Surface Markers on Leukemia and Lymphoma Cells: Recent Advances

By Kenneth A. Foon, Robert W. Schroff, and Robert Peter Gale

Recent advances in immunology have led to important insights into leukocyte differentiation and the cellular origin of leukemia. It is now possible to precisely define stages of human lymphocyte and granulocyte differentiation utilizing highly specific monoclonal antibodies that define cell surface antigens in conjunction with more traditional markers such as surface and cytoplasmic immunoglobulin on B lymphocytes, sheep erythrocyte (E) receptors on T lymphocytes, and cytochemical staining of myeloid cells. Five major subtypes of acute lymphoblastic leukemia (ALL) are now recognized, including unclassified or null ALL, common ALL (cALL), pre-B-ALL, B-ALL, and T-ALL. Within the T-ALL subgroup, there is considerable heterogeneity based on the presence or absence of the E-receptor and various T-cell surface membrane antigens defined by monoclonal antibodies. Cells from patients with chronic lymphocytic leukemia, non-Hodgkin's lymphoma, and Sézary syndrome also can be classified by their reactivity with monoclonal antibodies. Acute myelogenous leukemia (AML) cells are generally classified by morphological and cytochemical features. Recently, monoclonal antibodies reactive with granulocytic and monocytic subtypes of AML have been developed. In addition to their utility in leukemia classification, monoclonal antibodies that identify leukemia-associated antigens have also been used therapeutically. Monoclonal antibodies have been infused intravenously into patients with leukemia and lymphoma. They have also been used in vitro with complement to lyse residual leukemia cells from remission bone marrows removed from leukemia patients. These treated bone marrows were later reinfused into the same patients to "rescue" them following high-dose chemotherapy and radiation therapy.

IT IS NOW POSSIBLE to more precisely define stages of human lymphocyte and granulocyte differentiation utilizing cell surface markers and intracellular enzymes. In addition to the traditional cell surface markers, such as surface membrane immunoglobulin and receptors for sheep erythrocytes, that define B and T lymphocytes, highly specific monoclonal antibodies that distinguish cell surface membrane antigens are used. Careful analysis of the phenotypic profiles of normal and malignant cells has provided important insights into leukocyte differentiation and the cellular origin of leukemia. In this review we summarize advances in the classification of lymphocytic and granulocytic leukemias, including recent data using monoclonal antibodies. The relevance of these advances to our understanding of normal leukocyte differentiation and leukemia therapy is discussed.

CELL MARKERS

B Lymphocytes

Cell surface markers useful in studying leukocytes are indicated in Table 1. Lymphocytes are commonly divided into bone marrow-derived (B) lymphocytes and thymus-dependent (T) lymphocytes. B lymphocytes are identified by the presence of surface membrane immunoglobulin (SmIg). Progenitors of B lymphocytes, referred to as pre-B lymphocytes, are present in normal bone marrow. Pre-B lymphocytes possess cytoplasmic \( \mu \) heavy chain (C\( \mu \)) but lack intracytoplasmic light chain and SmIg. B and pre-B lymphocytes may also have receptors for the third component of complement (C'3) and for the Fc portion of immunoglobulin (Ig). Fc and C'3 receptors are not specific for the B cell lineage and are also found on other cell types such as monocyte-macrophages and some nonhematopoietic cells. Plasma cells are the most differentiated B lymphocytes. They often will have no detectable SmIg.
but will have cytoplasmic immunoglobulin (CIg). Unlike the CIg found in pre-B lymphocytes, the CIg in plasma cells includes both heavy and light chains.

Human B lymphocytes have also been reported to have immune-related antigens (Ia) on their surface. The Ia antigens are glycoproteins composed of a heavy chain of 35,000 daltons and a light chain of 27,000 daltons. Preliminary data suggested that the Ia antigens were unique to B lymphocytes, but it is now evident that Ia antigens are also present on monocytes, immature myeloid and possibly erythroid cells, activated T lymphocytes, a subpopulation of peripheral blood T lymphocytes and some nonhematopoietic tissues such as sperm or epidermal cells. There appears to be a close relationship between the Ia antigens and gene products of the HLA-D locus; the term HLA-D related or (HLA-DR) is sometimes used to indicate Ia antigens on human cells.

Monoclonal antibodies and heteroantisera that identify B cell antigens that are not Ia related and that are distinct from SmIg and receptors for C'3 and FeC have recently been described. Patterns of reactivity for several of the monoclonal antibodies in this group are summarized in Table 2.

### T Lymphocytes

T lymphocytes can be identified by their ability to spontaneously bind sheep erythrocytes (E rosette) and by reactivity with T cell-specific antisera and anti-T monoclonal antibodies. Anti-T antisera are commonly produced in rabbits by the injection of human T lymphocytes or thymocytes. Monoclonal anti-T antibodies have been developed with use of the hybridoma technique (summarized in Table 3). The two most widely studied groups of anti-T monoclonal antibodies are referred to as OKT (Ortho Pharmaceutical Corporation, Raritan, N.J.) and Leu (Becton-Dickinson & Co., Mountain View, Calif.). The OKT6, OKT9, and OKT10 antibodies identify antigens that are present on thymocytes and certain leukemic cells and are not restricted to the T cell lineage.

### Granulocytes, Monocytes, and Platelets

Several investigators have described heteroantisera that react with monocytes, granulocytes, blasts, and acute myelogenous leukemia (AML) cells. We reported a rabbit heteroantiserum that reacts with normal myelomonocytic cells, platelets, and AML cells. The antigen defined by this antiserum may be the same as that previously described by Roberts and Greaves and referred to as the "M" antigen. While the myelomonocytic and M antigens are not leukemia specific, they may be useful in distinguishing myeloid and lymphoid leukemias.

