American Journal of Pathology, Vol. 129, No. 3, December 1987

RAPID COMMUNICATION

Discordant Expression of CD3 and T-Cell Receptor Beta-Chain Antigens in T-Lineage Lymphomas

LOUIS J. PICKER, MD, MICHAEL B. BRENNER, MD, LAWRENCE M. WEISS, MD, STEPHEN D. SMITH, MD, and ROGER A. WARNKE, MD

From the Departments of Pathology and Pediatrics, Stanford University School of Medicine, Stanford, California, and the Division of Tumor Virology, Dana–Farber Cancer Institute, and the Department of Rheumatology and Immunology, Brigham and Womens' Hospital, Harvard Medical School, Boston, Massachusetts

Using an immunoperoxidase technique that identifies both surface and cytoplasmic antigen expression, the authors examined 28 benign reactive lymphoproliferative lesions and 55 T-lineage lymphomas for reactivity with CD3 (Leu-4; T-cell receptor-associated antigen) and βF1 antibodies, the latter recognizing nonpolymorphic determinants on T-cell receptor beta chains. Consistent with previous observations that these two antigens are co-expressed on the vast majority of thymocytes, peripheral blood T cells and tonsillar T cells, all 28 reactive lymphoproliferations showed essentially identical patterns of CD3 and βF1 expression. In contrast, only 29 of 55 T-lineage lymphomas displayed coexpression of these antigens. Among 33 peripheral T-cell lymphomas, 11 cases showed CD3/βF1 discordance (7 $CD3^+/\beta F1^-$; 4 $CD3^-/\beta F1^+$), and 5 showed absence of both these antigens. Nine of 22 T-lymphoblastic lymphomas showed CD3/βF1 discordance (all $CD3^+/\beta F1^-$), and 1 case was $CD3^-/\beta F1^-$. These patterns of CD3/βF1 expression, along with the patterns of CD2, CD4, CD5, CD7, and CD8 antigen expression in these neoplasms, indicate that T-cell lymphomas can manifest phenotypes not apparently reflective of normal T populations and suggest the presence of abnormal gene expression in these malignancies. The existence of aberrant phenotypes in T-cell neoplasia suggests caution in interpretation of investigations using T-lineage malignancies as models of normal T-cell biology. Finally, the identification of phenotypic abnormalities in T-lineage populations can be of great diagnostic usefulness in the delineation of benign versus malignant T-cell proliferations. (Am J Pathol 1987, 129:434–440)

THE ADVANCES in immunohistochemical and molecular genetic techniques in the past decade have yielded conclusive evidence that non-Hodgkin's lymphomas are clonal malignancies of the immune system, phenotypically resembling normal subsets of lymphocytes.[1–4] Some authors have gone so far as to suggest that lymphomas represent neoplastic expansions of lymphocytes "frozen" in differentiation and have used these tumors as models of normal lymphocyte biology.[5–7] However, recent immunophenotypic studies of non-Hodgkin's lymphoma, using well-characterized monoclonal antibodies against lymphocyte differentiation antigens, have pointed out the existence of apparently aberrant antigen profiles in malignant lymphoid populations, profiles not reflecting known lymphocyte subsets.[8] For example, while benign T-cell populations uniformly express CD5, CD3, and CD2, T-lineage lymphomas often lack these antigens.

To further investigate the phenomenon of "abnormal" antigen expression in malignant lymphoid populations, we examined the expression of the T-cell antigen receptor (TCAR) complex by both benign lymphoproliferations and T-lineage lymphomas. The TCAR complex consists of an antigen-specific recog-

Supported in part by NCI Grants CA34233, AR36308, and ACS-NY-IM-425.

Accepted for publication October 6, 1987.

Address reprint requests to Louis J. Picker, MD, Department of Pathology, Stanford University Medical School, Stanford, CA 94305.

nition component (usually an alpha/beta chain heterodimer), and an invariant transmembrane signaling component—the T-cell receptor-associated proteins (CD3 antigens).[9-11] Coexpression of these components is essential for antigen specific T-cell function. We previously reported that βF1, a monoclonal antibody specific for a common determinant of TCAR beta chains, reacts with the great majority of $CD3^+$ peripheral blood T cells, tonsillar T cells, and thymocytes.[12] In this report we expand these observations to include an additional 28 cases of histologically reactive lymphoproliferation and 55 cases of T-lineage lymphoma. Our results indicate that while βF1 and CD3 are coexpressed in benign reactive T-cell proliferations, T-lineage lymphomas frequently show discordant expression of these antigens or, more rarely, lack them altogether.

