Correlation of Two In Vitro Tests With Clinical Response to Immunosuppressive Therapy in 54 Patients With Severe Aplastic Anemia

By Beverly Torok-Storb, Kristine Doney, Susan L. Brown, and Ross L. Prentice

Two in vitro tests were applied to 54 consecutive patients with severe aplastic anemia who were treated in Seattle with antithymocyte globulin. In the first test, peripheral blood mononuclear cells were collected from each patient before antithymocyte globulin therapy and then treated with a panel of monoclonal antibodies and complement. The treated peripheral blood mononuclear cells were assayed for erythroid burst-forming units (BFU-E). This test was designed to determine whether removing various subpopulations of peripheral blood mononuclear cells would increase the number of detectable BFU-E. In the second test, peripheral blood was collected within 48 hr after completion of antithymocyte globulin therapy, and cells were immediately assayed for BFU-E without any further treatment. Data from both tests were analyzed to determine whether the in vitro results correlated with patient response to therapy. Binary logistic regression analyses indicate that a modest correlation \( p = 0.04 \) exists between test 1 in vitro results and patient response to therapy. However, the strength of this association appears to decrease as the interval between diagnosis and treatment increases. In contrast, test 2 had a very significant correlation \( p = 0.001 \) with response to therapy among patients diagnosed more than 1 mo prior to treatment, whereas such an association was not apparent among patients treated within 1 mo of diagnosis.

The techniques of detecting committed hematopoietic precursors in vitro as colony-forming units have been applied by many investigators to the study of aplastic anemia (AA). The purposes of such studies were generally twofold. First, they were aimed at understanding the etiology of aplasia; second, such studies were generally twofold. First, they were aimed at developing assays that would identify patients likely to respond to immunosuppressive therapy.

In regard to the first goal, it has been well established that colony-forming units of any kind (CFU-C, BFU-E, CFU-E) are either not detectable or are found in significantly reduced numbers in the marrow and blood of AA patients. Such a reduction in the quantity of committed progenitors is not surprising, given the hypoplastic marrow characteristics of this disease. The questions remain, though, as to how progenitor cell numbers are initially reduced and why they do not regenerate.

The concept of "immune-mediated" aplasia was first supported by the observation that some AA patients recovered autologous marrow function after immunosuppression. Several investigators tried to corroborate these clinical observations with in vitro studies that showed that lymphocytes from AA patients inhibited the growth of myeloid colonies when added to cultures of normal marrow. This, however, was not a consistent observation, and in many cases, there was no effect of adding lymphocytes. Nevertheless, inhibition of normal colony growth by AA lymphocytes was interpreted to indicate that an immune mechanism was responsible for the patient's aplasia. Subsequent studies, however, indicated that this reduction of normal colony growth was probably due to transfusion-induced sensitization of patient cells against major and/or minor histocompatibility antigens present on precursors. It became apparent, from these later studies, that assays designed to detect "autoimmunity" should be restricted to autologous cell combinations. This concept was incorporated into the design of more recent efforts in studying the effect of T cell depletion on colony growth from the AA patient's cells. However, as these cell depletion experiments preceded an understanding of how such manipulations affect in vitro growth of normal colonies, the observations made with patient cells have not necessarily been accurately interpreted. In addition, the validation of in vitro observations by correlation with clinical response has been limited to a sporadic sampling of a small number of patients.

The study presented in this article was designed to overcome some of the limitations of previous studies discussed above. Two in vitro tests were developed and applied in a prospective study to all patients with severe aplastic anemia treated in Seattle with antithymocyte globulin (ATG). The study continued for 2 yr to allow for the accrual of 54 patients. At the time of this writing, the minimum follow-up time is 18 mo.

From the Fred Hutchinson Cancer Research Center and the Departments of Medicine and Biostatistics, University of Washington, Seattle, WA.

Supported in part by Grants CA 30924, CA 15704, CA 18029, and CA 18221 awarded by the National Cancer Institute, DHHS. and by Grant HL 24439 from the National Heart, Blood and Lung Institute, DHHS.

Submitted March 17, 1983; accepted July 8, 1983.

