DDNEWS
PHARMA, BIOTECH & LIFE SCIENCE
MARCH 2015 : VOLUME 11 : NUMBER 3
PUBLISHED SINCE 2005
03.15

Industry-academia attack on GM1-gangliosidosis

Trio of Lysogene, UMass Medical School and Auburn University announce collaboration in CNS disease

BY LLOYD DUNLAP

PARIS—Lysogene, a clinical-stage gene therapy biotechnology company in France, has entered into a strategic collaboration with the University of Massachusetts Medical School (UMMS) in Worcester and Auburn University (AU) in Alabama. Through the collaboration, the three organizations will develop IND-supporting preclinical studies in GM1-gangliosidosis, a rare inherited disorder characterized by severe neurological impairment, using adeno-associated virus (AAV) gene therapy technology.

The collaboration will combine Lysogene's translational and clinical expertise in gene therapy for central nervous system (CNS) disorders with the unique preclinical expertise and infrastructure of UMMS and AU to design and test innovative AAV-based gene therapy approaches to treat GM1-gangliosidosis.

The development of a potential treatment for GM1-gangliosidosis using AAV gene therapy was initiated in 2005 by Dr. Miguel Sena-Esteves, associate professor in the neurology department and the Gene Therapy Center at UMMS, and Dr. Douglas R. Martin, associate professor in the Scott-Ritchey Research Center and department of anatomy, physiology and pharmacology at AU. The approach developed by the investigators uses AAV vectors to treat the entire brain and spinal cord after injection at only a few intracranial sites.

Lysogene and the two U.S academic institutions forged their collaboration on their shared interest for AAV-based gene therapies in CNS disorders, Karen Aiach, founding president and CEO of Lysogene, tells *DDNews*. "More specifically," she adds, "in lysosomal storage disorders (LSDs). Based on in-depth due diligence performed by the company to identify a new, robust and commercially viable target for its pipeline, the two U.S. institutions attracted

TRIO CONTINUED ON PAGE 20

CREDIT: UNIVERSITY OF MASSACHUSETTS

The University of Massachusetts Medical School, the Aaron Lazare Medical Research Building of which is pictured here, is engaged in a collaboration with Paris-based Lysogen and fellow U.S. academic and research institution Auburn University to develop IND-supporting preclinical studies in GM1-gangliosidosis.

TRIO

CONTINUED FROM PAGE 18

Lysogene's interest because of particularly compelling preclinical proof-of-concept data in GM1-gangliosidosis, a model disease for neurological disorders with motor impairment."

Lysogene's ultimate mission is to translate the initial proof of concept into a viable drug development program to the benefit of patients in urgent need. The parties are collaborating on IND-supporting preclinical studies. Under the agreements, Lysogene-sponsored efficacy studies will be performed at both UMMS and AU. The company will also design and execute translational activities, i.e. GMP vector manufacturing, toxicity and biodistribution studies, regulatory affairs, IND procedure and clinical development.

Preclinical studies demonstrated a remarkable extension in lifespan from eight months in untreated GM1 cats to greater than 4.5 years in AAV-treated cats, with dramatic improvements in quality of life. Results were published in *Science Translational Medicine* in 2014.

"We are thrilled by our collaboration with UMMS and AU, which constitutes a significant step towards the development of a treatment for patients affected with GM1-gangliosidosis. For each of these patients and their families, there is currently no option and an urgent need for a safe and effective therapy," according to Aiach. "AAV-based therapies are particularly suitable for inherited disorders of the CNS. In this new program, Lysogene will leverage its unique capacity to develop these therapies and bring them to patients with unmet needs. We will also reinforce our scientific and technology base through our collaboration with leaders in the field."

"Collaborating with Lysogene will allow us to leverage their clinical and translational expertise and advance the development of a gene transfer therapy for treating patients affected with GM1-gangliosidosis," said Sena-Esteves. "In our minds, what ultimately matters is the ability to deliver a treatment to the children suffering from this horrible disease."

GM1-gangliosidosis is a rare, inherited neurodegenerative disorder characterized by severe cognitive and motor developmental delays resulting in death of most patients at a very young age. It is caused by mutations in the GLB1 gene, which encodes an enzyme called beta-galactosidase necessary for recycling of a molecule (GM1-ganglioside) in neurons. This brain lipid is indispensable for normal function, but its overabundance causes neurodegeneration, resulting in the severe neurological symptoms of GM1-gangliosidosis.

LSDs are attractive candidates for gene replacement therapy because they are monogenetic conditions, and genetic correction of a small subset of neural cells may be sufficient to target large regions of the CNS, as secreted lysosomal enzymes can diffuse and be captured by adjacent and distal cells (cross-correction mechanism). Moreover, tight regulation of produced enzyme levels is not required because a low level of enzyme activity (around 10 percent) may be sufficient to have therapeutic effects and conversely supraphysiological levels of many of the acidic hydrolases have no deleterious effect.

In the past decade, recombinant adeno-associated virus (rAAV) approaches have rapidly advanced to the forefront of gene therapy, with hundreds of subjects injected and with no serious adverse events yet reported. According to Lysogene, rAAV vectors are excellent tools in gene therapy for treatment of neurological diseases as they transduce post-mitotic cells that mediate the sustained, long-term gene expression that is required to treat chronic diseases. Injected in the CNS, AAVs can be transported along neuronal connections to distal sites and secreted enzymes can be transported antero and retrograde to cross-correct cells distal from the injection site.

Other AAV serotypes with different expression cassette constructs will be tested in GM1 murine and feline models, as well as new injections routes to determine the optimal approach to be translated to human patients. ■

EDITCONNECT: E031515