Table 13-5 Some Immune Cell Antigens Detected by Monoclonal Antibodies

Antigen Designation	Normal Cellular Distribution
Primarily T-Cell Associated	
CD1	Thymocytes and Langerhans cells
CD3	Thymocytes, mature T cells
CD4	Helper T cells, subset of thymocytes
CD5	T cells and a small subset of B cells
CD8	Cytotoxic T cells, subset of thymocytes, and some NK cells
Primarily B-Cell Associated	
CD10	Pre-B cells and germinal-center B cells
CD19	Pre-B cells and mature B cells but not plasma cells
CD20	Pre-B cells after CD19 and mature B cells but not plasma cells
CD21	EBV receptor; mature B cells and follicular dendritic cells
CD23	Activated mature B cells
CD79a	Marrow pre-B cells and mature B cells
Primarily Monocyte or Macrophage Associated	
CD11c	Granulocytes, monocytes, and macrophages; also expressed by hairy cell leukemias
CD13	Immature and mature monocytes and granulocytes
CD14	Monocytes
CD15	Granulocytes; Reed-Sternberg cells and variants
CD33	Myeloid progenitors and monocytes
CD64	Mature myeloid cells
Primarily NK-Cell Associated	
CD16	NK cells and granulocytes
CD56	NK cells and a subset of T cells
Primarily Stem Cell and Progenitor Cell Associated	
CD34	Pluripotent hematopoietic stem cells and progenitor cells of many lineages
Activation Markers	
CD30	Activated B cells, T cells, and monocytes; Reed-Sternberg cells and variants
Present on All Leukocytes	
CD45	All leukocytes; also known as leukocyte common antigen (LCA)

CD, Cluster designation; EBV, Epstein-Barr virus; NK, natural killer.

lymphoid cells also recirculate through the lymphatics and peripheral blood to distant sites; as a result most lymphoid tumors are widely disseminated at the time of diagnosis. Notable exceptions to this rule include Hodgkin lymphomas, which are sometimes restricted to one group of lymph nodes, and marginal zone B-cell lymphomas, which are often restricted to sites of chronic inflammation.

- **Hodgkin lymphoma spreads in an orderly fashion, whereas most forms of NHL spread widely early in their course in a less predictable fashion.** Hence, while lymphoma staging provides generally useful prognostic information, it is of most utility in guiding therapy in Hodgkin lymphoma.

We now turn to the specific entities of the WHO classification. We will begin with neoplasms of immature lymphoid cells, and then discuss the more common Non-Hodgkin lymphomas and plasma cell neoplasms, followed by a selection of rarer lymphoid neoplams that are pathogenically informative or of particular clinical importance. Some of the salient molecular and clinical features of these neoplasms are summarized in Table 13-6. We will finish by discussing the Hodgkin lymphomas.

Precursor B- and T-Cell Neoplasms

Acute Lymphoblastic Leukemia/Lymphoma

Acute lymphoblastic leukemia/lymphomas (ALLs) are neoplasms composed of immature B (pre-B) or T (pre-T) cells, which are referred to as *lymphoblasts*. About 85% are B-ALLs, which typically manifest as childhood acute "leukemias." The less common T-ALLs tend to present in adolescent males as thymic "lymphomas." There is, however, considerable overlap in the clinical behavior of B- and T-ALL; for example, B-ALL uncommonly presents as a mass in the skin or a bone, and many T-ALLs present with or evolve to a leukemic picture. Because of their morphologic and clinical similarities, the various forms of ALL will be considered here together.

ALL is the most common cancer of children. Approximately 2500 new cases are diagnosed each year in the United States, most occurring in individuals younger than 15 years of age. ALL is almost three times as common in whites as in blacks and is slightly more frequent in boys than in girls. Hispanics have the highest incidence of any ethnic group. B-ALL peaks in incidence at about the age of 3, perhaps because the number of normal bone marrow pre-B cells (the cell of origin) is greatest very early in life. Similarly the peak incidence of T-ALL is in adolescence, the age when the thymus reaches maximum size. B- and T-ALL also occur less frequently in adults of all ages.

Pathogenesis. **Many of the chromosomal aberrations seen in ALL dysregulate the expression and function of transcription factors required for normal B- and T-cell development.** Up to 70% of T-ALLs have gain-of-function mutations in *NOTCH1*, a gene that is essential for T-cell development. On the other hand, a high fraction of B-ALLs have loss-of-function mutations in genes that are required for B-cell development, such as *PAX5*, *E2A*, and *EBF*, or a balanced t(12;21) involving the genes *ETV6* and *RUNX1*, two genes that are needed in very early hematopoietic precursors. All of these varied mutations disturb the differentiation of lymphoid precursors and promote maturation arrest, and in doing they induce increased self-renewal, a stem cell–like phenotype. Similar themes are relevant in the genesis of AML (discussed later).

In keeping with the multistep origin of cancer (Chapter 7), single mutations are not sufficient to produce ALL. The identity of these complementary mutations is incomplete, but aberrations that drive cell growth, such as mutations that increase tyrosine kinase activity and RAS signaling, are commonly present. Emerging data from deep sequencing of ALL genomes is rapidly filling in the remaining gaps. Early returns suggest that fewer than 10 mutations are sufficient to produce full-blown ALL; hence, compared to solid tumors, ALL is a genetically simple tumor.