PREFACE

Nowhere has our favorite edict "Chance favors the prepared mind" been better illustrated than in the corridors of the pharmaceutical industry. From its conception as fungal spores contaminating a laboratory culture, to the rapid and sophisticated automated technologies of the present day, successful drug discovery continues to combine scientific breakthroughs with an element of luck and serendipity. We have witnessed huge technological developments in the automation and miniaturization of high throughput screening, as sources of chemical diversity in lead explosion, and genome-wide sequencing and proteomics programs in the supply of drug targets. Despite the indisputable benefits that these advances have brought to bear on improving efficiency and the probability of successful drug discovery, there remains unanimous recognition among drug discoverers that validated therapeutically relevant protein targets that contribute to the disease process provide an essential starting point for success.

For human health care, though we are witnessing considerable improvements in treating certain prevalent disease conditions, cancer remains a disease where there is a clearly unmet clinical need. Cancer is a devastating and incurable disease that affects all ages. Statistics tell us that, in the Western world, 1 in 3 people will suffer from cancer, and that 1 in 4 people will die from the disease. Its prevalence will soon outstrip cardiovascular disease. Indeed, though current cancer treatments may halt disease progression, the side effects are often severe and debilitating, and the therapeutic benefit to the patient frequently of limited value. Lack of tissue specificity, widespread nonspecific cytotoxicity and necrosis, and drug resistance are observed with many current clinical regimens. There is an undeniable need for better medicines and for redesigning cancer treatment.

It is becoming increasingly recognized that intracellular proteins provide an untapped source of therapeutic targets. Although most remain to be validated as drug targets, the large body of research evidence that has accumulated in recent years includes many examples of proteins that exhibit abnormalities in tumor cells. Elucidating the signal transduction pathways that govern the mitogenic response of cells to growth factors, together with the huge developments in understanding the cell cycle and gene expression control, are examples of research areas that have provided important insights into abnormalities that occur in cancers. However, cancer results from a multistep process in which the mutation of different genes culminates in the cell acquiring the capacity for continual growth, and thus numerous targets may be available for therapeutic intervention in a single tumor cell. Many of these genetic events occur in proto-

oncogenes, causing them to acquire increased activity and provide a permanent growth-promoting signal, or tumor suppressor genes, resulting in a loss of growth suppressing activity. The overriding consequence of these genetic abnormalities is a cancer cell that is liberated from its normal tightly regulated growth cycle.

We have seen important developments in understanding the mechanism of action of oncogenes and tumor suppressors, together with the pathways of control through which their effects on proliferation are mediated. For example, two of the most frequently inactivated tumor suppressor genes, the retinoblastoma gene Rb and p53, function as nuclear transcription factors that target genes involved in growth control. The mechanism of action indicates that pRb and p53 regulate transcription through chromatin-associated mechanisms. Oncogenes such as *myc* and *mdm2*, which frequently exhibit increased activity in tumor cells, act in a similar fashion.

The developments in understanding how oncoproteins and tumor suppressors exert effects provide a great resource that can be exploited in drug discovery. We know very well that aberrant control by these proteins provides the fundamental basis for a normal cell to become tumorigenic. Therapeutic approaches that target these proteins are therefore likely to offer new opportunities in the search for innovative, more specific, and efficacious medicines for treating the cancer patient.

Targets for Cancer Chemotherapy: Transcription Factors and Other Nuclear Proteins provides a series of authoritative and compelling accounts on selected examples of transcription factor oncoproteins and tumor suppressors, together with other nuclear and chromatin-associated proteins that are central to the phenotype of the tumor cell. By bringing together this group of expert commentaries, we aim to provide a detailed understanding of the latest research developments and the impact of this knowledge for cancer drug discovery.

Our book opens with a discussion from Kaelin on the E2F transcription factor, which plays an instrumental role in regulating progress into the S phase of the proliferative cycle, and clearly is of great relevance to the cancer cell owing to its frequent, if not universal, deregulation in human tumors. Berwanger and Eilers follow by describing Myc, a nuclear oncoprotein that functions as a transcription regulator and where recent research information has provided new mechanistic insights into growth control through the regulation of chromatin.

