

**Harvard Medical School Department of  
Continuing Education and the Cardiovascular  
Division of the Department of Medicine,  
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***Cardiology Rounds***  
**November 2002**

**Rescuing the Failing Heart by Targeted Gene Transfer**  
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**Objectives:** The objective of gene transfer to selectively alter the genotype of targeted tissue is currently a reality. The objective of this issue of *Cardiology Rounds* by Dr. Hajjar, an expert in this field, is to assist practicing cardiologists in understanding the principles, objectives, and methods employed in gene transfer. Our readers should have an improved understanding of the capability and limitations of this investigational approach. This issue also underscores some potential targets for gene transfer relative to the failing heart. The reader will have a better understanding of potential vectors for use in cardiovascular gene transfer, as well as the rationale for producing myocyte-specific gene alterations. Our readers will also obtain a better understanding of the background and opportunities for gene transfer in research and for targeting and pinpointing lesions and disease processes, as well as potential therapeutic implications. Defects in myocardial calcium handling in the failing heart lead to elevated diastolic calcium levels, decreased systolic calcium levels, and a prolonged relaxation phase – fundamental problems in heart failure. Our readers will gain an understanding of the rationale behind animal studies employing the transfer of sarcoplasmic reticulum calcium ATPase gene to attempt to restore these abnormalities. Improving the understanding of the principles of targeted gene transfer should assist our readership in preparing and interpreting novel discoveries and potential therapeutic approaches.

**TEST:**

1. What are the most commonly used viral vectors for cardiovascular gene therapy?
  - A. Inactivated poliomyelitis virus
  - B. Baculovirus
  - C. Herpesvirus
  - D. Adenovirus
2. Which class of virus elicits the least immune reaction from the body when injected into muscle, conferring long-term expression?
  - A. Adeno-associated virus
  - B. Baculovirus
  - C. Herpesvirus
  - D. Adenovirus

3. What are the main difficulties in applying gene transfer to the heart?
  - A. Delivery system
  - B. Specificity of the vectors to the heart
  - C. Inflammatory response and transience of expression
  - D. Inefficiency of gene transfer
  - E. All of the above
  
4. What was the reason for the most catastrophic death based on a gene therapy trial at the University of Pennsylvania in 1999?
  - A. Immune reaction to the virus leading to ARDS
  - B. Incorporation of the inserted gene into a tumor suppressor region
  - C. The recombinant virus became virulent
  - D. None of the above
  
5. In failing hearts, calcium transients can be characterized as having elevated diastolic  $Ca^{++}$  levels, decreased systolic  $Ca^{++}$  levels, and a prolonged relaxation phase.  
True\_\_\_ False\_\_\_
  
6. A deficiency in  $Ca^{++}$  uptake by the sarcoplasmic reticulum is a major cause of abnormal  $Ca^{++}$  handling in the failing myocyte.  
True\_\_\_ False\_\_\_
  
7. In an experimental model of heart failure, adenoviral gene transfer has been used to restore sarcoplasmic reticulum  $Ca^{++}$ -ATPase activity (SERCA 2a) resulting in:
  - A. More normal intracellular  $Ca^{++}$  handling
  - B. Improved contractility
  - C. Prolonged survival
  - D. All of the above

To receive AMA category 1 credit, you must correctly answer 60% of the test questions.

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