Address reprint requests to Dr. Beverly Torok-Storb, Fred Hutchinson Cancer Research Center, 1124 Columbia Street, Seattle, WA 98104.

\( 0006-4971/84/02-0155$01.00/0 \)
The purposes of this study were the same as those mentioned above—to gain some understanding of the mechanism of AA and to develop a method of identifying patients who might respond to immunosuppressive therapy.

**MATERIALS AND METHODS**

**Patients**

Included in this study were 54 patients who met the criteria for severe aplastic anemia. All patients were treated with horse ATG (ATGAM, Upjohn Co., Kalamazoo, MI), 16 mg/kg q.d. for 10 days and oxymethone, 3 mg/kg for 3 mo. Thirty of these patients also received an HLA-haploididentical marrow infusion. A more detailed analysis of the patients’ hematologic status before and after ATG therapy is presented in the accompanying report (Doney et al., this issue).

**Preparation of Cells**

A quantity of 20–50 ml of heparinized whole blood was collected from each patient before and within 2 days after ATG therapy. Blood was diluted 1:1 in Hanks’ balanced salt solution and layered over Ficoll-Hypaque (Lymphoprep, Nyegaard Co., Oslo, Norway). After centrifugation at 400 g for 30 min at 22°C, the peripheral blood mononuclear cells (PBMC) that remained at the interface were collected, washed 3 times, and suspended in tissue culture medium (RPMI 1640) with 20% fetal bovine serum.

**Complement (C’) Mediated Cytolysis**

Cells were resuspended at a concentration of 1-4 x 10^6 in 0.1 ml of tissue culture medium (RPMI 1640) containing 20% heat-inactivated fetal bovine serum. An equal volume of monoclonal antibody (MoAb) (ascites fluid) diluted 1:1,000 was added and the cells incubated at room temperature for 30 min. Pooled, prescreened normal rabbit serum (0.2 ml undiluted) (Pelfreeze lot 1342) was then added as a source of complement (C’), and the incubation was continued an additional 60 min. Fifteen lots of pooled rabbit serum were screened to identify a reagent that gave greater than 95% antibody (a-HLA class I antigen)-dependent cytotoxicity and minimum nonspecific (antibody-independent) cytotoxicity. All lots of rabbit serum gave some degree of nonspecific killing, usually directed at late erythroid precursors, erythrocytes, and some monocytes (data not shown). Titration studies indicated that maximum specific killing with MoAb used in this study was achieved under conditions described above. After washing 3 times, cells in all groups were resuspended to the same volume to equal 10^6 cells/ml, based on the original cell concentrations. It is important to note that after lysis, cell concentrations were not readjusted to 10^6 viable cells/ml, thus eliminating the possibility of detecting colony growth by merely increasing the concentrations of stem cells plated. Cells were resuspended in supplemented alpha-medium for use in BFU-E assays.

**BFU-E Assay**

PBMC resuspended in alpha-medium were plated at a final concentration of 4–8 x 10^4 cells in 0.1-ml plasma clots. Erythropoietin was added at a concentration of 2 U/ml (Connaught step III, lots 3031 and 3034). No exogenous source of burst-promoting activity was added. Clots were incubated for 14 days at 37°C in 5% CO₂, then harvested, fixed on glass slides, and stained with benzidine.

**Monoclonal Antibodies**

Table 1 summarizes the characteristics of the MoAb used in this study. Briefly, antibodies 7.28, 9.6, 35.1, and 10.2 are specific for various populations of T lymphocytes, whereas antibody 20.3 reacts with monocytes. Antibody 7.2 is specific for the human Ia-like antigen. All six antibodies listed above fix complement and have been shown, with the exception of MoAb 7.2, not to react with BFU-E.

**Experimental Design**

Test 1 was designed to determine whether the number of detectable BFU-E grown from patient PBMC could be increased by removing various subpopulations of cells. PBMC used for this test were isolated from peripheral blood obtained from the patient prior to ATG therapy. Selected populations of cells were removed by C'-mediated cytotoxicity after treatment with specific monoclonal antibodies. Two control groups were included in this study: in one, PBMC were incubated with medium only, and in the other, PBMC were incubated with C’ only.