Materials and Methods

Fifty-five cases of histologically diagnosed non-Hodgkin's lymphoma classified as T-lineage on the basis of immunohistologic staining patterns with lineage-specific monoclonal antibodies were selected for study. Cases of lymphoma were considered T-lineage if the malignant lymphoid population expressed one or more pan-T antigens in the absence of B antigens, as previously described.[8] These cases included 33 cases of peripheral T-cell lymphoma (PTL; including 6 cases of mycosis fungoides and 27 cases of non-mycosis fungoides PTL) and 22 cases of T-lymphoblastic lymphoma/leukemia. Cases were selected to include examples of both $CD3^+$ and $CD3^-$ neoplasms. Cases of non-mycosis fungoides PTL were histologically subclassified as previously described.[13] Twenty-eight cases of histologically reactive lymphoproliferative processes, including 19 predominantly follicular hyperplasias (12 lymph node, 2 nasopharynx, 3 skin and subcutaneous tissue, 1 spleen, and 1 lung), 8 predominantly paracortical hyperplasias (all lymph node), and one granulomatous reaction in a lymph node were studied as benign controls.

Cryostat sections from each case were examined for reactivity with a panel of monoclonal antibodies against T-lineage differentiation antigens (Table 1). Additional monoclonal reagents designed to delineate the B-cell, dendritic reticulum cell/macrophage, and proliferating-cell compartments within the tissue were utilized to facilitate case analysis, as previously described.[8] The recorded phenotypes represent the staining pattern for the majority of cells in the T-cell compartment (antigens recorded as negative therefore required less than 50% of cells in the T-cell compartment bearing the antigene in question). This method of analysis takes into account the phenotypically normal T cells that often infiltrate lymphoid neoplasms. However, minor subpopulations of tumor cells with a different antigenic profile cannot be excluded. In all cases interpreted as $CD3^+/\beta F1^-$ or $CD3^-/\beta F1^+$ at least 50% of the cells were discordant for expression of these two antigens.

Specimens were processed and stained as previously described.[8,14] Briefly, application of the murine antibodies was followed by a second stage of a biotin-conjugated horse anti-mouse antibody (Vector Laboratories, Inc., Burlingame, Calif), which, in turn, was followed by a third stage of avidin-conjugated horseradish peroxidase (Vector). The sections were then developed with diaminobenzedine, followed by copper sulfate to darken the reaction product, and finally counterstained with methylene blue.

Results

All 28 cases of benign lymphoproliferation studied, including 2 cases with a predominant $CD4^-/CD8^+$ T-cell population, showed essentially identical patterns of βF1 and CD3 expression (Figure 1A and

Table 1—Monoclonal Antibodies Reactive with T-Lineage Differentiation Antigens*

Antibody	CD	Comment	Source/reference
Pan-T			
F1	—	Beta chain of TCAR	Reference 12
Leu-4	3	TCAR-associated antigen	Becton Dickinson (BD)
Leu-1	5	67-kd, also on B-CLL	BD
Leu-5	2	Sheep red blood cell receptor	BD
Leu-9	7	Probable Fc receptor	BD
T-Subset			
Leu-2	8	Class I MHC restricted T cells (Cytotoxic/suppressor cells)	BD
Leu-3	4	Class II MHC restricted T cells (Helper/inducer cells)	BD
Leu-6	1	Cortical thymocytes	BD

*Abbreviations: TCAR, T-cell antigen receptor; B-CLL, B-cell chronic lymphocytic leukemia; MHC, major histocompatibility complex.

