

PREFACE

Through experience we know only appearances ..., but not the modum noumenon ..., not things as they are in themselves.

—Immanuel Kant

Could cancer be treated, perhaps cured, by targeting and effectively removing its “cause”? A possible answer to this question is often as difficult to conceptualize as is the very essence of this life-threatening disease. In this regard, a reductionist viewpoint emphasizes properties of a “cancer cell” (1,2) or evolving and transformed clones of such cells (3), each of these entities typically equated with a “unit of malignancy.” On the other hand, cancer can also be viewed as a heterogeneous “society” of freely interacting but phenotypically altered cells and cell subpopulations. Each of such co-existing cell subsets, in and of itself, does not define the malignant process as a whole, but rather such definition is encoded in the (aberrant) functional interplay between its constituents (4). An even more “holistic” approach invokes a contribution of deregulated host responses, which either fail to control the “spontaneous” emergence of cancer cells (e.g., immunity) (5), or become subverted by the latter to support unrestricted tumor growth, invasion, and metastasis (e.g., angiogenesis) (6). In the latter instance, the vascularized, multicellular conglomerate involving both transformed and nontransformed (stromal) cells could be viewed as a different type, more complex tumorigenic “unit” (1,7). Could these vastly diverse concepts accommodate a common denominator, a unifying “causal” influence that drives multifaceted pathological processes and is responsible for the multitude of clinical manifestations of malignancy? Could such influence(s) be controlled therapeutically?

Breathtaking developments in cancer genetics over the last two to three decades seem to suggest that the answer to this crucial question may be affirmative. Indeed, intrinsic genetic lesions in cancer cells are now thought to be the *primum movens* behind expression of all major “hallmarks of cancer” (1), including formation of the vascular tumor stroma. In this sense, “cancer-causing” mutant genes are ultimately responsible for the development and progression of the malignant disease as we know it (2). It is, of course, possible that such overt genetic changes are preceded by more subtle epigenetic events affecting tissue or cellular homeostasis. It is also possible that the “cancer-causing” effects of mutant genes may be either direct or indirect in nature. Nevertheless, once they occur, the biological impact of “broken genes” transcends cellular boundaries, and emanates into the local and systemic realms of cancer-associated pathology.

Up to seven independent genetic “hits” are thought to be associated with development and progression of an overt malignant tumor (8). However, recent studies suggest that abnormal expression of only three genes might be sufficient, at least in some cases, for a complete conversion of normal human cells into their cancerous counterparts (9). Incidentally, all three of the “cancer-causing” genes implicated in such a process (i.e., *H-ras*, *hTERT*, *SV40-LT*) are known to induce “gain-of-function” type changes and thereby could be traditionally classified as dominant acting, transforming *oncogenes* (1,2). Moreover, inactivation of even a single oncogene (e.g., mutant *ras*) in the context

of a full-blown malignant tumor in vivo, can result in profound growth inhibition and/or tumor regression (10,11). Thus, despite a multitude of genetic and epigenetic influences and complexities associated with tumor formation, at least in some cases, sustained expression of certain oncoproteins is clearly functionally important, nonredundant, and virtually indispensable for continued tumor growth and “maintenance” (10,11). Indeed, it is difficult to formulate a better definition of an (almost) ideal therapeutic target.

In recent years, oncogenes have attracted a great deal of interest as prospective molecular targets for anticancer therapy. The tremendous amount of work and thought that went into exploration of this concept culminated in the recent FDA approval of at least two oncogene-targeted anticancer agents—Herceptin/trastuzumab and STI571/Gleevec—with several other compounds and approaches still in the “pipeline.” All of these efforts hold great promise, but there are also challenges ahead. These challenges have to be fully understood to be properly met in the future. For these various reasons, it is difficult to imagine a more appropriate time for the publication of a comprehensive overview on *Oncogene-Directed Therapies*. In the past, cancer *research* and cancer *treatment*, although motivated by similar long-term goals and objectives, have been developing along somewhat different trajectories influenced by their respective focus on either current or future challenges in dealing with human malignancies. In 2002, we can claim with some degree of credibility that with regards to the rational, causality-based, scientifically sound cancer treatment, “the future is now.” The advent of new Protein Kinase Inhibitors (PKI), Farnesyltransferase Inhibitors (FTIs), and other types of “anti-oncogenic” signal transduction antagonists heralds a significant change in the practice of oncology by bringing together the results of basic, translational, and clinical research. It continues to be a fascinating pursuit and many more potential targets for oncogene-directed therapies still remain unexplored (Table 1).

Although the nominal focus of this book is on targeting *oncoproteins*, it is important to realize that traditionally, antithetical concepts of “oncogenes” and “tumor suppressor genes” are gradually being replaced by more sophisticated models in which cellular transformation and tumor progression can be explained more accurately by analysis of interactive molecular circuitry involving protein products of both types of genes. We attempted to highlight this conceptual shift in this book.

