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Enzymic Markers in Lymphoproliferative Disorders

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INTRODUCTION

The classification of lymphoproliferative disorders utilizing cellular morphologic and immunologic characteristics has provided a biologically pertinent framework in which clinical prognostic indices continue to be identified. To this assessment has recently been added cellular biochemical profiles which appear to complement the established markers of these disorders. This review highlights some of the more clinically relevant advances in this expanding area and a synopsis of these data is presented in Table I.

PYRIMIDINE PATHWAY ENZYMES

Enzymes of pivotal importance in the cellular disposition of thymidine are thymidine kinase and thymidine phosphorylase (Fig. 1) and recent studies suggest that determination of the activity of these pyrimidine salvage enzymes has clinical relevance.

Thymidine Kinase (TK)

TK, which catalyzes the phosphorylation of thymidine to thymidine-5′-monophosphate may be a rate-limiting enzyme for the incorporation of thymidine into cellular DNA and thus is thought to have an important role in the regulation of cell proliferation. The human enzyme occurs as two isozymes designated TK1 and TK2, which are readily distinguished on the basis of different biochemical properties [1]. TK1 activity parallels cell DNA synthesis, while TK2 activity remains relatively constant during the cell cycle [1].

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TABLE I. Clinical Significance of Enzymic Markers in Lymphoproliferative Disorders

Enzymic activity	Levels		Clinical utility
	Elevated	Decreased	
Thymidine kinase	Isozyme TK1 T-ALL and T-CLL Blastic crisis of CML Aggressive B-CLL Intermediate and high grades NHL	Isozyme TK2 B-CLL	Elevated TK1 activity in serum or involved tissue is predictive for aggressive disease in NHL and B-CLL.
Thymidine phosphorylase		T-ALL and T-CLL	? Decreased TP activity is a marker for responsiveness to thymidine therapy.
Terminal transferase	T-ALL Non T, non B-ALL Lymphoid blastic crisis of CML Lymphoblastic lymphoma		Predictive for clinical response to vincristine and prednisolone Classification of undifferentiated leukaemias. ? Marker for early relapse of ALL.
Adenosine deaminase	T-ALL and T-CLL Non T non-B-ALL Lymphoid blastic crisis of CML T-lymphoma Aggressive B-CLL	B-CLL	? Increased ADA activity is a marker for cytotoxicity to ADA inhibitors. ? Marker for residual disease in ALL.
Purine nucleoside phosphorylase		T-ALL B-CLL	None demonstrated
Purine 5′-nucleotidase	Lymphoid blastic crisis of CML	T-ALL X-linked and common variable immunodeficiency B-CLL	Differentiating myeloid and lymphoid blastic crisis of CML.
Lactic acid dehydrogenase	Intermediate and high grades NHL ALL		Predictor of tumour mass and potential CNS involvement.

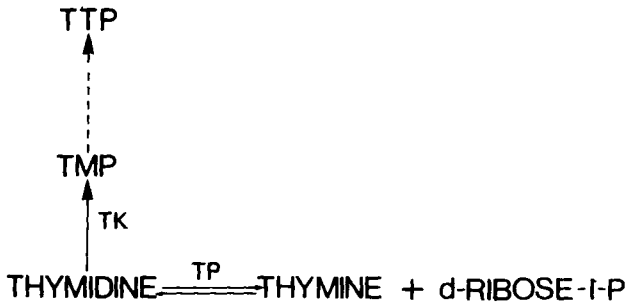

Fig. 1. Thymidine salvage pathway. TK, thymidine kinase; TP, thymidine phosphorylase.

Interest in the TK activity of lymphoproliferative diseases has arisen mainly from the use of the enzyme as a marker of cell proliferation and by implication of clinical aggressiveness. Early studies only measured total enzyme activity, but recorded low levels in normal peripheral blood lymphocytes and chronic lymphocytic leukemic cells, while peripheral blood lymphoblasts were found to have high enzyme activity [2]. A more recent study has determined both total enzyme activity and isozyme type in malignant lymphoid cell extracts, and correlated thymidine kinase activity and histopathology [1]. Normal peripheral blood lymphocytes, chronic lymphocytic leukemic cells, and the solid tissue counterpart diffuse well-differentiated lymphocytic lymphoma were found to have TK2 activity only, a finding consistent with the mature cytology and low proliferative rate of these cells. In contrast, non-Hodgkin lymphomas composed of less differentiated cells, and lymphosarcoma leukemia cells exhibited predominantly TK1 isozyme activity. When the non-Hodgkin lymphomas were grouped according to a modified Rappaport classification [3], there was a stepwise increase in the mean TK activity with the progressive degree of cellular immaturity expressed in the subtypes of this scheme. Furthermore, there was considerable variation in the TK activity of tumors of the same histological type, implying that this biochemical probe for clinical aggressiveness may apply not only to each subtype but to individual patients within the subtype.

