and chemotherapy can be enhanced further by combinations with another targeted monoclonal antibody (pertuzumab), which prevents dimerization of the HER2 receptor with other HER family members including HER3.

Although targeted therapies have not yet resulted in cures when used alone, their use in the adjuvant setting and when combined with other effective treatments has substantially increased the fraction of patients cured. For example, the addition of rituximab, an anti-CD20 antibody, to combination chemotherapy in patients with diffuse large B cell lymphoma improves cure rates by 15–20%. The addition of trastuzumab, antibody to HER2, to combination chemotherapy in the adjuvant treatment of HER2-positive breast cancer reduces relapse rates by 50%.

A major effort is under way to develop targeted therapies for mutations in the *ras* family of genes, which are the most common mutations in oncogenes in cancers (especially *kras*) but have proved to be very difficult targets for a number of reasons related to how RAS proteins are activated and inactivated. Targeted therapies against proteins downstream of RAS (including mitogen-activated protein [MAP] kinase and ERK) are currently being studied, both individually and in combination. A large number of inhibitors of phospholipid signaling pathways such as the phosphatidylinositol-3-kinase (PI3K) and phospholipase C-gamma pathways, which are involved in a large number of cellular processes that are important in cancer development and progression, are being evaluated. The targeting of a variety of other pathways that are activated in malignant cells, such as the MET pathway, hedgehog pathway, and various angiogenesis pathways, is also being explored.

One of the strategies for new drug development is to take advantage of so-called oncogene addiction. This situation (Fig. 102e-3) is created when a tumor cell develops an activating mutation in an oncogene that becomes a dominant pathway for survival and growth with reduced contributions from other pathways, even when there may be abnormalities in those pathways. This dependency on a single pathway creates a cell that is vulnerable to inhibitors of that oncogene pathway. For example, cells harboring mutations in *BRAF* are very sensitive to MEK inhibitors that inhibit downstream signaling in the BRAF pathway.

Targeting proteins critical for transcription of proteins vital for malignant cell survival or proliferation provides another potential target for treating cancers. The transcription factor nuclear factor-κB (NF-κB) is a heterodimer composed of p65 and p50 subunits that associate with an inhibitor, IκB, in the cell cytoplasm. In response to growth factor or cytokine signaling, a multi-subunit kinase called IKK (IκB kinase) phosphorylates IκB and directs its degradation by the ubiquitin/proteasome system. NF-κB, free of its inhibitor, translocates to the nucleus and activates target genes, many of which promote the survival of tumor cells. Novel drugs called *proteasome inhibitors* block the proteolysis of IκB, thereby preventing NF-κB activation. For unexplained reasons, this is selectively toxic to tumor cells. The antitumor effects of proteasome inhibitors are more complicated and involve the inhibition of the degradation of multiple cellular proteins. Proteasome inhibitors (e.g., bortezomib [Velcade]) have activity in patients with multiple myeloma, including partial and complete remissions. Inhibitors of IKK are also in development, with the hope of more selectively blocking the degradation of IκB, thus "locking" NF-κB in an inhibitory complex and rendering the cancer cell more susceptible to apoptosis-inducing agents. Many other transcription factors are activated by phosphorylation, which can be prevented by tyrosine kinase inhibitors or serine/threonine kinase inhibitors, a number of which are currently in clinical trials.

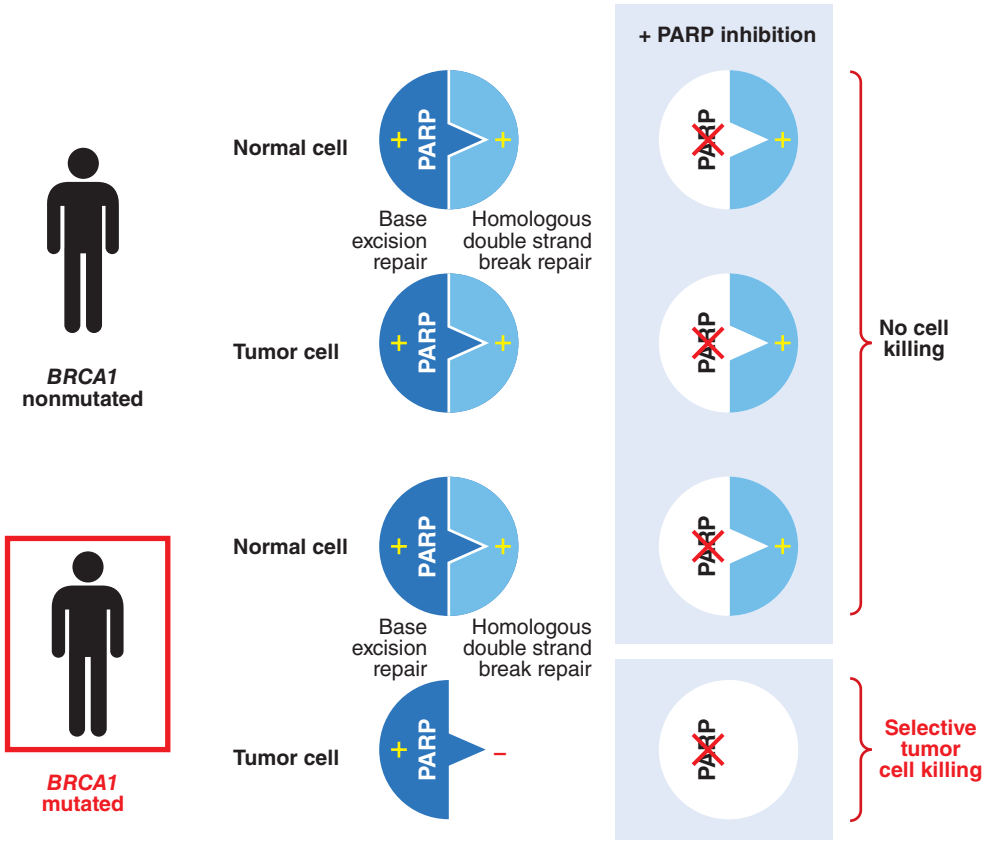

FIGURE 102e-3 **Synthetic lethality.** Genes are said to have a synthetic lethal relationship when mutation of either gene alone is tolerated by the cell but mutation of both genes leads to lethality, as originally noted by Bridges and later named by Dobzhansky. Thus, mutant *gene a* and *gene b* have a synthetic lethal relationship, implying that the loss of one gene makes the cell dependent on the function of the other gene. In cancer cells, loss of function of a DNA repair gene like *BRCA1*, which repairs double-strand breaks, makes the cell dependent on base excision repair mediated in part by *PARP*. If the PARP gene product is inhibited, the cell attempts to repair the break using the error-prone nonhomologous end-joining method, which results in tumor cell death. High-throughput screens can now be performed using isogenic cell line pairs in which one cell line has a defined defect in a DNA repair pathway. Compounds can be identified that selectively kill the mutant cell line; targets of these compounds have a synthetic lethal relationship to the repair pathway and are potentially important targets for future therapeutics.