Oncogene-Directed Therapies is a result of the concerted effort of a number of devoted individuals who have made significant contributions to this promising field of cancer research. The content of the book is composed in such a way as to give readers a balanced blend of fundamental science, basic research, experimental therapeutics, and early clinical experiences. The first section (Chapters 1–7) is devoted to the “concept” of an *oncogene* and *oncogenesis*. The reader will be presented with a series of up-to-date overviews on “how” and “why” certain proteins can acquire the ability to transform eukaryotic cells, and under what conditions. The many mechanisms, pathways, and complexities of the cell transformation process will be the main themes of this section. Chapters 8–13 are meant to introduce the crucial biological consequences of the oncogenic transformation, particularly for cellular mitogenesis, survival, differentiation, migration, proteolysis, or angiogenic competence. This is meant to open the discussion on how oncogene-directed therapies may work to obliterate essential elements of cancer pathogenesis. Chapters 14–22 are devoted to premises, principles, techniques, and approaches to oncogene targeting in vari-

Table 1		
Functional Classification of Oncoproteins [adapted from R. Hesketh (12)].		
Oncoproteins	Biological functions	Examples
Class 1	Growth factors	HSTF1, INT2, PDGFB/SIS, WNT1-3
Class 2	Tyrosine kinases	HER-2/NEU, EGFR, ABL-1, TRK, SRC,
Class 3	Non-kinase receptors	MAS, MPL
Class 4a	Membrane G-proteins	H-RAS, K-RAS, N-RAS, TC21, G _{α12} , G _{α13}
Class 4b	Guanine nucleotide exchange proteins	SDC25, OST
Class 4c	RHO/RAC binding proteins	BCR, DBL, TIAM1, VAV, TIM, ECT2
Class 5	Cytoplasmatic protein serine kinases	BCR, MOS, RAF, PKC , CLK, TPL-2
Class 6	Protein series, threonine (and tyrosine) kinases	AKT1, AKT2, STY
Class 7	Cytoplasmatic regulators	BCL1, CRK, NCK, PEM, ODC1
Class 8	Cell cycle regulators	INK4A, INK4B, INK4C, CyclinD1, CDC25
Class 9	Transcription factors	ETS, JUN, FOS, MYC, REL, TAL-1, E2F1
Class 10	Transcription elongation factors	ELL
Class 11	Intracellular membrane factors	BCL2
Class 12	Nucleoporins	NUP98, NUP214
Class 13	Adapter proteins	SHC
Class 14	RNA binding proteins (Translation factors)	EWS (eIF-4E)
Class 15	Unknown function	MEL, MAF, DAN, DLK, LBC

ous types of human cancer by using signal transduction inhibitors, immunological targeting methods, and/or antisense gene therapy. These chapters also review the results of preclinical and clinical testing of some of the most advanced therapeutic agents already developed (e.g., Gleevec, Herceptin, IMC225). It is also noteworthy that inhibition of oncoprotein activity could sensitize cancer cells to more traditional forms of anticancer therapy (e.g., radio- or chemotherapy) and, possibly, to inhibitors of angiogenesis. Therefore, oncogene targeting agents are likely to be used not instead of, but rather in addition to, already established treatment modalities. The discussion on each of these subjects is supported by an extensive survey of the relevant literature, providing a resource to those seeking more detailed information.

Many individuals have made their mark on this book and deserve thanks and gratitude. In particular, I am deeply indebted to all the contributors to this volume for their outstanding work and cooperation, to the publisher for a great deal of patience, to my colleagues, particularly Drs. Petr Klement and Jeffrey Weitz, for their encouragement and support, to my daughter Anna and wife Dana for their forgiveness and help, as well as to my mother Stanislaw for pretty much everything.

I would like to include another personal note. While this volume was in preparation, someone posed to me the following question: Why would an expert in a particular field of research contribute a book chapter these days? Why would such an individual risk the somewhat longer publication cycle and forgo the instant relief and gratification of much

faster publication in a scientific journal? My experience, with this book and otherwise, has taught me that scientists who agree, or else can be persuaded, to write a book chapter are a different breed. Perhaps these are the people who believe that in today's reality often illuminated by limelights of scientific "fashion," flashes of information snapshots, and the glow of ever changing research headlines, something qualitatively different is also needed. Working on a book inherently entails a more collegial process and results in something more lasting, more complete and comprehensive, and perhaps more mature than the "last minute" research report. Books are more about ideas and directions than about "hot" results. We hope that *Oncogene-Directed Therapies* will possess at least some of these lasting qualities and that it will help to accurately reflect the emerging new "climate" in oncology. We believe such understanding will benefit academics, students, physicians, and ultimately, the patients.

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