DNX-2401 (also known as Ad5 Delta-24-RGD-4C) is an oncolytic adenovirus that selectively replicates in cancer cells defective in the Rb/p16 tumor suppressor pathway. The *Rb* gene product and the cyclin-dependent kinase inhibitor p16 are integral components of the late G_1 restriction point. DNX-2401 has an RGD-4C peptide motif, inserted into the adenoviral fiber, that allows it to anchor directly to integrins in a receptor-independent infection of tumor cells where its active replication may induce oncolysis.[104] It is in phase I/II trials for recurrent GBM. When combined with temozolamide, it is much more effective than any other treatment against GBM stem cells, which supports the initiation of clinical studies for this combination.

Talimogene laherparepvec (T-VEC, OncoVEX®) is an oncolytic virus engineered from the herpes simplex-1 virus that has undergone phase III clinical study for the treatment of melanoma as a single therapy, although it failed to significantly improve survival rates.[105] A talimogene laherparepvec–ipilimumab combination is also under study, and phase I data have shown good tolerability at the doses administered.

JX-594 is a multitargeted oncolytic poxvirus that was tested in phase II in patients with hepatocellular carcinoma and demonstrated increased survival as compared to patients treated with sorafenib.

Pelareorep (Reolysin®) is a proprietary formulation of the human reovirus that is under development for the treatment of various cancers. A phase II study has been completed in patients with sarcomas metastatic to the lung.

5.2 GENE TRANSFER (SUICIDE GENE) THERAPY

As previously mentioned, viral vectors that selectively infect dividing tumor cells can be modified to carry a gene for an enzyme that activates an antitumor prodrug so that after its administration the prodrug is preferentially bioactivated in the tumor cells. For this reason, this approach is known as virus-directed enzyme prodrug therapy (VDEPT). For instance, sitimagene ceradenovec (Cerepro®) uses the adenoviral vector Ad5 to introduce the gene that causes tumor cells to express the herpes simplex virus thymidine kinase (TK) and activate ganciclovir to its triphosphate. Because of the absence of the 3′-OH deoxyribose group, when this compound is incorporated into DNA, it behaves as a chain terminator, blocking DNA synthesis and killing the cell (Figure 12.12).[106]

The combination of Cerepro® and ganciclovir entered clinical trials for treatment of the malignant brain tumor glioblastoma multiforme. Following the standard surgery to remove the solid tumor mass, Cerepro® was injected into the surrounding healthy brain tissue and ganciclovir was administered 5 days after surgery. Based on the results of three clinical trials performed from 1998 to 2004, it

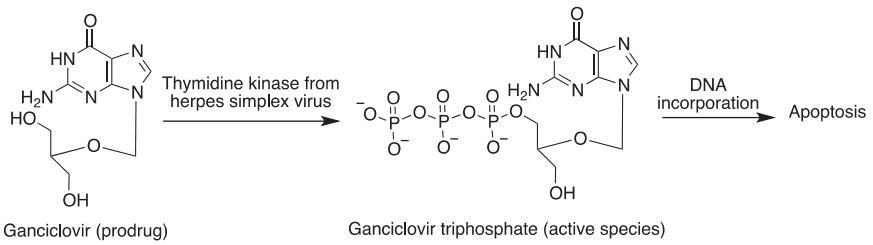

FIGURE 12.12

Activation of ganciclovir by the thymidine kinase from herpes simplex virus.