A number of monoclonal antibodies that react with myeloid cells have also been described. Some of these antibodies are restricted to monocytes or to granulocytes, while others react with both. Although
Table 2. Monoclonal Antibodies Reactive With Human B Lymphocytes

<table>
<thead>
<tr>
<th>Monoclonal Antibody</th>
<th>BA-1</th>
<th>B1</th>
<th>B2</th>
<th>FMC1</th>
<th>FMC7</th>
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<tr>
<td>B lymphocytes</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+ / - *</td>
</tr>
<tr>
<td>T lymphocytes</td>
<td></td>
<td>-</td>
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<td>Granulocytes</td>
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<td></td>
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<tr>
<td>Platelets</td>
<td></td>
<td>NR</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Erythrocytes</td>
<td></td>
<td>NR</td>
<td>NR</td>
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</tbody>
</table>

Leukemias

- B-chronic lymphocytic leukemia (CLL) + + + + +
- Prolymphocytic leukemia (PLL) NR + NR + / - +
- Hairy cell leukemia (HCL) + / - † NR NR NR + +
- Burkitt’s lymphoma NR + - NR NR NR NR
- Non-Hodgkin’s lymphoma + + + / - NR - +
- Waldenström’s macroglobulinoma NR + - NR NR NR
- Multiple myeloma - - NR NR -
- Pre-B acute lymphoblastic leukemia (pre-B-ALL) + + NR NR NR +
- B-ALL + + NR + NR +
- CALL + / - + - - - +
- Unclassified ALL + / - - - - - + /
- T-CLL - - - NR - -
- T-ALL - - - - - -
- Acute myelogenous leukemia (AML) - - - - - -

Molecular Weight of Antigen (daltons) NR 30,000 120,000 NR NR NR
140,000

Isotype

<table>
<thead>
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</tr>
</thead>
<tbody>
<tr>
<td>12</td>
</tr>
</tbody>
</table>

*FMC7 reacts with <50% of B lymphocytes.
†NR, not reported.
‡Twenty percent of HCL react with BA-1.

most of these reagents clearly distinguish myeloid from lymphoid leukemias, some may distinguish the granulocytic subtypes of AML (M1, M2, and M3) from the monocytic subtypes (M4 and M5) as defined by the French–American–British (FAB) criteria.39,40 We have studied another monoclonal antibody designated CALL 1 that reacts with platelets, megakaryocytes, and acute lymphoblastic leukemia (ALL) cells. This antibody inhibits platelet aggregation and serotonin release and does not react with normal lymphocytes, restricted in its pattern of reactivity to platelets.39

A monoclonal antibody has been described that is

Table 3. Monoclonal Antibodies Reactive With Human T Lymphocytes

<table>
<thead>
<tr>
<th>Antibody *</th>
<th>T Lymphocyte and Thymocyte Reactivity Pattern</th>
<th>Molecular Weight of Antigen (daltons)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OKT1, Leu-1, 17F12, T101, 10.2 (Lyt-2), SC1, A50</td>
<td>Pan-T lymphocyte, pan-thymocyte</td>
<td>65,000-69,000, 65,000-69,000, 22-24, 31, 35, 37-40</td>
</tr>
<tr>
<td>OKT3, Leu-4</td>
<td>Pan-T lymphocyte</td>
<td>19,000, 19,000</td>
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<tr>
<td>OKT4, Leu-3</td>
<td>Helper/inducer-T</td>
<td>62,000, 62,000</td>
</tr>
<tr>
<td>OKT5, OKT8, Leu-2</td>
<td>Cytotoxic/suppressor-T</td>
<td>76,000, 30,000 + 32,000</td>
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<tr>
<td>OKT6, NA1/34</td>
<td>Common thymocyte (stage I) †</td>
<td>49,000, 49,000</td>
</tr>
<tr>
<td>OKT9, SE9</td>
<td>Immature thymocyte (stage II) †</td>
<td>190,000, 94,000</td>
</tr>
<tr>
<td>OKT10</td>
<td>Pan-thymocyte †</td>
<td>37,000, 45,000</td>
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<tr>
<td>OKT11, Leu-5, 9.6 (Lyt-3)</td>
<td>E receptor</td>
<td>50,000</td>
</tr>
<tr>
<td>9.3 (Lyt-1)</td>
<td>Subsets of T-lymphocytes and thymocytes</td>
<td>44,000</td>
</tr>
<tr>
<td>3A1</td>
<td>Inducer T and Con-A suppressor-T and pan-thymocyte</td>
<td>40,000</td>
</tr>
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</table>

*The OKT series of antibodies are commercially prepared by Ortho Pharmaceutical Corporation, the Leu series by Becton-Dickinson & Co., T101 by Hybritech Inc., and the Lyt series by New England Nuclear.
†Not restricted to thymocytes.
monocytes, granulocytes, or erythrocytes (personal communication, Dr. C. Deng).

**Leukemia Cells**

The common acute lymphoblastic leukemia antigen (cALL or CALLA) was originally defined by antisera produced in rabbits by immunization with SmIg-negative, E-rosette negative ALL cells. The antigen defined by these antisera has a molecular weight of 98,000 daltons and is present on normal peripheral blood lymphocytes, it is not described. Although the cALL antigen is not present on normal circulating cells but is present on leukemia cells.67 The anti-p24/BA2 monoclonal antibody has been postulated to be the lymphohematopoietic precursor cell.74 Although the cALL antigen is not present on normal peripheral blood lymphocytes, it is not leukemia-specific, as it is present on normal bone marrow cells that are TdT and Ig positive. These cells have been postulated to be the lymphohematopoietic precursor cells.75 The J-5 monoclonal antibody has also been shown to react with renal tubular and glomerular cells, fetal small intestine epithelial cells, and myoepithelial cells of the adult breast.76

Another leukemia-associated antigen is the p24/BA-2 antigen, with a molecular weight of 24,000 daltons, defined by the BA-2 monoclonal antibody.77 BA-2 reacts with most unclassified ALL cells. Similar to the cALL antigen, the p24/BA-2 antigen is not detected on normal circulating cells but is present on approximately 3% of bone marrow mononuclear cells which are E rosette negative, SmIg negative, TdT positive. This also may represent a bone marrow derived lymphoid progenitor cell.

The RFB-1 monoclonal antibody reacts with hematopoietic precursor cells in human bone marrow as well as thymic blast cells. Similar to the cALL and p24/BA2 antigens, double marker studies showed that TdT-positive cells were also RFB-1 positive.

