BIOCENTURY
Innovations
FROM IDEA TO IND

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PRODUCT R&D

A BUG ABOUT ALZHEIMER'S

By Lauren Martz, Associate Editor

Cortexyme Inc. believes it has connected the dots between Alzheimer's and gum disease, outlining a path from the bacteria that cause periodontitis to chronic brain infection with hallmarks of AD. But in a field that has struggled for unity on a causal mechanism, skeptics argue the company's hypothesis leaves too many unanswered questions, and will hit the same clinical hurdles that have confounded β-amyloid inhibitors.

In a *Science Advances* study published last month, Cortexyme and collaborators from eight academic institutions offered a new explanation for the etiology of AD, suggesting it stems from proteolytic enzymes released in the brain by *Porphyromonas gingivalis*.

A constellation of hypotheses for AD have been put forward, centered around β-amyloid and tau, with varying other targets proposed to play a role inside and outside those pathways (see "After Amyloid".)

The idea of a pathogenic trigger dates to the disease's origin in the early 1900s. But while the literature contains numerous studies identifying pathogens that correlate with AD, there have been no convincing papers showing a causal connection.

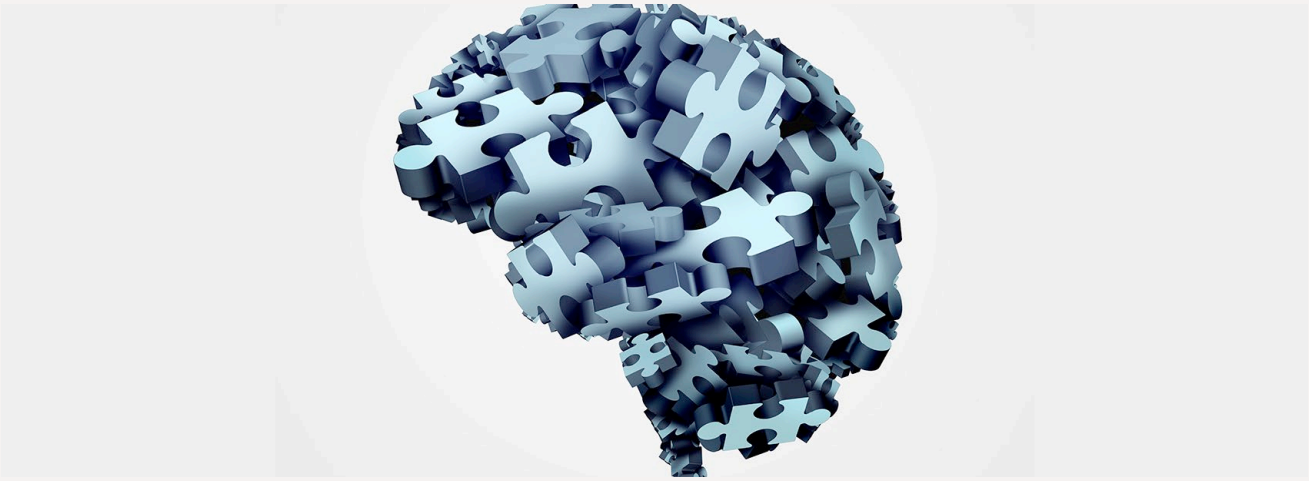
Cortexyme's paper both corroborated a previously reported link between gum disease and AD in humans and connected the two mechanistically, via experiments in cells and mice.

The study showed oral infection with *P. gingivalis* in mice can spread to the brain, where the bacteria release toxic peptidase enzymes — dubbed gingipains — that trigger β-amyloid aggregation and tau tangles. Cortexyme's small molecule gingipain inhibitors blocked neurodegeneration in the animals.

"No other pathogens have triggered the β-amyloid cascade that I'm aware of," co-founder and CSO Stephen Dominy told BioCentury.

On the back of this evidence, Cortexyme has taken the program into the clinic. The company has completed a Phase I trial, and plans to start a Phase II/III trial next half in over 500 mild-to-moderate AD patients.

The company raised a $76 million series B round in 2018 led by Sequoia Capital. At the time Sequoia's Michael Dixon told BioCentury the firm was attracted by the novel mechanism, against the backdrop of clinical failures in the disease. Cortexyme started out in a JLABs incubator



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operated by Johnson & Johnson, and raised $15 million in a series A round led by Pfizer Inc. in 2016 (see "Bacterial Brain").

However, several experts interviewed by BioCentury are doubtful the results will translate.

They suspect *P. gingivalis* infection is only involved in a small subset of AD cases, and don't see how the new mechanism will get around the fundamental problem that has dogged all Alzheimer's interventions to date — identifying patients early enough to have an effect on disease course.

HUMAN INTEREST

Cortexyme used human data as the starting point, rather than relying solely on animal models, which have been poorly predictive in the disease.

The biotech showed 51 of 53 (96%) brain tissue samples from AD patients tested positive for the gingipain RgpB, and 49 of 54 (91%) tested positive for Kgp gingipain; 39% and 52% of samples from non-dementia controls were positive for RgbP and Kgp, respectively.

For each toxin, patient levels were about five times higher than the average in controls ($p<0.0001$ for both toxins).

Gingipain levels were not elevated in postmortem brain samples from patients with Parkinson's disease, Huntington's disease or amyotrophic lateral sclerosis (ALS), suggesting the mechanism is not universal for neurodegeneration.

"Our study stands out because we've shown this to be such a prevalent factor among AD patients," Cortexyme CEO and co-founder Casey Lynch told BioCentury.

But neuroimmunologists who spoke to BioCentury were doubtful that brain infection with *P. gingivalis* is really as common in AD as Cortexyme's data suggest.

"We've seen about 25 or 26 previous studies linking periodontitis to Alzheimer's disease, and none have found the kind of prevalence these guys are reporting. Their study was not that big and needs to be repeated," said Robert Moir, assistant professor in neurology at Massachusetts General Hospital and Harvard Medical School.

However, the large number of variables makes it difficult to draw comparisons across studies, he added.

Dominy noted those other studies did not look for *P. gingivalis* or its peptidases in the brain.

"Studies have shown that approximately 25% of people can harbor low levels of *P. gingivalis* in their mouth without evidence of gum disease," and it is possible for those bacteria to enter the bloodstream and reach distant organs such as the brain, he said.

Another issue is that Cortexyme's human data come from postmortem tissue samples that reflect the state of the brain at the end of the disease and therefore say little about whether the bacteria trigger the pathology.

"The problem is you're dealing with two things so common in old age that you can't prove causality from epidemiological studies. Lots of people have periodontitis, and lots of people get Alzheimer's disease," Howard Fillit, founding executive director and CSO of the Alzheimer's Drug Discovery Foundation, told BioCentury.

"Patients with Alzheimer's have very poor oral health and a weakened blood-brain barrier easily penetrated by pathogens,"

added Moir. "This paper is just one of so many showing pathogens in the AD brain, but it still doesn't answer the question of what came first, the infection or Alzheimer's."

Moir was one of the first scientists to hypothesize that β-amyloid might function as anti-microbial peptide that accumulates in the brain as a byproduct of its role in fighting infection, a view that Cortexyme shares. However, Moir's working hypothesis is that the presence of various microbes in the brain accelerates, rather than initiates, amyloidosis.

Richard Ransohoff, an entrepreneur-in-residence at Third Rock Ventures and former VP and senior research fellow of neuroimmunology at Biogen Inc., noted that the paper failed to describe how the patients and brain samples were characterized to ensure they had bona fide AD. Given the variability in how the disease is diagnosed, "that needs to be done before spending any more money on this mechanism," he said.

When delivered orally to mice, *P. gingivalis* was capable of spreading to the brain. Pre-treatment with two of the company's gingipain inhibitors, or gingipain knockout from *P. gingivalis,* drove down bacterial load in the brain.

