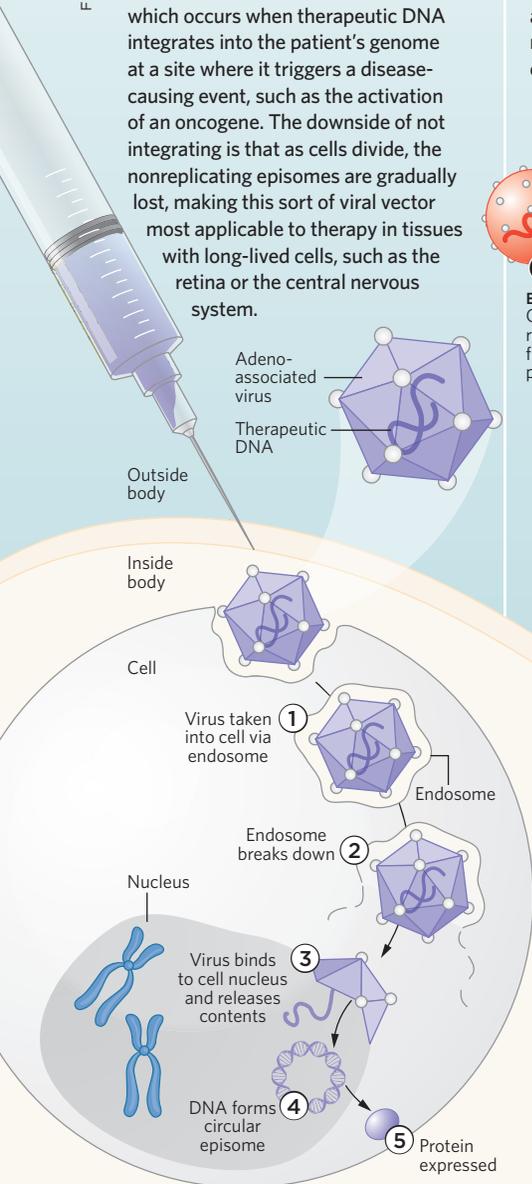


DELIVERING NEW GENES

Gene therapies typically involve the introduction of genetic material into target cells to replace or supplement an existing, usually dysfunctional, gene. Techniques for delivering the corrective payload vary widely. Many gene therapies utilize modified viruses, excising viral genes involved in replication and virulence before incorporating therapeutic DNA or RNA.

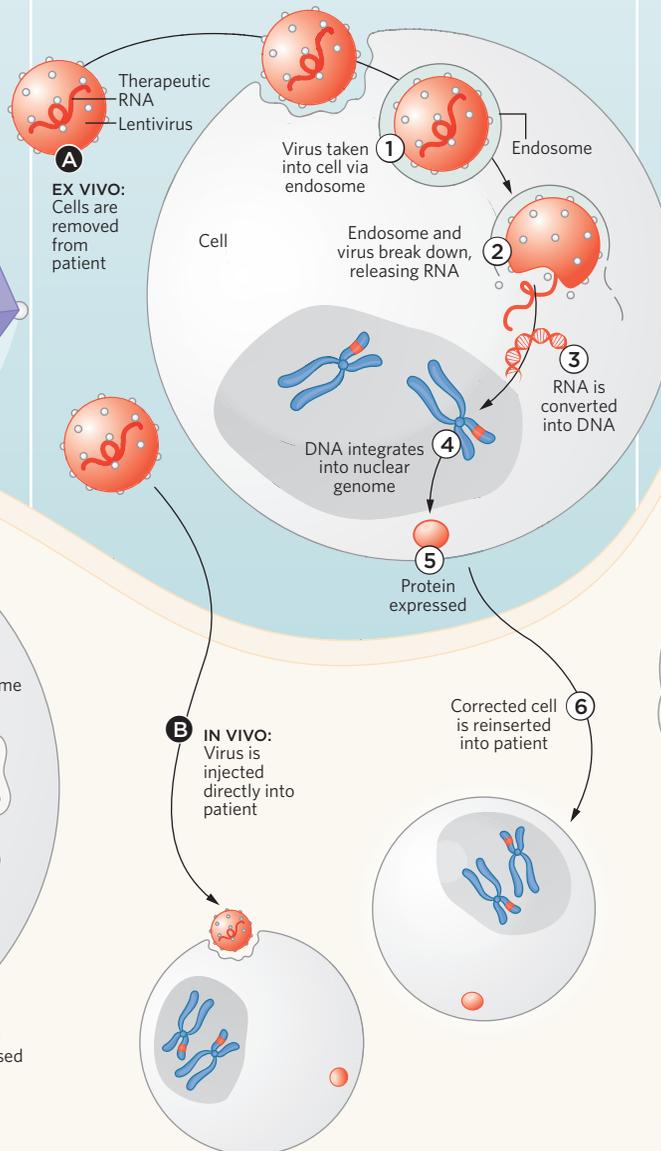
NONINTEGRATING VIRUSES

A common virus used for gene therapies is the modified adeno-associated virus (AAV), a small virus that doesn't cause disease and elicits only very minor immune responses. Importantly, AAVs deliver their payloads without integrating them into the genome. The DNA simply makes its way to the cell nucleus, where it forms a small circle, or episome, that acts as a mini-chromosome. This eliminates the chance of insertional mutagenesis, which occurs when therapeutic DNA integrates into the patient's genome at a site where it triggers a disease-causing event, such as the activation of an oncogene. The downside of not integrating is that as cells divide, the nonreplicating episomes are gradually lost, making this sort of viral vector most applicable to therapy in tissues with long-lived cells, such as the retina or the central nervous system.



INTEGRATING VIRUSES

In contrast to AAVs, integrating viruses insert their DNA into the host-cell genome. The lentivirus, for example, is a type of RNA retrovirus that delivers its payload to the cytoplasm, where a reverse transcriptase converts it into DNA. The DNA then enters the nucleus, where it inserts into the genome. This integration ensures that the therapeutic DNA will be passed onto daughter cells, thus lentiviruses can be used to target tissues with both low and high rates of cell turnover. As an alternative to injecting the viral vector directly into a patient, researchers can extract a patient's cells, such as those of the bone marrow, infect them with the lentivirus vector in culture, then infuse the modified cells back into the patient's body. The risk that integration will trigger a disease-causing mutation is reduced because, unlike some retroviruses, lentiviruses don't tend to integrate into oncogenes or growth-related genes.



ONCOLYTIC VIRUSES

In the field of cancer therapeutics, researchers are taking advantage of an old weapon—oncolytic viruses—to preferentially infect and kill cancer cells. Oncolytic viruses have been used to target tumors since the mid-20th century. Recently, however, researchers have been using gene therapy techniques to arm oncolytic viruses with even more powerful payloads, including genes to initiate apoptosis and to increase the immune system's attack on the cancer. These potent oncolytic viruses in development include those that fight liver, colon, kidney, lung, breast, and pancreatic cancers and melanoma.

