Lack of Autologous Mixed Lymphocyte Reaction in Patients With Chronic Lymphocytic Leukemia: Evidence for Autoreactive T-Cell Dysfunction Not Correlated With Phenotype, Karyotype, or Clinical Status

By Tin Han, Marvin L. Bloom, Barbara Dadey, Gregory Bennett, Jun Minowada, Avery A. Sandberg, and Howard Ozer

In the present study, there was a complete lack of autologous MLR between responding T cells or T subsets and unirradiated or irradiated leukemic B cells or monocytes in all 20 patients with CLL, regardless of disease status, stage, phenotype, or karyotype of the disease. The stimulating capacity of unirradiated CLL B cells and CLL monocytes or irradiated CLL B cells was significantly depressed as compared to that of respective normal B cells and monocytes in allogeneic MLR. The responding capacity of CLL T cells was also variably lower than that of normal T cells against unirradiated or irradiated allogeneic B cells and monocytes. The depressed allogeneic MLR between CLL B cells or CLL monocytes and normal T cells described in the present study could be explained on the basis of a defect in the stimulating antigens of leukemic B cells or monocytes. The decreased allogeneic MLR of CLL T cells might simply be explained by a defect in the responsiveness of T lymphocytes from patients with CLL. However, these speculations do not adequately explain the complete lack of autologous MLR in these patients. When irradiated CLL B cells or irradiated CLL T cells were cocultured with normal T cells and irradiated normal B cells, it was found that there was no suppressor cell activity of CLL B cells or CLL T cells on normal autologous MLR. Our data suggest that the absence or dysfunction of autoreactive T cells within the T<sub>non</sub>-subset account for the lack of autologous MLR in patients with CLL. The possible significance of the autologous MLR, its relationship to in vivo immunoregulatory mechanisms, and the possible role of breakdown of autoregulation in the oncogenic process of certain lymphoproliferative and autoimmune diseases in man are discussed.

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) is a malignancy characterized by the proliferation of monoclonal lymphocytes of B-cell origin in almost all instances. There is currently a controversy in the literature regarding both the ability of leukemic B cells from CLL patients to proliferate and differentiate into mature plasma cells as well as the ability of apparently normal T cells from these patients to perform immunoregulation of normal allo- genetic B-cell differentiation. In a recently completed study, we observed that the majority of leukemic CLL B cells are incapable of further differentiation in the presence of normal allogeneic T cells and pokeweed mitogen as measured by total ³H-thymidine incorporation. This lack of differentiative capacity is unaffected by clinical stage, therapy, or the phenotype of the leukemic cell population. Since the leukemic B cells do not suppress normal allogeneic B-cell differentiation, the maturation deficit is evidently intrinsic to the leukemic clone, rather than a result of non-T suppressor cell activity. T helper function is also variably depressed in CLL patients, and this depression does not correlate with clinical stage, therapy, or degree of lymphocytosis.

Opelz et al. and Kuntz et al. recently observed that non-T-cells from normal subjects are capable of stimulating autologous T lymphocytes to proliferate in the autologous mixed lymphocyte reaction (MLR). It has been postulated that the autologous MLR may represent an in vitro manifestation of an immunoregulatory mechanism by which B-lymphocyte function is controlled. The autologous MLR has recently been shown to be absent in patients with CLL.

The present study examined not only autologous MLR in CLL patients and healthy subjects, but also allogeneic MLR between healthy subjects and CLL patients, utilizing isolated subsets of T lymphocytes, B lymphocytes, and monocytes in order to elucidate the functional defects of specific mononuclear cell subpopulations involved in autologous and allogeneic MLR in this B-cell malignancy.

MATERIALS AND METHODS

Patient Population

Twenty patients with CLL were studied. There were 12 males and 8 females. A majority of patients (17/20) were over 50 yr old. All patients had active disease at the time of initial study. Clinical staging indicated that 10 patients had advanced disease (stage III or IV) and 10 patients had limited disease (stage 0–II). Of the 10 patients with stage 0,1, or II initially, 2 patients (one each with stage...
I and stage II) were found to have progression of the disease to advanced stages within 6 mo of an initial study. Twelve patients were previously untreated and 8 patients were previously treated. Lymphocytosis ranged from 20,000 to over 100,000/cu mm in these patients. Phenotypic analysis of leukemic cells showed that 18 of 20 patients were classified as either μ or μ, and the remaining 2 patients were classified as γ heavy chain type. Of these 20 patients, 12 were classified as α and 8 were classified as δ light chain type. Of 15 patients studied for chromosome analysis by Q- and G-banding techniques of B-cell mitogen-stimulated peripheral blood lymphocytes, 9 had a normal diploid karyotype, 1 had no mitosis, and 5 had a hyperdiploid with 47 chromosomes (trisomy 12 in 2 patients and trisomy 16, 18, and 19 in one each).