Oral infection with *P. gingivalis* increased levels of β-amyloid 42 in a mouse model of the disease ($n=40$, $p<0.001$). When mice were infected with bacteria lacking either of the gingipains, there was no change in the level of β-amyloid 42 over mock-infected controls. β-amyloid 42 is the primary form of the protein that deposits in the brain.

The group tied the mechanism to tau pathology by infecting a neuroblastoma cell line with *P. gingivalis,* which decreased concentrations of soluble tau. In the presence of isolated gingipains, tau cleavage products appeared, suggesting the pathogen cleaved tau into a aggregation-prone form.

> "No other pathogens have triggered the β-amyloid cascade that I'm aware of."
>
> Stephen Dominy, Cortexyme

Last year, NIH's National Institute on Aging and the Alzheimer's Association released a framework for pathologically defining AD called the ATN system, which suggests assessing β-amyloid, tau and neurodegeneration (see "New Framework Advocates Biomarker-Based Definition of AD").

Dominy told BioCentury an independent neuropathologist analyzed the samples for AD pathology and assigned them a pathological grade, which together with a history of dementia confirmed the diagnosis.

In addition, the paper showed higher gingipain levels correlated with tau and ubiquitin load, the latter indicating an increase in misfolded proteins in cells. While not conclusive, those results are consistent with AD and support the claim the toxins are directly tied to the neurotoxicity.

PRECLINICAL POC

Cortexyme performed a series of *in vitro* and mouse studies to establish a mechanistic link and establish preclinical proof of concept for its molecules.

In the same model, one of Cortexyme's gingipain inhibitors decreased cell death compared with vehicle. Neither a broad spectrum antibiotic nor a γ-secretase inhibitor were effective.

Finally, injection of gingipains directly into mouse brains triggered neurodegeneration, and pre-treatment with an oral gingipain inhibitor decreased the number of degenerating cells compared with vehicle.

ATOP THE AMYLOID CASCADE

Cortexyme thinks *P. gingivalis* is an early driver of AD and provided evidence in the paper supporting the hypothesis that β-amyloid is an anti-microbial peptide.

When *P. gingivalis* was incubated with β-amyloid 42, the proportion of dead and dying bacteria increased by about 50% over incubations using a scrambled peptide or vehicle control.

However, Ransohoff, who is highly skeptical of the anti-microbial theory, does not believe the experiment supports the hypothesis.

"These peptides are very sticky. Proving that when they stick to something in a dish it's biologically meaningful is very difficult, so you need to maintain a healthy skepticism," he said.

Moir also isn't convinced. "I'm completely skeptical an endotoxin produced by the bacteria is the trigger here. It flies in the face of so much genetic, biochemical, pathological and histological data" suggesting β-amyloid accumulates independently of the endotoxin, he said.

> "I'm completely skeptical an endotoxin produced by the bacteria is the trigger here. It flies in the face of so much genetic, biochemical, pathological and histological data."
>
> Robert Moir, Harvard Medical School

By placing gingipains atop the amyloid cascade model, Cortexyme runs into additional problems, he said. Chief among them is that if β-amyloid inhibitors are ever going to work, the current thinking is that patients would need treatment as early as possible to see benefit, possibly even before disease onset.

If gingipains act upstream of β-amyloid that logic could extend to their inhibition as well.

"If this infection is accelerating amyloidosis and they can stop it by killing the infection, the only problem is they probably have to do it prodromally," said Moir. "What's come out of the 400+ trials targeting [β-amyloid] is that the field accepts now that once clinical symptoms have popped up, it's too far along in disease progression to help."

But Cortexyme's Lynch thinks early treatment may be less important for the new mechanism because of evidence of disease reversal.

"We think you should be able to help people at any stage by intervening with a gingipain blocker. In mice, toxicity stops, neurodegeneration recedes when it's administered," she said.

Moir countered that animal models of AD haven't been predictive. "Getting rid of [β-amyloid] cures the mouse every time, but it just doesn't in humans."

CORTEXYME'S PATH

Cortexyme's clinical candidate COR338 is an optimized version of the lysine gingipain inhibitor used in the paper. If the upcoming Phase II/III trial is successful, the company will consider testing it in a preventative setting, said Lynch.

She noted the trial will go beyond evaluating the efficacy of the molecule in AD. It will also validate a diagnostic assay for AD, assess effects on patients' periodontal disease and enable the company to dig deeper into the mechanism.

The company's diagnostic assay detects DNA fragments from *P. gingivalis* in the CSF as an indicator of whether the pathogen is present in the brain. The idea is to use the test to identify patients likely to benefit from COR338.

The assay detected *P. gingivalis* DNA in all nine patients in the company's Phase Ib trial, and in 50 out of 50 patient CSF samples from various vendors examined in a separate, larger cohort. Cortexyme will validate the assay further in its next trial.

Mechanistically, Cortexyme will study whether certain strains of *P. gingivalis* are more virulent and likely to cause AD than others, and how much oral and brain infection correlate in humans.

"Our data is indicating oral infection may increase risk, but there is no real direct correlation between the two," said Lynch.

Cortexyme may pursue other neurological indications as well. Because *P. gingivalis* infection was found specifically in the medial temporal gyrus of AD patients, the company is investigating whether infection in other parts of the brain may be behind other conditions.

COMPANIES AND INSTITUTIONS MENTIONED

Alzheimer's Association, Chicago, Ill.
Alzheimer's Drug Discovery Foundation (ADDF), New York, N.Y.
Biogen Inc. (NASDAQ:BIIB), Cambridge, Mass.
Cortexyme Inc., South San Francisco, Calif.
Harvard Medical School, Boston, Mass.
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Massachusetts General Hospital, Boston, Mass.
National Institute on Aging (NIA), Bethesda, Md.
National Institutes of Health (NIH), Bethesda, Md.
Pfizer Inc. (NYSE:PFE), New York, N.Y.

TARGETS

tau (MAPT; FTDP-17) - Microtubule-associated protein τ

WHO_I_AM/ISTOCK/GETTY IMAGES

TOOLS & TECHNIQUES

HEARTENING PREDICTORS IN DIABETES

By Karen Tkach Tuzman, Associate Editor

New biomarkers of cardiovascular risk could relieve a decade-old bottleneck for diabetes drug development, but validating them will require companies to invest in strategic trial designs, and public and private stakeholders to pool thinking.

As diabetes companies await new FDA guidelines that might do away with the blanked requirement for costly post-market cardiovascular outcomes trials (CVOT) that have hampered progress over the last ten years, they also anticipate increased pre-market CV requirements that could negate some of the savings, making it unclear how much new development the change will spur (see "Cashing Out CVOT").

Better biomarkers for predicting major adverse cardiac events (MACE) could trim development costs for both pre- and postmarket diabetes trials. Translational research is starting to identify candidates that, if validated, could enable smaller, shorter trials through improved enrichment for high-risk patients.

A common refrain among experts interviewed by BioCentury is that the CV field needs to take a page from the cancer playbook in its approach to biomarkers.

"There are examples in oncology, for example in breast cancer treatment, where biomarkers are not only used for diagnosis, but also for establishing prognosis and selection of specific therapies," said James Januzzi, professor of medicine at Harvard Medical School and cardiologist at Massachusetts General Hospital. "In cardiovascular disease, there's no reason why we could not do the same."

According to Januzzi, the key to predictive power will be measuring multiple signals at once.

"What we've seen repeatedly is these machine learning-leveraged, multiple-marker panels out-perform traditional single biomarkers every single time," he said.

His retrospective CASABLANCA study of 1,251 patients referred for catheterization laid the groundwork for CV proteomics panels being developed by Prevencio Inc.

The challenge, said Januzzi, is moving from retrospective analyses of previously collected samples to prospectively defined validation studies of biomarker signatures.