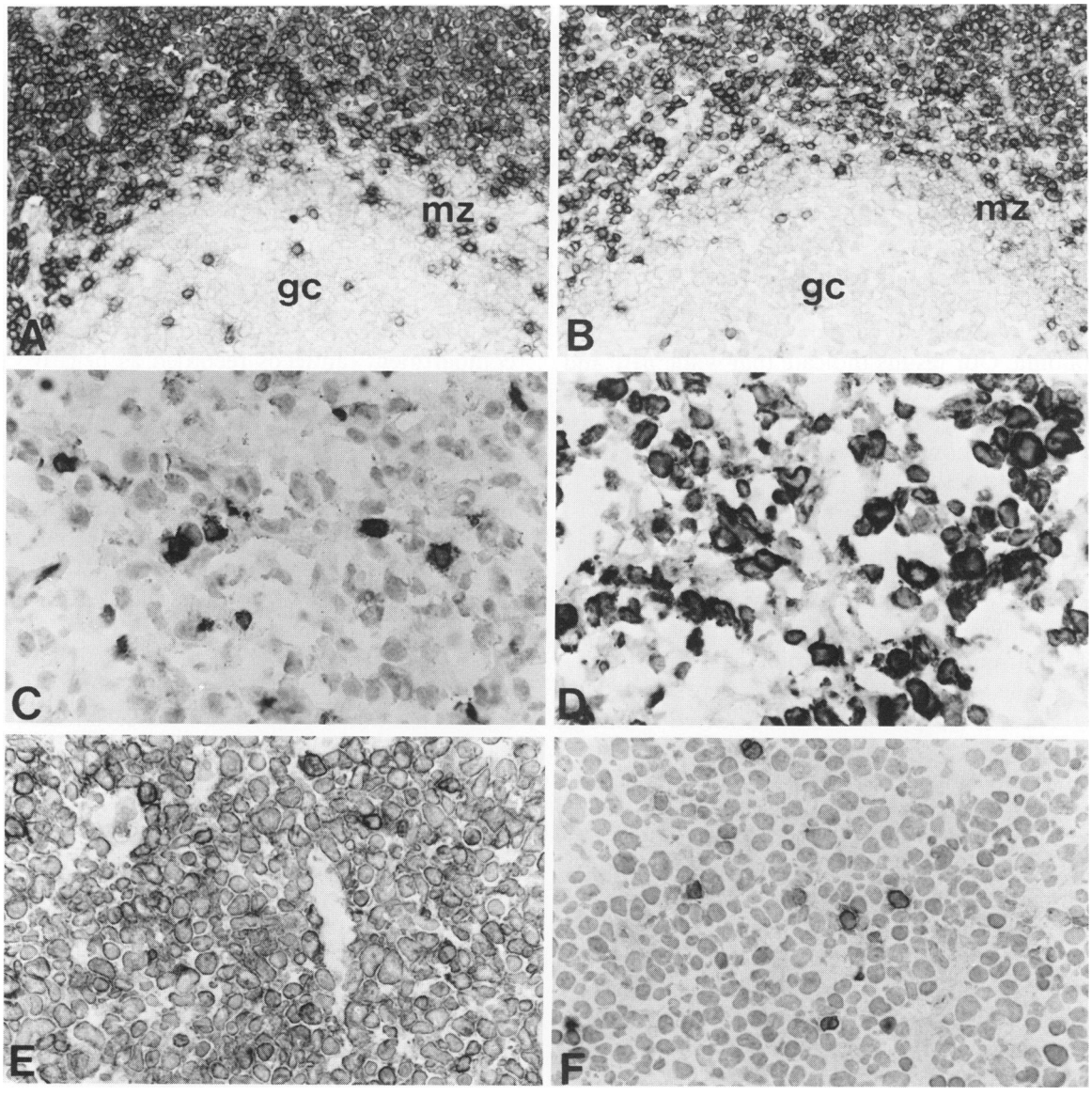

Figure 1A and B—Reactive lymph node showing similar patterns of CD3 (**A**) and βF1 (**B**) expression. Paracortical T cells and scattered T cells within the germinal centers (*gc*) and mantle zones (*mz*) are positive. **C and D**—$CD3^-$ (**C**), $\beta F1^+$ (**D**) peripheral T-cell lymphoma. **E and F**—$CD3^+$ (**C**), $\beta F1^-$ (**F**) T-lymphoblastic lymphoma.

B). Appreciable numbers of $CD3^+/\beta F1^-$ T-cells could not be observed with immunohistologic analysis. The $CD3^+/\beta F1^+$ population included most paracortical T cells (both small T cells and paracortical immunoblasts), as well as the majority of intrafollicular T cells. Patterns of CD2 and CD5 antigen expression were identical with CD3 and βF1, whereas the numbers of CD7 cells averaged between 70% and 90% of the $CD2^+/CD3^+/CD5^+/\beta F1^+$ population.