Test 2 was designed to determine whether BFU-E could be grown from patient PBMC after the patient had received ATG. PBMC used in this test were isolated from peripheral blood obtained within 48 hr of completion of ATG therapy. The cells received no additional treatment before they were assayed for BFU-E growth.

During the course of this study, 54 patients with severe AA were treated with ATG. Four of these patients were accidentally omitted from this study because their blood samples were not drawn. One patient who was studied is not included in this analysis because he received a fetal liver transplant at another institution before his response to ATG could be assessed. Of the remaining 49 patients, 47 were studied before they received ATG (test 1) and 41 were studied after ATG (test 2). A total of 39 patients were studied both before and after receiving ATG.

The clinical response to ATG therapy was assessed 3 mo after treatment, and patients who had evidence of hematologic improvement within this period of time were considered to have responded to therapy. The degree of response was defined by the sustained level of improvement rated from 1 to 4: (1) a return of a normal hematocrit and granulocyte count with a platelet count >100,000/cu mm; (2) a

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Isotype</th>
<th>Specificity (Effect on BFU-E)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.2</td>
<td>IgG2p</td>
<td>Monomorphic determinant on HLA-DR p29,34 bimolecular complex (6% ± 2%)</td>
</tr>
<tr>
<td>7.28</td>
<td>IgM</td>
<td>Determinant variably expressed on most peripheral blood T cells (180% ± 14%)</td>
</tr>
<tr>
<td>20.3</td>
<td>IgM</td>
<td>Determinant on monocytes, platelets, nucleated red cells, p85 (102% ± 6%)</td>
</tr>
<tr>
<td>9.6/35.1</td>
<td>IgG4a</td>
<td>E receptor on T cells, p50 (70% ± 6%)</td>
</tr>
<tr>
<td>10.2</td>
<td>IgG4a</td>
<td>Determinant on T cells, p67 (136% ± 20%)</td>
</tr>
</tbody>
</table>

*Effect on BFU-E growth of treating normal peripheral blood mononuclear cells with antibody and complement; data are represented as mean ± SE of control growth. Control growth is determined by treating cells with complement only. Treatment of normal peripheral blood mononuclear cells with this particular lot of complement consistently resulted in a 5%–10% increase in BFU-E growth compared to growth obtained from cells incubated with media only.
IN VITRO STUDIES OF APLASTIC ANEMIA

partial response with improvement in all three cell lines, a granulocyte count >500/cu mm, and no transfusion requirements; (3) a minimal response with improvement in at least one cell line but transfusions still required; and (4) no response.

Statistical Methods

To facilitate analysis, the in vitro data were simplified so that the observation of no BFU-E growth in test 1 was coded negative (−) and growth in response to any monoclonal antibody treatment was coded positive (+). The same code was applied to test 2. Standard contingency table methods were used to relate clinical response scores of 1–4 to in vitro test results. In particular, uncorrected chi-square statistics, based on a comparison of observed to "expected" cell frequencies, were used to test hypotheses of no association between in vitro results and clinical results. Binary logistic regression methods were used to accommodate other patient or disease characteristics (e.g., time from diagnosis to treatment) in analyses that relate in vitro test results to a binary clinical response (complete or partial response versus minimal or no response). These latter analyses also permit a quantification of the strength of association. Specifically, the odds for a complete or partial clinical response (probability of response divided by 1 minus probability of response) were estimated as a function of in vitro test results and time from diagnosis to treatment.

