RESEARCH & DEVELOPMENT

BRIEFS

Chemotherapy side effects collaboration underway

RUTHERFORD, N.J.—Cancer Genetics Inc. recently announced a series of multiyear collaborative studies with Moffitt Cancer Center to examine genetic variants to determine their potential as predictors of the most common side effects associated with chemotherapy treatment. The first study will work to validate and improve existing risk prediction indices of acute and delayed chemotherapy-induced nausea and vomiting. The study will ascertain if inclusion of variations of genes involved in metabolizing antiemetic drugs improves the ability to accurately predict patients that are more susceptible to chemotherapy side effects. The second collaboration will investigate how individual genetics variants affect the effectiveness of pain control for cancer patients and will seek out genetic associations for patient-reported pain outcomes. Genetic biomarkers found to be clinically significant in these studies will be integrated into Cancer Genetics' comprehensive pharmacogenomics panels.

Five Prime and bluebird ink CAR T license agreement

CAMBRIDGE, Mass. & SOUTH SAN FRANCISCO, Calif.—An exclusive license agreement was announced in late May between bluebird bio Inc. and Five Prime Therapeutics Inc. for the research, development and commercialization of chimeric antigen receptor (CAR) T cell therapies using Five Prime's proprietary human antibodies. Per the terms of the agreement, bluebird bio gains exclusive rights to Five Prime's human antibodies to an undisclosed cancer target, and will use its own proprietary lentiviral gene therapy platform and CAR T capabilities to develop therapies against the target. bluebird bio will pay $1.5 million up front to Five Prime, as well as subsequent milestone payments.

IN THIS SECTION

ANTI-AMYLOID ANSWER?

Human antibody has potential for treating Alzheimer's disease

BY ILENE SCHNEIDER

WYNNEWOOD, Pa.— An international research team, led by scientists at the Lankenau Institute for Medical Research (LIMR), a non-profit biomedical research organization, reported that it has discovered a human antibody that shows promise as a treatment for Alzheimer's disease (AD). The researchers, who shared their findings in the April 22, 2015, issue of *The Journal of Neuroscience* ("A Human Monoclonal IgG That Binds Aβ Assemblies and Diverse Amyloids Exhibits Anti-Amyloid Activities In Vitro and In Vivo"), said that "naturally occurring human IgGs can recognize a conformational, amyloid-specific epitope and have potent anti-amyloid activities, providing a rationale to test their potential as antibody therapeutics for diverse neurological and other amyloid diseases."

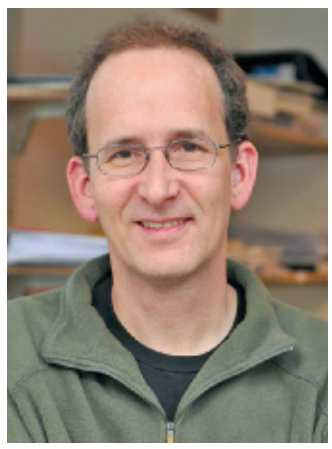
The research was supported by the Sharpe-Strumia Research Foundation of Bryn Mawr Hospital, the Edward N. and Della Thome Memorial Foundation, NIH Grant AG18454 and Science Foundation Ireland.

Building on previous research showing that human serum contains antibodies that recognize and neutralize activity of the toxic beta-amyloid proteins implicated in AD, the researchers wanted to isolate a single human antibody that is highly specific for beta-amyloid aggregates and to determine its possible protective effects in animal models. They discovered such an antibody by studying the immune response of a healthy young volunteer.

LIMR scientist Dr. Scott Dessain has developed a method of isolating and replicating human antibodies produced by the human body to fight infection in their native configurations. The objective is to customize therapy for infectious diseases in a way that circumvents resistance issues usually associated with conventional antibiotics.

Dessain and his LIMR colleagues collaborated with an international research team that included Dr. Yona Levites and Dr. Todd Golde of the University of Florida in Gainesville, Dr. Brian O'Nuallain and Dr. Dominic Walsh of Brigham and Women's Hospital in Boston and Dr. Tomas Ondrejcak and Dr. Michael

LIMR CONTINUED ON PAGE 13



Dr. Scott Dessain of the Lankenau Institute for Medical Research has developed a method of isolating and replicating human antibodies produced by the human body to fight infection in their native configurations; this work may have important implications in the treatment of Alzheimer's disease.

