

Inhalable gene therapy may help pulmonary arterial hypertension patients

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The deadly condition known as pulmonary arterial hypertension (PAH), which afflicts up to 150,000 Americans each year, may be reversible by using an inhalable gene therapy, report an international team of researchers led by investigators at the Cardiovascular Research Center at Icahn School of Medicine at Mount Sinai.

In their new study, reported in the July 30 issue of the journal *Circulation*, scientists demonstrated that [gene therapy](#) administered through a [nebulizer](#)-like inhalation device can completely reverse PAH in rat models of the disease. In the lab, researchers also showed in [pulmonary artery](#) PAH patient [tissue samples](#) reduced expression of the SERCA2a, an enzyme critical for proper pumping of [calcium](#) in calcium compartments within the cells. SERCA2a gene therapy could be sought as a promising [therapeutic intervention](#) in PAH.

"The gene therapy could be delivered very easily to patients through simple inhalation—just like the way nebulizers work to treat [asthma](#)," says study co-senior investigator Roger J. Hajjar, MD, Director of the Cardiovascular Research Center and the Arthur & Janet C. Ross Professor of Medicine and Professor of Gene & Cell at Icahn School of Medicine at Mount Sinai. "We are excited about testing this therapy in PAH patients who are in critical need of intervention."

This same SERCA2a dysfunction also occurs in heart failure. This new study utilizes the same gene therapy currently being tested in patients to reverse congestive heart failure in a large phase III clinical trial in the

United States and Europe.

"What we have shown is that gene therapy restores function of this crucial enzyme in diseased lungs," says Dr. Hajjar. "We are delighted with these new findings because it suggests that a gene therapy that is already showing great benefit in congestive heart failure patients may be able to help PAH patients who currently have no good treatment options—and are in critical need of a life sustaining therapy."

When SERCA2a is down-regulated, calcium stays longer in the cells than it should, and it induces pathways that lead to overgrowth of new and enlarged cells. According to researchers, the delivery of the SERCA2a gene produces SERCA2a enzymes, which helps both heart and lung cells restore their proper use of calcium.

"We are now on a path toward PAH patient clinical trials in the near future," says Dr. Hajjar, who developed the gene therapy approach. Studies in large animal models are now underway. SERCA2a gene therapy has already been approved by the National Institutes of Health for human study.

A Simple Inhalation Corrects Deadly Dysfunction

PAH most commonly results from heart failure in the left side of the heart or from a pulmonary embolism, when clots in the legs travel to the lungs and cause blockages. When the lung is damaged from these conditions, the tissue starts to quickly produce new and enlarged cells, which narrows pulmonary arteries. This increases the pressure inside them. The high pressure in these arteries resists the heart's effort to pump through them and the blood flow between the heart and lungs is reduced. The right side of the heart then must overcome the resistance and work harder to push the blood through the pulmonary arteries into the lungs. Over time, the right ventricle becomes thickened and enlarged

and heart failure develops.

The gene therapy that Dr. Hajjar developed uses a modified adeno-associated viral-vector that is derived from a parvovirus. It works by introducing a healthy SERCA2a gene into cells, but this gene does not incorporate into a patient's chromosome, according to the study's lead author, Lahouaria Hadri, PhD, an Instructor of Medicine in Cardiology at Icahn School of Medicine at Mount Sinai.

"The clinical trials in congestive heart failure have shown already that the gene therapy is very safe," says Dr. Hadri. Between 40-50 percent of individuals have antecedent antibodies to the adeno-associated vectors, so potential patients need to be screened before gene therapy to make sure they are eligible to receive the vectors. In patients without antibodies, the restorative enzyme gene therapy does not cause an immune response, according to Dr. Hadri.

The clinical application of the gene therapy for patients with PAH will most likely differ from those with heart failure. The replacement gene needs to be injected through the coronary arteries of [heart failure](#) patients using catheters, while in PAH patients, the gene will need to be administered through inhalation.

Provided by The Mount Sinai Hospital

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