Ultrasound-Mediated Gene Therapy - Philips and Glygenix Team Up

One of the clearest trends in medical care is the transition from invasive medical procedures, such as open surgery, to minimally-invasive interventions that typically result in faster procedures with less patient trauma and better outcomes. New minimally-invasive interventions may also enable the treatment of conditions for which no adequate therapy is currently available. Imaging and related technologies are key to guiding minimally-invasive procedures, providing visualization of the target area for treatment, assisting in the proper placement and operation of instruments, and monitoring the progress of the intervention. In a one-of-a-kind collaboration of technologies, Philips Research and GlyGenix Therapeutics are teaming up to research the feasibility of using ultrasound technologies to guide, monitor and control the delivery of therapeutic DNA to the liver in preclinical studies for the treatment of Glycogen Storage Disease Type 1a (GSD-1a).

The collaboration will research the treatment of Glycogen Storage Disease Type 1a (GSD-1a) in preclinical studies. The collaboration unites Philips’ expertise in medical imaging technologies for diagnosis and minimally-invasive medical procedures with GlyGenix’s expertise in correcting the genetic defect in GSD-1a.

Glycogen Storage Disease Type 1a (GSD-1a) is caused by a defective G6Pase gene that prevents the body from producing an enzyme called glucose-6-phosphatase. This enzyme plays a critical role in the conversion of glycogen to glucose in the liver as the body attempts to maintain an adequate blood sugar level between meals. Absence of the enzyme can therefore lead to potentially life-threatening periods of acute hypoglycemia (severely reduced blood sugar). Because the defective gene only impairs the body’s ability to convert glycogen into glucose and not its ability to convert excess glucose into glycogen, the disease also results in excessive glycogen storage – hence the name Glycogen Storage Disease. This typically results in enlargement of the liver, kidneys and small intestine, often with a range of other debilitating comorbidities.

At present, GSD-1a is only managed, not cured. Disease management normally involves stringent dietary regimes to ensure that the body has a continuous but not excessive supply of glucose from dietary sugar and starch. This therapy often involves continuous feeding via nasogastric or gastrostomy tubes, or regular feeding every few hours throughout the day and night. Because treatment must be carried out from a very early age, the disease is particularly distressing in infants and children.

GSD-1a is an inherited disease, with children born to parents who are both carriers of the defective G6Pase gene having a one-in-four chance of suffering from it. Although GSD-1a is a rare disease, currently affecting around 1 in every 100,000 to 200,000 births in the USA, its debilitating nature and impact on quality of life make it a disease that demands worthwhile specialist effort to find better treatments.

One potential cure for GSD-1a is gene therapy, in which non-defective G6Pase gene is introduced into liver cells in the form of a plasmid (a typically circular DNA molecule that is capable of independent replication). By restoring production of the glucose-6-phosphatase enzyme in GSD1a patients, the rigid dietary regimen and associated complications are eliminated, leading to a cure for the disease.
The challenge is to find a way of delivering the G6Pase gene to liver cells. One method that has been explored is to use viral vectors to transport the gene into the cells. Candidate viruses do exist, such as the adeno-associated virus (AAV). However, current gene therapies that use viral vectors to infect cells may carry the risk of an antiviral immune or inflammatory response.

“The potential to deliver genes using a targeted approach will be a significant advance for correcting genetic defects and could offer the prospect of curing hereditary diseases such as GSD-1a,” commented William Fodor, CSO of GlyGenix Therapeutics, Inc. “Philips’ ultrasound-mediated DNA delivery techniques offer the opportunity to deliver genes without the size constraints and limitations of viral packaging systems, and thus open the door to the development of more robust and effective therapeutic genes.”

“Medical imaging systems already play a crucial role in minimally-invasive medical procedures such as opening obstructed arteries, correcting heart rhythm disorders, or sampling tissue biopsies of suspected lesions,” said Henk van Houten, senior vice president of Philips Research and head of the Healthcare research program. “The development of ultrasound techniques that could non-invasively target the delivery of drugs, genes and stem cells to specific parts of the body opens up further possibilities to advance patient care.”

Current gene therapies that rely solely on the bloodstream to deliver corrective gene molecules typically fail to deliver sufficient quantities to the target organs. However, by directing focused ultrasound to target organs following DNA delivery, an increase in uptake via a process known as sonoporation has been successfully demonstrated in pre-clinical studies.

Sonoporation involves the use of microbubbles (microscopic gas-filled spheres made of a biocompatible material such as phospholipid) that will be co-injected into the bloodstream along with the G6Pase gene. Because these microbubbles act as an ultrasound contrast agent, their arrival in the liver (and by inference, the arrival of G6Pase at the liver) can be tracked with an ultrasound scanner.

When they arrive at the liver, the microbubbles will then be subjected to high-energy focused ultrasound pulses at their resonant frequency, causing them to rapidly expand and contract. If the microbubbles are close to a cell wall, their physical deformation or fragmentation increases the porosity of the cell wall to the G6Pase gene. The exact mechanisms involved are not yet fully understood, but it may be that the oscillating microbubbles induce cavitation or microscopic water jets in the surrounding fluid, while fragmentation of the microbubbles may create ballistic fragments that pierce the cell walls. In this application, the microbubbles therefore act as both an imaging agent for guided intervention and as a delivery mechanism for non-invasive therapy. The same ultrasound scanner will also be used to image the liver during the procedure.
Compared to current gene therapies that use viral vectors to infect cells, this ultrasound-mediated technique carries no risk of an anti-viral immune or inflammatory response. In addition, this targeted approach could reduce side effects.

The proposed treatment is known as ultrasound-mediated plasmid DNA (pDNA) delivery. The research program into it will specifically target the expression of a functional human G6Pase therapeutic pDNA to the liver, the primary organ responsible for glycogen storage and glucose release. Pre-clinical studies to investigate the feasibility of the technique will be carried out by Philips Research and GlyGenix Therapeutics in collaboration with the Duke University School of Medicine’s Division of Medical Genetics (Durham, North Carolina, USA) – a recognized leader in GSD-1a diagnosis, managed care, pediatric genetics and experimental models.

GlyGenix Therapeutics, Inc. holds a worldwide exclusive license to the G6Pase gene, protein, and related mutations for the treatment of GSD-1a. GlyGenix will seek to obtain orphan drug designation for the treatment of GSD-1a, which would provide 7 years of market exclusivity.

For Philips, involvement in this joint research work is one of a number of partnerships that will exploit its advanced focused-ultrasound technology. In addition to using co-injected microbubbles to induce sonoporation, it is also exploring the possibility of using focused ultrasound to release drugs from drug-loaded microbubbles and nanoparticles to achieve targeted drug delivery, and the possibility of using it for thermal ablation therapy. These initiatives include Philips’ leadership of the European Union (EU) SonoDrugs project.