Preparations of Purified T Lymphocytes, B Lymphocytes, and Monocytes

Peripheral blood mononuclear cells were isolated from 30–35 ml of heparinized venous blood by centrifugation over a Ficoll-Hypaque gradient. One percent (v/v) sheep erythrocyte suspension was incubated with Vibrio cholerae neuroaminidase (25 U/ml) at 37°C for 30 min. The cells were then washed twice with RPMI 1640 culture medium containing antibiotics (100 U of penicillin and 50 μg of streptomycin/ml). Samples of 0.25 ml of leukocyte suspension (10^6/ml), 0.25 ml of fetal calf serum, and 0.5 ml of neuraminidase-treated sheep erythrocytes (10^7/ml) were added to plastic test tubes, which were centrifuged for 5 min at 200 g and further incubated at room temperatures for 60 min. The cell pellets of all tubes containing rosetted and nonrosetted cells were pooled, gently resuspended, and centrifuged over a Ficoll-Hypaque gradient at 400 g for 30 min. The T lymphocytes rosetted with sheep erythrocytes formed the pellet, and nonrosetted cells remained at the interface between the layers. The T cells were washed once with culture medium. The two T-cell suspensions were then pooled and resuspended in culture medium. Sheep erythrocytes were lysed by treating with ammonium chloride (0.84%) at 4°C for 10 min. The cells were then washed twice and resuspended in culture medium.

Both T- and B-enriched preparations were incubated with iron particles (carbonyl iron, GAF Corp., Chemical Division, New York, N.Y.) for 60 min at 37°C. Monocytes ingested the iron particles, and these cells were separated from lymphocytes by centrifugation over a Ficoll-Hypaque gradient. Monocytes in the pellets were pooled and resuspended in culture medium.

Viability by trypan blue dye exclusion of each enriched fraction of cells ranged from 95% to 99%. The T-enriched fractions contained an average of 95% E-rosette-forming cells, with ranges of 92–98%. The monocyte-enriched fractions contained an average of 98% nonspecific esterase-positive cells, with ranges of 96–100%. The T-enriched or B-enriched fractions contained an average of only 2% E-rosette-forming cells, with ranges of 92–98%. Thus, the T-enriched fractions or monocyte-enriched fractions from both healthy subjects and CLL patients contained more than 90% purity of respective cell types. Although the B-enriched fractions from healthy subjects were virtually devoid of T cells or monocytes, these fractions also contained some SmIg-negative null cells.

Separations of Ty and T Non-γ Subpopulations

Ty cells were isolated by positive selection with bovine erythrocytes coated with the IgG fraction of rabbit anti-bovine erythrocyte antibody (N.L. Cappel Laboratories, Cochranville, Pa.). This antibody was screened for titer and class specificity and further purified on Sephadex G-150 columns as necessary. γγ-rosette-forming cells were prepared by a modification of the technique of Moretta et al.33 Briefly, washed bovine erythrocytes were incubated with a 1:7 dilution of anti-bovine erythrocyte IgG for 30 min at 37°C in normal saline with occasional mixing, washed twice in saline, and stored at 4°C for use within 4 days. Isolated T cells were incubated for 2 hr with IgG-coated bovine erythrocytes at a 1:150 ratio in RPMI 1640 with 10% FCS. The rosettes were resuspended with extremely gentle agitation, layered on Ficoll-Hypaque gradients, and centrifuged for 15 min at 200 g.