In contrast to the benign processes, 26 of 55 T-lineage lymphomas (47%) lacked either one or both of the CD3 and βF1 antigens. Of these, 11% lacked both antigens, while 36% showed discordant expression of the two antigens (Tables 2 and 3). Among the 33 PTL cases examined, examples of both $CD3^+/\beta F1^-$ (7 cases) and $CD3^-/\beta F1^+$ (4 cases; Figure 1C and D) phenotypes were observed, whereas among the βF1/CD3 discordant lymphoblastic malignancies only $\beta F1^-/CD3^+$ cases were identified (Figure 1E and F).

Within the PTL group, phenotypic profiles with other T-cell differentiation antigens were extremely diverse. There was no significant correlation of CD3/βF1 expression with histologic subtype or with expression of either T subset or other pan-T antigens.

Table 2—Immunophenotypes: Peripheral T-Cell Lymphomas*

Case	Histology	Pan T-antigen expression					T-subset antigen expression	
		βF1	CD3	CD2	CD5	CD7	CD4	CD8
βF1/CD3 concordant								
1	IBL	+	+	−	−	+	+	−
2	IBL	+	+	+	−	+	−	+
3	IBL	+	+	+	+	−	+	−
4	IBL	+	+	+	+	−	+	−
5	LCL	+	+	+	+	+	+	−
6	AILD-like	+	+	+	+	−	−	+
7	AILD-like	+	+	+	+	−	+	−
8	AILD-like	+	+	+	−	+	−	−
9	AILD-like	+	+	+	+	+	−	+
10	AILD-like	+	+	+	−	−	+	−
11	Mixed	+	+	+	+	+	NI	NI
12	Mixed	+	+	+	−	−	+	+
13	Mixed	+	+	+	−	−	+	−
14	SLL	+	+	+	+	+	−	+
15	MF(P/P)	+	+	+	+	−	−	+
16	MF(P/P)	+	+	+	+	+	+	−
17	MF(P/P)	+	+	+	+	−	+	−
18	IBL	−	−	+	−	+	−	−
19	LCL	−	−	+	−	+	+	−
20	LCL	−	−	+	+	−	+	−
21	Mono med	−	−	+	−	−	+	−
22	Mono med	−	−	+	−	+	−	−
βF1/CD3 discordant								
23	IBL	−	+	+	+	−	+	−
24	IBL	−	+	+	+	−	+	−
25	AILD-like	−	+	+	+	−	−	+
26	Mixed	−	+	+	−	+	+	−
27	Mixed	−	+	−	−	−	−	−
28	MF(P/P)	−	+	−	−	−	−	−
29	MF(P/P)	−	+	+	−	−	+	−
30	IBL	+	−	+	−	−	+	−
31	IBL	+	−	+	−	−	+	−
32	LCL	+	−	+	−	−	+	−
33	MF (tumor)	+	−	−	−	−	+	−

IBL, immunoblastic lymphoma; LCL, large cell lymphoma; AILD-like, angioimmunoblastic lymphadenopathy-like lymphoma; mixed, mixed small and large cell lymphoma; SLL, small lymphocytic lymphoma; mono med, monomorphic medium-sized cell lymphoma; MF, mycosis fungoides (either patch/plaque or tumor stage); NI, not interpretable.

Among the T-lymphoblastic neoplasms, there was a tendency for the $\beta F1^-$ cases to display an immature thymic phenotype ($CD4^-/CD8^-$), as opposed to the $\beta F1^+$ cases (5 of 9 $\beta F1^-$ cases were $CD4^-/CD8^-$, versus only 3 of 11 $\beta F1^+$ cases). However, this correlation was not absolute: βF1 antigen was absent in 3 cases of lymphoblastic lymphoma with a double positive ($CD4^+/CD3^+$) thymic phenotype and in 1 case of a $CD4^+/CD8^-$ (mature helper) phenotype. Interestingly, the single $CD3^-/\beta F1^-$ case displayed a $CD4^+/CD8^+$ common cortical thymocyte phenotype, rather than a more immature double negative phenotype. Cases of lymphoblastic lymphoma lacking βF1 were more likely to lack other pan-T antigens. In fact, of the 7 lymphoblastic neoplasms lacking one of the pan-T antigens CD2, CD3, or CD7, 6 also lacked βF1, suggesting that in lymphoblastic lymphoma "abnormalities" in antigen profiles may be restricted to a subset of cases.

