INTRODUCTION

More than 10 years have passed since we conceived the idea to use gene therapy in the treatment of arthritis. The original concept of delivering therapeutic genes to the synovial linings of arthritic joints (Fig. 1) (1) was quickly joined by additional strategies, including the systemic delivery of genes to extra-articular locations (2). Subsequent evaluation of these possibilities in animal models of disease (reviewed in refs. 3 and 4), confirmed that both approaches have merit. However, for a variety of technical and safety reasons, we decided to develop local gene delivery to the synovium for the first clinical trials (5), while continuing to investigate other strategies at a preclinical level.

As a result of this decision, considerable effort was devoted to evaluating the abilities of different vectors to deliver genes to the synovial lining of rabbits’ knee joints by in vivo and ex vivo means (6). These studies confirmed the efficiency of adenovirus as a vector for in vivo synovial delivery, as first observed by Roessler et al. (7), and a growing number of subsequent investigators are using this technique for preclinical studies (8–14). However, although experimentally very useful, this means of gene transfer did not seem well-suited to early human application because of inflammatory
responses to adenoviral infection and the brevity of gene expression. Retroviral, ex vivo methods, although more tedious, gave longer gene expression, albeit at a lower level, and were not associated with inflammation. Moreover, ex vivo gene delivery brings advantages of safety, because no transducing agents are introduced directly into the body and all genetically modified cells can be thoroughly tested before reimplantation.

The remainder of this chapter describes the development of the ex vivo gene therapy protocol used in the first human clinical trial. Additional information can be found in refs. 5 and 15.

**PATHOGENIC MECHANISMS THAT RATIONALIZE THE THERAPEUTIC TARGET**

In general terms, pathophysiological events in rheumatoid arthritis (RA) are driven by a series of interrelated processes involving inappropriate immune reactivity, and the excessive production of immunostimulatory, inflammatory, and destructive mediators (3). Agents that restore immune homeostasis and interfere with the activities of arthritogenic mediators are of obvious potential utility in treating RA. In recent years, it has become clear that biology provides a number of such agents (16). Many of them, however, are proteins and thus awkward drugs in chronic conditions such as RA. Gene therapy was primarily suggested as a means of solving the delivery problem (1), but it may bring additional advantages. For example, there is growing evidence that molecules