**Biochemical Markers**

Several membrane biochemical markers of leukemic cells have also been described. The glycolipid asialo GM1 is found on cells from patients with acute lymphoblastic leukemia (ALL) (non-B non-T, and T-ALL) but not on cells from patients with other forms of leukemia. Alterations in membrane carbohydrates, such as decreased complex gangliosides, and carbohydrate-containing antigens, and receptors for cholera toxin have been reported on leukemic cells.

**Intracellular Enzymes**

The most widely studied intracellular enzyme is TdT. TdT is found in thymocytes and in a small percentage of bone marrow cells but not in mature lymphocytes. Other intracellular enzymes useful in the diagnosis of ALL including hexosaminidase, adenosine deaminase, 5'-nucleotidase, and acid phosphatase are discussed below.

**ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)**

ALL can be divided into five major subgroups using B and T markers such as SmIg, Cu, E rosettes, and monoclonal antibodies that identify T cell antigens and the cALL antigen: unclassified ALL, cALL, pre-B-ALL, B-ALL, and T-ALL (Table 5). Lymphoblasts from most patients with ALL lack SmIg and Cig and do not form E rosettes or react with monoclonal anti-T antibodies. Two subgroups are identified among these patients: including unclassified ALL, whose cells do not express the cALL antigen,

### Table 4. Monoclonal Antibodies Reactive With Human Monocytes and Granulocytes

<table>
<thead>
<tr>
<th>Monoclonal Antibody</th>
<th>OKM1/M01</th>
<th>Mo2</th>
<th>63D3</th>
<th>DSD6</th>
<th>Mac-120</th>
<th>D5</th>
<th>TA-1</th>
<th>1/12/13</th>
<th>MY3</th>
<th>MY4</th>
<th>MY7</th>
<th>MY8</th>
<th>SF1</th>
<th>1G10</th>
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<td>Granulocytes</td>
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<tr>
<td>B lymphocytes</td>
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<td>T lymphocytes</td>
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<tr>
<td>AML (M1, M2, M3)</td>
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<td>+/-</td>
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<tr>
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<td>+/-</td>
<td>§</td>
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<table>
<thead>
<tr>
<th>Molecular weight of antigen (daltons)</th>
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<tbody>
<tr>
<td>Isotype</td>
<td>IgG2/igM</td>
<td>IgM</td>
<td>IgG1</td>
<td>IgM</td>
<td>IgM2</td>
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<td>IgM</td>
<td>IgM</td>
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<td>IgG2a</td>
<td>IgG</td>
<td>IgM</td>
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</table>

*Present on 23%-37% of peripheral blood monocytes.
†OKM 1 reacts with a small proportion of T lymphocytes and most null lymphocytes.
§Subclassifications of AML were not reported.
†10% of M1, M2, and M3 patients cells tested were positive.
Personal communication, Dr. H. V. Raff.
and cALL, whose cells express the cALL antigen. Cells from patients with unclassified ALL (sometimes referred to as null or non-B non-T ALL) generally express the Ia antigen, have elevated TdT, and intracellular levels of hexosaminidase isoenzyme 1, 5'-nucleotidase, and purine nucleoside phosphorylase.\(^8\) Unclassified ALL cells may express the BA-i and BA-2 antigens, however, the BI, B2, and cALL antigens are not present.\(^8\) The majority of ALL cells that lack SmIg, C1g, and T cell markers express the cALL antigen and are referred to as cALL or CALLA.\(^9\) These cells also express Ia and B1 antigens, usually the BA-1 antigen, and have enzyme patterns similar to unclassified ALL. Recent data from Korsmeyer and coworkers suggest that even though cALL cells have not yet acquired the capacity to synthesize cytoplasmic immunoglobulin, they have undergone immunoglobulin gene rearrangements indicating a commitment to B-cell differentiation.\(^9\) These data suggest that cALL cells may be very immature B-cells.

A third subgroup of ALL is identified by the presence of intracytoplasmic \(\kappa\) and \(\lambda\) light chains and SmIg are absent. These cells are referred to as pre-B cells.\(^8\) Cells from patients with pre-B-ALL have TdT and express the cALL, Ia, Ba-1, and B1 antigens. These features are similar to those seen in cALL.

The B-cell form of ALL (B-ALL) is rare, accounting for 1%-5% of cases. Leukemic cells from patients with B-ALL have SmIg that is usually IgM. The cells are also Ia, B1, and BA-1 antigen positive. B-ALL in children is probably a leukemic phase of non-Hodgkins or Burkitts lymphoma.\(^9\)

The T cell form of ALL (T-ALL) represents 15%-25% of cases.\(^9\) Clinical features of T-ALL include a high blast count, male predominance, older age, and a mediastinal mass.\(^9\) T-ALL can be identified by E rosette formation and/or reactivity with T-cell antisera or pan-T monoclonal antibodies such as OKT1/Leu-1 and OKT11/Leu-5. OKT3/Leu-4 identifies a pan-T antigen that is found on more mature T lymphocytes and is only occasionally identified on T-ALL cells.

T-ALL cells are generally TdT and acid phosphatase positive and have elevated levels of adenosine deaminase.\(^9\) These cells do not react with B cell monoclonal antibodies such as BA-1, B1, and B2 and only rarely have the Ia or cALL antigens. T-ALL cells are reported to form rosettes with sheep erythrocytes at both 4°C and 37°C, whereas mature T lymphocytes form stable E rosettes only at 4°C.\(^9\)

We recently reported that reactivity with anti-T antisera or monoclonal anti-T antibodies such as Leu-1 are more sensitive indicators of T-ALL cells than is E rosette formation.\(^9\) Lymphoblasts from nearly one-half of the patients with T-ALL do not form E rosettes but react with the Leu-1 monoclonal antibody. These cells do not react with B cell monoclonal antibodies and only rarely express the Ia antigen. Most of these patients have clinical features associated with T-ALL such as a mediastinal mass and high blast count. It seems likely that these Leu-1 positive, E rosette negative cells, are pre-T cells. Several T-ALL
cell lines with features similar to pre-T ALL cells have been described. Upon in vitro exposure to appropriate stimuli such as phorbol esters or dimethyl sulfoxide (DMSO), these cells increase their E rosetting capability. This is associated with a decrease in intracellular TdT and the expression of surface antigens typical of mature T lymphocytes. These enzyme patterns are summarized in Table 5.