The clinical value of measuring TK activity in lymphoproliferative diseases, has been emphasized by the finding that the detection of peripheral blood plasma or lymphocyte TK1 activity is an independent indicator of clinically aggressive non-Hodgkin lymphoma and chronic lymphocytic leukemia [4,5].

Thymidine Phosphorylase (TP)

TP catalyzes the reversible conversion of thymidine to thymine, and is thought to play a role in cellular pyrimidine metabolism by salvaging the bases thymine and uracil. Interest in the clinical importance of human lymphocyte TP activity has occurred because of two recent developments. The marked differences in the sensitivity of cultured leukemic lymphocytes, particularly human malignant T- and null cells and not B-lymphocyte cell lines, to thymidine has been ascribed to differences in TP, with the high thymidine sensitivity of leukemic cells correlating with low TP activity [6], and the introduction of thymidine as an investigational chemotherapeutic agent in the treatment of leukemia and lymphoma.

Preliminary clinical data suggest that these differences in in vitro sensitivity to thymidine may be extrapolated to patients. To date temporary clinical responses to thymidine have been observed in patients with T-cell leukemia but not in B-cell malignancies [7,8]. These clinical responses correlated with markedly reduced leukemic cell TP activity.

The overall value of thymidine as a chemotherapeutic agent in the treatment of lymphoproliferative diseases remains to be established. However it seems likely with the availability of rapid and simple radiometric assay [9] that TP activity in malignant lymphoid cell extracts will be an important determinant of its use. Initial findings have disclosed markedly reduced TP activities in T-ALL and T-CLL cells [10].

TERMINAL DEOXYNUCLEOTIDYL TRANSFERASE (TdT)

Terminal deoxynucleotidyl transferase is a unique DNA polymerase enzyme, in that it is able to catalyze DNA strand synthesis without template direction [11]. Although the precise physiological function of TdT is unclear, the enzyme has been shown to be a very specific biochemical marker of immature lymphocytes, and as such, its activity has been studied extensively in the lymphoproliferative disorders [11].

TdT positivity is a feature of the vast majority of cases of acute lymphoblastic leukemia and in a substantial number this activity is markedly elevated [11,12]. TdT activity exhibits variability within the different types of ALL, with the level in T-lymphoblasts being lower than that of null-lymphoblasts, while B-ALL is negative for TdT [11–14]. A high level of TdT activity is also a biochemical feature of the lymphoid crisis of chronic myelocytic leukemia and some instances of therapy related leukemia or that complicating polycythemia rubra vera and myeloid metaplasia [12,15]. In these circumstances a high level of TdT is predictive of a clinical response to vincristine, prednisone combination therapy [15]. Within the malignant lymphomas TdT is a marker of the lymphoblastic lymphoma type which confirms the close relationship between this tumor, and ALL [16]. TdT is rarely detected in other types of malignant lymphoma [16].

Present data indicate that the measurement of TdT activity in the lymphoproliferative disorders has value in differentiating in the main between acute lymphoid and myeloid leukemias; identifying the lymphoid crisis of CML, which differentially responds to vincristine and prednisone therapy; categorizing undifferentiated leukemias and as a marker of lymphoblastic lymphoma. The potential use of the biochemical, indirect immunofluorescent or histochemical assays for TdT to predict lymphoblastic leukemia marrow remission has been disappointing but remains subjudice [17–20]. The immunological technique, however, appears to be a valuable tool in identifying extramedullary disease such as testicular and central nervous system involvement in ALL [21]. The recent correlation of a progressive rise in the proportion of TdT positive cells in the peripheral blood of patients with ALL and subsequent systemic relapse [22] suggest that TdT determinations in this fashion may have clinical value in the prediction of leukemic relapse. Finally, the relevance of multiple molecular forms of TdT to clinical practice remains to be established [23,24].

