Preface

No other hematopoietic malignancy has attracted the degree of attention and investigative passion as what is still termed "leukemia." The condition was first described by John Hughes Benett in October 1845 and by Rudolf Virchow in November 1845 as the "white blood" disease, following earlier reports by Alfred Velpeau (1827) and others. Virchow coined the term "Leukaemie" in 1847. This was only shortly after Henri Dutrochet had discovered that "the cell is the fundamental element of organization," thus formulating the underlying tenet of cell theory (1824), and Theodor Schwann and Matthias Jakob Schleiden had proposed (in 1839) that cells were the basic units of life. Thus, the discovery of leukemia was closely linked, personally and historically, to the most revolutionary new concepts of modern biology and medicine. Ten years later, Virchow, plagiarizing earlier work of Robert Remak, declared that cells originate from pre-existing cells by cell division and founded the field of cellular pathology. He also distinguished between splenic and lymphatic leukemias, which was of great value for the subsequent subclassification of what was initially thought to be a uniform entity.

Although cytogenetic and molecular analyses have dissected leukemias into an ever expanding universe of distinct maladies, the clinical designation of acute myeloid leukemia (AML) has so far survived further dissection, perhaps because of its life-threatening acuity. The immediate clinical challange to the physician is to establish the correct diagnosis and to cope with complications that can engage all medical subspecialties, ranging from blood-product replacement to the treatment of septic shock and renal failure. In the center of the evolving drama is the individual patient, who, with no antecedent warning has to suddenly face his own mortality.

In the early 1900s, Paul Ehrlich started developing drugs to treat infectious diseases and developed the first "chemotherapy." About 100 years later we are still following the paradigm that he established.

The modern era of chemotherapy evolved with the observation that the accidental exposure of humans to sulfur mustards resulted in the depletion of bone marrows and lymph nodes. Goodman and Gillman at Yale, following experiments in animals, initiated treatment of patients with non-Hodgkin's lymphoma with nitrogen mustard. The first responses were observed in 1943 and stimulated the development of alkylating agents after the war. Farber treated children with leukemia with folate

antagonists (methotrexate) and Hitchings and Elion developed inhibitors of adenine metabolism (thiopurines) and observed major, although short-lived responses. Charles Heidelberger introduced 5-fluorouracil, the first "targeted" anticancer therapy. L-asparaginase is another example and once the double-helical structure of DNA was discovered, DNA-targeted agents such as cytosine arabinoside and daunomycin were successfully developed.

These chemotherapies were brought into clinical practice over the past 50 years and were based on evolving insights into the chemistry and biochemistry of the leukemic cell. Then as now, therapeutic strategies are attempting to exploit evolving scientific insights into metabolic and molecular abnormalities of the leukemia cell; therefore most therapies were "targeted" from their inception.

Subsequent steps in the development of targeted therapies were based on the discovery of tumor-associated antigens and monoclonal antibodies, on the plethora of newly identified mutations, evolving insights into the mechanisms of epigenetic gene regulation and the functions of oncogenic kinases. Much effort is now being focused on kinase inhibitors, following the spectacular success of the bcr-abl tyrosine kinase inhibitor Gleevec in Philadelphia-chromosome positive chronic myeloid and acute lymphoblastic leukemias.

What we are facing today is an exponential gain in our knowledge of the cell and molecular biology, immunology and epigenetic gene regulation of leukemias, which is fortunately matched by the zeal of laboratory and clinical investigators to translate scientific insights into clinical success. In addition, numerous treatment options have evolved and are being explored in clinical investigations even without clear identification and understanding of their targets. This approach is fueled by the notion that leukemia cells have an uncanny ability to evade highly specific targeted therapies and that less specific, multipotent "dirty" drugs may be more effective. Both approaches may have merits and are likely to contribute to the development of our therapeutic arsenal for the next decades.

Finally, it is becoming increasingly clear that many of the classical therapies are causing genetic damage in surviving cells that actually contribute to relapse. Hence, the development of nongenotoxic agents is paramount, such as BH3-mimetics and MDM2 inhibitors, that activate apoptosis pathways, presumably without causing DNA damage.

Targeted therapy also needs to define its cellular, not just molecular target. The concept of a highly drug resistant leukemia stem cell that contributes to relapse is now being accepted, but needs more attention by drug developers and clinicians alike It has also become increasingly clear that the leukemia microenvironment is a partner of equal importance to leukemia cell-intrinsic resistance mechanisms for the survival, expansion and relapse of leukemia stem cells, leading to clinical relapse. Early attempts are under way to address both sides of this "Yin-Yang" equation, which is dramatically put in focus by the recent discovery that molecular changes in the microenvironment can cause, and not just support, leukemia development.

