INTRODUCTION

Despite the safety issues with human gene therapy clinical trials (1), this approach to the treatment of specific disease states continues to hold enormous promise. This is based on the recently reported remarkable scientific achievement of deciphering most of the human genome (2), and the potential impact of utilizing the novel gene expression microarrays both at the RNA and protein levels (3,4). Considerable published evidence shows that the transfer of genes to humans is feasible, with expression varying from a few days to several months and years (5,6). Cystic fibrosis, adenosine deaminase deficiency, and familial hypercholesterolemia are some diseases where a partial correction of the abnormality via gene therapy has already been obtained. Although the ultimate goal of a stable, tissue-specific, and efficient production of the recombinant protein is currently difficult to achieve, prospects are promising.

In comparative terms, gene therapy of the diseases of the urogenital system has not obtained the same attention that has been directed toward other nonurogenital conditions. However, in the case of prostate cancer, several clinical trials are currently under-
way including suicide genes, immunomodulatory genes, autologous vaccines, tumor-suppressor genes, antisense strategies, and antioncogenes (7,8). The same strategies are being tested with bladder cancer (9). Also, in the case of bladder reconstructive surgery and incontinence, the possibility of combining tissue engineering based on autologous cells with ex vivo gene transfer opens other avenues where gene therapy may be applicable (10). Similar approaches are being applied to renal transplantation, certain kidney diseases, and renal hypertension (11–13).

Within this background of considerable clinical and scientific interest with substantial promise for the treatment of life-threatening diseases, male erectile dysfunction (ED) appears at first sight as an unlikely candidate for gene therapy in men. The main reason is that impotence is a condition that seriously hampers the quality of life, but does not involve physical pain or endangers life, and therefore the perceived risks of gene therapy may not justify yet this approach. In this chapter, we will provide evidence showing that far from this being the case, gene therapy for the treatment of ED is a logical and well thought-out concept, where specific molecular targets and pathways for safe biological modulation are available, and where the easy accessibility of the penis to external manipulation provides a good approach for cDNA delivery.

GENERAL STRATEGIES OF GENE THERAPY

Most of the gene therapy trials are focused on the treatment of inborn errors of metabolism and cancer (5,6,14,15), with several hundred on-going clinical studies and a large number of preclinical trials in animal models. The main objective is to identify a biochemical pathway that is crucial for the desired physiological or pharmacological response, and then a gene encoding a protein that controls the overall output of the selected pathway. The recombinant cDNA must be transfected or infected into the selected tissue, organ, or the body in general, and the expression of the active recombinant mRNA and protein must occur as preferentially as possible in the target tissue or organ, for as long as it is necessary.

In some cases, the desired effect is to correct an inactivating mutation, in which case the cDNA has to be transfected to replace the silent gene by homologous recombination. In other cases, the protein is active but it is expressed at low levels or its biological activity is downregulated, so that the recombinant cDNA aims to hyperexpress the normal protein. Finally, in many conditions, it is fundamental to block the expression of a noxious protein either because of its direct pharmacological effects or because it controls complex processes such as cell replication, death, and so on. In this case, it is necessary to apply the antisense cDNA that blocks its mRNA translation, or the ribozyme that cleaves specifically this mRNA. Alternatively, antisense oligonucleotides representing a fraction of the coding sequence, rather than whole cDNAs, may be used to achieve the same inhibition.

The success of gene therapy depends essentially on six main factors:

1. Efficient delivery of the cDNA construct or oligonucleotide.
2. Preferential tissue or organ targeting of the cDNA construct or oligonucleotide.
3. Selective tissue or organ expression.
4. Persistent hyperexpression or inhibition of the desired active protein.
5. Absence of immune responses against the proteins encoded by the recombinant vector or cDNA.
6. Conditional activation of protein expression to permit selective time frames of biological effects.