Autologous and Allogeneic MLR

Purified T lymphocytes, B lymphocytes, and monocytes were suspended in RPMI 1640 culture medium containing 10% fetal calf serum and antibiotics (100 U of penicillin and 50 μg of streptomycin/ml) at a 2 x 10^7/ml concentration. One milliliter of responding T-lymphocyte suspension was transferred to 16 x 125 mm Falcon disposable plastic culture tubes. To some culture tubes containing the responding T lymphocytes, 1 ml of unirradiated or irradiated (6000 rad) autologous or allogeneic stimulating cells, making a 1:1, 1:2, 1:4 or 1:8 ratio of responders to stimulators, was added. In addition to mixed-cell cultures, each experiment included single-cell cultures containing responding T lymphocytes or stimulating cells only. The experiments were carried out in duplicate. Cultures were incubated for 7 days. Incorporation of "H-thymidine into DNA was measured as previously described.34

Autologous MLR and allogeneic MLR were conducted for all 20 patients at the time of presentation to RPMI and prior to institution of chemotherapy. Autologous MLR was conducted again in 5 patients with stable disease (stage 0, 1, stage I, 1, and stage II, 3) 2–3 mo later and in 5 patients (stage II, 3 and stage III, 2) after a clinical remission was induced by chlorambucil-prednisone therapy.

RESULTS

Autologous MLR

The results of autologous MLR between responding T lymphocytes and stimulating B lymphocytes or monocytes at a 1:1 ratio of responders to stimulators in healthy subjects are shown in Table 1. The stimulating capacity of B lymphocytes on autologous T lymphocytes was somewhat higher than that of monocytes.

<table>
<thead>
<tr>
<th>Composition of Culture**</th>
<th>No. of Experiments</th>
<th>T-lymphocyte Incorporation of [3H]-Thymidine (cpm) (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT</td>
<td>30</td>
<td>1,392 ± 1,368</td>
</tr>
<tr>
<td>NB</td>
<td>30</td>
<td>1,362 ± 1,329</td>
</tr>
<tr>
<td>NT ± NB</td>
<td>30</td>
<td>17,405 ± 16,604</td>
</tr>
<tr>
<td>NB†</td>
<td>19</td>
<td>284 ± 19</td>
</tr>
<tr>
<td>NT ± NB†</td>
<td>19</td>
<td>10,879 ± 9,651</td>
</tr>
<tr>
<td>NT</td>
<td>10</td>
<td>561 ± 531</td>
</tr>
<tr>
<td>NM</td>
<td>10</td>
<td>1,168 ± 1,088</td>
</tr>
<tr>
<td>NT + NM</td>
<td>10</td>
<td>12,485 ± 10,959</td>
</tr>
<tr>
<td>NM†</td>
<td>10</td>
<td>323 ± 159</td>
</tr>
<tr>
<td>NT + NM†</td>
<td>10</td>
<td>5,749 ± 5,268</td>
</tr>
</tbody>
</table>

* A 1:1 ratio of responders to stimulators was utilized. (NT, normal T lymphocytes; NB, normal B lymphocytes; NM, normal monocytes.) †Irradiated with 6000 rad.
although the difference was not statistically significant. Irradiation of stimulating cells with 6000 rad resulted in a decrease in the stimulating capacity of both B lymphocytes and monocytes in autologous MLR.

When B lymphocytes were used as responding cells and irradiated T cells were used as stimulating cells in autologous MLR, it was found that normal B lymphocytes were not induced to proliferate by irradiated autologous T lymphocytes (means ± SD of 19 experiments, NB alone = 1962 ± 2396 cpm; irradiated NT alone = 326 ± 149 cpm; NB + irradiated NT = 2097 ± 2675 cpm). We also carried out 10 experiments in which unirradiated responding T cells were cocultured with an equal number of irradiated autologous T cells, B cells, and monocytes. In each experiment, irradiated T cells were found to be nonstimulating, whereas irradiated B cells or monocytes were capable of stimulating the autologous responding T lymphocytes to proliferate (Table 2).

In contrast, there was no autologous MLR between responding T cells and unirradiated or irradiated B cells or monocytes at a 1:1 ratio of responders to stimulators of active CLL patients in every experiment performed (Table 3). Autologous MLR was also absent when cultures were incubated for 3 days or 10 days instead of 7 days in all 3 patients with active CLL tested (not shown). In 2 active CLL patients utilizing higher numbers of CLL B cells or CLL monocytes (making a 1:2, 1:4, or 1:8 ratio of responders to stimulators) or lower numbers of CLL B cells and CLL monocytes in combination (making a 1:0.5:0.5 ratio of responders to stimulators) the autologous MLR was completely absent (Table 4). When irradiated CLL B cells or irradiated CLL T cells were cocultured with normal T cells and irradiated normal B cells, it was found that there was no suppressor cell activity of CLL B cells or CLL T cells on normal autologous MLR (Table 5).