In this book it is attempted to summarize and interpret targeted AML therapies by pairing chapters describing the basic molecular biology of major targets with clinical results of targeted therapies, thus rendering the translational and clinical

researcher a useful tool to apply recent research data available to him in a more specific way. The exponential growth in knowledge exceeds the ability of any researcher to be up-to-date and we do hope that this collection of 43 chapters from the leading experts in their fields will make a difference in how we approach the ever-growing complexity of AML-directed therapeutics. Topics and targets are evolving with further elucidation of the underlying basic science, as the tools at our disposal.

The introductory chapters present updated contemporary classification systems of myeloid leukemias, their genetic defects and the proteomic alterations characteristic of AML. The basic mechanisms of apoptosis disregulation described in these chapters include the roles of BCl-2, IAP and p53 families of proteins and exemplify the concept of pairing basic science with evolving therapeutics such as BH3 and SMAC mimetics and MDM2 inhibitors that can reactivate p53 signaling.

Tyrosine kinase controlled cell signaling pathways have been elucidated in a large number of investigations following the spectacular success of Gleevec and its successors in the treatment of chronic myeloid leukemias. The book then transitions into a discussion of PIM, FLT3, NPM1, Ras/Raf/MAPK, PI3K/AKT/mTOR and aurora kinase functions and therapeutic targeting—a field which is rapidly developing as exemplified by the recent successes reported for IDH2 inhibitors but could not be included here.

Epigenetic modulators of acetylation and methylation are being covered and discussed along with epigenetic therapies which have already yielded significant therapeutic impact but will only increase with improved specificities and more precise definition of their targets. Although the underlying mechanisms of action are well studied, much work still needs to be done until we will have the ability to selectively affect the epigenetic regulation of specific genes.

PML-RARa and orphan nuclear receptors such as nor1 and nur77 have provided fascinating targets in leukemias, as is best exemplified in the improvement of the survival rates of patients with acute promyelocytic leukemias from 30 to 90 % in just a few years, following the introduction of ATRA and arsenic trioxide. Nur77 may provide another target which is universally dysregulated in AML, not just in APL.

Rapid advances in tumor immunology led to the development of monoclonal antibodies that resulted in impressive response rates, alone or in combination with immunotoxins, in chronic and acute lymphocytic leukemias. These achievements have been more modest in AMLs, but recent advances in leukemic stem cell biology may make antibodies the most effective tools in the elimination of AML stem cells.

The leukemia microenvironment has graduated from supportive bystander to therapeutic target with the discovery that changes in bone marrow stroma cells, such as deletions of DICER which regulates microRNAs, results in the development of AMLs. First attempts to disrupt leukemia/stroma interactions by blockade of CXCR4 and VLA-4 signaling are yielding successes, but this field is clearly in more need of development. The recent identification of pronounced hypoxia in AML bone marrows makes hypoxia and hypoxia-induced genes novel targets in leukemia therapy.

MicroRNAs are also becoming attractive targets, as their complex regulatory control of many pathways of vital importance for leukemia proliferation and survival is being better understood.

All genetic and epigenetic alterations in leukemias finally result in metabolic alterations. Cancer metabolism, a field founded originally by Otto Warburg, has recently evolved in unexpected ways and will become of critical importance for the eradication of leukemias. Glycolysis, oxidative phosphorylation and fatty acid oxidation are at the center of leukemia metabolomics. The above mentioned development of IDH2 mutation inhibitors and their initial activity in patients whose AML cells carry this mutation provide an impressive example on how molecular genetics can be linked to epigenetic and metabolic functions and then be applied to the small subset of patients who may benefit.

The development of specific immunotherapies employing NK^{-}, and T-cells is making its own way in the therapy of AML. CAR T-cell have yielded dramatic and sustained responses in certain leukemias and it is hoped that these concepts can be carried over into the treatment of AMLs. Hematopoietic transplantation has been refined and improved after half a century of unrelenting efforts and may be complemented by strategies utilizing mesenchymal stem cells as well.

All contributing authors hope that this book will serve as a useful guideline and provide inspiration and support to all scientists working in a field with high challenges but also great potential and importance for our collective future.

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