The prospect of using genes as therapeutic agents presents myriad opportunities. No physician could fail to appreciate the power of this approach: why not abandon the shackles of the limited pharmacological and device repertoire and focus instead on reengineering the culprit tissue by somatic gene transfer? The explosion of genomic information leaves us with an embarrassment of riches in terms of potential therapeutic agents. Why draw the line at nature’s own genes expressed in their usual settings? Genes can readily be tailored to exhibit special properties not found in nature, altering the function of their protein products for specific ends. Alternatively, wild-type genes can be expressed in tissues where they are normally silent.

In this issue, Weig et al.1 describe a clever application of the latter approach: V2 vasopressin receptor genes, usually expressed only in kidney, were delivered to myocardium packaged in recombinant adenoviruses. Expression of these adenyl cyclase–activating receptors in the myocardium converted the basal negative inotropic response to infused vasopressin into a positive one. Because vasopressin levels are elevated in heart failure, a situation in which \( \beta \)-receptors are uncoupled from cyclase,2 ectopic expression of V2 receptors would logically be predicted to recruit cAMP-mediated inotropy, we have also learned of the concept that ectopically expressed V2 receptors can uncouple from cyclase,3–6 recruit cAMP-dependent inotropy,3–4 a crucial step toward routine catheter-mediated gene delivery to myocardium.

The work of Weig et al1 illustrates elegantly the power of animal studies in gene therapy. Not only has there been proof of the concept that ectopically expressed V2 receptors can recruit cAMP-dependent inotropy, but we have also learned about the normal heart’s reaction to such intervention. We must beware, however, of being so seduced by what we find in preliminary animal studies as to deceive ourselves into thinking that we can readily translate our accomplishments to the clinic. The notion that ectopically expressed V2 receptors might be helpful in heart failure is plausible, but it has yet to be tested in a relevant disease model. Even if the results of such studies looked promising in the short term, long-term studies would be crucial: there is good reason to doubt that sustained cAMP elevation, by whatever proximal signaling route, will be salutary in heart failure.5–6 Extrapolation from long-term studies with the same genes in transgenic mice will not suffice and may potentially mislead, particularly when myocardial diseases such as heart failure are the focus. The fundamental properties of excitability7 and contractility8 differ so greatly between mice and larger mammals (including humans) that conclusions so derived can only be tentative. Nevertheless, mice can help us to prioritize among various candidate genes, and larger animal studies offer a perfect platform for pushing the envelope.

No matter how smart we think we are, and how extensive our animal studies may be, we will inevitably make mistakes when it comes to real therapeutics. The recent past is littered with well-reasoned but ultimately disastrous pharmacological misadventures, notably with antiarrhythmics in postinfarction patients9 and with phosphodiesterase inhibitors for heart failure.5 In such cases, at least the treatment could be terminated as soon as adverse effects became evident. Gene therapy has the potential danger of persistence, not to mention dosing difficulties. Such concerns are arguably less germane to the application of gene therapy for monogenic disorders, such as hemophilia; the culprit gene is clear, and the presence of a secreted protein, even without tight control of its expression, may suffice to correct the phenotype. In contrast, the use of gene transfer to alter the function of the heart differs fundamentally in its philosophy. Here the goal is not to correct a well-defined genetic disorder; instead, genes are used to manipulate the very workings of the diseased organ, in ways that may have no relationship to underlying changes of gene expression. The use of V2 receptors to boost cardiac contractility illustrates this paradox: no one would suggest that deficient expression of these receptors is culpable in heart failure, yet Weig et al1 argue that their overexpression represents a logical therapeutic approach. Such reasoning...
must be encouraged, as it will lead to increasingly creative applications of gene therapy. However, in proceeding toward clinical application, we must be brutally honest and recognize that such ideas are also fraught with potential pitfalls, because we are simply not smart enough to anticipate all the likely adverse outcomes. When it comes to alterations of cardiac excitation or contraction, I believe it would be unethical to initiate gene therapy trials without extensive prior animal experimentation and without the use of proven mechanisms for the tight control of transgene expression. That way, genes that turn out to be detrimental can be silenced; moreover, inducible systems offer the potential for dose-dependent titration of expression levels, a critical advantage when one has the temerity (and hubris) to alter the very substrate of the heart itself. Several systems for inducible gene expression in the context of gene therapy vectors are currently in development (eg, References 10 and 11), but none is quite ready for prime time.

How close are we to practical application of gene therapy for myocardial diseases? Given the caveats that I have highlighted, as well as many that I have not even mentioned (eg, inflammation, oncogenesis, mutational integration into the host genome, gene expression in nontarget organs, and the potential to trigger autoimmunity), caution is merited before we start putting genes into human hearts with a view to modifying contractility or excitability. The time has come to push forward with inducible vector development and proof-of-concept studies. The more promising approaches will have to undergo long-term validation in appropriate animal models. Such work will undoubtedly continue to dazzle us with its spectacular potential. Along the way, the temptations to jump directly into human studies will be akin to those Odysseus faced with the Sirens. The song we hear is all the more seductive because it originates deep within ourselves. Nevertheless, our roles as physicians and as guardians of the public trust dictate that we do all we can to resist the temptation to jump into human studies until we have gathered overwhelming evidence for both safety and efficacy. For the time being, the best we can do is to tie ourselves to the mast and listen to the song.

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References


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