Anticancer drug discovery has historically been done empirically, screening for compounds that inhibit the growth of tumor cells in culture, or that are effective against implanted tumors in mice. This approach is analogous to the highly effective screens carried out in the 1950s and 1960s for antimicrobial agents and has had its successes – indeed, many of the anticancer drugs currently in clinical use were developed in this fashion. However, as our understanding of the molecular mechanisms underlying the development and growth of cancer cells has improved, new approaches to drug discovery have begun to build on this knowledge. The recognition that not all tumors arising in the same tissue are due to the same underlying defects calls for treatments regimes that will be tailored to these molecular alterations. The drug screen described in this chapter was initiated with the hypothesis that single gene changes that are often associated with particular hereditary and sporadic forms of cancer may serve as determinants of drug sensitivity [27]. In principle, there are two possible mechanisms by which a drug can be more toxic to a cell containing a particular genetic alteration. First, by a mechanism in which damage caused by the drug is normally repaired in a wild-type cell by a protein that has been deleted or altered in the mutant. An example of this is the sensitivity of mutants defective in recombinational repair of DNA double-strand breaks (DSBs) (e.g., yeast rad50 mutants) to agents that cause DSBs (e.g., the topoisomerase poison...
etoposide). The second mechanism is more interesting and potentially more important as a anticancer therapy strategy. In this scenario, genes that are normally nonessential are made essential by the deletion of the cancer-related gene. Inhibition of the normally nonessential gene product by a small molecule leads to cell death in the mutant background. This phenomenon is called synthetic lethality and is an example of context-specific cytotoxicity. By screening for agents that elicit synthetic lethality in cells harboring cancer-related mutations, we may be able to identify a new armamentarium of context-specific anticancer agents.

The drug discovery effort described here began in 1997 as a collaboration between the Developmental Therapeutics Program (DTP) of the National Cancer Institute (NCI) and the Fred Hutchinson Cancer Research Center (FHCRC) and used the yeast *Saccharomyces cerevisiae* to screen a large number of compounds for those that are selectively toxic to cells with alterations in defined genes. This screen utilized a panel of yeast strains, each with defined alterations in DNA repair genes or in cell cycle control genes. Differential sensitivity of various DNA repair mutant strains to a compound can identify pathways important for repair of damage caused by that agent. DNA damage repair pathways represented in this screen included DNA DSB repair (*rad50* and *rad52*), ultraviolet (UV)-excision repair (*rad14*), DNA mismatch repair (*mlh1*), removal of O6-methylguanine (*mgt1*), and post-replication repair (*rad18*). Alterations in human homologs of these genes have been identified in human tumors. The DNA mismatch repair gene hMLH1 is mutated or silenced in hereditary and sporadic forms of colon cancer, and is one source of the “Microsatellite Instability” (MIN) phenotype. Defects in UV-excision repair lead to the cancer-prone syndrome Xeroderma pigmentosum. The breast cancer predisposing gene BRCA1 associates with components of the DSB repair pathway. The screen also included strains altered in cell cycle control – again, these reflect alterations observed in human tumors. Bub3p is a component of the mitotic spindle checkpoint, which ensures that chromosomes are attached to the mitotic spindle before allowing passage through mitosis. Defects in a component of this checkpoint have been seen in some human tumors, giving rise to the “Chromosome Instability” (CIN) phenotype. The *RAD53* gene is part of two checkpoints, monitoring completeness of S-phase DNA synthesis, and also arresting cell growth in response to DNA damage in G2. The screen also includes a strain overexpressing the G1 cyclin, *CLN2*, which controls entry into S-phase. Finally, the *SGS1* gene is involved in an ever-growing list of DNA transactions, including DNA replication, recombination, and telomere function. There are several human homologs of *SGS1*, two of which, BLM and WRN, lead to cancer-prone diseases, Bloom’s and Werner’s syndromes, respectively.