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## Preface

The mature T- and NK-cell lymphomas are rare, comprising approximately 10 % of all malignant lymphomas. The incidence of T-cell lymphoma is variable around the world, with a higher incidence compared to B-cell lymphomas in the Asian basin. While the overall incidence of B-cell lymphomas has begun to decline in the United States, the incidence of T-cell lymphomas continues to rise. The evolution of T-cell lymphoma biology and therapy has lagged behind that of B-cell lymphomas, partly due to the fact that in the lymphoproliferative world, T-cell lymphomas have only recently been identified as distinct from their B-cell counterparts. Early lymphoma classification systems made no distinction between B- and T-cell lymphomas. The Working Formulation grouped lymphomas by size and grade and identified them based on clinical behavior (aggressive vs. indolent). In the mid-1990s, the Revised European American Lymphoma Classification attempted to identify distinct clinicopathologic entities based on immunophenotypic and molecular features and included the subset of T-cell lymphomas. More recently, the World Health Organization (WHO) has attempted to further classify lymphomas based on clinical, morphologic, phenotypic, and molecular genetic features to define disease entities and provisional entities. Within the mature T/NK-cell neoplasms, there are 20 entities or provisional entities, with the most common types being the nodal T-cell lymphomas.

The history of T-cell lymphomas is rich and significant advances have been made over the past few years. The identification of the first human retrovirus HTLV-1 was made in 1980, the setting of a patient with aggressive T-cell leukemia/lymphoma from whom the HUT102 cell line was derived, and the first application of a T-cell-targeted monoclonal antibody, the anti-TAC antibody directed against the CD25 epitope, was conducted by the Waldmann group at the NCI in patients with HTLV-1-associated T-cell leukemia. The propagation of the HTLV-1 retrovirus in vitro was facilitated via a HUT78/H9 cell line representing a mature CD4+ cutaneous T-cell lymphoma. More recently, molecular profiling has identified and distinguished distinct subsets of aggressive nodal T-cell lymphomas within the group of peripheral T-cell lymphomas which are “not otherwise specified” and has led to the identification of a follicular dendritic cell origin for angioimmunoblastic T-cell lymphoma. The importance of the Notch signaling pathway has been shown in T-ALL by the presence of activating NOTCH mutations in over 50 % of patients. Expression of ALK fusion proteins in anaplastic large cell lymphoma has been associated with an adverse outcome and may identify yet

another unique subset of T-cell lymphomas. The demonstration of in vitro cytotoxicity of L-asparaginase in NK/T-cell lymphoma cell lines has led to clinical trials using this active agent in refractory NK/T-cell lymphoma patients and has largely changed the therapeutic landscape for these diseases.

From a therapeutic perspective, these and other advances have led to an explosion in the development of novel therapeutic approaches for the T-cell lymphoproliferative disorders. Currently there are a number of FDA-approved therapies for T-cell malignancies, including the IL2 fusion toxin denileukin diftitox, the RXR retinoid bexarotene, the histone deacetylase inhibitors vorinostat, and romidepsin for cutaneous T-cell lymphomas, and pralatrexate, a folate antagonist and romidepsin for peripheral T-cell lymphomas, brentuximab vedotin, a CD30-targeted fusion toxin for anaplastic large cell lymphomas, and the nucleoside analog nelarabine for T-cell ALL. A number of new agents targeting specific receptors and metabolic pathways are currently in clinical trials and are on the horizon.

This book is a comprehensive overview of the T-cell lymphoproliferative disorders both in adults and in children and includes both the cutaneous and the systemic T-cell malignancies. The experts in the field have done an excellent job summarizing the highlights in each disorder with the intent to introduce the reader to the salient clinical and biological features of these diseases as well as future directions for research and novel approaches. I would like to thank all of my collaborators for their insights and ongoing tireless efforts to address the unmet needs within the field of T-cell lymphoproliferative disorders.

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