'Homing beacon' for pathogens

UCSD research leads to tool that might help researchers to track and attack pathogenic bacteria

BY ZACK ANCHORS

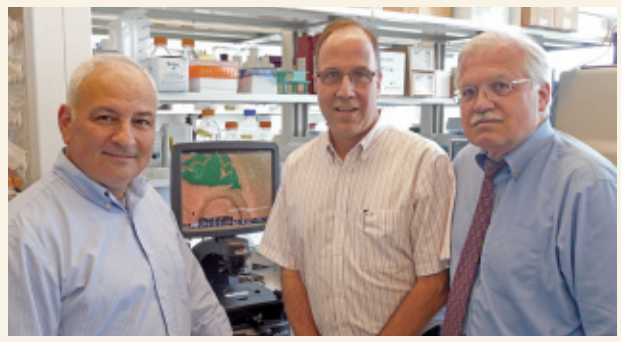
SAN DIEGO—Homing beacons are regularly used to track planes, packages, animals and people, but there's been little effort to use the devices to track bacterial pathogens. A recent study that explored using homing beacons to fight multidrug resistance suggests that may not be the case for long. Researchers at University of California, San Diego's School of Medicine and Skaggs School of Pharmacy and Pharmaceutical Sciences have reported preliminary success tagging bacteria with a "molecular homing beacon" that attracts preexisting antibodies to attack the harmful pathogens.

The researchers involved tell *DDNews* that their study potentially opens up a completely new approach to fighting multidrug resistant bacteria and infectious diseases more generally.

"This is the first essential proof of principle of an entirely novel approach to infectious

UCSD CONTINUED ON PAGE 13

"This is the first essential proof of principle of an entirely novel approach to infectious disease therapy: that natural antibodies present in our body can be redirected to target a pathogen by using the Alphamer as a linker," says Victor Nizet, professor of pediatrics and pharmacy at the University of California, San Diego.



CREDIT: ILSE

Pictured here (left to right) is the ILSE management team in the NJCSTM building labs: Dr. Scott A. Siegel, vice president of business development; Dr. Michael P. Graziano, vice president of research; and Dr. Keith A. Bostian, interim CEO.

A new player in New Jersey

ATCC and ILSE announce establishment of translational microbiology center

BY KELSEY KAUSTINEN

UNION, N.J. & MANASSAS, Va.—In its inaugural partnership, the Institute for Life Science Entrepreneurship (ILSE), a non-profit translational science research integrator, accelerator and incubator, is collaborating with ATCC to establish the ATCC Center for Translational Microbiology (CTM) at ILSE. Per the terms of the multi-year, multi-million-dollar partnership, initial funding to ILSE will enable the recruitment of a 10- to 12-person scientific team and the start-up of research operations. Once the new center is established, additional funding

JERSEY CONTINUED ON PAGE 14

LIMR

CONTINUED FROM PAGE 12

Rowan of Trinity College in Dublin. The team analyzed the immune response of a healthy young person and cloned one antibody, called 3H3, that specifically bound to beta-amyloid aggregates. Not only did 3H3 prevent the formation of toxic aggregates of beta-amyloid protein *in vitro*, it also strongly inhibited the toxic effect of these aggregates in a mouse brain model of human AD.

One of the significant features of the study was the use of an adeno-associated virus to express a 3H3 antibody fragment in the brains of mice prone to developing beta-amyloid deposition similar to AD. In experiments performed by Levites, the antibody was shown to reduce the load of toxic beta-amyloid in this mouse model of AD. Levites then extended the study to show that 3H3 also reduces deposition of a similar aggregated amyloid protein

"This exciting study demonstrates the potential power of the human immune system to make antibodies we can use to treat diseases. After all, the human immune system has evolved to protect us, and the antibodies it makes reflect that critical role. Artificial systems for making antibodies, using rodents or single-celled organisms, have a much harder time replicating such unique and valuable molecules."

Dr. George Prendergast, president and CEO of the Lankenau Institute for Medical Research

in a mouse model of familial Danish dementia. These results suggest that the antibody 3H3 may have value as a potential treatment for AD and other amyloid-related diseases in humans.

Until recently, antibodies have failed to show promise as a potential treatment for AD in clinical trials. However, in March 2015, Biogen released an interim analysis of data from a Phase 1b trial of aducanumab, which, like 3H3, is an antibody with high affinity for binding toxic beta-amyloid aggregates. The early analysis showed that in patients with AD, aducanumab resulted in a reduction in the levels of amyloid plaques in the brain and significant slowing of cognitive and functional decline, compared to placebo.

