

1. Record Nr.	UNINA9910830571103321
Titolo	Targeting oncogenic drivers and signaling pathways in lymphoid malignancies : from concept to practice // edited by Owen A. O'Connor, Stephen Ansell, and John Seymour
Pubbl/distr/stampa	Hoboken, New Jersey : , : John Wiley & Sons, Inc., , [2023] ©2023
ISBN	1-119-81995-4 1-119-81993-8
Descrizione fisica	1 online resource (514 pages)
Collana	Precision cancer therapies ; ; Volume 1
Disciplina	616.99406
Soggetti	Cancer - Treatment Precision Medicine Lymphoma - therapy Signal Transduction
Lingua di pubblicazione	Inglese
Formato	Materiale a stampa
Livello bibliografico	Monografia
Nota di bibliografia	Includes bibliographical references and index.
Nota di contenuto	Intro -- Precision Cancer Therapies -- Contents -- List of Contributors -- Volume Foreword -- Volume Preface -- Series Preface -- Section I Biological Basis of the Lymphoid Malignancies -- 1 Fundamental Principles of Lymphomagenesis -- Take Home Messages -- Introduction -- How to Study Lymphomagenesis -- Before Lymphoma: The Gray Frontier Between Physiology and Pathology -- Driver Without Disease -- From In Situ Neoplasms to Asymptomatic Lymphomas -- Chronic Antigenic Stimulation as an Early Step of Lymphomagenesis -- The Cell of Origin Concept: A Classification Based on Physiology -- What Are the Hallmarks of Lymphoma? -- Epigenetics and Metabolism -- Apoptosis Escape -- Proliferation -- TCR/BCR Signaling -- Immune Escape -- Trafficking -- Microenvironment -- Conclusion -- Must Read References -- References -- 2 Identifying Molecular Drivers of Lymphomagenesis -- Take Home Messages -- Introduction -- Sequencing and Bioinformatics Methods -- Functional Validation of Drivers -- Common Themes in B- and T-cell Lymphoma -- Genetic Landscapes of Lymphomas -- Mature B-cell Lymphomas -- T-cell

Lymphomas -- Genomic Subgrouping Approaches in DLBCL -- Challenges of Incorporating Genomic Subgrouping Approaches in Clinical Trials -- Leveraging Underlying Pathophysiology to Inform Therapeutic Consideration -- Conclusion -- Must Read References -- References -- 3 Characterizing the Spectrum of Epigenetic Dysregulation Across Lymphoid Malignancies -- Take Home Messages -- Introduction: Epigenetics and Lymphoid Malignancies -- Dysregulation of DNA Methylation and Modification of Histone Proteins -- Genes Involved in Histone Modification Implicated in Lymphomagenesis -- Enhancer of Zeste Homolog 2 (EZH2) -- CREB-binding Protein (CREBBP) and Histone Acetyltransferase P300 (EP300) -- The H3K4 Methyltransferase Family. The Bromodomain and Extra-Terminal Domain (BET) Family -- Genes Involved in DNA Methylation Implicated in Lymphomagenesis -- DNA Methyltransferase 3A (DNMT3A) -- Ten-Eleven Translocation 1/2 (TET1/2) -- Isocitrate Dehydrogenase 2 (IDH2) -- The Epigenetic Landscape of Specific Lymphoid Malignancies -- Follicular Lymphoma -- Diffuse Large B-cell Lymphoma -- Marginal Zone Lymphoma -- Burkitt's Lymphoma -- Acute Lymphoblastic Leukemia -- Chronic Lymphocytic Leukemia -- Mantle Cell Lymphoma -- Hodgkin's Lymphoma -- Multiple Myeloma -- Peripheral T-cell Lymphoma - Not Otherwise Specified -- Angioimmunoblastic T-cell Lymphoma and PTCL with TFH Phenotype -- Anaplastic Large Cell Lymphoma -- Adult T-cell Leukemia/Lymphoma -- Intestinal T-cell Lymphoma -- Hepatosplenic T-cell Lymphomas -- NK/T Cell Lymphoma -- Mycosis Fungoides and Sezary's Syndrome -- Summary -- Must Read References -- References -- 4 Animal Models of Lymphoid Malignancies -- Take Home Messages -- Introduction -- Optimal Animal Models to Study Lymphoid Neoplasms -- Zebrafish Model -- Zebrafish Model of T-cell Neoplasms -- Zebrafish Model of B-cell Neoplasms -- Zebrafish Model of NK-cell Neoplasms -- Patient-Derived Xenograft Models in Zebrafish -- Fruit Fly Model -- Non-human Primate Model -- Mouse Models of Lymphoid Neoplasia -- Use of Animal Models in Translational Research -- Conclusions -- Must Read References -- References -- Section II Targeting the PI3 Kinase-AKT-mTOR Pathway -- 5 Principles of PI3K Biology and Its Role in Lymphoma -- Take Home Messages -- Introduction: Overview -- Four Decades of PI3K Signaling Research -- Class I PI3K Enzymes -- Isoforms -- Structural Organization -- Isoform-specific Functions -- The Essential Phospholipid Second Messenger PIP3 -- PI3K Pathway Effectors -- AKT, FOXO, and mTORC1 -- TEC Tyrosine Kinases -- Network Topology and Signal Robustness. Dynamic PI3K Signaling in Lymphocyte Biology -- B-cell Development and Survival -- The Germinal Center (GC) Reaction -- TFH Cell Function -- Naïve and Effector T-cells -- Lessons from Monogenic Disorders -- Genetic PI3Kd Inactivation -- Genetic PI3Kd Hyperactivation -- Corrupted PI3K Signaling in Cancer -- The Success of PI3Kd Inhibition in Lymphoid Malignancies -- Quantitative Biology and Therapeutic Considerations -- Concluding Remarks -- Acknowledgments -- Must Read Reference -- References -- 6 Pharmacologic Differentiation of Drugs Targeting the PI3K-AKT-mTOR Signaling Pathway -- Take Home Messages -- Introduction -- PI3K Inhibitors Approved by the US Food and Drug Administration (FDA) -- PI3K Inhibitors in Clinical Development -- AKT Inhibitors -- mTOR Inhibitors -- Conclusions -- Must Read References -- References -- 7 Clinical Experience with Phosphatidylinositol 3-Kinase Inhibitors in Hematologic Malignancies -- Take Home Messages -- Introduction -- Idelalisib -- Copanlisib -- Duvelisib -- Umbralisib -- Parsaclisib -- Zandelisib -- Amdizalisib