RESULTS

Test 1

In all cases tested, there was no detectable BFU-E growth from patient cells incubated with media only. However, BFU-E were detected in PBMC from 10 patients after cells were treated with C' only. The numbers of BFU-E ranged from 1 to 9 BFU-E/10^5 cells plated. After treatment with MoAb and C', BFU-E growth was detected in 10 of the 47 patients tested. The numbers of BFU-E obtained ranged from 2 to 19/10^5 cells plated. In the 10 cases that showed BFU-E growth after incubation with C' alone, there was an additional increase in the number of BFU-E after MoAB + C', although this increase was not necessarily statistically significant. Table 2 lists the 19 patients who were positive in test 1 and shows which MoAb treatments increased BFU-E growth. No clear pattern emerged to suggest that one MoAb was more useful than another for detecting BFU-E. In seven cases, BFU-E growth occurred after treatment with either MoAb 9.6 or 35.1, both of which will cause lysis of E-rosette-positive cells. Treatment with 10.2 plus C' detected growth in nine patients, only four of whom showed a response to 9.6 or 35.1. BFU-E growth was detected in ten cases after treatment with MoAb 7.28, and nine of these showed a response to one of the other MoAb. Incubation with MoAb 20.3, which reacts with monocytes, increased BFU-E growth in six patients, and five of these showed a similar response to other MoAb tested.

Incubation of cells with 7.2 and C' was designed to test the effect of eliminating La-positive, activated T cells. However, since the La molecule is also expressed on BFU-E, it is necessary to combine the 7.2-treated cells with another cell population containing BFU-E but not T cells. This was achieved by coculturing equal volumes of 7.2-treated and 10.2-treated cells. Following this procedure, BFU-E were detected in five patients, four of whom also showed growth in response to other MoAb treatment.

Test 2

Test 2 was designed to determine whether BFU-E could be grown from patient PBMC after the patient had received ATG. In this test, Ficoll-Hypaque-separated PBMC were washed and then immediately cultured for BFU-E growth without any further treatment. This approach was based on the assumption that lymphocytes had already been depleted in vivo. Samples from 41 patients were collected and studied, and in 16 cases, BFU-E growth was detected. Growth in test 2 ranged from 1 to 32 BFU-E/10^5 cells plated.

Statistical Analyses

The correlation between in vitro response (+ or −) and clinical response (1–4) was first analyzed by uncorrected chi-square tests, with the significance levels corresponding to the hypothesis that the clinical response rates are independent of the in vitro test
Table 3. Aplastic Anemia Patients’ Responses to Therapy in Relation to In Vitro Test Results: Tests 1 and 2 Analyzed Separately*

<table>
<thead>
<tr>
<th>Clinical Response</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>In vitro test 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>–</td>
<td>2</td>
<td>5</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>( \chi_1^2 = 3.71, p = 0.29 )</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In vitro test 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>8</td>
<td>4</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>–</td>
<td>0</td>
<td>5</td>
<td>4</td>
<td>16</td>
</tr>
</tbody>
</table>
| \( \chi_1^2 = 17.68, p = 0.0005 \)

*Data indicate the number of patients with positive (+) or negative (–) in vitro test scores for each grade of clinical response (1, complete response; 2, partial response; 3, minimal response; and 4, no response).

Table 4. Aplastic Anemia Patients’ Response to Therapy in Relation to Combined In Vitro Tests 1 and 2*

<table>
<thead>
<tr>
<th>Clinical Response</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A) In vitro test score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>9</td>
<td>6</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>–</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>16</td>
</tr>
</tbody>
</table>
| \( \chi_1^2 = 9.92, p = 0.02 \)
| (B) In vitro test score |   |   |   |   |
| +                 | 5 | 2 | 0 | 2 |
| –                 | 2 | 4 | 2 | 2 |
| –                 | 0 | 3 | 3 | 14 |
| \( \chi_1^2 = 19.21, p = 0.004 \)

* A combines tests 1 and 2 such that ‘+’ indicates a positive score in either test, and ‘–’ indicates a negative score in both tests. B considers both test scores in combination.

The relationship between clinical response and test 1 has significance level \( p = 0.04 \). Note also that the odds for clinical response are estimated to decline by a factor of 0.56 \( p = 0.02 \) for each additional month postdiagnosis, up to 6 mo.

The second column of Table 5 shows a strong association between test 2 and clinical response \( p = 0.003 \) after adjusting for time from diagnosis to treatment. In fact, patients who are positive on test 2 have odds for clinical response that are estimated to be 10.19 times that for patients with negative test 2 results. After accommodating the test 2 result, the clinical response rate is still estimated to decline with increasing months from diagnosis to treatment, but this association is no longer significant \( p = 0.16 \).

