transaminases if untreated. The phase 1 study showed that this could be controlled using a course of corticosteroids begun 1 day before the vector infusion and continued for 30 days, with tapering at that point and carried out with monitoring of liver transaminases. Patients receiving the approved treatment are followed in a registry designed to assess effectiveness, long-term safety, and overall survival of patients with spinal muscular atrophy. An alternative treatment, intrathecal administration of an antisense oligonucleotide designed to increase expression of functional SMN from a mostly nonfunctional *SMN2* gene, was approved during the course of the gene therapy studies, but the efficacy data in the clinical trial were less robust, and the drug requires intrathecal administration every 4 months. Clearly, the gene therapy approach is a disease-modifying one, for a disease that previously lacked treatment. Additional follow-up in this population should address questions of long-term safety and efficacy.

GENE THERAPY FOR CANCER

The majority of clinical gene transfer experience has been in subjects with cancer. The intent has been to increase the precision of cancer therapies and thereby make them less toxic and more effective. Most approaches have either modified the tumor directly or altered the host's response to the malignancy to produce immune effector cells that are precisely targeted to the tumor phenotype.

■ MODIFYING THE CANCER

Since cancer is an (acquired) genetic disorder, initial efforts were directed at correcting the genetic deficits of the tumor or introducing lethal genes. Two major and persisting obstacles, however, are the poor biodistribution and transduction efficiency of all currently available vectors and the heterogeneity and genetic instability of the tumor targets themselves, so that correction of single driver mutations does not preclude the evolution of a resistant population.

Tumor Correction One widely used direct intratumoral approach was adenoviral-mediated expression of the tumor suppressor p53,