



New Data Support Use of EKOS Technology for Improving Delivery of Gene Therapy; Novel Approach May Help Overcome Limitations of Current Delivery Techniques

BOTHELL, Wash., July 18, 2001-A new study indicates that ultrasound could play an important role in delivering gene therapy to target sites in the body, potentially making such treatment safer and more effective. The research appears in the current issue of the Journal of the American College of Cardiology.

The preclinical study found that applying ultrasound directly in the area where gene therapy was administered resulted in greater uptake of the gene into tissue compared to standard administration without ultrasound. This improvement was manifested by a dramatic increase in the amount of gene-encoded protein produced in the region of treatment, proving that the genes not only reached the target site but were also viable and functioning.

"These findings are exciting because they suggest that ultrasound may provide a useful method to enhance the delivery of therapeutic genes, and thus could help move us to a point where gene therapy can finally become a practical and effective treatment option," said Michael Dake, MD, chief of cardiovascular and interventional radiology at Stanford University Medical Center and the study's lead investigator.

Need for New Approaches

Gene therapy holds much promise to dramatically alter the treatment of many types of medical conditions, including vascular disease. Typically, the specific genes needed to treat the disease are inserted into viruses that serve as the vectors, or carriers, of the genetic information. The vectors are then injected into patients, where the altered virus is taken up into target tissue. Once there, the gene makes, or expresses, the encoded protein.

Although the viruses used to carry genes are partially inactivated, they can still cause tissue injury when administered in the doses necessary for effective gene delivery. In an attempt to overcome this problem, researchers have turned to the use of plasmids as an alternative vector. Plasmids are small pieces of viral material that react less with human tissue because they are not complete organisms. However, plasmid-mediated gene therapy has previously proved too inefficient for practical use; that is, not enough of the gene reaches the target tissue to produce the desired effect. As a result, one of the biggest obstacles to more widespread use of gene therapy has been finding a mechanism to deliver genes more efficiently and more safely.

Ultrasound offers one possible solution. Ultrasonic energy causes a temporary change in the structure of many types of tissue. When this occurs, small gaps are created that allow the genetic vector to more readily penetrate into the tissue where its effects are needed.

More Efficient than the Current Standard

One of the most immediate potential uses of gene therapy is to prevent restenosis, or reblockage, of heart arteries after angioplasty or stenting. Because of this, the Stanford study was designed to assess how the use of ultrasound affected the expression of genes in vascular tissue -- in this case, a leg artery -- after the vessel had been exposed to angioplasty. To test the approach, gene therapy was first administered in one of two ways, either using a virus or a plasmid as the vector. Then within these two groups, half of the arteries were treated only with gene therapy and the other half were treated with gene therapy combined with ultrasound using EKOS' LYSUS™ system.

Researchers found that in the plasmid group, the addition of ultrasound enhanced gene expression by 12-fold compared with nonultrasound controls. The result was even more dramatic in the viral group, where ultrasound resulted in a 19-fold increase. Furthermore, the use of plasmid-mediated gene therapy plus ultrasound was found to be more efficient than the current standard of viral-mediated gene therapy alone. All of these differences were statistically significant. The researchers also demonstrated that the addition of ultrasound was safe, especially in the plasmid group.

"This study suggests that ultrasound is a flexible tool that could be used in conjunction with gene therapy either to decrease the amount of virus to safer levels or, more promisingly, to employ safer nonviral strategies with enhanced efficiency," Dr. Dake noted. "These options now require further study to confirm and quantify the effects in a human model."

The LYSUS System

The LYSUS device is a miniaturized catheter that is placed directly at the treatment site. A drug or therapeutic molecule is infused through the catheter to the tip, where a tiny ultrasound transmitter is located. The system allows ultrasound and agent to be administered simultaneously, enhancing movement of the therapy into target tissue.

In addition to its potential application in gene therapy, the LYSUS system is currently undergoing initial clinical evaluation for the treatment of stroke, where the device is being tested in conjunction with clot-dissolving therapy.

EKOS Corporation, located in Bothell, Washington, develops proprietary ultrasound-based systems and devices for local drug delivery. Such "active drug delivery" is designed to enhance drug action, reduce dosage requirements and toxicity, and deliver drugs to areas where none can effectively penetrate with standard techniques. EKOS is currently focusing its research and development efforts in the areas of ultrasound-enhanced thrombolysis for treatment of stroke and peripheral vascular occlusion as well as in gene therapy for prevention of coronary restenosis.