(HMPL-689) -- Conclusion -- Must Read References -- References -- 8 Clinical Experiences with Drugs Targeting mTOR -- Take Home Messages -- Introduction -- Rapamycin (Sirolimus) Rapamune® (Pfizer) and Generic Sirolimus -- The Rapamycin Analogs (Rapalogs) -- Temsirolimus (CCI-779 -- Torisel) -- Everolimus (RAD-001 -- Afinitor, Zortress, Evertor) -- Summary of Lymphoma Studies of Everolimus -- Ridaforolimus -- Dual Inhibitors of mTORC1 and mTORC2 -- Side Effects of mTORC1 Inhibitors -- Future Directions for mTOR Inhibitors in Lymphoma -- Must Read References -- References -- 9 PI3 Kinase, AKT, and mTOR Inhibitors -- Take Home Messages -- Introduction -- PI3K Structure and Functions -- AKT Structure and Functions -- mTOR Structure and Functions -- PTEN as a Regulator of the PI3K/AKT/mTOR Pathway.

mTOR Inhibitors -- Temsirolimus: Phase 3 Trials -- PI3K and Dual PI3K/mTOR Inhibitors -- PI3K Isoforms and Expression Throughout the Body -- Immune Toxicity and Management -- Colitis -- Hepatitis -- Pneumonitis -- Skin Rash -- Homeostatic Toxicity -- Hypertension and Hyperglycemia -- Myelosuppression and Opportunistic Infection -- Myelosuppression -- Atypical Infection -- Vaccination -- Neuropsychiatric Problems -- PI3K Treatment in NHL -- AKT Inhibitors -- Conclusion -- Must Read References -- References -- Section III Targeting Programmed Cell Death -- 10 Principles for Understanding Mechanisms of Cell Death and Their Role in Cancer Biology -- Take Home Messages -- Introduction -- A Historical Perspective -- Apoptotic Pathways -- Other Cell Death Pathways -- The Role of Intrinsic Apoptosis in Normal Cells - Lessons from Gene Knockout Mice -- BCL2 Family Pro-survival Proteins -- BCL2 -- BCL-XL -- MCL-1 -- A1/BFL-1 -- BCL-W -- Combined Knockout of Pro-survival Proteins -- BCL2 Family Pro-apoptotic Effector Proteins -- BH3-only Proteins -- The Dysregulation of Apoptosis in Cancer -- Must Read References -- References -- 11 Pharmacologic Features of Drugs Targeting BCL2 Family Members -- Take Home Messages -- Introduction -- Historical Perspective: From the Discovery of BCL2 to Therapeutic Applications -- BCL2 as a Biomarker -- Targeting BCL2 Family Members -- Antisense Approaches for Targeting BCL2 -- Natural Anti-apoptotic Compounds -- Small Molecule Inhibitors of BCL2 Family Members -- Novel BCL2 Inhibitors on the Horizon -- Mechanisms of Resistance to BCL2 Inhibitors -- Novel Mechanisms to Overcome BCL2 Resistance -- Targeting MCL1 -- PROTAC Strategies for Targeting Apoptotic Family Members -- Conclusions -- Must Read References -- References -- 12 Clinical Experience with Pro-Apoptotic Agents -- Take Home Messages -- Introduction.