That could involve incorporating biomarker validation into Phase II trial designs. But the need for extensive validation data suggests companies might do best to work together in data-sharing consortia.

"In order to not reinvent the wheel, you need to invest in collaborative efforts," said Klaus Romero, director of clinical pharmacology and quantitative medicine at the Critical Path Institute.

There's also an opportunity for closer collaboration between consortia in the CV and diabetes fields, given the large overlap and co-morbidity between the two diseases.

MARKING HEARTS

In the decade since a spate of diabetes studies raised safety concerns that prompted FDA to require CVOTs for all non-insulin diabetes therapies, the number of clinical candidates entering Phase II and Phase III trials has been slashed by about two thirds (see "CVOT Damage in Diabetes").

Yet none of the 15 CVOT studies completed since 2009 found substantial safety hazards, according to a review published last month in *Diabetologia*, while studies of SGLT2 and GLP-1R agonists showed CV benefit. Estimates of the trials' costs come in at $200-$500 million apiece.

Last October, FDA's Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) argued CVOTs should be obligatory only when a safety concern arises in the clinic, but panelists thought premarket safety evaluations should become more thorough in exchange. FDA has not said when it will update its guidance.

The field has already begun enriching CVOT studies for patients with high CV risk using established clinical parameters, but better biomarkers are still needed, said Allan Vaag, VP of early clinical development in the CVRM Translational Medical Unit of AstraZeneca plc.

"Current CV risk factors and markers, including blood pressure and lipids, do not fully account for the excess CV risk in diabetes," said Vaag in comments emailed to BioCentury.

Vaag said AZ is working to identify biomarkers that predict residual CV risk in diabetes patients, which could also be useful for determining which drugs may have CV benefit and identifying new therapeutic targets.

He did not disclose specific biomarkers on the pharma's radar, but said it is exploring multiple data types, including metabolomics, genomics and imaging. "These approaches are often combined," he said.

A group at the University of California San Francisco (UCSF) is using artificial intelligence to mine CV ultrasound data for potential biomarkers (see Box: "Sound Signals").

AZ's diabetes portfolio contains marketed GLP-1R and amylin receptor agonists and SGLT2 and DPP-4 inhibitors. Its clinical pipeline includes a next-generation GLP-1R agonist in Phase

TOOLS & TECHNIQUES

SOUND SIGNALS

Artificial intelligence could enable more reproducible and predictive analyses of CV ultrasounds, a widely used but notoriously noisy imaging modality.

"It's the cheapest, most ubiquitous cardiac imaging test. The problem is, it's the most complex from an image analysis standpoint," said Rima Arnaout, a professor of medicine at University of California San Francisco.

CV ultrasounds are collected by running a probe over ultrasound gel on patients' chests. Because the probe is controlled manually, there are "many degrees of freedom" that lead to images that are noisier and grainier compared with those captured via more formulaic techniques like MRIs and CT scans, said Arnaout.

Arnaout's team is using machine learning to standardize analysis of CV ultrasounds for better accuracy and reproducibility, making it easier to use the approach in large-scale clinical trials.

Such analyses could identify new biomarkers from vast troves of retrospective data. "We might find information in images that is very useful, and already sitting right in front of us, that the human eye doesn't naturally see," said Arnaout.

That could include early predictors of MACE outcomes, but "what specific outcomes you'll be able to predict from what specific images remains to be seen," she said.

She thinks extracting CV outcomes data from a test that's routinely done as part of any CV patient's care will also "lower the activation energy to rigorous prospective research" by avoiding the need for expensive core facilities.

Arnaout said there's still a long way to go before CV ultrasound biomarkers are ready for prime time. "The name of the game is going to be validation, mapping potentially novel biomarkers to well-trusted and well-studied biomarkers."

Her team is open to collaborating with industry, academia and community hospitals. "The way this work is going to move forward is if we break down data silos and expertise silos," said Aranout.

— Karen Tkach Tuzman

II testing, a triple-combination of metformin plus SGLT2 and DPP-4 inhibitors in Phase I, and a β cell regeneration factor in preclinical development.

Based on the CVOT results, AZ is seeking a label extension of CV benefit for its SGLT2 inhibitor Farxiga dapagliflozin and its GLP-1R agonist Bydureon exenatide.

NIH's Ahmed Hasan, acting deputy chief and program director of the Atherothrombosis and Coronary Artery Disease Branch of the National Heart, Lung, and Blood Institute (NHLBI), thinks the most informative biomarkers will be those that can both stratify patients and measure therapeutic response to treatment, similar to some used in cancer. The T790M mutation in EGFR, for example, is used for both purposes in non-small cell lung cancer (NSCLC).

Hasan said several lines of evidence point to inflammation as a key driver of MACE, with CRP emerging as a promising stratification and response marker for CV risk.

Though Januzzi said FDA has been "somewhat conservative" about accepting biomarkers as alternative outcome measures, he thinks the mounting costs of CVOT "megatrials" might lead regulators to consider new evidence.

COLLECTIVE OUTCOMES

Hasan said the history of CV biomarkers like LDL and coronary calcium suggests any new marker will require extensive, repeated validation in large studies.

"After all this work for many years and so much heated debate, coronary calcium was finally accepted as a good biomarker" in the 2018 American Heart Association (AHA) guidelines, he said. "It took a lot of time to prove that point, even though it was visible on CT scans very clearly."

This suggests consortia may be the way to go. And as CV risk biomarkers stand to benefit both the cardiovascular and diabetes fields, it could make sense for stakeholders to collaborate to find biomarkers that meet the requirements for FDA's Biomarker Qualification Program, which would allow the same marker to be used across multiple drug development programs.

So far, all eight biomarkers approved under the program have been submitted by consortia or academic centers, rather than individual companies (see "Biomarkers' Road Less Traveled"). One of the qualified markers is serum levels of cardiac troponin proteins in rats, dogs or monkeys, a readout of preclinical cardiotoxicity that can help pick first-in-human doses. The others relate to respiratory disease, renal function or infectious disease.

> "Current CV risk factors and markers, including blood pressure and lipids, do not fully account for the excess CV risk in diabetes."
>
> Allan Vaag, AstraZeneca

"Alternative means by which to predict outcomes in drug trials, such as the use of biomarkers, is a very testable and plausible approach," said Januzzi.

He wants to see biomarker validation incorporated into late-stage trials.

"The information gained in Phase II with respect to how the drugs affect biomarker panels would be then leveraged to help determine powering considerations for Phase III," he said.

FDA did not return requests for comment in time for publication.

The Cardiac Safety Research Consortium (CSRC) is organizing an April meeting on driving efficiencies in clinical trials through the use of cardiac biomarkers. CSRC is also planning a meeting evaluating heart failure as an off-target event in diabetes drug development, but has not announced a date.

Among the consortium's goals are facilitating research to inform regulatory processes involving cardiac safety. The group participated in the Comprehensive *In Vitro* Proarrhythmia Assay (CiPA) initiative, which worked to replace clinical, electrocardiogram-based thorough QT (tQT) studies with a

faster, less expensive and more specific preclinical assay system. In April, FDA said it would recommend using new method (see "QT Replacement Plan").

Foundation for the National Institutes of Health (FNIH) has sponsored two biomarker consortia related to CV biomarkers. One is assessing the predictive power of pro-hormone NT-proBNP, which is made in response to heart stress and myocardial ischemia, and two troponin complex components on total mortality in the general U.S. population; the other is estimating risk reduction from statin therapy based on *in silico* modeling of biomarkers of atherosclerosis.

Hasan, who participated in the latter consortium, said the group surveyed 88 CV biomarkers and ultimately converged on nine, including NT-proBNP, the inflammatory markers CRP and IL-6, and six clinical measures reflecting blood lipids, hypertension and blood pressure.