The remainder of Table 5 divides patients according to whether the time from diagnosis to treatment exceeded 1 mo. This analysis showed a very strong association between test 2 and clinical response among patients diagnosed more than 1 mo prior to treatment.
Many investigators have studied colony-forming units from patients with severe AA. For the most part, they agree that, in AA patients, these precursor cells are significantly reduced in number and that in some cases, optimal growth of patient colonies can be limited by patient lymphocytes.\(^1\)\(^{6,11\,}\)\(^{14,15,31,32}\) This latter observation has been interpreted in many instances to indicate an immune mechanism for aplasia. "Immune mechanism" is usually taken to mean that patient lymphocytes are reacting against patient stem cells. The fact that some patients recover autologous marrow function after ATG therapy would seem to support this concept. However, there is increasing evidence that lymphocytes and monocytes play a role in regulating normal hematopoiesis. If this proves true, the potential role of lymphocytes in mediating AA extends beyond the classical one of "autoreactivity" to include the possibility of defective regulation.

Recently, hybridoma technology has led to the development of MoAb that can be used to identify and separate lymphohematopoietic cells. With these tools, it has been possible to show that two functionally distinct populations of T cells modulate in vitro erythropoiesis: one functions to stimulate growth and the other functions to limit this stimulation.\(^24\)\(^\,\)\(^33\) The possible role that an abnormality in this type of regulation might play in mediating aplasia is purely speculative. Nevertheless, insights gained through the use of monoclonal probes prompted the application of MoAb to the study of aplasia.

Fifty-four consecutive AA patients were entered into this study, of whom 49 are available for analysis. Two in vitro tests were done on these patients. In test 1, patient PBMC were collected before ATG treatment and treated with various MoAB and C'. This test was designed to determine whether C'-mediated lysis of various mononuclear cell subpopulations would cause increased growth of immature erythroid progenitors (BFU-E). In PBMC from 28 of the 47 patients studied, there was no evidence of BFU-E growth after cells were treated with any of the MoAb and C'. This absence of growth can be explained in several ways: first, the number of BFU-E could be reduced below a detectable range; second, BFU-E could be present, but abnormal, and therefore not capable of growing in vitro; and third, BFU-E could be present and normal, but "auxiliary" cells needed to elaborate growth factors are absent or abnormal. This last possibility is of particular interest, as exogenous burst-promoting factors were not added to the cultures.

In PBMC from 19 of 47 patients tested, some BFU-E did grow after cells were treated with antibodies and C'. In ten samples, BFU-E grew after treatment with C' only. Increased growth of patient BFU-E after treatment with antibody and/or C' can also be explained in several ways. Increased BFU-E growth could have resulted from foreign protein (mouse ascites and rabbit serum) stimulating the in situ pro-

### Table 5. Binary Logistic Regression Analysis of Clinical Response* in Relation to In Vitro Test Results and Time from Diagnosis to Treatment

<table>
<thead>
<tr>
<th>Factor</th>
<th>Analysis 1 (All Patients)</th>
<th>Analysis 2 (Patients With Diagnosis to Treatment &lt; 1 mo)</th>
<th>Analysis 3 (Patients With Diagnosis to Treatment &lt; 1 mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test 1 (-, +)</td>
<td>4.55† (0.04)</td>
<td>2.02 (0.33)</td>
<td>—§</td>
</tr>
<tr>
<td>Test 2 (-, +)</td>
<td>10.19 (0.003)</td>
<td>37.49 (0.001)</td>
<td>1.67 (0.68)</td>
</tr>
<tr>
<td>Months from diagnosis to treatment (truncated at 6 mo)</td>
<td>0.56 (0.02)</td>
<td>0.71 (0.16)</td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>47</td>
<td>41</td>
<td>29</td>
</tr>
</tbody>
</table>

*The binary response in these analyses is clinical response 1 and 2 versus clinical response 3 and 4.
†Each column represents a distinct analysis. For example, the first column involves all 47 patients with available test 1 results.
‡The table gives odds ratio estimates for clinical response in relation to each factor included in the analysis. Significance levels for the hypothesis of no association between clinical response and the factors are given in parentheses.
§Odds ratio estimate does not exist, as all patients with a positive test 1 response had a 1 or 2 clinical response. The corresponding significance level is based on Fisher's exact test.
duction of burst-promoting activity. This is unlikely, however, since C' treatment is carried out at room temperature and cells are washed thoroughly before they are cultured for BFU-E growth. The more appealing explanation is that C' lysis, whether specific or nonspecific, removed cells that were limiting BFU-E growth. The "inhibition" of BFU-E growth could have been affected either directly or indirectly via inhibition of "auxiliary" cell function.