Angel and colleagues cover an equally important transcription factor in signal transduction, AP1, followed by Bhattacharya on the importance of the hypoxia-inducible transcription HIF factor that regulates angiogenesis required for tumor growth, and which offers great potential as a drug target. Trepel and colleagues overview recent developments in the β-catenin/TCF pathway, potentially of huge significance in cancer cells.

Research into chromatin control has shed light on the mechanisms that influence gene expression and accessibility to the transcription machinery. In turn, these studies have elucidated novel and interesting proteins that are endowed with enzyme activities required for chromatin modulation, and that play key roles in growth control. Thomson and Mahadevan describe the importance of histone acetylases, followed by Jung on the potential of deacetylases as cancer drug targets. Here, we know already of clinical trials underway with drugs that act as deacetylase antagonists.

Phosphorylation is known to have an important influence upon the activity of many transcription factors and other nuclear proteins, and several examples are discussed in which protein kinase regulation of transcription factors influences growth control. Rao and Patel overview cyclin-dependent kinases, frequently aberrantly regulated in tumor cells where they target and act through the pRb/E2F pathway, to drive early cell cycle progression. Mitogen-activated protein kinases, reviewed by Chiloeches and Marais, are an established group of drug targets that relay signals from growth factors to the nucleus, and regulate growth through the targeted phosphorylation of certain transcription factors.

Other nuclear mechanisms that influence growth could offer great value as cancer targets. The product of the tumor suppressor locus ink4/arf locus, the ARF protein, impedes the activity of the MDM2 oncoprotein to degrade p53, thereby facilitating the p53 response, representing an interaction that has attracted considerable interest in cancer drug discovery. Furthermore, we now understand that MDM2 regulates p53 activity by stimulating p53 breakdown through an ubiquitin-dependent pathway, and Klotzbücher and Kubbutat review recent progress in this area. In this respect, MDM2 mimics the action of certain viral oncoproteins, such as the oncogenic human papilloma virus E6 protein, a topic, and its application to new therapies, that is discussed in detail by Pim and colleagues.

Moreover, approaches that manipulate the mechanisms of DNA repair in response to DNA damage may alter the sensitivity of tumour cells to conventional chemotherapy, an exciting idea that is raised in the account from Gabriel and Ashworth on the role that the BRCA1/2 tumour suppressor proteins may play in DNA repair, and the opportunities for therapy that arise.

A review of an important series of developments surrounding the remarkable VP3 protein, known as apoptin, from the chicken anemia virus is provided by Noteborn. Apoptin causes apoptosis in cells that are malignant or transformed, but not in normal cells. Understanding the route through which apoptin stimulates apoptosis will likely open up new avenues for drug discovery in tumor cells.

In the final chapters, we conclude with reviews that move the emphasis from laboratory and pre-clinical-based anticancer drug discovery, to focus on the clinical disease, and address current knowledge of therapeutic applications for

E2F (Bertino) and HIF1 (Harris). Without doubt, it is pleasing and encouraging that application of these key targets has progressed to the clinical setting.

Our final review underscores the important contribution that drugs targeting transcription factors have made in current cancer treatments. Here, Oosterkamp and Bernards describe the mechanism of action of the nuclear hormone estrogen and androgen receptors and their value as anticancer targets.

Many of the proteins considered in this volume fulfill one of the most important and fundamental criteria in drug discovery, namely a validated target that contributes to the pathology of the disease. By providing this information in a single volume, together with the scientific and therapeutic rationale that justifies the approach and value of each target to cancer drug discovery, the cancer patient, and the pharmaceutical industry, we hope to have provided an authoritative account of an innovative scientific area that we believe could lead to a new class of specific target-based medicines for treating what remains an incurable disease. In completing the volume, we have tried at the very least to have prepared the mind of the cancer drug discoverer. After all, as all scientists know, chance does indeed favor the prepared mind.

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