A concept fundamental to human gene therapy is efficient and specific somatic gene transfer. A generous assessment of the field would conclude that most vectors fall short of the mark, although a few illustrative exceptions indicate some progress has been made. Recombinant adenoviruses have provided the most encouraging results as of late (1). Vectors based on human adenoviruses are extraordinarily efficient gene transfer vehicles in a wide variety of cells both in vitro and in vivo. A glaring exception is hematopoietic derived cells which seem virtually impenetrable to these vectors (2). Chen et al. describe in this issue of *The Journal* a potential application of adenoviruses to purge bone marrow of tumor cells that is based on the relative resistance of bone marrow progenitors to adenoviral vectors (3).

Autologous bone marrow transplantation is having an expanding role in the treatment of malignancies such as breast cancer. Patients are treated with high dose chemotherapy and the resulting pancytopenias are corrected by transplanting autologous bone marrow cells harvested before the therapy. Patients receiving autologous bone marrow tolerate doses of chemotherapy that otherwise would be lethal. Remission has been achieved in some patients although virtually all eventually relapse. A potential source of relapse is outgrowth of tumor cells that contaminate the transplanted bone marrow cells. This problem has led to strategies to selectively purge the bone marrow of tumor cells before transplantation; most approaches suffer from insufficient specificity resulting in incomplete purging of cancer cells and clinical relapses, or toxicity to the bone marrow and incomplete hematopoietic reconstitution.

The study by Chen et al. describes a novel approach for purging breast cancer cells from bone marrow that is based on somatic gene transfer (3). They exploited the apparent failure of adenoviruses to infect hematopoietic cells to selectively target the more infectable breast cancer cells with a "suicide gene." Human bone marrow contaminated with variable quantities of breast cancer cells was exposed to an adenoviral vector expressing the thymidine kinase (TK) gene from Herpes Simplex Virus. Selective ablation of vector transduced cells was achieved in the presence of ganciclovir which, in cells expressing TK, is converted to a toxic phosphorylated metabolite (4). The specificity by which this was achieved was impressive, infecting ~ 1 cancer cell in 5×10^5 bone marrow cells. This was accomplished without compromising the viability of bone marrow progenitors.

The application of adenoviral vectors for bone marrow purging in humans should consider several issues. The adenoviral capsid proteins, per se, have demonstrated toxicity to a variety of cells independent of transduction. It will be necessary to assure that the ability of stem cells to fully reconstitute in all lineages is not affected by the ex vivo infection protocol. Furthermore, it remains to be seen if the purging efficiency is sufficient to eliminate the contaminating tumor cells. In vitro studies have demonstrated significant variation in the relative

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infectability of different tumor isolates, suggesting there may be heterogeneity in clinical responses.

The study by Chen et al. is important to the field of gene therapy for several reasons. Despite the caveats noted above, this application of gene transfer technology has real therapeutic potential. The problem of relapse following autologous bone marrow transplantation in cancer is a substantial clinical problem with no obvious solutions, thereby justifying novel approaches. All manipulations occur ex vivo so that immunologic responses to the vector and vector gene products, a problem that has plagued in vivo approaches (5), are irrelevant. The actual weakness of the vector (i.e., poor gene transfer in hematopoietic cells) is exploited to improve specificity. Finally, there is a growing experience in humans confirming the safety of adenoviral vectors (6).

This use of adenoviral vectors in this application is a poignant example how far the field of gene therapy has come since the 1980s when it was solely considered in the context of gene replacement for the treatment of autosomal recessive diseases. A full spectrum of more common acquired diseases has been considered for gene therapy. Substantial effort has been directed to the use of gene transfer in the treatment of malignancy with some of the most promising strategies attempting to enhance anticancer immunity through vaccines or adoptive transfer. Similarly creative programs have been developed for the genetic treatment of cardiovascular diseases, AIDS, and auto-immune diseases.

Gene transfer vectors have emerged as powerful tools to study and potentially treat diseases. The concept is fundamental and the technology is evolving in step with the spectacular evolution of biomedical research. The challenge is to identify those clinical situations in which value is gained by incorporating the transfer of genetic material. The study by Chen et al. is an elegantly simple application. Only time will tell if it will impact on the outcome of autologous bone marrow transplantation for cancer.

James M. Wilson Institute for Human Gene Therapy Department of Molecular and Cellular Engineering University of Pennsylvania and The Wistar Institute

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