AZ is participating in both consortia. While neither is focused on diabetes, AZ's Vaag thinks the findings will still be relevant. "Any knowledge generated from the consortia will benefit the strong CV focus we have in our diabetes drug development," he said.

CSRC and FNIH did not respond to requests for comment.

Romero said C-Path "would be thrilled to explore the starting of consortia-type efforts" on CV risk for diabetes drugs, if stakeholders can align around the right questions and resources.

C-Path's quantitative researchers use machine learning methods to generate hypotheses about sources of variability in patient populations, and incorporate those variables into mathematical models to probe their effects on disease progression or drug response.

But Romero said it's critical to first "fully articulate the drug development need in regulatory terms" by identifying the main issues sponsors and regulators are faced with, and consider a broader array of solutions beyond new surrogate biomarkers.

Sometimes simpler solutions arise that take less time and fewer resources than developing a new biomarker, he said. He cited an example of an undisclosed consortium that combined its members' resources to fill knowledge gaps about how levels of an established biomarker changed over time, which was sufficient to better define clinical endpoints for the disease.

"There is a tendency to jump to the conclusion that all that is needed is new surrogate markers or some novel way of defining the primary endpoints for studies," said Ramos. "If you can get to that point, those will be super valuable solutions," but he added, "you could be missing other attainable goals that could provide same value in a shorter amount of time."

A consortium to address regulatory needs for diabetes drug development would also require companies to pitch in funding and integrate their data, said Ramos. But the payoff would be the ability to learn from past work and develop new resources to optimize the design of future clinical studies, such as a synthetic control arms.

> "What we've seen repeatedly is these machine learning-leveraged, multiple-marker panels out-perform traditional single biomarkers every single time."
>
> James Januzzi, Harvard Medical School

"Why do I need to keep doing the same thing over and over again when I could leverage the power of existing information in a robust and documented way, with a very rigorous regulatory review component behind it, to generate something that sponsors and regulators can use?" said Ramos.

HART NUMBERS

At least one company thinks it could get a CV biomarker qualified on its own, without the help of a consortium. Diagnostics company Prevencio has developed six proteomics-based blood tests for CV signals, including HART CVE, which measures one-year risk of heart attack, stroke or cardiac death: three major underpinnings of MACE composite endpoints.

Prevencio's HART CVE was created via machine learning analyses of 109 serum proteins in 927 patients; 70% of the patients were used in a training set, and the remaining 30% were used for validation.

The analysis identified a four-protein signature in the blood that predicted MACE at one year with an AUC of 0.79 in the validation cohort, along with 64% sensitivity, 76% specificity, 28% positive predictive value and 93% negative predictive value. Data were published in *The American Journal of Cardiology* in 2017.

The four proteins are NT-proBNP; KIM-1, a protein upregulated by kidney cells after renal injury; Opn, a calcium-binding protein

involved in vascular plaque inflammation and calcification; and TIMP1, which inhibits matrix metalloproteases and is associated with plaque rupture.

In a subset of 167 patients with diabetes in the CASABLANCA study, HART CVE predicted one-year MACE with an AUC of 0.80, a sensitivity of 78%, specificity of 69%, positive predictive value of 47% and negative predictive value of 90%. Results were presented at an American Diabetes Association study session last June.

> "There is a tendency to jump to the conclusion that all that is needed is new surrogate markers or some novel way of defining the primary endpoints for studies."
>
> Klaus Ramos, Critical Path Institute

CEO Rhonda Rhyne told BioCentury Prevencio will present data for an additional validation cohort for HART CVE at the American College of Cardiology meeting in March.

Rhyne said Prevencio is in discussions with undisclosed drug developers to use its tests as predictors of outcomes in recent CVOT trials for diabetes drugs and other therapies, and to use multi-protein biomarkers to better understand drug MOAs.

Rhyne said the tests can be used to enrich for high-risk patients, or track whether a drug has cardiotoxic or cardioprotective effects.

She thinks the company's aggregate data on HART CVE could be enough to qualify as a surrogate biomarker under FDA's December guidance document on biomarker qualification, even without the help of a consortium.

"Looking at the guidance, we feel we have the evidence needed to go FDA," said Rhyne.

COMPANIES AND INSTITUTIONS MENTIONED

American College of Cardiology, Washington, D.C.
American Diabetes Association, Arlington, Va.
American Heart Association Inc., Dallas, Texas
AstraZeneca plc (NYSE:AZN; LSE:AZN), London, U.K.
Boehringer Ingelheim GmbH, Ingelheim, Germany
Cardiac Safety Research Consortium, Durham, N.C.
Critical Path Institute, Tuscon, Ariz.
Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
Foundation for the National Institutes of Health, Bethesda, Md.
Harvard Medical School, Boston, Mass.
Massachusetts General Hospital, Boston, Mass.
National Heart, Lung, and Blood Institute (NHLBI), Bethesda, Md.
National Institutes of Health (NIH), Bethesda, Md.
Novo Nordisk A/S (CSE:NOVO B; NYSE:NVO), Bagsvaerd, Denmark
Prevencio Inc., Kirkland, Wash.
University of California San Francisco, San Francisco, Calif.
U.S. Food and Drug Administration (FDA), Silver Spring, Md.

TARGETS

CRP - C-reactive protein
DPP-4 (CD26) - Dipeptidyl peptidase-4
GLP-1R (GLP1R) - Glucagon-like peptide-1 receptor
IL-6 - Interleukin-6
KIM-1 - Kidney injury molecule 1
NT-proBNP - N-terminal pro-brain natriuretic peptide
Opn (Spp1) - Osteopontin
SGLT2 - Sodium-glucose cotransporter 2
TIMP1 - Tissue inhibitor of metalloproteinases 1

EMERGING COMPANY PROFILE

INDALO: INTEGRAL TO FIBROSIS

By Sandi Wong, Staff Writer

Indalo Therapeutics Inc. is targeting the root causes in fibrosis by antagonizing multiple integrins simultaneously to disrupt disease-associated processes, not just those driven by a single integrin or TGFβ signaling.

Indalo President and CEO Robert Jacks said other fibrosis companies focus on the process by which integrins, particularly integrin $\alpha_v\beta_6$, activate transforming growth factor β (TGFβ), but do not address other integrin-mediated fibrotic processes, such as the promotion of fibroblast migration and survival by stiff extracellular matrix (ECM). "We at Indalo are focused on multiple processes in the fibrotic cascade that are all modulated by integrins."

He said targeting a single integrin like $\alpha_v\beta_6$ doesn't affect TGFβ activation by other integrins, some of which may enable TGFβ-independent activation of fibroblasts via direct fibroblast-ECM interactions — a factor not addressed by other therapies.

The company believes that targeting a key set of integrins will have greater antifibrotic efficacy and allow Indalo to target a broader range of tissue types and fibrotic diseases. The strategy could also yield "a better therapeutic index by not having to lean so hard on just one target," said Jacks.

In addition, TGFβ is a master regulator of multiple processes including cell proliferation and migration, immune modulation and wound healing, and according to Jacks, directly targeting TGFβ could induce inflammation and epithelial neoplasia.

Indalo formed with the 2016 merger of Antegrin Therapeutics LLC and Cascadia Therapeutics LLC. Antegrin had a portfolio of small molecule integrin antagonists licensed from St. Louis University; Jacks said Indalo is still working on those compounds. Indalo has in-licensed additional compounds from the university and developed its own portfolio of integrin antagonists.

Its main program encompasses small molecules that inhibit the site integrins use to bind RGD, an ECM peptide motif recognized by many integrins, and thereby antagonize multiple integrins simultaneously. "We want to disrupt key cellular processes that rely on contact of our target integrins with RGD sites on proteins found in pathologic matrix," Jacks said.

