1. INTRODUCTION

Although it is always tempting to skip the history of a field, this is particularly unwise for a discipline as young as cancer gene therapy. Indeed, it is the history of the last few years that is largely dictating the research directions that will likely be both profitable and permitted in the future. This brief introductory chapter outlines the early days of cancer gene therapy—the successes and the setbacks—and suggests how the remaining challenges may be faced.

2. BACKGROUND

When the possibility of human gene therapy was first mooted (and illicitly attempted) in the 1970s, it was assumed that inherited single-gene disorders would be the target of the approach (1). The obvious elegance of repairing or replacing the root cause of a disease had and retains an enormous appeal to researchers, patients, and public alike. Unfortunately, it soon became obvious that the tools available were simply not up to the job.

Effective gene therapy of genetic disorders requires a vector that can efficiently transduce the desired cell type, in a targeted manner, preferably in vivo. Moreover, the gene product usually would need to be produced in substantial quantities for a long time, often in a regulated manner. Above all, the process and consequences of gene transfer should be safe.

Sadly, the gene transfer vectors available for clinical use, then as now, possess none of these desirable properties. They are diffusely targeted, inefficient at making transgene products, and difficult to regulate. As the gene therapy community has painfully learned, they are not even all that safe for they have the potential to produce immediate (adenovectors) or delayed (retroviral vectors) severe or lethal adverse events.

Many of these limitations were obvious to early workers in the field and led them to concentrate on disorders in which low-frequency transduction of stem cells would lead to a selective growth advantage and repopulation of the host and in which unregulated expression of even small quantities of the transgenic material would be of therapeutic benefit. The group of disorders that most clearly met these criteria was the inherited severe combined immunodeficiency syndromes. But, although these remain of great interest as a possible “proof of principle” for establishing the value of this new technology, they are exceedingly rare, and there was a strong feeling that the technology should be applied to more common conditions. Although these included more widespread inherited genetic disorders such as cystic fibrosis, the prospect of treating cancer with gene therapy grew increasingly justifiable in the 1980s.
Several factors led to this change in perception:

1. The realization that cancer too was a genetic disorder, albeit one that was acquired and multigenic.
2. The existence of a profoundly unmet therapeutic need because conventional treatments were toxic, ineffective, or, most commonly, both.
3. The high incidence of the disorder, making it an appealing area for research and development support from industry.
4. The availability of an established community of researchers used to clinical trial development and monitoring.
5. A general agreement that the risk-to-benefit ratio was likely to be acceptable to patients, regulatory agencies, and the general public given the immediate life-threatening nature of most of these disorders and the paucity of safe alternatives.

As a consequence, the very first gene transfer protocol approved was in cancer patients (2), and the dominance of this area in gene therapy has persisted to this day, with more than 80% of gene transfer subjects falling into this disease category (3). However, it must also be pointed out that cancer gene therapy has a number of drawbacks, and as evident from the chapters in this book, these have led to an underappreciation of its achievements to date and an underestimation of its likely future importance.

Cancer, even of a single cell type in a single organ, is a molecularly heterogeneous disease. Although there is extensive categorization of the molecular basis of hematologic malignancies, this process is just beginning in solid tumors. Hence, no single therapeutic approach is likely to be effective in more than a minority of patients with a given broad histologic category of disease, so that a low success rate even for effective gene therapies is currently to be expected.

Even when effective, single therapies are rarely curative. Cancers evolve and escape from all therapeutic agents. Instead, combined modalities must be used in which resistance to one does not predicate resistance to the others. Although gene therapies have the great advantage of non-cross-resistance to most conventional treatments, combination clinical studies that convincingly show the benefits of adding gene therapy are slow and expensive to perform. End points are often either vague (e.g., increased tumor “response” rates) or delayed for months or years (e.g., prolongation of survival).

Most cancer patients have received multiple other toxic therapies. Their responsiveness to gene therapies designed, for example, to boost immunity may be deficient. Similarly, when toxic events occur, it may be difficult to discern whether they are attributable to the disease, to prior or concurrent therapy, or to the investigational gene drug.

It is these difficulties that lead to the failure or abandonment of many of the historically early studies in gene therapy. However, as is apparent from succeeding chapters, the ability to compensate for some of these problems now underlies many of the successes seen, together with improvements in the transgenes used and the ways in which they are delivered.

The earliest studies using gene transfer to treat cancer were all designed to compensate for the remarkable inefficiency of the available adenoviral, retroviral, and plasmid vectors. Gene-marking studies were the first out of the gate (2,4–6). These were implemented not with any direct therapeutic intent, but rather to use the transferred marker gene as a means of tracking normal or malignant cells and help validate and improve interventions already in use. The principle of gene marking is the transfer and integration of a unique deoxyribonucleic acid (DNA) sequence (e.g., a nonhuman gene) into the DNA of a host cell (e.g., T cell, hematopoietic stem cell), allowing the gene or the gene product to be detected easily, thereby serving as a marker for these labeled cells (5).

In 1988, Rosenberg proposed a protocol to genetically mark lymphocytes derived from tumor patients (tumor-infiltrating lymphocytes, TILs). These lymphocytes appeared to have antitumor activity and could be expanded ex vivo and returned to patients with tumors. However, it was unclear whether the infused cells were able to traffic to tumor sites and produce antitumor activity. Rosenberg’s group planned to expand TIL cells ex vivo, transduce them with a Moloney retroviral vector encoding the neomycin phosphotransferase gene (NEO or, as it was then written, NeoR) and return them to the patient. Any transduced cells infused and all their progeny could then be detected by subsequent