In two experiments the autologous MLR was examined utilizing normal and CLL T-cell subsets isolated for presence or absence of Fc receptors for IgG as responders and B cells as stimulators. There was a significant autologous MLR between normal T<sub>non-γ</sub> cells and B cells, whereas there was no autologous MLR between normal Tγ cells and B cells. However, the autologous MLR was absent between either CLL T<sub>non-γ</sub> cells or CLL Tγ cells and CLL B cells in both instances (Table 6). In 5 patients with CLL, the autologous MLR remained absent when the experi-
ments were repeated after a clinical remission was induced (Table 7). In 5 patients with stable disease (stage 0–II), repeat autologous MLR was again absent (not shown).

**Allogeneic MLR**

Table 8 show the comparison between the stimulating capacity of normal B lymphocytes and CLL B lymphocytes. The stimulating capacity of unirradiated or irradiated CLL B cells was significantly depressed as compared to that of respective normal B cells in allogeneic MLR. Table 9 shows the comparison between the stimulating capacity of normal monocytes and CLL monocytes. Although the stimulating capacity of unirradiated CLL monocytes was significantly depressed as compared to that of unirradiated normal monocytes, the stimulating capacity of irradiated CLL monocytes was almost identical to that of irradiated normal monocytes in allogeneic MLR.

The responding capacity of normal T cells was found to be higher than that of CLL T cells stimulated by unirradiated or irradiated normal B cells (Table 10). Likewise, the responding capacity of normal T cells was higher than that of CLL T cells against unirradiated or irradiated normal monocytes (Table 11).

**DISCUSSION**

It has generally been accepted that the T lymphocytes are the responding cells and that B lymphocytes, null cells, and monocytes are stimulators in human allogeneic MLR. Currently, the non-T-cell population from healthy subjects has also been shown to represent the stimulatory cells in autologous MLR. The present study provides further confirmation for the observation that B lymphocytes or monocytes from healthy subjects are capable of stimulating normal T lymphocytes in autologous MLR, whereas there is no autologous MLR between CLL T lymphocytes and either CLL B lymphocytes or monocytes when used as stimulators in this assay. Our results provide further new information that the autologous MLR is absent in all patients with CLL regardless of disease status, stage, phenotype, or karyotype of the disease. Quesada et al. recently reported that patients with CLL in remission also fail to elicit autologous MLR. Fernandez et al. recently observed that during the stable phase of the disease, the T lymphocytes from...
LACK OF AUTOLOGOUS MLR IN CLL

either at the time of initial study or during subsequent
of Fernandez et al.,'8 we observed no autologous MLR
disease progression from stage I and II to stage III and
gressive disease and during a 6-mo follow-up period,
study, 10 patients (stage III or IV) 'exhibited pro-
developed progressive disease, a significant autologous
populations from normal subjects and CLL patients. The
capacity of unirradiated or irradiated leukemic B cells, whereas in 7 patients who have
developed progressive disease, a significant autologous
MLR could be demonstrated. At the beginning of our
stimulating capacity of leukemic B lymphocytes in the
surface determinants resulting from surface mem-
brane alterations during the process of leukemogene-
sis. Although it is also possible that the depressed
stimulating capacity of leukemic B cells in the allogeneic or autologous MLR could be explained by
some suppressor activity of these cells, this appears
unlikely since leukemic B lymphocytes from patients
with CLL fail to suppress T-lymphocyte response to
mitogens and do not suppress in normal autologous
MLR when added in coculture (Table 5).

The T lymphocytes from patients with CLL have
been shown to be functionally normal in responding to
mitogens such as PHA. In the present study, the
responding T lymphocytes from patients with CLL
proliferated subnormally against unirradiated or irra-
diated B lymphocytes or monocytes from healthy sub-
jects in the allogeneic MLR. However, normal
responding capacity of T lymphocytes from patients
with CLL in the allogeneic MLR has recently been observed.