Indalo's lead compound, IDL-2965, antagonizes multiple undisclosed integrins, inhibiting consequent TGFβ activation and promotion of fibroblast migration and survival. Jacks said IDL-2965 has shown potent antifibrotic activity in multiple preclinical models, including non-alcoholic steatohepatitis (NASH) and idiopathic pulmonary fibrosis (IPF), at low, oral, once-daily doses. The company has also conducted formal safety and toxicity studies and is "confident we have achieved the optimal benefit-risk profile."

Indalo expects to begin Phase I testing of IDL-2965 for NASH and IPF in healthy volunteers this half and in patients this year. It also expects to present preclinical data for the compound at a scientific meeting as early as 3Q19.

INDALO THERAPEUTICS INC., Cambridge, Mass.
Technology: Small molecules inhibiting RGD binding sites to antagonize multiple integrins
Disease focus: Pulmonary, hepatic
Clinical status: Preclinical
Founded: 2016 by Peter Ruminski, David Griggs, Bill Bradford and Scott Seiwert
University collaborators: St. Louis University
Corporate partners: None
Number of employees: 10
Funds raised: $26 million
Investors: Atlas Venture, F-Prime Capital, BioGenerator, Missouri Technology Corporation and iSelect Fund
CEO: Robert Jacks
Patents: Undisclosed

According to BioCentury's BCIQ database, no other companies are targeting integrins for NASH but at least two have integrin $\alpha_v\beta_6$ inhibitors for IPF: Biogen Inc. has BG00011, a humanized mAb, in Phase II testing; and Pliant Therapeutics Inc. has a small molecule in preclinical development.

No companies have disclosed inhibitors of TGFβ signaling for NASH or liver fibrosis but at least five companies target TGFβ signaling pathway components for other fibrotic indications. The most advanced is Esbriet pirfenidone, a dual TGFB1/TNFα inhibitor Roche markets for IPF. According to the drug's label, common side effects include nausea, abdominal pain, upper respiratory tract infection and skin rash.

The other four have inhibitors in Phase I or Phase II testing for IPF, actinic keratosis, myelofibrosis, pulmonary fibrosis and/or scleroderma.

Indalo has raised $26 million and Jacks said it may raise more funds this year to enable pipeline expansion and support development of IDL-2965.

COMPANIES AND INSTITUTIONS MENTIONED

Biogen Inc. (NASDAQ:BIIB), Cambridge, Mass.
Indalo Therapeutics Inc., Cambridge, Mass.
Pliant Therapeutics Inc., Redwood City, Calif.
Roche (SIX:ROG; OTCQB:RHHBY), Basel, Switzerland
St. Louis University, St. Louis, Mo.

TARGETS

TGFB1 - Transforming growth factor β 1
TNFα - Tumor necrosis factor α

TRANSLATION IN BRIEF

STORM'S RNA MODIFICATION SOFTWARE

By Michael Leviten, Senior Writer

Storm Therapeutics Ltd. has created an algorithm to extend the use of mass spectrometric data to RNA epigenetics. Making it open source, the company plans to put the algorithm in as many hands as possible to yield new therapeutic targets.

In a December paper published on the preprint server *bioRxiv*, Storm scientists teamed up with bioinformatics scientists at the University of Tübingen to describe an open-source algorithm known as NucleicAcidSearchEngine (NASE). This computational platform borrowed from the OpenMS platform used by mass spectrometry operators in the proteomics space and will boost the discovery power of RNA modification teams (see "Taking RNA Epigenetics by Storm").

> "We're trying to make this space accessible to drug discovery and this lets us investigate the role of RNA modifications in disease."
>
> Oliver Rausch, Storm Therapeutics

Storm CSO Oliver Rausch told BioCentury that with over 100 possible RNA modifications, it's a daunting task to analyze mass spec data to uncover each modification on a transcript.

Since RNAs have only four bases it's more difficult to assign a mass spec fragment to the correct parent RNA than it is to proteins that have 20 distinct amino acids.

"We're trying to make this space accessible to drug discovery and this lets us investigate the role of RNA modifications in disease," said Rausch. "We can't do without it."

Storm Senior Scientist Bioinformatics Hendrik Weisser told BioCentury his team developed NASE by adding functions to programs freely available from OpenMS.

The researchers validated the software with three increasingly complex experiments.

First, the team synthesized a 21-base microRNA molecule, added methyl groups at different sites and optimized the program to analyze this relatively simple standard. Next, they showed they could evaluate methylated cytidines throughout a 321 nucleotide long non-coding RNA (lncRNA). And finally, they validated the software using a complex mix of heavily modified human transfer RNAs (tRNAs).

"We looked at over 20 modifications in our tRNA analysis, which is far beyond any previous studies," said Weisser.

Weisser's team compared its algorithm to existing software and concluded NASE was more sensitive and lets researchers track more modifications. It also assigns a statistical significance score so it's quantitatively superior to other programs, Weisser said.

Chuan He told BioCentury the Storm algorithm could be particularly useful for characterizing modifications on relatively abundant RNA species. He is a chemistry professor at University of Chicago and a founder of Accent Therapeutics Inc. (see "Accent on RNA").

In a *Nature* paper published Feb. 6, He's group at University of Chicago showed the transcription factor YTHDF1 is required for optimal PD-1 therapy in mice. The researchers also showed antigen presentation by dendritic cells to cytotoxic T cells is regulated through adenosine methylation of the YTHDF1 RNA.

He's research used mass spectrometry to uncover the RNA modification-related MOA for YTHDF1.

Accent CEO Robert Copeland said: "We believe that much of the rapid innovation and advancement the community has realized over the past decade can be credited to these types of resources."

Targets: PD-1 (PDCD1; CD279) - Programmed cell death 1; YTHDF1 - YTH N6-Methyladenosine RNA binding protein 1

STABILIZING MUTANT PROTEINS

By Sandi Wong, Staff Writer

A team from Novartis Institutes for BioMedical Research (NIBR) and University of British Columbia has hit upon a strategy for treating diseases caused by loss-of-function protein mutations: target allosteric pockets on the mutant proteins to stabilize them.

> "We hope this work can inspire similar precision medicine approaches."
>
> Jean Quancard, NIBR

The team showed the strategy worked on the W580S mutation of MALT1, which causes a form of immunodeficiency, and thinks it can apply to other proteins and diseases.

MALT1 is required for lymphocyte activation and proliferation driven by NF-κB. Loss of MALT1 function caused by the W580S mutation results in low MALT1 levels and activity and low B cell counts. Conversely, aberrantly high wild-type MALT1 activity is associated with some lymphomas and autoimmune diseases.

As reported in a *Nature Chemical Biology* paper last month, the NIBR-UBC team set out to find allosteric inhibitors of wild-type MALT1 for lymphoma and other diseases and identified two compounds, MLT-747 and MLT-748, that inhibited the wild-type protein by binding the allosteric pocket containing the W580 residue. The compound also bound W580S-mutant MALT1; but instead of inhibiting it, the compounds stabilized the protein by acting as a substitute for the indole structure lost in the mutation from tryptophan to serine.

Consequently, the compounds raised levels and activity of mutant MALT1 protein and increased NF-κB signaling in a B cell line derived from a combined immunodeficiency patient homozygous for the W580S mutation (see Distillery).

MLT-748 also increased level of mutant protein and NF-κB activation and signaling in T cells from the patient.

In the paper, the authors wrote that bone marrow transplantation cured the patient from whom the B and T cells were derived, suggesting the compound could help treat patients harboring the W580S mutation as they await transplantation.

They also named methylmalonic aciduria, phenylketonuria and cystic fibrosis as diseases that allosteric stabilizers of mutant proteins might treat.

"We hope this work can inspire similar precision medicine approaches," said study co-leader Jean Quancard, who is NIBR's head of chemistry, musculoskeletal disease.