Purine Pathway Enzymes

Changes in purine salvage pathway enzymes (Fig. 2) have received considerable attention in lymphoproliferative disorders. This has primarily occurred because of the

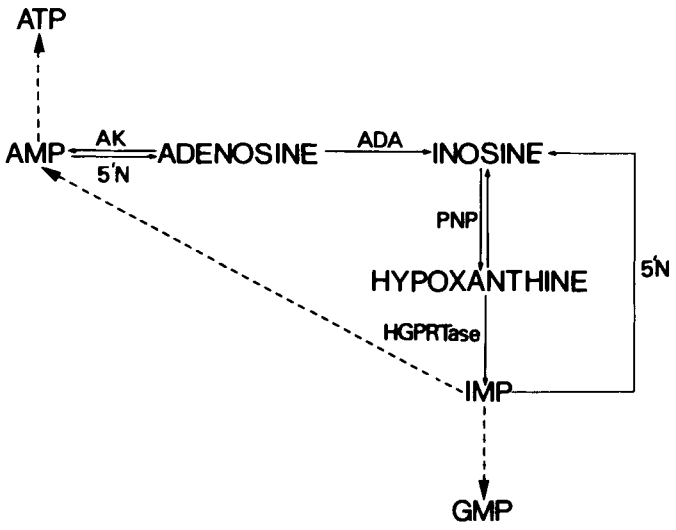

Fig. 2. Purine salvage pathway. ADA, adenosine deaminase; PNP, purine nucleoside phosphorylase; 5'N, 5'purine nucleotidase; AK, adenosine kinase; HGPRTase, hypoxanthine guanine phosphoribosyl transferase.

reduced or absent adenosine deaminase, purine nucleoside phosphorylase, and 5' purine nucleotidase activities in specific immunodeficiency diseases suggesting that abnormalities of these activities might also exist in malignant lymphoid cells.

Adenosine Deaminase

Adenosine deaminase (ADA) promotes the irreversible conversion of adenosine and deoxyadenosine to inosine and deoxyinosine. In lymphoid tissue its level broadly reflects the T-cell or B-cell origin of the lymphoid tissue and has some biologic significance for the proliferation and maturation of these cells. This is reflected in the higher ADA levels in human thymocytes and proliferating T cells [25,26], the profound impairment of T cell function and varying B cell dysfunction in ADA deficient severe combined immunodeficiency disease [27] and the cytotoxic susceptibility of human T lymphoblasts to metabolic inhibition of ADA either in vitro or in vivo [28–30].

In acute lymphoblastic leukemia a number of reports have attested that for malignant lymphoblasts mean ADA activity is higher for T ALL cells compared with that of non T, non B ALL cells [13,31,32] whether C-ALL antigen is positive or not, and an inverse relationship exists between mean ADA levels and those for TdT [32]. Despite this delineation the considerable overlap of individual ADA activities within these subgroups has negated the value of ADA as an immunologic discriminator. Not all studies have supported the findings of divergent distributions of ADA activity in T- and non-T, non-B-ALL lymphoblasts [33,34] and although normal or subnormal ADA levels typify B-ALL cells [13], paradoxically high levels have also been reported [35]. This activity heterogeneity suggests that determinants for cellular ADA levels other than immunologic derivation exists. One such factor appears to be the cellular proliferative capacity as for abnormal lymphoid leukemia, a parallel relationship exists between increased spontaneous cellular tritiated thymidine uptake and ADA levels [10].

Normal or subnormal ADA levels occur in peripheral blood lymphocytes of individuals with B-CLL [36,37], multiple myeloma, and hairy cell leukemia [38], whereas in T-CLL and T cell prolymphocytic leukemia elevated levels occur [32]. For B-CLL cells the low ADA activity has been attributed to the abnormal clone [36]. Of interest is the sequential increase in ADA activity accompanying the accelerated phase of CLL which is associated with an increased spontaneous tritiated thymidine uptake and conversion of TK isoenzyme status by the abnormal B cells [5,10]. In solid malignant lymphoid tissue considerable ranges of ADA activity occur with the highest levels being found in T cell tumors of the lymphoblastic type; whereas in tumors exhibiting monoclonal B cell populations, the ADA levels vary directly with the proportion of T cells in the tumor [32]. Little information exists as to the value of cellular ADA levels in lymphoproliferative disorders as an independent prognostic marker, but higher levels appear to be predictive for in vivo cytotoxic responsiveness to inhibition of ADA with 2'deoxycoformycin, and measurement of ADA levels of marrow and blood mononuclear cells of individuals with T-ALL in apparent remission may be a valuable indicator for residual disease [39].