It has also been observed that cultured B lympho-
blasts stimulate autologous lymphocytes in the
MLR. Weksler suggested that the Ia-like anti-
gens on B cells are responsible for the proliferation of
autologous T lymphocytes. Bergholtz et al. showed
that HLA-DR antigens on B cells are involved in the
stimulation of autologous T lymphocytes. Since the
Ia-like or HLA-DR antigens are responsible for the
allogeneic T-cell proliferation, it appears that the
antigenic systems functioning in the autologous and
allogeneic MLR are closely related. On the other hand,
Smith et al. have shown that autologous and al-
logeneic MLR can be selectively blocked by different
serum samples from multiparous women. This observ-
ervation suggests that the stimulating antigen(s) in the
autologous and allogeneic MLR may be different. Of
particular interest is the fact that the leukemic B
lymphocytes from patients with CLL express Ia-like
antigens as do counterpart normal B lymphocytes,
although the stimulating capacity of these leukemic B
lymphocytes is markedly depressed. We have also
previously reported the lack of correlation between the
presence of Ia-like antigen and the stimulating capac-
ity of fresh or cultured leukemic lymphoid or myeloid
cells. These observations suggest that expression of
Ia-like or HLA-DR antigens and the stimulating anti-

<table>
<thead>
<tr>
<th>Table 10. Allogeneic MLR Between T Lymphocytes and B Lymphocytes in Healthy Subjects and CLL Patients: A Comparison Between Responding Capacity of Normal T and CLL T Lymphocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Composition of Culture</strong></td>
</tr>
<tr>
<td>-----------------------------</td>
</tr>
<tr>
<td>NT</td>
</tr>
<tr>
<td>NB</td>
</tr>
<tr>
<td>NT + NB</td>
</tr>
<tr>
<td>NB*</td>
</tr>
<tr>
<td>NT + NB*</td>
</tr>
<tr>
<td>CLL T</td>
</tr>
<tr>
<td>NB</td>
</tr>
<tr>
<td>CLL T + NB</td>
</tr>
<tr>
<td>NB*</td>
</tr>
<tr>
<td>CLL T + NB*</td>
</tr>
</tbody>
</table>

*irradiated with 6000 rad.
†p < 0.01 by the paired t test.
NS, not significant.

27 patients with CLL failed to respond to their own
leukemic B cells, whereas in 7 patients who have
developed progressive disease, a significant autologous
MLR could be demonstrated. At the beginning of our
study, 10 patients (stage III or IV) exhibited pro-
gressive disease and during a 6-mo follow-up period,
disease progression from stage I and II to stage III and
IV was seen in two patients. In contrast to the findings
of Fernandez et al.,18 we observed no autologous MLR
in any of these 12 patients with progressive disease
either at the time of initial study or during subsequent
follow-up.

In order to clarify a possible defective regulatory
role or a defect in stimulating capacity by CLL cell
populations, we have also compared allogeneic and
autologous MLR with different mononuclear cell pop-
ulations from normal subjects and CLL patients. The
stimulating capacity of unirradiated or irradiated leu-

<table>
<thead>
<tr>
<th>Table 11. Allogeneic MLR Between T Lymphocytes and Monocytes in Healthy Subjects and CLL Patients: A Comparison Between Responding Capacity of Normal T and CLL T Lymphocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comparison of Culture</strong></td>
</tr>
<tr>
<td>-----------------------------</td>
</tr>
<tr>
<td>NT</td>
</tr>
<tr>
<td>NM</td>
</tr>
<tr>
<td>NT + NM</td>
</tr>
<tr>
<td>NM*</td>
</tr>
<tr>
<td>NT + NM*</td>
</tr>
<tr>
<td>CLL T</td>
</tr>
<tr>
<td>NM</td>
</tr>
<tr>
<td>CLL T + M</td>
</tr>
<tr>
<td>NM*</td>
</tr>
<tr>
<td>CLL T + M*</td>
</tr>
</tbody>
</table>

