ENCODING GLUCOSE CONTROL

By Lauren Martz, Senior Writer

Renova Therapeutics has licensed a gene therapy technology for Type II diabetes from the University of California San Diego that could control blood glucose levels for years with only a single injection. By discovering a new role for the paracrine peptide UCN2, the company believes it has a fresh angle on the long search to bypass the peaks and troughs of standard therapies.

Renova’s lead product RT-100 (Ad5.hAC6), a Phase II gene therapy for congestive heart failure, is slated to enter a pivotal trial by year end. Now, the company is focusing on building its preclinical pipeline by using gene therapy to deliver paracrine factors.

Although researchers have been investigating gene therapy of insulin to treat Type I diabetes since the advent of the technology, there’s been little success and no companies have ongoing programs, according to BioCentury’s BCIQ database. In the last six years, the modality has been used to express leptin in the brain, or genes that promote β cell production in the pancreas, but none of those approaches has yet reached the clinic.

Last month, a team led by Renova founder and UCSD professor of medicine Kirk Hammond showed a single IV injection of a gene therapy vector expressing UCN2 normalized blood glucose levels in mouse models of diabetes for the full 18-week duration of the experiment.

The target is involved in arterial vasodilation, and had not previously been linked to downregulation of glucose levels. But Hammond’s lab at UCSD — which operates independently from Renova — discovered the association by accident when testing gene therapy of UCN2 in mouse models of heart failure, where the team expected the peptide would increase cardiac output and decrease blood pressure.

“During the course of those studies, we made the serendipitous discovery that fasting blood glucose levels were lower in normal mice treated with the gene therapy,” said Hammond. He noted that in the intended indication, UCN2 produced “marked positive effects on the failing heart.”

According to Hammond, the Regents of the University of California have filed several patent applications covering UCN2 gene transfer for Type II diabetes and Renova has exclusively licensed the IP.

GENETICALLY GOVERNING GLUCOSE

After finding that UCN2 delivery can decrease glucose levels in healthy animals, Hammond’s group tested whether the results would extend to models of diabetes.

The researchers used two rat models of Type II diabetes: one of insulin resistance induced by a high-fat diet and the other induced by genetic manipulation. In both models, a single IV infusion of an adeno-associated viral (AAV) serotype 8 (AAV8) vector expressing UCN2 decreased glucose levels and increased glucose tolerance compared with vehicle or an AAV8 vector encoding a control gene. The gene therapy also increased insulin sensitivity in the high-fat diet model.
While the term of this experiment demonstrated the glucose-lowering effect lasts at least 18 weeks, a previous study from Hammond’s group showed the therapy increased plasma levels of UCN2 for at least seven months. Hammond told BioCentury that he also has unpublished data suggesting the effects last the lifetime of the animal, which is about 20 months.

The AAV8 vector primarily accumulated in the liver, but also targeted the left ventricle, which suggested the two locations served as sites of UCN2 production and secretion.

To determine how UCN2 lowered glucose levels, the team cultured skeletal myotubes with the UCN2 peptide and found it induced plasma membrane translocation of GLUT4 as well as activation of AMPK — two effects that likely explain the improved glucose control, according to Hammond.

He noted that insulin causes the same GLUT4 translocation effect, which increases the uptake of glucose by skeletal muscle cells, whereas AMPK activation stimulates glucose uptake in several tissues.

Data were published in JCI Insight.

In addition to the long-lasting effects, the UCN2 gene therapy could provide at least three other advantages over insulin, Hammond said.

First, the therapy “appears also to attenuate weight gain, unlike insulin which increases weight gain,” said Hammond.

Second, the therapy decreased fatty infiltration of the liver in both diabetes models.

Finally, the treatment also had beneficial effects on both heart and β cell function.

Hammond’s group has completed biodistribution and toxicology studies on an AAV8 vector encoding UCN2 and will report the data by the end of the year.

Renova is developing the AAV8-encoded UCN2 for diabetes as RT-200. Richard McCloskey, EVP of clinical development at Renova, said the company is currently selecting the best vector to deliver the gene in the clinic.

Hammond said FDA has requested non-human primate studies, which will be conducted in the first half of 2017, prior to beginning a Phase II study in Type II diabetes patients. The company hopes to begin a clinical trial in the second half of next year.

PARACRINE POSITION

Hammond said the UCN2 product fits squarely in Renova’s strategy of using gene therapy to increase levels of paracrine factors that can help treat cardiovascular and metabolic diseases, such as those that control insulin production and glucose uptake.

Paracrine factors such as UCN2 are signals that cells secrete to communicate with other cells in their immediate vicinity. Hammond believes that using gene therapy can get around the short-range action and short half-lives that hamper development of the factors as peptide-based therapeutics.

“The UCN2 peptide would require continuous infusion because its plasma half-life is ten minutes. The therapy requires gene transfer,” said Hammond, adding, “the benefits last only as long as the peptide is present.”

Neurocrine Biosciences Inc. discontinued development of its urocortin 2 peptide for congestive heart failure. Hammond noted the UCN2 peptide’s short half-life limits its therapeutic benefit.

“The advantage of this treatment is that a single intravenous injection of AAV8 vector encoding UCN2 would work for years with no additional treatments required,” he said.
In addition, paracrine factors are good fit for gene therapy because they are secreted, said Hammond. Under normal conditions paracrine factors generally act locally and are not released into systemic circulation. But the gene therapy is designed to secrete the proteins from any target tissue into plasma. That means the vector doesn’t have to selectively deliver the gene to the target tissue, but can deliver it to any tissue, as long as it releases the peptide product into circulation — a particular benefit for conditions affecting hard-to-access organs like the heart.

The company has two other paracrine factor-based gene therapies in preclinical testing, RT-210 and RT-300, which are in development for Type II diabetes and congestive heart failure, respectively. The genes encoded are undisclosed.

COMPANIES AND INSTITUTIONS MENTIONED

Neurocrine Biosciences Inc. (NASDAQ:NBIX), San Diego, Calif.
Renova Therapeutics, San Diego, Calif.
University of California San Diego, La Jolla, Calif.

TARGETS AND COMPOUNDS

AMPK - AMP-activated protein kinase
GLUT4 (SLC2A4) - Solute carrier family 2 facilitated glucose transporter member 4
UCN2 - Urocortin 2

REFERENCES


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