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## **Jefferson Scientists Use Gene Therapy to Reverse Heart Failure in Animals**

**Heart researchers at the Center for Translational Medicine at Jefferson Medical College have used gene therapy to reverse heart failure in animals. In addition, they found that this gene therapy strategy had “unique and additive effects” to currently used, standard heart failure drugs called beta-blockers.**

**Reporting in the American Heart Association journal *Circulation*, researchers led by Walter J. Koch, Ph.D., director of the Center for Translational Medicine and the George Zallie and Family Laboratory for Cardiovascular Gene Therapy in the Department of Medicine at Jefferson Medical College of Thomas Jefferson University in Philadelphia, used a virus to carry the gene for a protein, S100A1, into the heart cells of rats with heart failure. The virus expressed the S100A1 gene only in heart cells and not in other organs, essentially making it a tailored therapy. After 18 weeks, those animals that received the gene therapy had significantly improved heart function compared to animals that did not receive the treatment.**

**Specifically, the Koch team, including Patrick Most, M.D., and Joseph Rabinowitz, Ph.D., also in Jefferson’s Center for Translational Medicine, experimentally produced heart failure in the animals, which is characterized by a dramatic reduction in the heart’s pumping ability. The scientists then delivered a modified adeno-associated virus (AAV) that contained the S100A1 gene to the heart’s coronary arteries with the help of a novel heart-specific “gene promoter” that enabled the gene to be present only in heart cells.**

**The rats with heart failure were then followed for another two months, when their heart pumping function was monitored again. The animals that received the gene therapy had significantly better heart-pumping abilities compared to the pre-gene therapy level, and overall, the S100A1-treated rats had improved heart health. The researchers found this in both individual heart cells and in the whole animal as well.**

**The researchers also discovered that the S100A1 gene therapy changed the geometry of the heart. In heart failure, the heart tends to increase in size. The added S100A1 slowed down this process and actually reversed it.**

**According to Dr. Koch, who is also W.W. Smith Professor of Medicine at Jefferson Medical College, the added S100A1 appears to improve calcium signaling in heart cells, which is critical to the force of contraction of individual cells.**

**In another arm of the study, the scientists looked at the effects of beta-blockers alone or in combination with the S100A1 gene therapy. They found that beta-blockers only partially rescued the animals’ hearts in failure and that S100A1 gene therapy alone was significantly better at improving heart function in the model. “Importantly, the combination of the two was also therapeutic and in some indices studied there were additive effects,” Dr. Koch notes. “However, it should be stressed that the beta-blocker could stop progression of heart failure in this model. S100A1 gene therapy not only**

**stopped progression but reversed damage and actually improved the heart's performance."**

**Last fall, Dr. Koch and his team found that increasing levels of the protein S100A1 above normal helped protect animal hearts from further damage after simulated heart attacks. In some cases, the animals' heart function hardly changed at all even when a large percentage of the heart muscle had died. At the same time, other animals with heart cells lacking the gene for the protein couldn't handle the stress of part of the heart dying and went on to develop heart failure.**

**S100A1, part of a larger family of proteins called S100, is primarily found at high levels in muscle, particularly the heart. Falling levels of S100A1 are critical in the loss of heart-pumping strength after a heart attack and play an important role in the progression to heart failure. Previous studies by other researchers showed that the protein was reduced by as much as 50 percent in patients with heart failure.**

**Several years ago, Dr. Koch and his co-workers put the human gene that makes S100A1 into a mouse, and found a resulting increase in the heart cell's ability to contract. The mouse hearts worked better and had stronger beats. In subsequent work, he and co-workers used gene therapy to restore S100A1 levels – and heart function – to normal in failing animal hearts.**

**These results have significant implications for the future therapy of heart failure in humans, Dr. Koch says. "The use of the novel gene promoter to ensure the therapeutic gene is only expressed in heart cells increases the safety of the gene therapy for human use."**

**Congestive heart failure affects nearly five million Americans, many of whom have poor long-term prognoses, despite recent therapeutic advances.**