The discovery of cisplatin in the 1960s is a classic case of serendipity, when studies on the effect of an electric current on the growth of *Escherichia coli* showed that the inhibition of cell growth was not due to the electric current but, rather, to the production of a platinum complex in the electrodes. Two important anticancer drugs, doxorubicin and paclitaxel, were discovered in the screening of natural product extracts in mouse leukemia models. A more targeted approach to cancer chemotherapy was developed after the early discovery of the strong relationship between estrogens and some breast cancers.[23] The recognition that breast and prostate cancers are subject to hormonal regulation led to the introduction of antihormones that directly or indirectly target the estrogen or androgen receptors. This knowledge also led to the approval of the estrogen receptor modulator tamoxifen (Novaldex®) for cancer chemoprevention in 1998.[24,25]

Since the 1950s, the biological activities of many antitumor drug leads have been discovered through *in vitro* screening programs promoted by the NCI by using a range of cancer cell lines. In this early period, transplantable rodent tumor models characterized by a high growth rate were used for *in vivo* screening. Later, human tumor xenografts, based on transplantation of human tumor tissue into immune-tolerant animals, also became important tools for selecting antitumor drugs because these models allowed simulating a chemotherapeutic effect under conditions closer to humans. In the late 1970s and early 1980s, the role of chemotherapy was extended to preoperative and postoperative adjuvants, radiosensitizers to enhance radiation effects, and supportive therapy to increase the tolerance of the organism toward toxicity.[26] We have progressed in a few years from a lack of targets to having too many, as shown by the Cancer Gene Census, which catalogs those genes for which mutations have been causally implicated in cancer.[27] To use this information to design better drugs, improved methods for validation of these new targets are needed. In this respect, the use of high-throughput RNAi methods and genetically modified mouse models are very valuable, although removal of the target is not necessarily equivalent to its inhibition by a small molecule.

The rationale for the use of conventional cytotoxic agents as antitumor drugs was based on the notion that rapidly proliferating and dividing cells are more sensitive to these compounds that are normal cells.[28] However, as the interactions of these agents with DNA were better defined, new compounds targeting particular base sequences that may inhibit transcription factors in a more specific manner were studied. DNA was considered a molecular receptor capable of molecular recognition and triggering of response elements,[29] and the binding properties of the DNA ligands were rationalized on the basis of their structural and electronic complementarity with the functional groups present in the major and minor grooves of particular DNA sequences, which are mainly recognized by specific hydrogen bonds.[30] However, although DNA continues to be a target for anticancer chemotherapy, more recent efforts have been directed at discovering antitumor drugs specifically suited to target molecular aberrations that are specific to tumor cells.[31] This new generation of specific antitumor agents, or anticancer targeted drugs, is based on advances in molecular biology that occurred by the late 1980s, providing greatly increased understanding of regulatory and signaling networks that control fundamental cellular processes such as vascularization, cell growth and proliferation. It was then known that many of these signaling networks are enhanced in tumor cells in response to activated oncogenes.

The beginning of the twenty-first century was marked by the development of targeted therapeutics in the fight against cancer. Today, conventional chemotherapy is frequently replaced by monoclonal antibodies, kinase inhibitors, and cell differentiation or immunomodulatory agents. After the approval of trastuzumab (Herceptin®), other HER2-targeting agents, such as the small molecule lapatinib (Tykerb®) and the antibody pertuzumab (Perjeta®), were developed. Metastatic melanoma treatment