5′ Purine Neucleotidase

5′ purine neucleotidase (5′N) converts purine nucleotides such as AMP and IMP to the corresponding neucleotides (Fig. 2). Although the exact biologic role for these activities is unclear, the cellular compartmentalization of the AMP utilizing 5′N as an ectoenzyme and the IMP utilizing 5′N as a cytosolic enzyme suggest differing roles in nucleoside transport and purine nucleoside recycling [40–42]. Decreased 5′N activities occur in peripheral blood mononuclears of individuals with X linked and common variable immunodeficiency disease [43,44] and probably reflects the altered peripheral blood mononuclear composition [45]. Transient decrease in 5′N activity occurs in lymphocytes of individuals with infectious mononucleosis [46] and a uniform reduction in level of this activity typifies the abnormal cell of B-CLL [47].

In human T lymphoblasts and thymocytes the comparatively lower 5′N activities have been correlated with the capacity of these cells to expand deoxynucleoside triphosphate pools after exposure to the corresponding deoxynucleosides [48,49]. This differing 5′N activity of human T- and B-lymphoblasts is mirrored in acute leukemic lymphoblasts where 5′N levels are significantly reduced in T-ALL cells compared with those of non T non B lymphoblasts [50]. Paradoxically this reduced activity is not predictive for in vivo cytotoxicity with 2′deoxycoformycin [51]. In the accelerated phase of chronic myeloid leukemia elevated 5′N activity may be helpful in differentiating lymphoid from myeloid blastic crisis [52].

Purine Nucleoside Phosphorylase

Purine nucleoside phosphorylase (PNP) converts purine nucleosides such as inosine to their corresponding purine bases (Fig. 2) and complete or partial deficiency of this activity is associated with inherited defects of T cell function [53,54]. Although neither normal B cells nor those of B cell CLL stain histochemically for PNP [55], enzymatic analysis has demonstrated only a mild decrease of this activity in extracts of B-CLL and normal levels in T CLL cells [10,56].

For T ALL lymphoblasts the median PNP level is lower than that of non T non B lymphoblasts or normal peripheral blood lymphocytes [57], although this finding is not universal [10]. This heterogeneity in the PNP activity of ALL has yet to be

exploited with specific PNP inhibitors such as 8-aminoguanosine which has in vitro cytotoxicity for human T lymphoblasts [58].

LACTATE DEHYDROGENASE (LDH)

The glycolytic enzyme LDH, has long been considered to be an important tumor marker, but it is only in recent years that its clinical utility has been established in the lymphoproliferative disorders. Serum LDH level has been found to be an independent prognostic marker in American Burkitt's lymphoma [59], diffuse histiocytic lymphoma [60] and in a mixed group of histiocyitc and lymphocytic lymphomas [61], with an inverse relationship existing between the level of enzyme activity and survival. Similarly, serum LDH activity has been found to be a significant marker of the length of complete remission in adult acute lymphoblastic leukemia [62] and the risk of central nervous system involvement in this disease [63]. In general, a serum LDH level of greater than 400 IU/l appears to be a poor prognostic finding in the lymphoproliferative disorders. The reason(s) for the prognostic significance of the serum LDH activity are not well understood, but the available data does show a good correlation between the enzyme level and tumor load, which suggest that the LDH is probably derived from the neoplastic cells. In addition, the cellular LDH level also reflects the proliferative state of the cell, and it is likely that differences in the growth rates of the lymphoproliferative disorders contribute to the differences in serum LDH levels. Analysis of LDH isozyme patterns may clarify these points as the LDH isozyme pattern distinguishes normal T from B lymphocytes and normal lymphocytes from those of T- and B- CLL lymphocytes [64].

OTHER ENZYMES

Hexosaminidase is one of the acid hydrolases, and occurs as three isoenzymes (A.B.I.) which have distinct profiles in normal granulocytes, lymphocyes, and thymocytes. In non T non B ALL there is an increase in the isoenzyme I in 85% of cases and this disappears in remission and reappears during relapse, indicating a close association with the lymphoblast [65,66]. Quantitation and isoenzyme pattern of other lysosomal enzymes have also been helpful in delineating subtypes of leukemias and lymphomas. Cytochemical demonstration of acid phosphatase enzyme has been utilized to distinguish B cells from T cells. A "block" positivity for acid phosphatase predominating in the Golgi zone is a characteristic for T-cell tumors [67].

