

Public Lecture by H. Kirk Hammond, M.D., Professor
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“Gene Therapy for Heart Failure”
Wednesday, May 18, 2005 at 7:00 p.m. in the Garren Auditorium, Basic Science Building
Sponsored by the Sam & Rose Stein Institute for Research on Aging, UCSD

Heart failure affects 6 million patients in the United States, and is the most common diagnosis for urgent admission to the hospital in patients over 60 years old. It is the only cardiovascular disease that is increasing in prevalence, in part because of the growing numbers of older people in our population.

The symptoms of heart failure (fatigue, breathlessness, leg swelling, and fluid in the lungs) are caused by the heart muscle not pumping with enough force. Because of this, not enough blood can get to the tissues. Once these symptoms become severe enough that they occur at rest or with mild activity, the 4-year survival is less than 50%--a mortality rate that is worse than most cancers. This mortality rate is for patients on optimal therapy.

The most common cause of a poor pump is heart attack, but there are other causes too, such as high blood pressure and infections. The primary manner to treat severe heart failure is to use drugs that help to alleviate symptoms. Recent data show that pacing devices can also help to prevent dangerous heart rhythms. Cardiac transplantation provides help to only 3000 patients per year, a small minority of patients with this problem. Despite all these measures, prognosis remains dreadful for patients with severe heart failure. Clearly we need new treatments.

Normal hearts respond to catecholamines (the “flight and fright” hormones) by increasing the pumping strength and rate and the cardiac output goes up. Catecholamines exert their effects by interacting with receptor proteins on heart muscle cells. This eventually activates a molecule called adenylyate cyclase (AC) which leads to increased cAMP inside the cell which then causes the heart to beat stronger and more frequently. Patients with heart failure have hearts that respond very poorly to catecholamine stimulation. Their hearts are almost unresponsive, and this is a major liability and a cause for severe symptoms and shortened early mortality.

Patients with heart failure have abnormally low levels of AC and therefore low levels of cAMP. This is a major cause of poor pump function. We reasoned that if we could increase the amount of AC in the failing heart, it would increase heart function. We set about to explore this hypothesis about twelve years ago by conducting a series of experiments first in heart muscle cells in a Petrie dish, then in mice and pigs with heart failure. The results of these experiments will be discussed in detail during the lecture.

Based on the results of these experiments and the safety profile of this strategy, we will soon initiate a gene therapy trial in human patients with severe heart failure. This study will be conducted at UCSD Medical Center (Hillcrest) and at the VA San

Diego Healthcare System. Patients will be brought to the cardiac catheterization laboratory and we will inject an inactivated virus carrying the gene that makes AC into their coronary arteries. The virus carrying the gene then enters the cells of the heart and the AC protein is increased in amount. In animal experiments this same strategy has safely resulted in increased heart function within 6 days, an effect that lasts for at least eighteen weeks. The clinical trial design will be discussed in detail during the lecture.