Reinherz and colleagues have subclassified T-ALL according to the level of thymic differentiation. The most primitive thymocytes, prothymocytes or stage I thymocytes, account for approximately 10% of thymus cells; these cells react with OKT9 and OKT10 monoclonal antibodies. Most T-ALL cells posses antigens found on prothymocytes. We have identified Leu-1 reactivity on virtually 100% of thymocytes and all T-ALL cells. The next level of thymic differentiation includes the majority of thymocytes, referred to as stage II thymocytes, which lose OKT9, retain OKT10 and Leu-1, and acquire the OKT6, OKT4/Leu-3, and OKT5,8/Leu-2 antigens. Approximately 20% of T-ALL cells express this phenotype. With further maturation, stage III thymocytes no longer express OKT6 and segregate into OKT4/Leu-3 or OKT5,8/Leu-2 subsets similar to peripheral blood T lymphocytes. Only rarely do T-ALL cells have the phenotype of mature thymocytes. Similar results to those described above have been reported by other investigators.

Adults with ALL generally have a less favorable prognosis than children, but there remains an overall order of favorable prognosis based on immune markers: cALL > pre-B-ALL > unclassified ALL > T-ALL > B-ALL. Recent evidence suggests that pre-B-ALL has a less favorable prognosis than cALL. While these data remain controversial, there are a number of reports that the prognosis for patients with unclassified ALL is less favorable than that for patients with cALL. Patients with T-ALL and B-ALL have been shown to have an unfavorable prognosis.

Analysis of intracellular enzymes may also be useful in the classification of ALL. TdT, a nonspecific DNA polymerase, is elevated in unclassified ALL, cALL, pre-B-ALL, and T-ALL, but not in B-ALL. Hexosaminidase isoenzyme 1 is elevated above the level found in normal cells in cALL and in many cases of unclassified ALL and pre-B-ALL. Adenosine deaminase is elevated in T-ALL. 5’-Nucleotidase and purine nucleoside phosphorylase fall within the normal range in non-T-ALL cells but are markedly reduced in most T-ALL cells. Acid phosphatase is unique to T-ALL. These enzyme patterns are summarized in Table 5.

Several investigators have attempted to classify patients with ALL on the basis of morphological features of the leukemic cells by light microscopy. The FAB cooperative group has proposed a cytomorphological classification of ALL that divides patients into L1, L2, and L3 subgroups. The L1 subgroup is characterized by a homogenous population of predominantly small cells with a high nuclear-cytoplasmic ratio and few nucleoli. L1 is most common in children. The L2 subgroup is characterized by a heterogeneous population of large cells with a low nuclear-cytoplasmic ratio; L2 is more common in adults. The L3 subgroup represents the leukemic form of Burkitt’s lymphoma. The cells are large and homogeneous, with deeply basophilic cytoplasm and prominent nucleoli. Intracytoplasmic and intranuclear vacuoles are common. Cells in the L3 subgroup have SmIg similar to B-ALL. Except for the L3 subgroups, attempts to correlate morphologic subgroups and immune classification of ALL have been difficult to reproduce and largely unsuccessful.

**CHRONIC LYMPHOCYTIC LEUKEMIA**

Chronic lymphocytic leukemia (CLL) and diffuse well-differentiated lymphocytic lymphoma represent monoclonal proliferation of SmIg-positive B lymphocytes and are neoplastic expansions of the secretory B cell system. The surface membrane Ig is most often \( \mu \) and \( \Delta \) heavy chain and is usually associated with either a monoclonal \( \kappa \) or \( \lambda \) light chain. Surface membrane Ig density is very low, with a uniform distribution. The percentage of cells that form rosettes with mouse erythrocytes is elevated. These data suggest an arrest of B cell development at an early stage. B-CLL cells usually have C3 and Fc receptors and the B1, BA-1, and Ia antigens. In 3%-10% of patients with CLL, the disease may evolve into a diffuse histiocytic lymphoma (Richter’s syndrome). Most data suggest that this evolution involves transformed follicular center B cells rather than true histiocytes or macrophages. Some of these cases clearly represent a further differentiation of the malignant clone, with expression of the same monoclonal Ig and karyotypic abnormality found in the original CLL clone. In other cases, the lymphoma cells either lack SmIg or have different Ig markers; these cases probably represent the concomitant development of a B-cell lymphoma or a true histiocytic malignancy in patients with B-CLL.

Prolymphocytic leukemia (PLL) is probably a variant of CLL that is also derived from the medullary cords of the lymph node. Patients with PLL generally have extremely high blast counts and splenomegaly but lack significant lymphadenopathy. The PLL cells appear morphologically immature with a fine lacy nuclear chromatin and 1–2 nucleoli; they may contain...
intracytoplasmic granules. These cells generally have higher density SmIg than CLL cells, have Ia and B1 antigens, and rosette with mouse erythrocytes.122 PLL cells from 14 consecutive patients reacted with the FMC7 monoclonal antibody, which recognizes an antigen found on approximately 50% of normal B-lymphocytes, while cells from only 5 to 20 patients with CLL reacted with this antibody.14

Approximately 5% of cases of CLL and PLL result from a malignant proliferation of T cells rather than B cells. These cells react with T antisera, anti-T monoclonal antibodies, and form E rosettes; they lack SmIg.122,123 Many of these patients have diffuse organ and skin involvement.122 T-CLL cells have been reported to have helper and suppressor functions.124,125

We studied leukemia cells from several patients with T-CLL. In some patients, the phenotype of helper/inducer T lymphocytes (OKT1/Leu-1+, OKT3/Leu-4+, OKT4/Leu-3+) was found, whereas cells from other patients had the phenotypic features of suppressor/cytotoxic T lymphocytes (OKT1/Leu-1+, OKT3/Leu-4+, OKT8/Leu-2-). Rarely, neither of these phenotypes or a combination of the two were expressed.106 One unusual patient's cells E rosetted, expressed the Leu-2 antigen, and also had SmIg and CIg (IgMA).126 In most instances the surface markers of the leukemic T cells correlated with their functional activity in in vitro assays, including Ig synthesis following pokeweed mitogen stimulation of B lymphocytes (Schroff RW, unpublished data).