A tartrate resistant form of acid phosphatase is found in hairy cell leukemia [68]. It has also been demonstrated that the low grade lymphomas (Kiel classification) have the highest levels of acid phosphatase, whilst the high grade lymphomas have the least activity using isoelectric focusing technique [69].

The glycosyl transferases have been utilized to monitor the activity and remission status of non-Hodgkin lymphomas. The plasma level of galactose fucosyltransferase is elevated in nonresponding patients and has good correlation with tumor burden, whilst N-acetyl glucosaminide fucosyl transferase is elevated in all patients receiving chemotherapy regardless of disease status, but returns to normal levels during unmaintained remissions [70].

Histochemical demonstration of alkaline phosphatase has been utilized in the studies of malignant lymphoma [71]. In normal nodes ALP is found on the membranes

of follicular-cuff lymphocytes and not in other areas. The cell of nodular lymphoma, intermediate differentiated lymphocytic lymphoma, and Burkitt's lymphoma have ALP positivity whereas well-differentiated lymphocyte cells are negative. This would tend to suggest that nodular and intermediate differentiated lymphomas arise in follicular centers whereas CLL and well-differentiated lymphocytic lymphoma arises in the medullary cord.

CONCLUSION

The delineation of enzymic profiles of the involved cell in lymphoid disorders not only complements current morphologic and immunologic classification but more importantly yields indices predictive for clinical behavior and prognosis. The exploitation of some of these unique biochemical properties by specific enzyme inhibition with or without nucleoside therapy promises to be a new and exciting therapeutic option in the management of these disorders.

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REFERENCES

1. Ellims PH, Van Der Weyden MB, Medley G: Thymidine kinase isoenzymes in malignant lymphoma. Cancer Res 41:691–695, 1981.
2. Rabinowitz Y, Wilhite BA: Thymidine salvage pathway in normal and leukemic leukocytes with effects of ATP on enzyme control. Blood 33:759–771, 1969.
3. Berard CW, Dorfman RF: Hisotpathology of malignant lymphomas. Clin Haematol 3:39–76, 1976.
4. Ellims PH, Gan TE, Medley G, Van Der Weyden MB: Prognostic relevance of thymidine kinase isozymes in adult non-Hodgkin's lymphomas. Blood 58:926–931, 1981.
5. Ellims PH, Gan TE, Van Der Weyden WB: Thymidine kinase isoenzymes in chronic lymphocytic leukaemia. Br J Haematol 49:479–481, 1981.
6. Fox RM, Piddington SK, Tripp EH, Dudman NP, Tattersall MHN: Thymidine sensitivity of cultural leukemic lymphocytes. Lancet 2:391–393, 1979.
7. Kufe DW, Beardsley P, Karp D, Parker L, Rosowsky A, Canellos G, Frei E III: High-dose thymidine infusions in patients with leukemia and lymphoma. Blood 55:580–589, 1981.
8. Howell SB, Chu B, Mendelsohn J, Carson DA, Kung FH, Seegmiller JE: Thymidine as a chemotherapeutic agent: Pharmacologic, cytokinetic and biochemical studies in a patient with T-cell acute lymphocytic leukemia. J Natl Cancer Inst 65:277–284, 1980.
9. Gan TE, Hallam L, Pilkington GR, Van Der Weyden MB: A rapid and simple radiometric assay for thymidine phosphorylase of human peripheral blood cells. Clin Chim Acta 116:231–236, 1981.
10. Gan TE, Hallam L, Van Der Weyden MB: Purine and pyrimidine activities in acute and chronic leukaemia: Relation to cellular proliferative status. Leukemia Research 6:839–844, 1982.
11. Bollum FJ: Terminal deoxynucleotidyl transferase as a hematopoietic cell marker. Blood 54:1203–1215, 1979.
12. McCaffrey R, Lillquist A, Sallan S, Cohen E, Osband M: Clinical utility of leukemia cell terminal transferase measurements. Cancer Res 41:4814–4820, 1981.
13. Coleman MS, Greenwood MF, Hutton JJ, Holland P, Lampkin B, Krill G, Kastelic JE: Adenosine deaminase terminal deoxynucleotidyl transferase and cell surface markers in childhood acute leukemia. Blood 52:1125–1131, 1978.
14. Janossy G, Hoffbrand AV, Greaves MF, Ganeshaguru K, Pain C, Bradstock KF, Prentice HG, Kay HEM, Lister TA: Terminal transferase enzyme assay and immunological membrane markers in the diagnosis of leukemia: a multiparameter analysis of 300 cases. Br J Haematol 44:221–234, 1980.

