

# Mending the Broken Heart

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# Guest Editorial

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## MENDING THE BROKEN HEART

**W**hen David Hearse and Roberto Ferrari invited me to edit this issue and to contribute one of the articles I had mixed feelings. While the title proposed suggests a romantic paperback novel, the subject matter it incorporates is potentially groundbreaking: arguably, gene and cell therapies are fields that will apply to much of cardiovascular and other medical therapeutics in the future.

The beginnings have been rocky, especially with regard to gene therapy. This largely reflects the toxicity of viral vectors used in the initial gene therapies that were administered to patients. Cell therapy has had a more successful beginning, first appearing on the scene in 1956. In that year, E. Donnall Thomas obtained long-term survival by transplanting bone marrow into a patient with leukemia. Since that time both the efficacy and safety of bone marrow transplant have been documented and detailed for the treatment of certain cancers and immunodeficiency diseases. Obviously there are toxicities and shortcomings, but the life-saving nature of the therapy is unquestionable. And this history has provided assurance to subsequent investigators studying marrow-derived cells, assurance that the cells they deliver to patients likely will cause no harm. Important with regard to the safety issue is that in most instances the cells administered have been autologous.

Given the limited safety concerns, there has been rapid advancement of cell therapy in humans with myocardial infarction and/or with heart failure. There has been almost marginal benefit, with the occasional report looking hopeful, but the safety of the procedure appears to have been validated.

So if gene therapy has produced death and disease and cell therapy has been shown safe if not necessarily effective (except for bone marrow transplantation as stated above), why devote an issue to “Mending the Broken Heart?” My own prejudice is that ●●●

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gene and cell therapies are at a developmental stage not unlike antimicrobials in the 1930s. Sulfa drugs then appeared in a field that previously depended on folk medicine, carbolic acid, arsenicals, and the like. And although sulfa drugs were far from an ideal antimicrobial, they were not only a vast improvement, but they presaged the arrival of antibiotics in the clinic in the 1940s. To succeed, investigators had to accept the germ theory of disease, a nineteenth century concept verified scientifically by Koch in 1875, and then learn a new language: partly that of the germs themselves and partly that of the molds and other sources from which they made their antibiotics. Whereas Tyndall in 1875 had already noted the antimicrobial properties of *Penicillium*, it was not until 1928 that Fleming replicated the observation and did one essential additional experiment: he used the soup in which the mold grew to treat bacterial colonies, saw that it lysed them, called the soup penicillin and gave new impetus to a burgeoning field of therapy. All that remained was to develop a stable, clinically useful system to make penicillin, and this required another decade.

Those individuals now working in the field of cell and gene therapy are also having to learn a language; arguably a far more obscure language than that of the bacilli and molds that dot the antibacterial landscape. What are the signals and factors that determine stem cell growth and fate? How can these be manipulated safely? How reproducibly can cells be made to grow, to mature, but not to evolve into neoplasms? The list is almost endless. These issues and others relating to the use of cells to repair/regenerate myocardium are considered in this issue by **Ira Cohen** and **Glenn Gaudette**. The segue from the cells under investigation and problems in understanding their biology to their use in clinical settings of myocardial infarction and heart failure is considered by **Kai Wollert** and **Helmut Drexler**. Review of the types of cells available, the means for their administration and the clinical successes and limitations to date is both encouraging and chastening as it indicates how far we have to go to understand what we are doing in the clinic and how to do it better.

**Kirk Hammond** and **Tong Tang** look at another side of the coin: their area is the viral approaches to gene delivery in the setting of heart failure. They provide a summary of progress made as well as of the strengths and limitations of different viral approaches. They emphasize preclinical studies showing that gene transfer improves left ventricular contractility and attenuates deleterious remodeling in myocardial infarction-associated congestive failure, and express optimism that these outcomes will be replicated in patients with congestive failure. Finally, my own paper, authored with **Peter Danilo** and **Richard Robinson**, considers viral vector-delivered gene therapy as a means to insert novel ion channel constructs into the heart in attempting to prevent induction of lethal ventricular tachycardias. The goal here, in proof-of-concept experiments, is to provide local therapy with these constructs, thereby maintaining an antiarrhythmic action while limiting toxicity.



I encourage the reader to think of the lead article and the three accompanying papers as snapshots of a field that contains a lot of empty space. We are gathering islands of information, and when we have learned a sufficient amount, the continuum of what is needed for us to understand what cell and what therapy to use in any particular situation will have been clarified. But that day is still far off. In the meantime, we learn and we worry: worry that the pressure investigators feel to bring treatments to the clinic and the economic pressures of raising funds to perform research and deliver its benefits to human subjects may poison the field by leading to premature application and unforeseen toxicity or failure. This certainly was the case for gene therapy, even though we are now having another “go” at it; it would be devastating for the same thing to happen with cell therapy. A different concern, but no less dismaying, is the administration of various cell therapies to desperately ill patients in some countries with the same abandon that characterized the selling of snake oil to a gullible public 100 years ago.

Finally, I ask the reader to save this volume for about 20 years, not because of any pretensions about it, but to perform an easy experiment. The experiment is simply to open the volume in 20 years to see, with appropriate hindsight, the extent to which this bold new future we envision for gene and cell therapies has made its way into the mainstream of cardiovascular therapy.