It has been observed that cells from patients with typical B-CLL and B-PLL (SmIg−, E−) react with T cell antisera127 and the OKT1/Leu-1/T101 pan-T monoclonal antibodies.128,129,130 Immunoprecipitation experiments have demonstrated that this 65,000 dalton glycoprotein is present on these B-CLL cells; not just a small sequence of the molecule.17 Although the pan-T antibodies OKT1/Leu-1 react with B-CLL cells, other pan-T antibodies such as OKT3/Leu-4 and OKT11/Leu-5 and antibodies that identify T subsets such as OKT4/Leu-3 and OKT8/Leu-2 do not react with B-CLL cells.

SÉZARY CELL LEUKEMIA

The S é zary syndrome is a malignant proliferation of T lymphocytes. Clinical features include skin lesions or diffuse erythema, lymphadenopathy, and hepatosplenomegaly. S é zary cells are distinguished morphologically by their characteristic cerebriform nucleus. S é zary cells are T cells; they form E rosettes and react with T antisera.128,129 Most S é zary cells have the phenotype of normal helper/inducer T lymphocytes (OKT1/Leu-1+, OKT3/Leu-4+, OKT4/Leu-3+)106,130-134 and function as helper T lymphocytes in in vitro assays.135 Recently we identified a patient whose S é zary cells had a cytotoxic/suppressor T cell phenotype.106 The 3A1 monoclonal antibody that reacts with 85% of normal circulating T lymphocytes did not react with circulating S é zary cells in 5 patients studied.133 3A1 reactivity has been reported, however, with mycosis fungoides cells that infiltrate the skin.136 This disparity raises the question that antigen 3A1 may differentiate the phase of skin infiltration from the leukemic phase of this disease.

HAIRY CELL LEUKEMIA

Hairy cell leukemia (leukemic reticuloendotheliosi s) is characterized by invasion of the bone marrow and spleen by morphologically distinct mononuclear cells with "hairy" cytoplasmic projections. These cells contain an isoenzyme of acid phosphatase (isozyme 5) that is resistant to tartrate but is not unique to hairy cells as it is occasionally found in S é zary cells and other leukemia/lymphoma cells. The cellular origin of hairy cell leukemia is controversial. The presence of monoclonal SmIg, serum M-components, the capacity to synthesize Ig in vitro and reactivity with FCM7 monoclonal antibody suggests a B cell origin in most cases.14,137-139 These cells have a low percentage of mouse erythrocyte rosettes121 and only 20% react with BA-1 and BA-2 monoclonal antibodies.140 Cells from some patients with hairy cell leukemia resemble monocytes;141 in rare cases the cells have features of T cells.142,143

NON-HODGKIN'S LYMPHOMA

Lymphoblastic lymphoma comprises approximately 33% of the cases of non-Hodgkin's lymphomas in children and 5% of cases in adults. There is a male predominance and patients often present with a mediastinal mass. In some cases the disease may evolve into a leukemic phase, morphologically indistinguishable from T-ALL. The malignant cells are T cells. They form E rosettes and react with T cell antisera.144-146 Studies with monoclonal antibodies demonstrated a marked heterogeneity of these patients' cells. In most cases the cells have the phenotypes of stage II and stage III thymocytes, suggesting they may be derived from the thymus. In contrast, cells from patients with T-ALL usually have the phenotype of stage I thymocytes.147 Furthermore, 40% of these T cells express the cALL antigen, while less than 10% of T-ALL cells express the cALL antigen.148 These distinctions may be useful in identifying lymphoblastic lymphoma from T-ALL.

Burkitt's lymphoma cells express the cALL and Ia antigens and SmIg of the IgM class. Peripheral blood
and bone marrow Burkitt's cells are classified as L3 by the FAB criteria. Most cases of Burkitt's lymphoma from Africa are associated with Epstein-Barr virus (EBV) whereas, most American cases are EBV-negative. The t(14q;8q) chromosomal abnormality is commonly identified in Burkitt's lymphoma cells. The B1 antigen is identified on Burkitt's lymphoma cell. The B2 antigen which is generally absent from B cells in the later stages of differentiation, is not present on cells from patients with Burkitt's lymphoma.16

Nodular or follicular lymphomas most likely represent a neoplastic proliferation of lymph node follicular center B lymphocytes.114 The cell type may be small cleaved poorly differentiated cells, small non-cleaved well differentiated cells, or large cells previously referred to as "histiocytes." Follicular lymphoma cells may also be found in the peripheral circulation in a "leukemia" phase. These lymphoma cells have high-density monoclonal SmIg and have Ia, BA-i and Bi antigens.12,15,92,117,118,121 They may or may not have the B2 antigen16 and, unlike CLL cells, generally have a low percentage of mouse rosette formation.118,121 Nodular lymphoma cells commonly express the cALL antigen while most diffuse lymphoma cells do not. Similar to B-derived-CLL, we have identified reactivity of the pan-T monoclonal antibodies (Leu-1, TIO1) with some B-derived-CLL, we have identified reactivity of the pan-T monoclonal antibodies (Leu-1, TIO1) with some B-derived lymphocytes. Other investigators have reported conflicting results.