15. Marks SM, Baltimore D, McCaffrey R: Terminal transferase as a predictor of the initial responsiveness to vincristine and prednisone in blastic chronic myelogenous leukemia. N Engl J Med 298:812–814, 1978.
16. Donlon JA, Jaffe ES, Braylan RC: Terminal deoxynucleotidyl transferase activity in lymphomas. N Engl J Med 297:461–464, 1977.
17. Mertelsmann R, Koziner B, Fillipa A, Gupta S, Clarkson BD, Good RA, Siegal FP: Characterization of malignant lymphoma in leukemic phase by multiple differentiation markers of mononuclear cells. Am J Med 63:556–561, 1977.
18. Bradstock KF, Janossy G, Hoffbrand AV, Ganeshaguru K, Llewellin P, Prentice HG, Bollum FJ: Immunofluorescent and biochemical studies of terminal deoxynucleotidyl transferase in treated acute leukemia. Br J Haematol 47:121–131, 1981.
19. Stass SA, McGraw TP, Folds JD, Odle B, Bollum FJ: Terminal transferase in acute lymphoblastic leukemia in remission. Am J Clin Pathol 75:838–840, 1981.
20. Hecht T, Forman SJ, Winkler US, Santos S, Winkler KJ, Carlson F, Maslow WC, Borer W, Blume KG: Histochemical demonstration of terminal deoxynucleotidyl transferase in leukemia. Blood 58:856–858, 1981.
21. Bradstock KF, Papageorgiou ES, Janossy G: Diagnosis of meningeal involvement in patients with acute lymphoblastic leukemia: Immunofluorescence for terminal transferase. Cancer 47:2478–2481, 1981.
22. Froehlich TW, Buchanan GR, Cornet JAM, Sartain PA, Graham Smith R: Terminal nucleotidyl transferase-containing cells in peripheral blood: Implications for the surveillance of patients with lymphoblastic leukemia or lymphoma in remission. Blood 58:214–220, 1981.
23. Bollum FJ, Brown M: A high molecular weight form of terminal transferase. Nature 278:191–192, 1979.
24. Diebel MR, Coleman MS, Acree K, Hutton JJ: Biochemical and immunological properties of human terminal deoxynucleotidyl transferase purified from blasts of acute lymphoblastic and chronic myelogeneous leukemia. J Clin Invest 67:725–734, 1981.
25. Carson DA, Kaye J, Seegmiller JE: Lymphospecific toxicity in adenosine deaminase deficiency and purine nucleoside phosphorylase deficiency: Possible role of nucleoside kinase(s). Proc Natl Acad Sci USA. 74:5677–5681, 1977.
26. Hovi T, Smyth JF, Allison AC, William SC: Role of adenosine deaminase in lymphocyte proliferation. Clin Exp Immunol 23:395–403, 1976.
27. Meuwissen HJ, Pollara B: Combined immunodeficiency and inborn errors of purine metabolism. Blut 37:173–181, 1978.
28. Mitchell BS, Mejias E, Daddona PE, Kelley WN: Purinogenic immunodeficiency diseases: selective toxicity of deoxyribonucleosides for T cells. Proc Natl Acad Sci USA. 75:5011–5014, 1978.
29. Koller CA, Mitchell BS, Grever MR, Mejias E, Malspeis L, Metz EN: Treatment of acute lymphoblastic leukemia with 2 deoxycoformycin. Clinical and biochemical consequences of adenosine deaminase inhibition. Cancer Treat Rep 63:1949–1952, 1979.
30. Prentice HG, Smyth JG, Ganeshaguru K, Wonke B, Bradstock K, Janossy G, Goldstone A, Hoffbrand AV: Remission induction with the adenosine deaminase inhibitor 2 deoxycoformycin in Thy-lymphoblastic leukaemia. Lancet ii:170–172, 1980.
31. Smyth JF, Poplack DG, Holman BJ, Leventhal B, Jabro G: Correlation of adenosine deaminase with cell surface markers in acute lymphoblastic leukemia. J Clin Invest 59:710–713, 1978.
32. Ganeshaguru K, Lee N, Llewellin P, Prentice HG, Hoffbrand AV, Catovsky D, Hareshar JA, Robinson J, Greaves MF: Adenosine deaminase concentration in leukaemia and lymphomas: relationship to cell phenotypes. Leuk Res 5:215–222, 1981.
33. Lislo V, Tursi A, Specchia G, Troccoli G, Loria MP, Bonome L: Adenosine deaminase in acute lymphoblastic leukaemia: cytochemical, immunological, and clinical correlations. Scand J Haematol 21:167–175, 1978.
34. Simpkins H, Stanton A, Davis BH: Adenosine deaminase activity in lymphoid subpopulations and leukemias. Cancer Res 41:3107–3110, 1981.
35. Reaman GH, Blatt J, Poplack DG: Lymphoblast purine pathway enzyme in B cell acute lymphoblastic leukemia. Blood 58:330–332, 1981.
36. Tung R, Silber R, Quagliata F, Conklyn M, Gottesman J, Hirschhorn R: Adenosine deaminase activity in chronic lymphocytic leukemia: relationship to B- and T-cell subpopulations. J Clin Invest 57:756–761, 1976.