Discussion

As previously mentioned, the human TCAR complex can be functionally divided into two components: a dimeric polymorphic antigen recognition unit (alpha/beta chain heterodimers for the great majority of T cells; delta/gamma heterodimers for a small subpopulation) and an at least trimeric, nonpolymorphic component (CD3) which is thought to initiate the chain of molecular events leading to cellular activation.[9-11,15-17]

Prior studies, examining primarily cell surface expression of CD3 and TCAR antigens in tumor systems, have demonstrated coordinate expression of

Table 3—Immunophenotypes: T-Lymphoblastic Lymphoma/Leukemia

Case	Pan-T antigen expression					T-subset antigen expression		
	βF1	CD3	CD2	CD5	CD7	CD1	CD4	CD8
βF1/CD3 concordant								
1	+	+	+	+	+	+	+	+
2	+	+	+	+	+	+	+	+
3	+	+	+	+	+	+	+	+
4	+	+	+	+	+	+	+	+
5	+	+	+	+	+	+	+	+
6	+	+	+	+	+	+	+	+
7	+	+	+	+	+	+	+	−
8	+	+	+	+	−	+	+	−
9	+	+	+	+	+	−	−	−
10	+	+	+	+	+	−	−	−
11	+	+	+	+	+	+	−	−
12	+	+	+	+	+	−	+	−
13	−	−	+	+	+	+	+	+
βF1/CD3 discordant								
14	−	+	−	+	+	+	−	−
15	−	+	+	+	+	+	−	−
16	−	+	+	+	−	+	−	−
17	−	+	+	+	+	+	−	−
18	−	+	−	+	+	−	−	−
19	−	+	+	+	+	−	−	−
20	−	+	+	+	+	+	+	+
21	−	+	−	+	+	−	+	+
22	−	+	−	+	+	+	+	−

these molecules following a variety of experimental manipulations.[18–21] These studies have not, for the most part, addressed the issue of cytoplasmic expression of these antigens.

Using techniques that demonstrate both surface and cytoplasmic antigens, we have previously demonstrated coexpression of CD3 and TCAR beta chains in greater than 92% of peripheral blood T cells, greater than 90% of thymocytes, and most tonsillar T cells.[12] Since that study, we have examined additional normal thymi with both single- and double-label immunohistology and have demonstrated coexpression of CD3 and βF1 antigens in at least 95% of thymocytes (data not shown). In this report, we show similar patterns of CD3 and TCAR beta-chain expression in 28 cases of histologically varied, reactive lymphoproliferation. While we cannot rule out a small (less than 10%) population of normal T cells with a discordant βF1/CD3 phenotype, our results indicate that both TCAR beta chains and CD3 appear very early in thymocyte differentiation (probably cytoplasmic expression without surface expression in most cortical thymocytes), and that most peripheral T cells coexpress these antigens.

In contrast to benign populations, T-cell malignancies show discordant expression of CD3 and TCAR beta-chain antigens in 36% of the cases examined. Although it is possible that these neoplasms may have arisen from the uncommon normal $CD3^+/\beta F1^-$ population (these cells presumably expressing CD3 antigens with gamma/delta TCAR chains), several factors make this unlikely. First, 4 cases of PTL were identified with expression of TCAR beta chains without coexpression of CD3 ($\beta F1^+/CD3^-$), a phenotype with no known normal counterpart. Second, the normal $CD3^+/\beta F1^-$ population identified in peripheral blood has been reported to be composed predominantly, if not exclusively, of $CD8^+$ or $CD4^-/CD8^-$ T-cells.[12,22,23] Of the 16 $CD3^+/\beta F1^-$ tumors, 5 were $CD4^+/CD8^-$ (a phenotype not reported for TCAR gamma/delta cells). Finally, the majority of CD3/βF1 discordant cases also showed loss of other pan-T antigens such as CD2 and CD5. Because these antigens are expressed by all or nearly all thymocytes and peripheral T cells,[8,24] their absence reinforces our suspicion that the phenotypes observed in the cases in this study were abnormal. It seems unlikely that the myriad, disparate phenotypes demonstrated among these T-cell lymphomas (especially those cases lacking three or four pan-T antigens; eg, PTL Cases 27–33) represent expansions of normal populations "frozen" in differentiation. T-lymphoblastic lymphomas more closely follow putative normal phenotypic patterns than PTL, but still a significant subpopulation (up to

half of cases) displays phenotypes consistent with abnormal antigen expression.