According to Dr. George Prendergast, president and CEO of LIMR, "This exciting study demonstrates the potential power of the human immune system to make antibodies we can use to treat diseases. After all, the human immune system has evolved to protect us, and the antibodies it makes reflect that critical role. Artificial systems for making antibodies, using rodents or single-celled organisms, have a much harder time replicating such unique and valuable molecules." ■

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UCSD

CONTINUED FROM PAGE 12

disease therapy: that natural antibodies present in our body can be redirected to target a pathogen by using the Alphamer as a linker," Victor Nizet, professor of pediatrics and pharmacy at UC San Diego, tells *DDNews*. Nizet, whose laboratory studies how pathogens interact with the human immune system, participated in the research that resulted in a study published in *Journal of Molecular Medicine*.

The homing beacon used by researchers contains two ends with distinct components. One end is made up of a DNA aptamer, a small piece of DNA that can be selected from a pool of billions of candidates based on its ability to bind tightly to a particular target. In this test case, the aptamer specifically targeted group A *Streptococcus*, the bacteria that causes strep throat and invasive skin infections, while leaving human cells untouched. The other end of the homing beacon is alpha-Gal, a type of sugar molecule. Humans naturally produce antibodies against alpha-Gal, since alpha-Gal is foreign to humans, though other mammals and some microbes produce it. Humans have evolved antibodies against it from eating meat or being exposed to alpha-Gal-generating microbes in the environment.

The idea to use a homing beacon to fight pathogens came from Nobel laureate and study co-author Kary Mullis, who is known as a key pioneer in the area of polymerase chain reaction. Mullis is chief scientific advisor to Altermune Technologies, which funded the study. Nizet tells *DDNews* that Mullis developed the concept after considering the role of alpha-Gal in the human body. Most other animals and some bacteria express the sugar, says Nizet, and through eating meat and exposure to these microbes, humans develop a striking abundance of anti-Gal antibodies, a fact that was first discovered when attempts to transplant a pig heart into a human resulted in immediate rejection, apparently because the anti-Gal antibodies attacked the epitope present on the pig cells.

"Kary Mullis had the idea that instead of having these antibodies get rid of something we want in our body (the transplanted organ), can't we harness them to get rid of something we don't want in our bodies, like a drug-resistant bacterial pathogen. He had been working with aptamers, which can be evolved to bind targets with high affinity through the SELEX procedure, and saw them as a perfect platform to modify with alpha-Gal to direct these preexisting antibodies to their target."

Victor Nizet, professor of pediatrics and pharmacy at UCSD

"Kary Mullis had the idea that instead of having these antibodies get rid of something we want in our body (the transplanted organ), can't we harness them to get rid of something we don't want in our bodies, like a drug-resistant bacterial pathogen," says Nizet. "He had been working with aptamers, which can be evolved to bind targets with high affinity through the SELEX procedure, and saw them as a perfect platform to modify with alpha-Gal to direct these preexisting antibodies to their target."

Researchers tested the homing beacon against live strep bacteria and found that Alphamers can bind strep and recruit anti-Gal antibodies to the bacterial surface and also help human immune cells engulf and kill the Alphamer-coated bacteria. The researchers screened for Alphamers that strongly bound to strep and identifyied the molecular target of the Alphamer on the bacteria. They then showed that Alphamers could redirect preexisting antibodies from human blood/serum to the surface of the strep bacteria in an Alphamer sequence-specific and alpha-Gal-specific fashion. These antibodies promoted neutrophil and whole-blood killing of the bacteria.

According to Nizet, the homing beacon concept should theoretically work just as well for bacterial strains that are highly resistant to multidrug treatments. "A doctor could have a suitcase full of pathogen-specific aptamers to create instant immunity to the pathogen once it is diagnosed," he says. "This conceivably should work for even highly multidrug-resistant strains, as the principle is entirely different than antibiotics. Also, the aptamers would have no effect on the normal human microbiome—all those 'good citizen' bacteria that are so important to our health and immunity."

The study offers the first proof of concept that Alphamers have the potential to specifically redirect preexisting antibodies to bacteria and rapidly activate an antibacterial immune response.

"Our next step is to test Alphamers in animal models of infection with multidrug-resistant bacteria that pose a public health threat, such as MRSA," said first author Sascha Kristian, visiting research scholar at UC San Diego and associate research director at Altermune Technologies. "Meanwhile, we'll also be tweaking the Alphamer to make it more potent and more resistant to degradation by the body."

Nizet says that if Alphamers continue to show promise, researchers might be able to apply the same concept to attack any type of bacteria or virus, or perhaps even cancer cells. ■

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