PREFACE

This unique volume traces the critically important pathway by which a "molecule" becomes an "anticancer agent." The recognition following World War I that the administration of toxic chemicals such as nitrogen mustards in a controlled manner could shrink malignant tumor masses for relatively substantial periods of time gave great impetus to the search for molecules that would be lethal to specific cancer cells. We are still actively engaged in that search today. The question is how to discover these "anticancer" molecules. *Anticancer Drug Development Guide: Preclinical Screening, Clinical Trials, and Approval, Second Edition* describes the evolution to the present of preclinical screening methods. The National Cancer Institute's high-throughput, in vitro disease-specific screen with 60 or more human tumor cell lines is used to search for molecules with novel mechanisms of action or activity against specific phenotypes. The Human Tumor Colony-Forming Assay (HTCA) uses fresh tumor biopsies as sources of cells that more nearly resemble the human disease.

There is no doubt that the greatest successes of traditional chemotherapy have been in the leukemias and lymphomas. Since the earliest widely used in vivo drug screening models were the murine L1210 and P388 leukemias, the community came to assume that these murine tumor models were appropriate to the discovery of "antileukemia" agents, but that other tumor models would be needed to discover drugs active against solid tumors. Several solid tumor models were developed in mice that are still widely used today and have the advantage of growing a tumor in a syngeneic host. In the meantime, a cohort of immunodeficient mice was developed, including nude, beige, and SCID mice, allowing the growth of human tumor cell lines and human tumor biopsies as xenografts in the mice. Through the great advances in our knowledge of intracellular communication by secreted growth factors, cytokines, chemokines, and small molecules, the importance of the normal cellular environment, both stromal and organal, to the growth of malignant tumors has come to the fore. Now preclinical tumors in which malignant cells are implanted into the organ of origin, that is, in the orthotopic site, add this additional level of sophistication to drug discovery. In addition, new endpoints for preclinical testing, such as quantified tumor cell killing and detection of tumor cells in sanctuary sites, have been developed.

Of the hundreds of thousands of molecules passing through the in vitro screens, few reach clinical testing. In the United States, the FDA must grant permission to enter new investigational agents into human testing, whether the clinical testing is sponsored by an academic investigator, the NCI, or the pharmaceutical industry. Patient safety is the foremost concern. Nonclinical safety testing programs need to be carefully designed to allow identification of potential hazards so that they can be appropriately monitored and so that safe starting doses can be selected. The ongoing costs and timelines for toxicology studies need to be realistically factored into overall development plans so that clinical testing is not unnecessarily delayed. The phase I clinical trial allows the initial study of a candidate therapeutic's pharmacokinetics, pharmacodynamics, toxicity profile, and tolerated dose. In phase II clinical trials, the goal becomes demonstration of disease-

specific activity. In phase III clinical trials, statistically significant clinical benefit in well-designed and adequate clinical trials is required for success and FDA marketing approval. Phase III trial designs and statistical plans need to be appropriate relative to the current standard therapy for the intended indication. Poorly conceived and poorly executed clinical development can sabotage promising agents with recognizable activity. Much of the world's community of physicians and investigators now participate in clinical trials of potential new anticancer agents; however, the century-old goal of discovering molecules that control the growth and spread of malignancies as well as being viable as therapeutics in humans remains elusive.

The systems for finding molecules to manage malignancy are in place worldwide and our knowledge of cell growth and regulation is increasing daily; thus, one must remain optimistic of success in cancer drug discovery. This volume provides a guide for navigating the treacherous path from molecule discovery to a commercial therapy. This development path is mined with ample opportunity for failure. For anticancer drug development programs to succeed, promising compounds need to be expeditiously and intelligently selected; toxicology programs need to be thorough, relevant, timely, and informative; clinical development needs to be focused and executed with the highest scientific and administrative integrity; and FDA regulations and guidance have to be understood and followed. It is our hope that *Anticancer Drug Development Guide: Preclinical Screening, Clinical Trials, and Approval, Second Edition* will help all those engaged in developing new treatments for this dread disease to avoid the pitfalls that await. Our friends, colleagues, and family members who are burdened with a diagnosis of cancer await your successes.

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