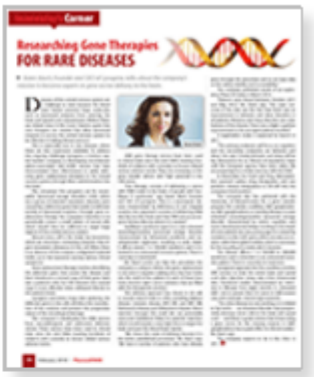
RooneyPartners

PharmaVOICE.com

February 1, 2016

http://www.pharmavoice.com/article/2016-02-gene-therapies-for-rare-diseases

Innovator's Corner



Contributed by:

Karen Aiach, Founder and CE, Lysogene

Researching Gene Therapies for Rare Diseases

Karen Aiach, Founder and CEO of Lysogene, talks about the company's mission to become experts in gene vector delivery to the brain.

Diseases of the central nervous system are a challenge to treat because the blood brain barrier prevents large molecules such as lysosomal enzymes from entering the brain and spinal cord compartment. (Editor's Note: see related story in this issue.) Experts agree that new therapies are needed that allow lysosomal enzymes to access the central nervous system to be effective in halting disease process.

This is especially true in rare diseases where there are few treatments available. To address this ongoing challenge, Lysogene, a venture capital backed company, is developing recombinant adeno-associated viral (rAAV) vectors that have demonstrated their effectiveness in safely delivering gene replacement therapies to the central nervous system, through direct administration into the brain.

The company's first programs are for neuropathic lysosomal storage disorders (LSD), which are a group of inherited metabolic diseases, each caused by a defective gene that results in deficient activity of lysosomal enzymes. Through gene replacement therapy the company's intention is to genetically correct a small subset of neural cells, which should then be sufficient to target large regions of the central nervous system.

Almost every cell in the body has lysosomes, which are structures containing enzymes that digest unwanted substances in the cell. When there is an absence of this enzyme, undigested material builds up in the lysosome causing various clinical symptoms.

Gene replacement therapy involves identifying the defective gene that causes the disease and then introduces a normal copy of that gene back into a patient's cells. For CNS diseases this normal copy is most effective when delivered directly to the patient's brain.

Lysogene executives hope that replacing the defective gene in the cells will allow the manufacture of the enzyme and prevent the progressive nature of the neurological damage.

The company is developing the rAAV vectors from non-pathogenic and replication deficient viruses. These vectors have been used in clinical trials since the mid-1990s treating hundreds of subjects with currently no known related serious adverse events.

rAAV gene therapy vectors have been used in clinical trials since the mid-1990s treating hundreds of subjects with currently no known related serious adverse events. They are emerging as the gene transfer vehicle with high potential in the CNS arena.

"Our therapy consists of delivering a vector with DNA inside to the brain of people with Sanfilippo A syndrome," says Karen Aiach, founder and CEO of Lysogene. "This is a monogenic disease characterized by deficiency in one singular enzyme. Our approach consists of delivering DNA directly into the brain and that DNA acts as an enzyme factory directly where it is needed."

Sanfilippo syndrome type A is a rare inherited neurodegenerative lysosomal storage disorder characterized by behavioral problems and developmental regression resulting in early death. It affects about 1 in 100,000 newborns and is inherited in an autosomal recessive pattern. There is currently no treatment.

Ms. Aiach points out that the procedure the company is using to deliver the gene replacement is not new. It requires making very tiny burr holes into the skull of the patient. In each of these burr holes, doctors inject micro catheters that are filled with the therapeutic product.

This delivery approach has shown to be safe in several clinical trials in LSDs, including Batten's disease, Canavan disease, MPS IIIA, and MPS IIIB; Parkinson's disease; and Alzheimer's disease. Direct injection through this small site can potentially overcome limitations linked to systemic injection, which would require a very high dose to target the brain and pass the blood-brain barrier.

"We chose this route of delivery because it is the better established procedure," Ms. Aiach says. "We have a number of patients who have already gone through the procedure and so we have data on the safety, viability, and acceptability."

The company published results of an exploratory Phase I/II study in March 2014.

"Patients were dosed between October 2011 and May 2012," Ms. Aiach says. "The main outcome of the trial was the fact that there was an improvement in behavior and sleep disorders in all patients. Behavior and sleep disorders are main features of this disease. There was a slight cognitive improvement in the youngest patient enrolled."

A registration study is expected to launch in 2017.

"The primary endpoint will focus on cognition and the secondary endpoints are behavior and sleep," she says. "Clearly behavior and sleep will be key dimensions for us. Almost all regulatory steps with the European agency have been taken. We are preparing for a similar exercise with the FDA."
In November, the Food and Drug Administration granted orphan drug designation and rare pediatric disease designation to LYS-SAF-302, the company's lead product.

The company also has partnered with the University of Massachusetts for a gene transfer program for a similar condition, GM1 gangliosidosis. GM1 gangliosidosis, or Landing disease, is a rare inherited neurodegenerative lysosomal storage disorder characterized by severe cognitive and motor developmental delays resulting in the 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, which is necessary for the recycling of a molecule in neurons.

The disease affects 1 in 100,000 to 200,000 newborns and is inherited in an autosomal recessive pattern. There is currently no treatment.
Lysogene's approach for this condition involves AAV vectors to treat the entire brain and spinal cord after injection using only a few intracranial sites. Preclinical studies demonstrated an extension in lifespan from eight months in untreated GM1 cats to greater than 4.5 years in AAV-treated cats, with dramatic clinical improvements.

"The other disease we are working on is related to Tay-Sachs — an inherited disorder that progressively destroys nerve cells in the brain and spinal cord — and there is great science that shows using a gene vector for the missing enzyme in GM1 gangliosidosis has a great effect in clinical studies," Ms. Aiach says.
The company expects to be in the clinic in 2017. (PV)