The data suggest that the phenotypic heterogeneity in these lymphomas is, at least in part, related to aberrant gene expression by malignant cells, rather than just clonal expansion of phenotypically normal T cells. This conclusion is supported by the observations of Winberg et al, who studied a case of T-cell lymphoma with multiple sequential biopsies and demonstrated that morphologic and clinical progression of the neoplasm was accompanied by progressive loss of T antigens.[25] Furthermore, we have identified a small subset of non-Hodgkin's lymphoid neoplasms displaying coexpression of T-cell, B-cell, and histiocytic antigens, often in association with T-cell receptor gene rearrangements (L. Weiss et al, manuscript submitted). The unusual nature of these phenotypes argues against the hypothesis that all non-Hodgkin's lymphomas phenotypically mimic normal lymphocyte populations. One important implication of the hypothesis that lymphomas manifest abnormal phenotypes is that tumor cell lines or freshly explanted lymphoma cells may not always be accurate models of normal T-cell biology. The possibility that observations made with neoplastic cells may be distorted by malignancy-induced alterations in phenotype suggests caution in the interpretation of studies using these cells as experimental models.

We have previously reported the diagnostic usefulness of pan-T antigen loss (CD2, CD3, CD5, and CD7) in the identification of about 80% of PTL and 26% of T-lymphoblastic neoplasms.[8,13] The inclusion of βF1 antibody in diagnostic panels would likely increase this yield, especially for T lymphoblastic lymphomas where the βF1 determinant is the most common antigen lost (45% of cases).

Finally, the finding that a significant percentage of T-cell lymphomas lack TCAR beta chains is relevant to possible attempts to treat patients with these neoplasms with monoclonal antibodies to TCAR variable regions (analogous to the treatment of B-lineage lymphomas with idiotype-specific anti-immunoglobulin).[26] Such therapeutic attempts would probably not benefit those patients whose neoplasms fail to express the TCAR beta chains.