37. Ramot B, Brok-Simoni F, Barnea N, Bank I, Holtzman F: Adenosine deaminase in lymphocytes of normal individuals and patients with chronic lymphocytic leukaemia. Br J Haematol 36:67–70, 1977.
38. Meier J, Coleman MS, Hutton JJ: Adenosine deaminase activity in peripheral blood cells of patients with hematological malignancies. Br J Cancer 33:312–319, 1976.
39. Glader BE, Link MP: Lymphocyte adenosine deaminase activity: A potential marker of minimal residual disease in T-cell leukemia/lymphoma. Blood 58:139a, 1981.
40. De Pierre JW, Karnovsky ML: Ectoenzymes of the guinea pig polymorphonuclear leukocyte. J Biol Chem 249:7121–7129, 1974.
41. Howard F, Conklyn M, Stebbins RD, Silber R: Function of 5′ nucleotidase in the uptake of adenosine from AMP by human lymphocytes. J Biol Chem 250:8890–8892, 1975.
42. Naito J, Itoh R, Isushima K: 5′ nucleotidase of chick liver: a comparison of soluble 5 nucleotidase activities in chicken and rat liver. Int J Biochem 5:807–810, 1974.
43. Johnson SM, North ME, Asherton GL, Allsop J, Watts RWE, Webster ADB: Lymphocyte purine 5′ nucleotidase deficiency in primary hypogammaglobulinaemia. Lancet 1:168–170, 1977.
44. Edwards NL, Magelary DB, Cassidy JT, Fox IH: Lymphocyte ecto-5-nucleotidase in agammaglobulinaemia. Science 201:628–630, 1978.
45. Thompson LF, Boss GR, Spiegelberg AL, Jansen IV, O'Conner RD, Waldmann TA, Hauterger RN, Seegmiller JE: Ecto 5 nucleotidase activity in T and B lymphocytes from normal subjects and patients with congential X linked agammaglobulinaemia. J Immunol 123:2475–2478, 1978.
46. Quagliata F, Faig D, Conklyn M, Silber R: Studies on the lymphocyte 5 nucleotidase in chronic lymphocytic leukemia, infectious mononucleosis, normal subpopulations, and phytohemagglutinin-stimulated cells. Cancer Res 34:3197–3202, 1974.
47. Lopes J, Zucker-Franklin D, Silber R: Heterogeneity of 5′ nucleotidase activity in lymphocytes in chronic lymphocytic leukemia. J Clin Invest 52:1297–1300, 1973.
48. Wortmann RL, Mitchell BS, Edwards NL, Fox IH: Biochemical basis for differential deoxyadenosine toxicity to T and B lymphoblasts: role for 5′ nucleotidase. Proc Natl Acad Sci USA. 76:2434–2437, 1979.
49. Carson DA, Kaye J, Wasson DB: The potential importance of soluble deoxynucleotidase activity in mediating deoxyadenosine toxicity in human lymphoblasts. J Immunol 126:348–352, 1981.
50. Poplack DG, Blatt J, Reaman G: Purine pathway abnormalities in acute lymphoblastic leukemia. Cancer Res 41:4821–4823, 1981.
51. Wortmann RL, Holcenberg J, Poplack DG: Relationship of 5′ nucleotidase activity and antileukemic effect of 2 deoxycoformycin therapy. Cancer Treat Rep 66:387–390, 1982.
52. Koya M, Kanoh T, Sawada H, Uchino H, Ueda K: Adenosine deaminase and ecto-5-nucleotidase activities in various leukemias with special reference to blast crisis: significance of ecto-5-nucleotidase in lymphoid blast crisis of chronic myeloid leukemia. Blood 58:1107–1111, 1981.
53. Giblett ER, Amman AJ, Wara DW, Sandman R, Diamond LK: Nucleoside phosphorylase deficiency in a child with severely defective T cell immunity and normal B cell immunity. Lancet 1:1010–1013, 1975.
54. Biggar WD, Giblett ER, Ozere RL, Grover DB: A new form of nucleoside phosphorylase deficiency in two brothers with defective T cell function. J Pediatr 92:354–357, 1978.
55. Bogers M, Verhaegen H, De Brabander M, De Cree J, De Cock W, Thone F, Geuens G: Purine nucleoside phosphorylase in chronic lymphocytic leukemia (CLL). Blood 52:886–895, 1978.
56. Ludwig H, Kuzmits R, Pietschmann H, Muller MM: Enzymes of the purine interconversion system in chronic lymphocytic leukaemia: decreased purine nucleoside phosphorylase and adenosine deaminase activity. Blut 39:309, 1979.
57. Blatt J, Reaman GH, Levin H, Poplack DG: Purine nucleoside phosphorylase activity in acute lymphoblastic leukemia. Blood 56:380–382, 1981.
58. Kazmers IS, Mitchell BS, Dadonna PE, Wotring LL, Townsend LB, Kelley WN: Inhibition of purine nucleoside phosphorylase by 8 aminoguanosine: Selective toxicity for T lymphoblasts. Science 214:1137–1139, 1981.
59. Arseneau JC, Canellos GP, Banks PM, Berard CW, Gralnick HR, De Vita VT Jr: American Burkitt's lymphoma: A clinicopathologic study of 30 cases. 1. Clinical factors relating to prolonged survival. Am J Med 58:314–321, 1975.
60. Schneider RJ, Seibert K, Passe S, Little C, Gee T, Lee BJ III, Mike V, Young CW: Prognostic significance of serum lactate dehydrogenase in malignant lymphoma. Cancer 46:139–143, 1980.