Safety and Toxicities of Pro-apoptotic Agents -- Tumor Lysis Syndrome -- Myeloid Compartment Toxicities and Infections -- Gastrointestinal Toxicities -- Thrombocytopenia and Navitoclax -- Efficacy of Venetoclax in Chronic Lymphocytic Leukemia/Small Cell Lymphoma -- Phase 1/2 Studies -- Combining Venetoclax with Conventional Chemotherapy in CLL/SLL -- Phase 3 Studies -- Venetoclax Re-treatment -- Efficacy of Venetoclax in Other B-cell Neoplasms -- Mantle Cell Lymphoma -- Follicular Lymphoma -- Diffuse Large B-cell Lymphoma and Other Aggressive B-cell Lymphomas -- Richter Transformation -- Waldenstrom's Macroglobulinemia -- Marginal Zone Lymphoma -- Acute Lymphoblastic Leukemia/Lymphoma -- Lessons from Venetoclax in Lymphoid Neoplasms Other than CLL/SLL -- Associations and Mechanisms of Resistance to Pro-apoptotic Agents -- Must Read References -- References -- 13 Promising Combinations of Drugs Targeting Apoptosis -- Take Home Messages -- Introduction: Background and Disease Perspective -- Clinical Development of BCL2

Inhibitors -- Venetoclax Monotherapy for CLL -- Venetoclax Plus CD20 Monoclonal Antibody for CLL -- Venetoclax Plus BTK Inhibitor for CLL -- Venetoclax Plus BTK Inhibitor and CD20 Monoclonal Antibody for CLL -- Venetoclax Plus Chemoimmunotherapy -- Venetoclax Toxicities and Side Effects in CLL -- TLS Risk Mitigation and Management in CLL -- Venetoclax-associated Neutropenia -- Risk for Progression and Resistance Mechanisms -- Current Knowledge Gaps and Opportunities for Future Work with Venetoclax -- Must Read References -- References -- Section IV Targeting the Cancer Epigenome -- 14 The Role of Epigenetic Dysregulation in Lymphoma Biology -- Take Home Messages -- Introduction: Germinal Center B (GCB)-cells and GCB-derived Lymphomas -- Mutations Altering DNA Modifications and Structure -- TET2. Mutations Altering Writers of Histone Post-translational Modifications.

Sommario/riassunto

"If one asks a cancer scientist a seemingly naive question such as what are the hallmarks of cancer cells, he-she will probably cite at first somatic mutations and genomic rearrangement, leading to excessive proliferation, resistance to apoptosis, and dissemination potential (Hanahan and Weinberg, 2011). Intriguingly, all of these hallmarks are physiological properties of B- and T-lymphocytes, selected by evolution because they ensure an efficient immune response against pathogens. So, it is a fascinating paradox to observe that lymphoma remains a relatively rare cancer as compared to epithelial cancers. Hence, understanding the tumor suppressor mechanisms that mitigate lymphomagenesis or eradicate lymphoma cells at preclinical stages appears an extraordinary challenge. After a short overview of the current models used to analyze lymphomagenesis, we will highlight that the frontier between reactive lymphoproliferation and overt lymphoma is not always clear. Then, we will present how the classification of lymphomas based on the concept of cell of origin might reveal important phenotypical properties of lymphoma subtypes. Finally, we propose an overview of the main hallmarks of lymphomas and discuss their contribution in the most frequent subtypes of lymphomas. How to study lymphomagenesis As in other scientific fields, the nature of our knowledge of lymphomagenesis is tightly linked to the tools used to produce this knowledge. Hence, it seems interesting to start this review with a methodological perspective, providing a brief overview of the different scientific approaches which have brought major contributions to our understanding of lymphomagenesis. Epidemiology was the first approach which shed light on the mechanisms of lymphomagenesis, by deriving statistical correlations from direct observation of cohorts of patients. First, epidemiology has established the link between lymphoma incidence and aging. The incidence of most lymphomas follows an exponential growth after the fifth decade as observed for most cancers, suggesting that common processes are shared with solid tumors (Sarkozy et al., 2015; Rozhok and DeGregori, 2016). In the case of Hodgkin lymphomas, the bimodal distribution of incidence suggests that specific mechanisms are occurring in young patients, which have not been fully elucidated to date. Second, epidemiology has also proven a counter-intuitive association of lymphomas with immunosuppression, either inherited (common variable immunodepression for example) or acquired after HIV infection, or immunosuppressive drugs (van Leeuwen et al., 2009; Kaplan, 2012). This association revealed the role of the immune system in repressing the growth of transformed lymphocytes, either by active eradication of tumor cells or by exerting a competition for resources. Third, the analysis of the geographic distribution of lymphoma subtypes also shows striking differences,

such as the higher incidence of T-cell lymphoma in Asia as compared to Western countries (Perry et al., 2016). These differences suggest two non-mutually exclusive hypotheses, related to environmental or genetic differences. The fourth major insight from epidemiological studies was to shed light on the role of pathogens such as *Helicobacter pylori*, HCV, EBV or HTLV1 in specific subtypes of lymphoma (Lecuit et al., 2004; Suarez et al., 2006; Couronne et al., 2018), which has been then confirmed experimentally. Besides pathogens, epidemiological studies have also demonstrated the role of environmental exposures such as herbicides in lymphomagenesis, which might have important consequences for health policies (Weisenburger, 2021). More recently, molecular epidemiology based on genome wide association studies have demonstrated the association of host genetic polymorphisms with the risk of specific lymphoma subtypes (Cerhan et al., 2014), highlighting unsuspected pathways which can then be experimentally explored"--