Diffuse lymphomas represent a wide diversity of cell types. Diffuse poorly differentiated lymphocytic lymphoma cells are usually B-derived with similar phenotypic characteristics to follicular lymphoma cells. Large cell lymphomas encompass "histiocytic," mixed lymphocytic-histiocytic and undifferentiated subtypes in the Rappaport classification. These tend to be more aggressive tumors and represent a morphologic end point for transformed cells of diverse origins.14 Fifty to 60% of these tumors are B cells with phenotypic characteristics similar to nodular lymphomas. Approximately 15% of large cell lymphomas have T cell markers and 15 to 25% are "null" cells.114

"Peripheral T lymphoma" presents clinically with generalized lymphadenopathy, weight loss and a high incidence of pulmonary involvement.114,149 Histologically there is a broad spectrum of morphologic types of lymphocytes all with T markers and an admixture of epitheliod histiocytes, plasma cells, eosinophils and a prominent vascular component.114

Another type of T cell leukemia/lymphoma has been described in patients from Japan.150 The disease generally follows an aggressive course and is often associated with skin involvement and diffuse organ infiltration. Phenotypically these cells most often express the helper/inducer associated antigen OKT4 but paradoxically have been reported to suppress B cell immunoglobulin secretion.151

MYELOMA AND RELATED DISORDERS

The malignant B cells found in Waldenström's macroglobulinemia, heavy chain disease, and multiple myeloma may represent a further step in the maturation of medullary cord B cells.114 Cells from patients with Waldenström's macroglobulinemia, similar to CLL cells, express surface Ig, and the Ia and B1 antigens.16 Unlike CLL cells, however, these cells do not express the B2 antigen or rosette with mouse erythrocytes.16 The plasma cell and its malignant counterpart, the myeloma cell, represent the most differentiated B lymphocytes. These cells synthesize large quantities of Ig. They have cytoplasmic Ig but usually lack SmIg, the B1, B2, and Ia antigen and do not form rosettes with mouse erythrocyte.16,152 Plasma cells and myeloma cells, like other mature B lymphocytes, lack the cALL antigen.153 Interestingly, plasma cells and myeloma cells intensely stain with the OKT10 monoclonal antibody.154,155

ACUTE MYELOGENOUS LEUKEMIA

Most classifications of AML are based on morphological and cytochemical features. The joint French-American-British (FAB) group proposed criteria for the classification of AML have been widely accepted.64,65 Six subtypes of AML (M1-M6) are identified in the FAB classification: M1 and M2 are progressive levels of myeloid maturation, M3, progranulocytic leukemia; M4 and M5, myelomonocytic and monocytic variants; and M6, erythroleukemia. There do not appear to be major prognostic differences between the subtypes. Some investigators have reported fewer remissions in patients with the M6 variant, briefer remissions in those with monocytic variants (M5), or longer remissions in those with progranulocytic leukemia (M3). These findings are controversial.156-159

Studies of cell surface markers have not yet proven useful in the classification of AML. Ia-like antigens have been detected on most AML cells. The B1, B2, and cALL antigens in contrast are not present on AML cells, and less than 5% of cells are TdT positive. Although these surface antigens and TdT are not useful for subclassifying AML, they are useful in distinguishing AML from ALL in some patients. Recently developed monoclonal antibodies to myeloid cells may have some utility in subclassifying AML. OKM1, Mol, TA-1, MY3, and MY4 react predominantly with monocytic variants of AML (M4 and M5) and not with the myeloid subgroups (M1, M2, and M3).54,55,60,62 Conversely, the 1/12/13 antibody reacts
predominantly with the myeloid subgroups but not with monocytic variants. Fc receptors can be detected on most promyelocytic and monocytic leukemia cells; because of nonspecific absorption of Ig to Fc-receptors, these cells may also appear to be SmIg positive in some assays.

CHRONIC MYELOGENOUS LEUKEMIA

Chronic myelogenous leukemia (CML) is a clonal proliferation of mature granulocytes and their progenitors. The chronic phase of CML is characterized by a marked overproduction of relatively mature granulocytes. Other myeloid cell lines, such as megakaryocytes and erythrocytes, may also be involved (Fig. 1). Because of the heterogeneity of cell types in the chronic phase of CML, surface marker phenotypes have not been useful. In most cases there is a specific chromosome abnormality, the Philadelphia (Ph') chromosome, resulting from a 22 to 9 translocation t(9q'::22q'). The Ph' chromosome is present in neutrophils, monocytes, normoblasts, megakaryocytes, basophils, and eosinophils of patients with CML. The clonal nature of the disease has been further established by detailed analysis of glucose-6-phosphate dehydrogenase (G6PD) isoenzyme patterns.

Most cases of CML evolve to an acute phase or "blast crisis" (CML-BC) characterized by decreasing cell maturity and additional chromosome abnormalities. Two types of CML-BC have been described: myeloid CML-BC and lymphoid CML-BC. Myeloid CML-BC cells have phenotypic markers similar to AML (Ia+, cALL-, B1-, MY7+, TdT-) (Fig. 1). Patients with myeloid CML-BC are generally unresponsive to chemotherapy, and their survival is generally less than 6 months.

Lymphoid blast crisis occurs in approximately 30% of patients. The cells phenotypically resemble cALL cells (Ia+, cALL+, B1+, MY7-, TdT-). Some cells also have Cμ, similar to pre-B-ALL cells. Patients with the lymphoid blast crisis may respond to

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**Fig. 1.** Schematic representation of the origin of chronic and blast crisis phases of chronic myelogenous leukemia (CML) from the target pluripotent stem cell. Phenotypes for various forms of CML—blast crisis (CML-BC) are shown. While most patients present in the chronic phase of CML, a minority present in the CML-BC phase and occasionally revert back to the chronic phase following therapy. Ph', Philadelphia chromosome; TdT, terminal deoxynucleotidyl transferase; Cμ, cytoplasmic μ heavy chain.
treatment with vincristine and prednisone. In some cases, the disease reverts to the chronic phase for several months.

Occasionally patients may present with Ph'-chromosome-positive forms of AML or ALL. These patients have no history typical of the chronic phase of CML. The prognosis for these patients is less favorable than that for patients who present with Ph'-chromosome-negative acute leukemia or with typical CML. Some of these patients may be in the acute phase of CML, whereas others have atypical forms of ALL or AML. This subject is reviewed in a recent article.