61. Ferraris AM, Giuntini P, Gaetani GF: Serum lactic dehydrogenase as a prognostic tool for non-Hodgkin's lymphomas. Blood 54:928–932, 1979.
62. Keating MJ, Smith TL, Gehan EA, McCredie KB, Bodey GP, Spitzer G, Hersh E, Gutterman J, Freireich EJ: Factors related to length of complete remission in adult acute leukemia. Cancer 45:2017–2029, 1980.
63. Stewart DJ, Keating MJ, McCredie KB, Smith TL, Youness E, Murphy SG, Bodey GP, Freireich EJ: Natural history of central nervous system acute leukemia in adults. Cancer 47:184–196, 1981.
64. Rambotti P, Davis S: Lactic dehydrogenase in normal and leukemia lymphocyte subpopulations: evidence for the presence of abnormal T cells and B cells in chronic lymphocytic leukemia. Blood 57:324–327, 1981.
65. Ellis RB, Rapson NT, Patrick AD, Greaves MF: Expression of hexosaminidase isoenzymes in childhood leukemia. N Engl J Med 298:476–480, 1978.
66. Besley GTN, Broadhead DM, Bain AD, Dewar AE, Dewar AE, Eden OB: Enzyme markers in acute lymphoblastic leukemia. Lancet 2:1311, 1978.
67. Mann RB, Jaffe ES, Berard CW: Malignant lymphomas. A conceptual understanding of morphologic diversity. Am J Path 94:105–174, 1979.
68. Yam LT, Li CY, Lam KW: Tartrate-resistant acid phosphatase isoenzyme in the reticulum cells of leukemic reticuloendotheliosis. N Engl J Med 284:357–359, 1971.
69. Schmidt D, Radjun HJ, Schwerge EW, Stein H, Parwaresch MR: Activity and isoenzymes of acid phosphatase in human B-cell lymphomas of low grade malignancy. A novel aid in the classification of malignant lymphoma. Cancer 46:2676–2681, 1980.
70. Khilanani P, Chou TH, Rafanatharathorn V, Kessel D: Evaluation of two plasma fucosyltransferases as marker enzymes in non-Hodgkin's lymphoma. Cancer 41:701–704, 1978.
71. Nanba K, Jaffe ES, Braylan RC, Saban EJ, Berard CW: Alkaline phosphatase-positive malignant lymphoma. Am J Clin Pathol 535–542, 1977.