PUBLICATION DETAILS: Ji, S.-G. et al. *Nat. Genet.*; published online Dec. 19, 2016

doi:10.1038/ng.3745

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