CELLULAR DIFFERENTIATION

There is substantial evidence that the phenotypes of most malignant leukemic cells are not unique but instead reflect the phenotypes of normal cells. None of the surface markers described above are leukemia specific; each can be identified on normal cells. Although the monocyte, granulocyte, and lymphoid antigens are found on a variety of mature and immature cells (Table 1), the cALL and BA-2 antigens are expressed only on immature bone marrow cells. This is consistent with the phenotypes of leukemic cells, in which the cALL and BA-2 antigens are present only on the most primitive leukemic cells (ALL and lymphoid CML-BC cells) and are not found on more mature leukemic cells. Distribution of the reactivity of the monoclonal T antibodies are also consistent with this hypothesis. The more primitive thymocyte markers OKT9 and OKT10 are found on most T-ALL cells, while OKT3/Leu-4, OKT8/Leu-2, and OKT4/Leu-3, which are found on more mature thymocytes and circulating T lymphocytes, are more often identified on the more mature cells of the chronic T cell leukemias.

A proposed scheme of lymphoid differentiation is presented in Fig. 2. This scheme is based on the concept that the phenotype of the normal lymphoid cell at each level of differentiation is comparable to the phenotype of its malignant counterpart. There are exceptions, however, in which the phenotype of the
leukemic cells does not appear to have a normal lymphoid counterpart, such as OKT1/Leu-1 reactivity with B-CLL cells. However, even in this unusual case 2%-3% of normal tonsil and lymph node B lymphocytes react with OKT1 and Leu-1 and rosette with mouse erythrocytes, similar to B-CLL cells.\textsuperscript{178}

The proposed phenotype of the lymphoid stem cell might have the same surface markers as the unclassified ALL cell (1a\textsuperscript{+}, cALL\textsuperscript{+}, BA-1\textsuperscript{+}, B1\textsuperscript{+}, B2\textsuperscript{+}). The cALL cell, which by immunoglobulin gene rearrangement and the presence of the BA-1 and B1 antigens, has been demonstrated to be a pre-pre-B cell, probably reflects the phenotype of the earliest B cell. Lymphoid cells whose phenotype is identical to that of the cALL cell have been identified in normal human bone marrow.\textsuperscript{77} The pre-B lymphocyte most likely shares the same phenotype as its malignant counterpart, the pre-B-ALL cell. As the B cell matures, it loses TdT and begins to express SmIg. Burkitt's lymphoma cells may be derived from the most primitive follicular center cell, expressing high-density SmIg of the IgM class and the B1 and cALL antigens. However, the B2 antigen, which is identified on some primitive B cells (cALL), is not usually found on Burkitt's cells, suggesting that Burkitt's lymphoma cells may arise from a more mature B cell. The poorly differentiated nodular and diffuse lymphoma cells and "histiocytic" lymphoma cells are also most likely derived from follicular center cells. Similar to Burkitt's cells, these cells have high-density SmIg. CLL, PLL, diffuse well differentiated lymphoma cells, and Waldenström's macroglobulinoma cells are probably derived from the medullary cords of the lymph node. The plasma cell, the most differentiated B lymphocyte, appears to express the same phenotype as myeloma cells. Although these cells produce Ig and have intracytoplasmic immunoglobulin, and express the OKT10 antigen; SmIg, 1a, and B cell antigens are generally not detected.\textsuperscript{16,152,154,155}

T cell differentiation follows a very different pathway. The immature or stage I thymocytes are OKT10\textsuperscript{+}, OKT9\textsuperscript{+} with the common thymocytes or stage II are OKT10\textsuperscript{+}, OKT6\textsuperscript{+}, OKT4\textsuperscript{+}, OKT5/8\textsuperscript{+}.\textsuperscript{21} Most patients with T-ALL express the phenotypes of stage I and stage II thymocytes.\textsuperscript{21} Many of these cells from all three stages of thymocyte differentiation will also express the OKT11 antigen.\textsuperscript{179} We have identified 100% reactivity of thymocytes and T-ALL cells with Leu-1. It remains undetermined why the Leu-1 antibody, which apparently identifies the same antigen as OKT1,\textsuperscript{37} reacts so differently. This is possibly related to the binding affinity of these antibodies or to their binding to different epitopes on the same antigen. Rarely, T-ALL cells will reflect the phenotype of mature thymocytes and peripheral blood T cells, i.e., OKT1/Leu-1\textsuperscript{+}, OKT3/Leu-4\textsuperscript{+}, OKT8/Leu-2\textsuperscript{+}, or OKT4/Leu-3\textsuperscript{+}.\textsuperscript{31,106}

Cells from patients with chronic T lymphoid leukemias generally have the same phenotype as normal circulating T lymphocytes. We have identified patients whose T-CLL cells have the phenotype of normal suppressor T lymphocytes (OKT1/Leu-1\textsuperscript{+}, OKT3/Leu-4\textsuperscript{+}, OKT8/Leu-2\textsuperscript{+}) and of normal helper T lymphocytes (OKT1/Leu-1\textsuperscript{+}, OKT3/Leu-4\textsuperscript{+}, OKT4/Leu-3\textsuperscript{+}). Cells from some patients with T-CLL do not fit easily into either of these groups.\textsuperscript{106}

The morphological subgroups of AML are usually defined by the dominant cell type present in the peripheral blood and bone marrow. Most of the morphological subgroups of AML, with the possible exception of erythroleukemia cells (M6), have la antigens and react with D5/D6 and MY7.\textsuperscript{77,62} The myelomonocytic and monocyteic subgroups (M4, M5) may uniquely react with OKM1, Mol, Mo2, MY3, and MY4.\textsuperscript{53,54,62} All of these cells lack the cALL, B1, B2, and BA-1 antigens. These phenotypes are most likely identical to those found on their normal, nonmalignant counterparts, as shown in Fig. 3.

TARGET CELL FOR MALIGNANT TRANSFORMATION

The leukemic target cell is responsible for the malignancy, and ultimately it is the drug susceptibility of this cell that determines the course of the disease. For example, while the phenotype of the circulating cells in cALL and lymphoid CML-BC are identical, the target cells for the leukemic transformation are clearly different. In lymphoid CML-BC, the target cell is a very primitive pluripotent stem cell that is extremely difficult to eradicate, while in cALL it can be eradicated by conventional chemotherapy in the majority of patients.

