

Preface

Cancer drug development is currently undergoing a profound shift. Drugs targeting fundamental cellular processes such as DNA–replication and microtubule function, often referred to as “chemotherapy” and still the backbone of most cancer treatment regimens, are increasingly being complemented by or replaced with kinase inhibitors. This new class of drugs targets enzymes which provide growth and survival signals to cancer cells by transferring phosphate groups from Adenosine-5'-triphosphate (ATP) to other proteins, lipids, nucleotides, and carbohydrates.

The earliest roots of kinase inhibitor therapy for cancer can be found in observations several decades ago that mutant kinases are often responsible for tumor inducing properties of certain animal viruses. The idea to develop drugs against these kinases was initially not pursued due to the important physiological functions of many of these enzymes and the concern that kinase inhibitors would be selective enough to provide a sufficiently wide “therapeutic window” between drug activity and drug toxicity. This concern was largely alleviated by the discovery that mutations in kinase encoding genes can render cancer cells uniquely “addicted” to signals provided by the mutant kinase. An early dramatic example for the paradigm of oncogene addiction was the durable remissions of BCR-ABL positive leukemias in response to the ABL kinase inhibitor imatinib (gleevec).

Since the first publication of the gleevec trials in the year 2001, much has happened. Pharmaceutical companies have designed and synthesized inhibitors against virtually all known human kinases and the genomes of many human cancer types have been surveyed for mutations that might result in oncogene addiction. These efforts have been rewarded by the development and regulatory approval of inhibitors against the ABL kinase (chronic myeloid leukemia), EGFR kinase (lung cancer), ALK kinase (lung cancer), PDGFR and KIT kinase (gastrointestinal stromal tumors), VEGFR (kidney cancer) and most recently the BRAF kinase (melanoma). As with any other cancer drug, responses to therapy are often not durable and acquired drug resistance has become a major challenge.

This book summarizes the current state of kinase inhibitor therapy for cancer. Successful drug development relies on the expertise and dedication of many experts. To reflect this team approach to finding new kinase inhibitors and defining

their optimal use for cancer treatment, we invited experts in academia and pharmaceutical industry to share their insights into various aspects of this process, ranging from the first chemical screens, to preclinical testing and disease-focused clinical drug development. We hope these lessons will be instructive for the novice as well as the expert.

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