Targets: MALT1 - Mucosa associated lymphoid tissue lymphoma translocation gene 1; NF-κB (NFKB1; p105; p50) - Nuclear factor of κ light polypeptide gene enhancer in B cells 1

NEW THERAPEUTIC TARGETS AND BIOMARKERS: JANUARY 2019

Select top therapeutic targets and biomarkers covered by BioCentury or added to the BCIQ database during January. 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				
Cancer				
Breast cancer	WW domain containing oxidoreductase (WWOX)	Patient sample, cell culture and mouse studies suggest promoting WWOX expression could help treat metastatic triple-negative breast cancer (TNBC)	**The Ohio State University**	Distillery Therapeutics
Colorectal cancer	Fibrinogen like 1 (FGL1)	Patient sample, cell culture and mouse studies suggest inhibiting FGL1 could help treat colorectal cancer	**Yale University**	Distillery Therapeutics
Liver cancer	Cyclin dependent kinase 20 (CDK20; CCRK)	Patient sample and mouse studies suggest inhibiting CDK20 could help treat non-alcoholic steatohepatitis (NASH)-associated hepatocellular carcinoma (HCC)	**Chinese University of Hong Kong**	Distillery Therapeutics
Renal cancer; lung cancer	Phosphogluconate dehydrogenase (PGD)	Cell culture and mouse studies suggest inhibiting PGD could help treat renal cell carcinoma (RCC) or non-small cell lung cancer (NSCLC)	**The University of Texas MD Anderson Cancer Center**	Distillery Therapeutics
Infectious disease				
Malaria	Plasmodium falciparum serine/threonine protein kinase (P. falciparum PK9)	In vitro and cell culture studies identified two P. falciparum PK9 inhibitors that could help treat malaria	**Duke University**	Distillery Therapeutics
Tuberculosis	Mycobacterium tuberculosis 4'-phosphopantetheinyl transferase (M. tuberculosis PptT)	Cell culture and mouse studies identified an M. tuberculosis PptT inhibitor that could help treat tuberculosis	**Weill Cornell Medicine**	Distillery Therapeutics
Viral infection	Powassan virus protein prM Powassan virus envelope protein E	Mouse studies suggest an mRNA vaccine based on Powassan virus protein prM and envelope protein E could help prevent infection by Powassan virus and other tick-borne flaviviruses	**Washington University School of Medicine**	Distillery Therapeutics
Zika virus	MicroRNA-202 (miR-202)	Mouse and non-human primate (NHP) studies suggest a live-attenuated vaccine engineered to express sequences targeted by four miRNAs, including miR-202, could help prevent Zika viral infection	**National Institutes of Health (NIH)**	Distillery Therapeutics
Musculoskeletal				
Bone repair	Hydroxysteroid 17-β dehydrogenase 2 (HSD17B2)	Cell culture and mouse studies identified a bicyclic HSD17B2 inhibitor that could help treat bone fractures	**ElexoPharm GmbH**	Distillery Therapeutics
Renal				
Renal damage	Aldo-keto reductase family 1 member A1 (AKR1A1)	Mouse studies suggest inhibiting AKR1A1 could help treat acute kidney injury (AKI)	**Case Western Reserve University**	Distillery Therapeutics
Biomarkers				
Infectious disease				
Malaria	Plasmodium falciparum sexual stage protein 17 (P. falciparum PSSP17; PF3D7_1218800)	An assay for detecting P. falciparum PSSP17 in saliva could help rapidly diagnose clinical and subclinical P. falciparum infection at the point of care.	**Johns Hopkins Bloomberg School of Public Health**	Distillery Techniques

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

INDICATION: Osteoarthritis

Patient sample and mouse studies suggest inhibiting the CH25H-RORA axis could help treat osteoarthritis. In patients, mRNA and protein levels of CH25H and RORA, two factors on the cholesterol metabolism pathway in chondrocytes, were higher in damaged cartilage than in adjacent intact cartilage. In two mouse models of osteoarthritis, systemic or joint tissue-specific knockout of CH25H decreased disease-associated cartilage destruction, osteophyte formation and thickening of subchondral bone plate compared with normal CH25H expression. In one of the models, systemic knockout of RORA or an RORA inverse agonist tool compound decreased disease-associated cartilage destruction, osteophyte formation and thickening of subchondral bone plate compared with normal RORA expression or vehicle, respectively. Next steps could include identifying and testing CH25H and RORA inhibitors in the models.

TARGET/MARKER/PATHWAY: Cholesterol 25 hydroxylase (CH25H); RAR-related orphan receptor A (RORA)

LICENSING STATUS: Patent and licensing status unavailable

PUBLICATION DETAILS: Choi, W.-S. et al. *Nature*; published online Feb. 06, 2019

doi:10.1038/s41586-019-0920-1

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CANCER

INDICATION: Acute lymphoblastic leukemia (ALL); melanoma

Mouse studies suggest inhibiting CD95 could help enhance the efficacy of adoptive T cell therapies for melanoma and ALL. In a mouse model of melanoma, adoptive transfer of T cells transduced with a dominant-negative mutant CD95 encoded in a retroviral vector decreased tumor growth and increased survival compared with T cells transduced with empty vector. In a syngeneic model of B cell ALL, T cells expressing the mutant CD95 decreased the number of leukemia cells in the bone marrow. Also in the ALL model, anti-CD19 CAR T cells transduced with the retroviral vector encoding dominant-negative mutant CD95 increased survival compared with CD19-targeting CAR T cells transduced with empty vector. Next steps could include testing the strategy in models of other solid tumors and hematologic malignancies.

Apogenix AG and Canbridge Life Sciences Ltd. have asunercept, a fusion protein consisting of the extracellular domain of CD95 fused to the Fc region of human IgG that inhibits CD95's interactions with its ligand, in Phase II testing for glioblastoma multiforme (GBM). Apogenix also has the product in Phase I testing for myelodysplastic syndrome (MDS) and solid tumors.

ONL Therapeutics Inc. has the CD95 inhibitor ONL101 in preclinical testing for retinal detachment.

ONL also has the CD95 inhibitor ONL1204 in preclinical testing for age-related macular degeneration (AMD) and retinal detachment.

TARGET/MARKER/PATHWAY: Fas receptor (CD95)

LICENSING STATUS: Patent and licensing status unavailable

PUBLICATION DETAILS: Yamamoto, T. et al. *J. Clin. Invest.*; published online Jan. 29, 2019

doi:10.1172/JCI121491

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THERAPEUTICS

CANCER

INDICATION: Bone cancer; sarcoma; brain cancer

Mouse studies suggest CAR T cells targeting B7-H3 could help treat pediatric osteosarcoma, Ewing sarcoma and brain cancer. In tumor samples from 388 patients with pediatric solid tumors and brain tumors, 325 (84%) were positive for B7-H3, with 70% showing high expression. In xenograft mouse models of pediatric osteosarcoma and Ewing sarcoma, CAR T cells targeting B7-H3 decreased tumor growth and increased survival compared with CD19-targeting CAR T cells. In a xenograft mouse model of osteosarcoma, amputation of the affected hind limb followed by the B7-H3-targeting CAR T cells increased survival compared with amputation alone. In two xenograft mouse models of pediatric medulloblastoma, the B7-H3-targeting CAR T cells decreased tumor growth compared with CD19-targeting CAR T cells, and in one of the models, the CAR T cells increased survival. Next steps include Phase I testing of the B7-H3 CAR T cells in adult patients with high-grade brain tumors.

Y-mAbs Therapeutics Inc. and Memorial Sloan Kettering Cancer Center have omburtamab, an iodine 131-radiolabelled humanized mAb targeting B7-H3 in Phase II testing for neuroendocrine tumors, Phase I/II testing for sarcoma and preclinical testing for B7-H3-positive leptomeningeal tumors.

