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GENE THERAPY TARGETS IN POSTINFARCTION REMODELING

To the Editor:

We are very happy that our recent article¹ has drawn so much interest and stimulated important discussion about using gene therapy in the setting of acute myocardial infarction in animal models. We really appreciate the questions raised and the comments made by Drs Ryan and Ghanta from Baylor College of Medicine, Dr Harken from the University of California, Dr Balsam from the University of Massachusetts, and Dr Anderson, one of the pioneers of gene therapy.

Substantial progress has been made in cardiac gene therapy research over the last several decades. It should be noted that many cardiac surgeons in the United States and other countries have also made huge contributions in the development of gene therapy. In fact, studies including cardiac angiogenesis with different growth factors, genetic manipulations with conduits before coronary grafting, evaluation of genetic molecular targets in coronary artery disease and heart failure, gene-based treatment to prevent allograft vasculopathy, and chronic rejection after heart transplantation were done mostly by cardiac surgeons.

Regarding our study, we strongly believe that calcium (Ca^{2+}) cycling protein is currently one of the most important potential molecular targets in ischemic heart failure that has proven effective in many preclinical gene therapy studies.² We focused on the gene-based treatment of abnormal Ca^{2+} cycling protein handling in ischemic heart failure. The logic behind this is based on the fact that excitation-contraction (EC) coupling of myocytes involves Ca^{2+} activation of contractile proteins and the subsequent removal of Ca^{2+} . During the cardiac action potential, Ca^{2+} enters through L-type Ca^{2+} channels that trigger Ca^{2+} release from the sarcoplasmic reticulum through

ryanodine receptors. The resulting rise in intracellular Ca^{2+} concentration causes sarcomere shortening and muscle contraction. In heart failure, the whole chain associated with EC is broken. Using the EF-hand Ca^{2+} sensor protein S100A1 restores the EC of myocytes by diminishing diastolic Ca^{2+} leak and reinforcing the function of ryanodine receptors.

Patients with left ventricular (LV) dysfunction caused by coronary artery disease represent at least 25% to 30% of patients in coronary surgery today. It is well known that surgical revascularization in 3-vessel disease with LV dysfunction is accompanied by a higher survival rate than other treatments. However, only a small number of these patients demonstrated improvements in LV function and LV ejection fraction. So far, there is not a strong explanation for why this happens. We believe that such patients may benefit after the delivery of gene products in combination with coronary artery bypass graft surgery. Thus, we and others think that gene therapy has potential in cardiac surgery, and that translational research in this area should proceed.³

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References

1. Katz MG, Gubara SM, Hadas Y, Weber T, Kumar A, Eliyahu E, et al. Effects of genetic transfection on calcium cycling pathways mediated by double-stranded adeno-associated virus in postinfarction remodeling. *J Thorac Cardiovasc Surg.* 2020;159:1809-19.e3.
2. Katz MG, Fargnoli AS, Kendle AP, Hajjar RJ, Bridges CR. Gene therapy in cardiac surgery: clinical trials, challenges, and perspectives. *Ann Thorac Surg.* 2016;101:2407-16.
3. Ikonomidis JS, Menasché P, Kreisel D, Sellke FW, Woo YJ, Colson YL. Attrition of the cardiothoracic surgeon-scientist: Definition of the problem and remedial strategies. *J Thorac Cardiovasc Surg.* 2019;158:504-8.

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