*irradiated with 6000 rad.
†p < 0.05 by the paired t test.
NS, not significant.
The depressed allogeneic MLR between leukemic CLL B cells and normal T cells described in the present study could be explained on the basis of a defect in the stimulating antigens of leukemic B cells or monocytes. The decreased allogeneic MLR of CLL T cells might similarly be explained by a defect in responsiveness of T lymphocytes from patients with CLL. However, these speculations do not adequately explain the complete lack of autologous MLR in patients with CLL. Ilfeld et al.35 recently demonstrated that marked suppression of the autologous MLR without any suppression of the allogeneic MLR could be induced by concentrations of hydrocortisone equivalent to those found in human plasma. These observations suggest that two or more distinct subsets of T lymphocytes may be responsible for the autologous and allogeneic MLR. It is possible that the lack of autologous MLR in patients with CLL may primarily be due to the absence of such an autoreactive T-cell subset. Very recently, Engleman et al.36 observed that Leu-3a\(^+\) T cells (inducer cells) proliferate in response to autologous non-T-cells, whereas Leu-2a\(^+\) T cells (suppressor/cytotoxic cells) do not. These authors concluded that inducer but not suppressor/cytotoxic T cells recognize autologous HLA-DR antigens, and the inducer and suppressor/cytotoxic T-cell subsets in man respond differentially to major histocompatibility complex antigens in a manner similar to murine Lyt-2\(^-\)3\(^+\) and Lyt-2\(^+\)3\(^-\) populations. In the present study, we observed that normal T\(\gamma\) cells do not proliferate in response to autologous B cells, while the T\(_{\text{non-}}\) subset (containing both the helper and radiosensitive mitogen-inducible suppressor subsets) respond to autologous B cells, whereas neither CLL T\(\gamma\) nor the normally responsive T\(_{\text{non-}}\) subset from these patients will proliferate in response to autologous leukemic B cells. Our observations indicate that the absence or dysfunction of autoreactive T cells within the T\(_{\text{non-}}\) population may account for the lack of autologous MLR in patients with CLL.

The possible significance of the autologous MLR, and its relationship to in vivo immunoregulatory mechanisms, remain highly speculative. Smith and Knowlton\(^3\) have shown that activation of suppressor T cells occurs in the autologous MLR of healthy subjects, whereas such suppressor T-cell activation does not occur in patients with CLL. Katz et al.\(^4\) and Vandestouwe et al.\(^5\) have shown that autocytotoxic T cells do not develop in the autologous MLR. Thus, the suppression caused by autologous MLR-activated T cells on secondary MLR seen in Smith and Knowlton’s study\(^6\) does not seem to be due to the development of autocytotoxic T cells. Smith and Pasternak\(^7\) have also failed to demonstrate an autocytotoxic response of T cells against either T or B target cells in syngeneic MLR in mice. Recently, however, Miller and Kaplan\(^8\) have reported evidence that autologous MLR-activated T cells can kill LPS-stimulated blast but not unstimulated B cells in a human system, and Tomonari\(^9\) demonstrated that cytotoxic T cells with broad specificity other than for MHC antigens are generated in the human autologous MLR. It has been shown that like Con-A-inducible suppressor cells, the autologous MLR-activated cells can suppress not only T-cell response but also the B-cell response in man.\(^10\)\(^,\)\(^11\)\(^,\)\(^12\)

Regardless of the mechanism, the available evidence suggests that the autologous MLR represents an important immunoregulatory mechanism. The lack of autologous MLR in patients with CLL\(^13\)\(^,\)\(^14\) as well as in patients with systemic lupus erythematosus\(^15\) and Hodgkin’s disease\(^16\) support the contention that the breakdown of autoimmunoregulation could play an important role in the oncogenic process of certain lymphoproliferative and autoimmune diseases.

REFERENCES


25. Han T, Daday B: T and B lymphocytes: Exclusive role as responders and stimulators in human "one-way" mixed lymphocytes reaction. Immunology 31:643–648, 1976


27. Han T, Daday B: Loss of stimulatory capacity of leukemia B lymphocytes from chronic lymphocytic leukemia in "one-way" mixed lymphocyte reaction. IRCS Med Sci 5:177, 1977


32. Han T, Orsini F, Minowada J: Unpublished observations


34. Han T, Daday B, Minowada J: Stimulating capacity of fresh and cultured human leukemia lymphoid and myeloid cells in "one-way" mixed lymphocyte reaction. Immunology 33:543–556, 1977


From www.bloodjournal.org by guest on October 21, 2017. For personal use only.
Lack of autologous mixed lymphocyte reaction in patients with chronic lymphocytic leukemia: evidence for autoreactive T-cell dysfunction not correlated with phenotype, karyotype, or clinical status

T Han, ML Bloom, B Dadey, G Bennett, J Minowada, AA Sandberg and H Ozer