MacroGenics Inc. has enoblituzumab, a humanized mAb against B7-H3, in Phase I testing for melanoma and B7-H3-expressing solid tumors.

MacroGenics also has a B7-H3 antibody-drug conjugate in preclinical testing for solid tumors.

TARGET/MARKER/PATHWAY: B7-H3 (CD276)

LICENSING STATUS: Patented; available for licensing

PUBLICATION DETAILS: Majzner, R. et al. *Can. Immun. Res.*; published online Jan. 17, 2019

doi:10.1158/1078-0432.CCR-18-0432

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INDICATION: Melanoma

In vitro, cell culture and mouse studies identified a quinazolinamine-based STK19 inhibitor that could help treat NRAS-mutant melanoma. *In vitro* screening of a small molecule library and optimization of the top hit yielded a quinazolinamine-based compound that inhibited STK19 with an IC_{50} of 24 nM. In two human NRAS-mutant melanoma cell lines, the compound decreased growth compared with no treatment. In a xenograft mouse model of NRAS-mutant melanoma, the compound decreased tumor growth and increased survival. Next steps include PK/PD studies of the compound.

TARGET/MARKER/PATHWAY: Serine/threonine kinase 19 (STK19); neuroblastoma Ras viral (v-Ras) oncogene (NRAS)

LICENSING STATUS: Patent application filed; unavailable for licensing

PUBLICATION DETAILS: Yin, C. et al. *Cell*; published online Jan. 31, 2019

doi:10.1016/j.cell.2019.01.002

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THERAPEUTICS

CANCER

INDICATION: Mesothelioma

Cell and mouse studies suggest GHRH receptor antagonists could help treat malignant pleural mesothelioma (MPM). In two human-derived MPM cell lines and patient-derived MPM cells, two previously identified GHRH receptor antagonists inhibited growth with IC_50 values of 2.35-3.92 µM. In a xenograft mouse model of MPM, subcutaneous delivery of the compounds decreased tumor growth compared with vehicle. Next steps could include testing the compounds in additional models of MPM.

Biscayne Pharmaceuticals Inc. has BIS-1602, a hypothalamic peptide GHRH receptor antagonist, in preclinical testing for breast, ovarian and prostate cancer.

TARGET/MARKER/PATHWAY: Growth hormone-releasing hormone (GHRH) receptor
LICENSING STATUS: Patented; available for licensing or partnering
PUBLICATION DETAILS: Villanova, T. et al. *Proc. Natl. Acad. Sci. USA*; published online Jan. 18, 2019
doi:10.1073/pnas.1818865116
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INFECTIOUS DISEASE

INDICATION: Cytomegalovirus (CMV)

Mouse studies suggest immune serum from individuals latently infected with CMV could help treat active CMV infection. In a mouse model of CMV reactivation after bone marrow transplant, immune serum from latently infected mice decreased viral replication in spleen, liver and lung compared with serum from infection-naïve mice. In mice with active infection of the K181 clinical isolate of CMV, serum from mice latently infected with K181 decreased viral load in the spleen, whereas in mice infected with three other clinical isolates, serum from the latent K181 mice did not. Next steps could include testing patient-derived immune serum in animal models of CMV.

TARGET/MARKER/PATHWAY: Not applicable
LICENSING STATUS: Patent application filed; licensing status unavailable
PUBLICATION DETAILS: Martins, J. et al. *Science*; published online Jan. 14, 2019
doi:10.1126/science.aat0066
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INDICATION: HIV/AIDS

Cell culture studies identified HIV reverse transcriptase inhibitors that could help treat HIV infection resistant to non-nucleoside reverse transcriptase inhibitors (NNRTIs). Chemical synthesis of dihydrofuropyrimidine-based NNRTIs and cell-based HIV-1 infectivity assays identified 10 compounds that inhibited cell death induced by an HIV-1 strain harboring two NNRTI-resistance mutations with EC_{50} values of 28.8-46.6 nM. *In vitro*, nine of the compounds inhibited wild-type HIV reverse transcriptase with IC_{50} values of 51-130 nM. In a cell-based HIV-1 infectivity assay, eight of the 10 compounds inhibited cell death induced by six other NNRTI-resistant viral strains with EC_{50} values of 0.9-42.3 nM. Next steps could include testing the compounds in mouse models of NNRTI-resistant HIV-1 infection.

TARGET/MARKER/PATHWAY: HIV reverse transcriptase
LICENSING STATUS: Patented; available for licensing
PUBLICATION DETAILS: Kang, D. et al. *J. Med. Chem.*; published online Jan. 9, 2019
doi:10.1021/acs.jmedchem.8b01656
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THERAPEUTICS

INFECTIOUS DISEASE

INDICATION: Infectious

In vitro and mosquito studies identified a quinazoline-based agonist of *A. aegypti* NPYLR7 that could help prevent *A. aegypti* mosquito bites and associated infections. *In vitro* screening of a compound library in agonistic assays, followed by screening of the top hits in an assay designed to detect response of *A. aegypti* mosquitoes to human host odors and carbon dioxide exhalation, yielded a quinazoline-based compound that decreased host-seeking behavior compared with vehicle. In *A. aegypti* mosquitoes exposed to mice, pre-feeding of mosquitoes with the compound decreased their feeding on mouse blood. Next steps include testing the compound in other mosquito species and ticks.

TARGET/MARKER/PATHWAY: Aedes aegypti NPY-like receptor 7 (A. *aegypti* NPYLR7)

LICENSING STATUS: Unpatented; licensing status not applicable; available for partnering

PUBLICATION DETAILS: Duvall, L. et al. *Cell*; published online Feb. 7, 2019

doi:10.1016/j.cell.2018.12.004

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INDICATION: Mycobacterium

Cell culture and mouse studies identified a carboxamide-based inhibitor of *M. tuberculosis* qcrB that could help treat Buruli ulcers, which are caused by *M. ulcerans* infection. In *M. ulcerans* growth assays, bacteria expressing mutant qcrB had lower sensitivity to a previously reported carboxamide-based compound than bacteria expressing the wild-type gene, indicating qcrB as the compound's probable target. In a mouse model of Buruli ulcers, the compound decreased disease-associated swelling and redness in the footpad and bacterial burden in the footpad tissue compared with the generic antibiotics rifampin and streptomycin. In mice, the compound had a plasma half-life of 17.7 hours. Next steps could include testing the efficacy and safety of the compound in mouse models with chronic, severe Buruli ulcers.

Qurient Co. Ltd. and Infectex Ltd. have Q203, an inhibitor of *M. tuberculosis* qcrB, in Phase I testing for tuberculosis.

TARGET/MARKER/PATHWAY: Mycobacterium tuberculosis cytochrome bc1 (M. *tuberculosis* qcrB)

LICENSING STATUS: Patent and licensing status unavailable

PUBLICATION DETAILS: Liu, Y. et al. *Nat. Commun.*; published online Jan. 31, 2019

doi:10.1038/s41467-019-08464-y

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THERAPEUTICS

INFECTIOUS DISEASE

INDICATION: Staphylococcus; Streptococcus; Gram-positive bacterial infection

In vitro, cell culture, mouse, rat and dog studies identified a spiropyrimidinetrione-based bacterial DNA gyrase inhibitor that could help treat *Staphylococcus*, *Streptococcus* and other Gram-positive bacterial infections. Optimization and testing in bacterial growth assays of analogs of a previously reported spiropyrimidinetrione yielded a compound that inhibited *S. aureus* DNA gyrase *in vitro* with an IC_{50} of 7.8 µM. In bacterial cultures, the compound inhibited growth of multiple strains of methicillin-resistant *Staphylococcus aureus* (MRSA) with minimum inhibitory concentration (MIC) values of 0.03-0.125 mg/L; inhibited growth of methicillin-sensitive *S. aureus* (MSSA) and *S. epidermidis*, methicillin-resistant *S. epidermidis*, and *Streptococcus pneumoniae* and *S. pyogenes* with MIC values ≤ 0.03 mg/L; and inhibited growth of *Neisseria gonorrhoeae* with an MIC of 0.06 mg/L. In mouse models of systemic MRSA or MSSA infection, the compound prolonged survival with greater potency than the DNA gyrase and topoisomerase IV inhibitor zoliflodacin (effective doses: 3.87 vs. 11.51 mg/kg and 8.37 vs. 11.03 mg/kg, respectively). The compound had a plasma half-life of 6.2 hours in mice; a plasma half-life and oral bioavailability of 3.71 hours and 22.6%, respectively, in rats; and a plasma half-life and oral bioavailability of 3.65 hours and 96.6%, respectively, in dogs. Next steps could include testing the compound in animal models of additional Gram-positive bacterial infections.