References

1. Stein H, Bonk A, Tolksdorf G, Lennert K, Rodt H, Gerdes J: Immunohistologic analysis of the organization of normal lymphoid tissue and non-Hodgkin's lymphomas. J Histochem Cytochem 1980, 28:746–760
2. Tubbs RR, Fishleder A, Weiss RA, Savage RA, Sebek BA, Weick JK: Immunohistologic cellular phenotypes of lymphoproliferative disorders: comprehensive evaluation of 564 cases including 257 non-Hodgkin's lymphomas classified by the International Working Formulation. Am J Pathol 1983, 113:207–221
3. Cleary ML, Chao J, Warnke R, Sklar J: Immunoglobulin gene rearrangement as a diagnostic criterion of B-cell lymphoma. Proc Natl Acad Sci, USA 1984, 81:593–597
4. Bertness V, Kirsh I, Hollis G, Johnson B, Bunn PA: T-cell receptor gene rearrangements as clinical markers of human T-cell lymphomas. N Engl J Med 1985, 313:534–538
5. Greaves MF, Rao J, Hariri G, Verbi W, Catovsky D, Kung P, Goldstein G: Phenotypic heterogeneity and cellular origins of T cell malignancies. Leuk Res 1981, 5:281–299
6. Van Donger JJM, Quertermous T, Bartram CR, Gold DP, Wolvers-TeHero ILM, Comans-Bitter WM, Hooijkaas H, Adriaansen HJ, Deklein A, Raghavachar A, Ganser A, Duby AD, Seidman JG, Van Den Elsen P, Terhorst C: T cell receptor-CD3 complex during early T cell differentiation: Analysis of immature T cell acute lymphoblastic leukemias (T-ALL) at DNA, RNA, and cell membrane level. J Immunol 1987, 138:1260–1269
7. Sangster RN, Minowada J, Suciu-Foca N, Minden M, Mak TW: Rearrangement and expression of the α, β, and γ chain T cell receptor genes in human thymic leukemia cells and functional T cells. J Exp Med 1986, 163:1491–1508
8. Picker LJ, Weiss LM, Medeiros LJ, Wood GS, Warnke RA: Immunophenotypic criteria for the diagnosis of non-Hodgkin's lymphoma. Am J Pathol 1987, 128:181–201
9. Acuto O, Hussey RE, Fitzgerald KA, Protentis JP, Meuer SL, Schlossman SF, Reinherz EL: The human T cell receptor: Appearance in ontogeny and biochemical relationship of α and β subunits on IL-2 dependent clones and T-cell tumors. Cell 1983, 34:717–726
10. Brenner MB, Trowbridge IS, Strominger JL: Cross-linking of human T cell receptor proteins: Association between the T-cell idiotype β subunit and the T_3 glycoprotein heavy subunit. Cell 1985, 40:183–190
11. Weiss A, Imboden J, Hardy K, Manger B, Terhorst C, Stobo J: The role of the T3/antigen receptor complex in T-cell activation. Ann Rev Immunol 1986, 4:593–619
12. Brenner MB, McLean J, Scheft H, Warnke RA, Jones N, Strominger JL: Characterization and expression of the human αβ T cell receptor using a framework monoclonal antibody. J Immunol 1987, 138:1502–1509
13. Weiss LM, Crabtree GS, Rouse RV, Warnke RA: Morphologic and immunologic characterization of 50 peripheral T-cell lymphomas. Am J Pathol 1985, 118:316–324
14. Bindl JM, Warnke RA: Advantages of detecting monoclonal antibody binding to tissue sections with biotin and avidin reagents in coplin jars. Am J Clin Pathol 1986, 85:490–493
15. Bank I, DePinho RA, Brenner MB, Cassimeris J, Alt FW, Chess L: A functional T3 molecule associated with a novel heterodimer on the surface of immature human thymocytes. Nature 1986, 322:179–181
16. Brenner MB, McLean J, Dialgnas DP, Strominger JL, Smith JA, Owen FL, Seidman JG, Ip S, Rosen F, Krangel MS: Identification of a putative second T-cell receptor. Nature 1986, 322:145–149
17. Borst J, Alexander S, Elder J, Terhorst C: The T3 complex on human T lymphocytes involves four structurally distant glycoproteins. J Biol Chem 1983, 258:5135–5141
18. Weiss A, Stobo JD: Requirement for the co-expression of T3 and the T cell antigen receptor on a malignant human T cell line. J Exp Med 1984, 160:1284–1299

19. Goldin RD, Boulton RA, Boylston AW: Qualitative relationship between T3 and the T-cell antigen receptor on a human leukaemic line. Immunol 1985, 56:295–300
20. Shackelford DA, Smith AV, Trowbridge IS: Changes in gene expression induced by a phorbol diester: expression of IL-2 receptor, T3 and a T-cell antigen receptor. J Immunol 1987, 136:613–619
21. Cantrell DA, Davis AA, Crumpton MJ: Activators of protein kinase C down-regulate and phosphorylate the T3/T-cell antigen receptor complex of human T lymphocytes. Proc Natl Acad Sci USA 1985, 82:8158–8162
22. Lanier LL, Weiss A: Presence of Ti(WT31) negative T lymphocytes in peripheral blood and thymus. Nature 1986, 324:268–270
23. Lanier LL, Federspiel NA, Ruitenberg JJ, Phillips JH, Allison JP, Littman D, Weiss A: The T cell antigen receptor complex expressed on normal peripheral blood $CD4^-$, $CD8^-$ T lymphocytes: A CD3-associated disulfide-linked γ chain heterodimer. J Exp Med 1987, 165:1075–1094
24. Hsu SM, Jaffe ES: Phenotypic expression of T lymphocytes in thymus and peripheral lymphoid tissues. Am J Pathol 1985, 121:69–78
25. Winberg CD, Sheibani K, Krance R, Rappaport H: Peripheral T cell lymphoma: Immunologic and cell-kinetic observations associated with morphologic progression. Blood 1985, 66:980–989
26. Miller RA, Maloney DG, Warnke R, Levy R: Treatment of B-cell lymphoma with monoclonal anti-idiotype antibody. N Engl J Med 1982, 306:517–522

Acknowledgments

The authors gratefully acknowledge the technical assistance of Virginia Rojas, Kathleen Dunn, Cedith Copenhaver, and Lourdes Villaneuva; the secretarial assistance of Margaret Beers; and the photographic assistance of Phil Verzola.