The target cell(s) for malignant transformation in the lymphoid leukemias is unknown. Some data suggest that malignant transformation may occur in a very primitive cell, a cell more primitive than those that predominate in the blood and bone marrow. These malignant cells retain the ability to undergo differentiation. Several data support this theory. First, leukemia cells are often heterogeneous; cells from patients with pre-B-ALL have variable numbers of C\textsubscript{u}-positive and C\textsubscript{u}-negative lymphoblasts.\textsuperscript{98} The C\textsubscript{u}-negative cells may be pre-B precursor cells or pre-B cells and may be the target of the malignant transformation, whereas the C\textsubscript{u}-positive cells result from partial but incomplete differentiation of a malignant precursor. Second, the phenotype of ALL may change following chemotherapy, possibly because of increased or decreased cell differentiation.\textsuperscript{180} Third, the phenotype has been demonstrated to change in
vitro following stimulation with phorbol esters and DMSO. Finally, identical monoclonal idiotypic Ig determinants have been detected on malignant myeloma cells and normal B and T lymphocytes in patients with multiple myeloma. Thus, the myeloma cells represent the most differentiated cells in a clonal disease that involves less mature B lymphocytes and possibly even T lymphocytes. This suggests that the malignant transformation occurred in an uncommitted lymphoid precursor cell.

The target cell for malignant transformation in AML is unknown. Chromosome and G6PD isoenzyme studies indicate that most cases of AML arise in an immature myeloid stem cell, suggesting that the malignant transformation occurs at this level (Fig. 3); however, other data suggest considerable heterogeneity. Fialkow and coworkers studied G6PD isoenzymes in four patients with AML. In all four patients, all myeloblasts had a single G6PD isoenzyme type, indicating derivation from the malignant clone. Two of 4 patients had both isoenzyme types in their red cells, however, indicating the persistence of some normal stem cells.

In AML, similar to ALL, the dominant leukemic cell type may reflect a level of maturational arrest, but not necessarily an arrest at the level at which the malignant transformation has occurred. This concept receives further support from the observation that AML blasts can be induced to differentiate following incubation in vitro with phorbol esters and retinoic acid.

In CML, the target cell for malignant transformation is a multipotential stem cell. The Ph' chromosome and G6PD studies have clearly demonstrated that granulocytes, eosinophils, erythrocytes, megakaryocytes, and possibly lymphocytes are part of the malignant clone. In most cases of CML, the chronic phase terminates in an acute phase, in which a rela-
tively primitive cell type predominates. For unknown reasons, the malignant pluripotent cell loses its capacity to differentiate normally during this blast crisis.

**CLINICAL UTILITY OF MONOCLONAL ANTIBODIES AND ANTISERA**

Monoclonal antibodies and antisera to leukemia-related antigens may have important diagnostic utility. For example, it is often difficult to distinguish undifferentiated forms of AML and ALL, and optimal therapies of the two diseases are quite different. Use of antisera or antibodies to identify the cALL antigen and the various myeloid, B cell, and T cell antigens may establish the correct diagnosis and thereby direct treatment.

The success of leukemia therapy is based on the achievements of a hematologic remission, usually a morphological evaluation. Patients with less than 5% blast cells in the marrow are defined as having achieved remission. The accuracy of this approach clearly is limited since it is impossible to distinguish 5% normal immature cells from leukemic blasts by morphological criteria alone. It may be possible to increase this accuracy using sensitive and specific immunologic or biochemical markers. Similarly, it may be possible to detect leukemia recurrence at an earlier stage than might be possible using morphological criteria alone. The sensitivity of such an approach is increased by the modern technology of flow cytometry. In a similar fashion, restricted numbers of malignant B cells in the bone marrow or peripheral blood exhibiting homogeneous amounts of surface immunoglobulin of one light chain class can be detected by use of flow cytometry.

Cell markers may eventually be useful in identifying cell types that can be induced to differentiate. Thus, there may be a new approach to the treatment of acute leukemia in which the objective is to encourage maturation of leukemic cells rather than to achieve leukemia eradication using cytotoxic drugs. Such an approach would most likely be limited by the inherent genetic abnormalities of leukemic cells.

Monoclonal antibodies and antisera may eventually by therapeutically useful as well. There has been considerable interest in autologous bone marrow transplantation in patients with leukemia; however, the value of this therapy is limited by the high risk of contamination of the transplanted “remission” bone marrow by leukemic cells. Monoclonal antibodies and antisera might conceivably be used to treat bone marrow prior to autologous transplantation, provided they are not cytotoxic to normal hematopoietic stem cells. Remission bone marrow from patients with cALL-antigen positive leukemia has been cryopreserved after antiserum or monoclonal antibody (J-5) treatment and used to “rescue” patients following high-dose chemoradiotherapy. cALL antisera and J-5 monoclonal antibody are not cytotoxic to stem cells, and the bone marrow of these patients recovered as expected. In the future it may be possible to remove leukemic cells by use of fluorescein-labeled antileukemic sera or monoclonal antibodies on a cell sorter. Another therapeutic possibility is infusion into patients of monoclonal antibodies that recognize antigens on leukemic cells. These antibodies could be coupled to highly toxic proteins such as ricin toxin or diptheria toxin or to chemotherapy drugs.

Perhaps the most interesting and innovative clinical study utilizing monoclonal antibodies is that recently reported by Miller and co-workers. Circulating lymphoma cells from a patient with a nodular lymphoma were fused with a murine myeloma line. This human-murine hybridoma secreted the human IgM found on the surface of the lymphoma cells. Mice were then immunized with this IgM and murine-murine hybridomas were developed that recognized the idiotype unique to the IgM. The patient who had entered an accelerated phase of his disease, and who was no longer responsive to conventional therapies, was treated with this murine anti-idiotypic monoclonal antibody. Following eight intravenous infusions, the patient entered a complete remission with disappearance of enlarged lymph nodes, return to normal size of his liver and spleen, and normalization of his blood counts. Nine months following this therapy the patient was still in complete remission. Clearly this remarkable experiment must be repeated, but these results are very promising.

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Surface markers on leukemia and lymphoma cells: recent advances

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