Entasis Therapeutics Inc. has zoliflodacin in Phase II testing for uncomplicated urogenital gonorrhea.

TARGET/MARKER/PATHWAY: DNA gyrase

LICENSING STATUS: Patent and licensing status unavailable

PUBLICATION DETAILS: Shi, C. et al. *J. Med. Chem.*; published online Jan. 30, 2019

doi:10.1021/acs.jmedchem.8b01750

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NEUROLOGY

INDICATION: Depression; neurology

In silico, cell culture and rat studies identified a methanamine-based agonist of 5-HT1A receptor that could help treat depression and other neuropsychiatric diseases. Chemical synthesis, cell-based screening of methanamine analogs in binding assays and *in silico* screening of top hits for measures of drug-likeness yielded a compound (NLX-204) that bound 5-HT1A receptor with a K_i of 26.4 nM. In a rat model of depression, the compound decreased depression-associated immobility compared with vehicle. Next steps by Neurolixis Inc. include testing NLX-204 in other neuropsychiatric indications, such as cognitive deficits in schizophrenia.

Bristol-Myers Squibb Co. markets Buspar buspirone, a 5-HT1A receptor partial agonist, for anxiety.

MediciNova Inc. and Mitsubishi Tanabe Pharma Corp. have the 5-HT1A receptor agonist MN-305 in Phase II/III testing for anxiety and Phase II testing for insomnia.

Neurolixis and Pierre Fabre Group have befiradol, a 5-HT1A receptor full agonist, in Phase II testing for Parkinson's disease (PD).

TARGET/MARKER/PATHWAY: Serotonin (5-HT1A) receptor

LICENSING STATUS: Patent application filed by Neurolixis Inc.; available for licensing or partnering

PUBLICATION DETAILS: Sniecikowska, J. et al. *J. Med. Chem.*; published online Feb. 5, 2019

doi:10.1021/acs.jmedchem.9b00062

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THERAPEUTICS

NEUROLOGY

INDICATION: Neurology

Mouse studies identified a peptide agonist of MAS receptor that could help treat vascular dementia. The compound consists of the first six residues of angiotensin(1-7) – an endogenous peptide ligand of the MAS receptor – linked to a glycosylated and amidated serine to increase the peptide's serum half-life. In a mouse model of inflammation-induced vascular dementia, the compound decreased cognitive impairment and markers of brain inflammation compared with vehicle. Next steps by ProNeurogen Inc. include testing the peptide agonist in patients with vascular dementia, mixed dementia and traumatic brain injury.

MorphoSys AG and Tarix Orphan LLC have TXA127, a lanthionine-stabilized angiotensin(1-7) agonistic peptide, in Phase II testing for muscular dystrophy, Phase I testing for stem cell transplant and preclinical testing for blistering disorder and amyotrophic lateral sclerosis (ALS).

Biophytis S.A. has the MAS receptor agonist Sarconeos in Phase II testing for muscular atrophy and muscular dystrophy.

Biophytis also has the MAS receptor agonist BIO103 in preclinical testing for muscular dystrophy.

TARGET/MARKER/PATHWAY: MAS receptor
LICENSING STATUS: Patented; available for licensing
PUBLICATION DETAILS: Hay, M. et al. *J. Pharmacol. Exp. Ther.*; published online Feb. 1, 2019
doi:10.1124/jpet.118.254854
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INDICATION: Pain

In vitro and rat studies identified a benzimidazole-based PTGER4 antagonist that could help treat pain. High throughput screening of Bayer AG's compound library, *in vitro* enzymatic activity assays and optimization of hits yielded a benzimidazolecarboxylic acid-based compound (BAY 1316957) that antagonized PTGER4 with an IC_{50} of 15.3 nM. In a rat model of prostaglandin E2 (PGE2)-induced pain, the compound decreased mechanical allodynia compared with vehicle. Next steps by Bayer could include testing BAY 1316957 in other mouse models of pain.

AskAt Inc. has the PTGER4 antagonist ARY-007 in Phase II testing for pain and Phase I testing for allergy. AskAt and Arrys Therapeutics Inc. have the compound in preclinical testing for cancer.

Rottapharm Biotech s.r.l. has CR6086, a PTGER4 antagonist, in Phase II testing for rheumatoid arthritis (RA).

Adlai Nortye Biopharma Co. Ltd. has the PTGER4 antagonist AN0025 in Phase I testing for solid tumors.

TARGET/MARKER/PATHWAY: Prostaglandin E2 receptor EP4 subtype (prostanoid EP4 receptor) (PTGER4)
LICENSING STATUS: Patent and licensing status undisclosed
PUBLICATION DETAILS: Bäurle, S. et al. *J. Med. Chem.*; published online Feb. 1, 2019
doi:10.1021/acs.jmedchem.8b01862
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THERAPEUTICS

NEUROLOGY

INDICATION: Pain

Cell culture and rat studies identified an N-acylamino acid-based inhibitor of SLC6A5 that could help treat chronic neuropathic pain. Chemical synthesis and testing of N-acylamino acid analogs in frog cell-based activity assays yielded a compound that inhibited SLC6A5 with an IC_{50} of 48.3 nM. In a rat model of chronic neuropathic pain, the compound decreased allodynia compared with vehicle. In rats, the compound had a plasma half-life of 10 hours. Ongoing work includes optimizing and testing the compound in other models of chronic neuropathic pain.

TARGET/MARKER/PATHWAY: Solute carrier family 6 member 5 (SLC6A5; GlyT2)

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

PUBLICATION DETAILS: Mostyn, S. et al. *J. Med. Chem.*; published online Feb. 4, 2019

doi:10.1021/acs.jmedchem.8b01775

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TECHNIQUES

DRUG DELIVERY

TECHNOLOGY: Other

An ingestible device could enable oral delivery of biologics for injection into the stomach lining. The device is a self-orienting millimeter-scale applicator (SOMA) with a tortoise shape to promote adoption of the correct orientation at the bottom of the stomach, and contains a drug-loaded biodegradable shaft about 1 mm in diameter; gastric fluid entering the shaft dissolves a sucrose and isomalt actuator to trigger spring-powered injection of drug cargo into the mucosa. In pigs, the PK profile of SOMA-delivered insulin was comparable to that of subcutaneously or intragastrically injected insulin. Also in pigs, SOMA-delivered insulin decreased blood glucose levels with potency comparable to the two other routes of injection. Next steps by Novo Nordisk A/S include test the SOMA device in clinical trials.

DESCRIPTION: Ingestible, self-orienting device for oral delivery of biologics for injection into the stomach lining

LICENSING STATUS: Patent applications filed; licensed to Novo Nordisk A/S

PUBLICATION DETAILS: Abramson, A. et al. *Science*; published online Feb. 8, 2019

doi:10.1126/science.aau2277

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