Efforts to treat cancer through immunization or deliberate infection with natural oncolytic viruses began in the mid-twentieth century, when the technology for creating a custom virus did not exist. These treatments induced significant morbidity and mortality, and the very frequent development of an immune response destroyed the virus, thus preventing its oncolytic function. For these reasons, this strategy was nearly abandoned for a time. Today, the technology required to modify viruses has been thoroughly developed, and systemic oncolytic viral therapy is a plausible alternative.[100] Adenoviruses have a low pathogenicity in humans and are relatively easy to manipulate using recombinant DNA techniques. Furthermore, their genome does not undergo rearrangement at a high rate, and the inserted foreign genes are maintained through multiple rounds of viral replication. During vector development, the viral surface proteins may be modified, removed, or replaced.[101] Once internalized into the cells, oncolytic viruses or viral vectors use a vesicular transport in which the viral envelope is metabolized and their content is released to the cytoplasm, enters the nucleus through a nuclear pore, and viral transgene expression occurs.

To improve patient safety and increase the gene transfer efficiency of viral vectors, the target cells may be removed from the patient, transduced with viral vectors, and reintroduced into the patient. However, this method is limited to cells available either by extraction or by growing from the stem cells *in vitro*. Excluding this *ex vivo* approach, the vectors need to be directly injected into the patient or delivered and retained in target areas with vector reservoirs. Among other administration methods, the inclusion of the antibody into paramagnetic particles enables the physical concentration of viral vectors by applying a local magnetic field.[102] Several potential strategies for cancer therapy based on gene therapy that are being explored in clinical trials are summarized here.

5.1 REPLACEMENT OF DEFICIENT OR ABSENT TUMOR SUPPRESSOR GENES: ONCOLYTIC VIRUSES

Oncolytic virus therapy is based on the concept of using live viruses to selectively replicate in cancer cells, with minimal destruction of normal tissue. Replication amplifies the input dose of the oncolytic virus and helps spread the agent to adjacent tumor cells. This strategy is very important in cancer therapy because tumor suppressor gene-inactivating mutations predominate over oncogene-activating mutations in the most common solid tumors. The first gene-based products were Gendicine® and Oncorine®, which entered the Chinese market in 2003 and 2006, respectively. Gendicine® is a recombinant human adenovirus vector containing the therapeutic *P53* gene. It is used in China for the treatment of various cancers,[103] and its combination with radiotherapy favors the control of nasopharyngeal carcinoma. Oncorine® is a genetically modified oncolytic adenovirus that was approved in China for the treatment of head and neck cancer. Oncorine® and the very similar ONYX-015 have been engineered to remove a viral defense mechanism that involves the human gene *P53*. Many viruses exploit the defects of cancer cells in the p53 tumor suppressor pathways to replicate, package its genome, lyse the cell, and spread to new cells. To do so, they produce E1B proteins that bind to and degrade p53 transcription factors, preventing cell apoptosis. In the ONYX-015 and Oncorine® adenoviruses, the *E1B* gene has been knocked out and the infected cells are unable to block the p53 function. If ONYX-015 or Oncorine® infect a normal cell with a functioning p53 gene, their multiplication will be prevented by the action of the p53 transcription factor, but if they infect a p53-deficient cell, they should be able to survive and replicate, resulting in selective destruction of cancer cells.