It is obvious that, for any individual patient, an increase from no BFU-E growth in the media-treated control group to some small number of BFU-E in the MoAb + C'-treated group may not be a biologically meaningful event. Such an event, however, may be important if it correlates with the patient's positive response to therapy. Binary logistic regression analyses indicated that the in vitro observation of increased BFU-E growth after treatment with MoAb and C' (test 1) appeared to correlate with the patients' response to ATG therapy ($p = 0.04$). This association decreased, however, as disease duration increased. Rather different results were obtained for test 2. In this study, patient PBMC were collected within 48 hr of the completion of ATG therapy. Cells were cultured for BFU-E growth without further treatment. A positive response to test 2 had, overall, a very significant correlation with clinical response, except for a small group of patients tested and treated within 1 mo of diagnosis.

It appears from these data that test 1 and test 2 are detecting different phenomena. BFU-E growth after MoAb + C' treatment (test 1) may reflect an "immune" disease mechanism, and the correlation with clinical response decreases as disease duration increases because the patient's ability to respond also decreases with time postdiagnosis. This could explain the large numbers of false positive in vitro scores obtained with test 1. Test 2 may be detecting the actual response to ATG, which would explain the significant correlation with clinical response. This, however, is an important observation, as in the majority of patients, test 2 scores were obtained 4–6 wk before there was any indication of recovery in the peripheral blood. The failure of test 2 to accurately predict response in patients less than 1 mo postdiagnosis might be due to the fact that patients early postdiagnosis, regardless of the etiology of their disease, may have more circulating BFU-E than patients with longer disease history. In such cases, BFU-E growth would be detected after ATG therapy not necessarily because the patient is responding, but because the therapy decreases the absolute number of lymphocytes and thereby increases the concentration of BFU-E in PBMC up to detectable levels.

One purpose of this research was to develop an in vitro test that would identify patients likely to respond to ATG therapy, preferably a test that would be done prior to treatment. Although statistical analysis has shown that test 1 has some predictive value, it is not sufficiently accurate to warrant a decision for or against ATG therapy. It is possible that the predictability of this test can be improved if more patients are studied and treated within 1 mo of diagnosis. For this reason, test 1 is being continued and the panel of antibodies extended to include specificities against activated and suppressor T cells. Test 2, however, has a very significant correlation with clinical response and may prove useful for identifying those patients who are unlikely to respond and should therefore be considered for additional therapy without waiting 3 mo for a clinical response.

The second purpose of this study was to gain some understanding of the mechanisms of AA. In this regard, the combined data do suggest that some cases of AA may be "immune-mediated." This is not to say, however, that lymphocytes are attacking progenitor cells, but only that lymphocytes are adversely affecting hematopoiesis. The exact nature of this effect is currently unknown. At this time, the real value of the correlation between in vitro and in vivo observations is that it suggests that some of the manipulations done in vitro to modulate growth may actually have physiologic relevance.

ACKNOWLEDGMENT

The authors thank Drs. John A. Hansen and Paul J. Martin for providing monoclonal antibodies, and Dr. Rainer Storb for his contribution of various resources, including thoughtful criticism. The authors also thank Lisa Eldred for her help in preparing the manuscript.

REFERENCES

IN VITRO STUDIES OF APLASTIC ANEMIA

Presence in human bone marrow of cells that suppress myelopoiesis. Proc Natl Acad Sci USA 73:2890, 1976


Correlation of two in vitro tests with clinical response to immunosuppressive therapy in 54 patients with severe aplastic anemia

B Torok-Storb, K Doney, SL Brown and RL Prentice