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# BLOOD

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# The Interleukin-2 Receptor: A Target for Monoclonal Antibody Treatment of Human T-Cell Lymphotrophic Virus I–Induced Adult T-Cell Leukemia

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**Adult T-cell leukemia (ATL) is a malignancy of mature lymphocytes caused by the retrovirus human T-cell lymphotrophic virus-I (HTLV-I). It is an aggressive leukemia with an overall mortality rate of 50% within 5 months; no conventional chemotherapy regimen appears successful in inducing long-term disease-free survival in ATL patients. However, ATL cells constitutively express high-affinity interleukin-2 receptors (IL-2Rs) identified by the anti-Tac monoclonal antibody, whereas normal resting cells do not. To exploit this difference in receptor expression, we administered anti-Tac intravenously (IV) to 19 patients with ATL. In general the patients did not suffer untoward reactions, and in 18 of 19 cases did not have a reduction in normal formed elements of the blood. Seven patients developed remissions that were mixed (1 patient), partial (4 patients), or complete (2 patients), with partial and complete remissions lasting from 9 weeks to more than 3 years as assessed by routine hematologic tests, immunofluorescence analysis, and molecular genetic analysis of T-cell receptor gene rearrangements and of HTLV-I proviral integration. Furthermore, remission was associated with a return to normal serum calcium levels and an improvement of liver function tests. Remission was also associated in some cases with an amelioration of the profound immunodeficiency state that characterizes ATL. Thus the use of a monoclonal antibody that blocks the interaction of IL-2 with its receptor expressed on ATL cells provides a rational approach for treatment of this aggressive malignancy.**


THE HYBRIDOMA TECHNIQUE of Köhler and Milstein[1] rekindled interest in the use of antibodies targeted to cell surface antigens to treat cancer patients. Immune-receptor–directed therapy has been applied clinically to an array of human disorders. However, effective therapy using unmodified murine monoclonal antibodies has been elusive because these antibodies are not cytocidal against human cells and in most cases are not directed against a vital cell surface structure required for tumor cell proliferation and survival.[2] We readdressed this issue using the interleukin-2 receptor (IL-2R) as the target for immune intervention. The scientific basis for this approach using the IL-2R as a target for immunotherapy is that resting normal cells do not express the high-affinity IL-2R, whereas this receptor is expressed by a proportion of the abnormal cells in certain forms of lymphoid neoplasia, select autoimmune disorders, and in individuals rejecting allografts.[3-7] The IL-2R consists of at least three IL-2–binding peptide chains, as follows: IL-2R$\alpha$, a 55-Kd peptide identified by the monoclonal antibody anti-Tac[8,9]; IL-2R$\beta$, a 75-Kd subunit[10,11]; and the recently discovered IL-2R$\gamma$, a 64-Kd protein.[12] Identification and characterization of the IL-2R$\alpha$ subunit was facilitated by our development of a monoclonal antibody, anti-Tac, that binds to IL-2R$\alpha$ and prevents the interaction of IL-2 with this subunit.[8] Resting T cells, B cells, and monocytes in the circulation do not display IL-2R$\alpha$. In contrast to this lack of IL-2R$\alpha$ expression in normal resting mononuclear cells, this receptor subunit is expressed by a proportion of the abnormal cells in certain forms of neoplasia including certain T-cell, B-cell, monocytic, and even granulocytic leukemias. Furthermore, the serum concentration of the soluble form of IL-2R$\alpha$ released by the abnormal cells is increased in patients with these disorders.[13] Specifically, a proportion of the leukemic cells of patients with chronic or acute myelogenous leukemia express IL-2R$\alpha$ identified by the anti-Tac monoclonal antibody.[14] Furthermore, malignant B cells of virtually all patients with hairy cell leukemia and a proportion of patients with large- and mixed-cell diffuse lymphomas express IL-2R$\alpha$.[15] The IL-2R$\alpha$ is also expressed on Reed-Sternberg cells of patients with Hodgkin's disease and on malignant cells of patients with true histiocytic lymphoma.[16] Similarly, a proportion of patients with cutaneous T-cell lymphomas express the Tac peptide on their malignant cells. Finally, virtually all patients with human T-cell lymphotrophic virus-I (HTLV-I)–associated adult T-cell leukemia (ATL) constitutively express very large numbers of IL-2R$\alpha$.[17-19]

These results suggested that anti–IL-2R antibodies might be effective agents for the treatment of certain neoplastic diseases. We have focused our therapeutic studies of malignancy on the disordered IL-2R expression of a distinct form of T-cell leukemia, ATL.[19] ATL is an aggressive malignancy of lymphocytes displaying a multilobulated nucleus with dense chromatin and expressing a $CD3^+$, $CD4^+$, $CD8^-$, $CD7^-$, and $CD25^+$ (IL-2R$\alpha$, $Tac^+$) phenotype.[17,18] The disease exhibits a striking clustering of cases in certain geographic regions, notably southwestern Japan, the Caribbean basin, northeastern South America, Central America, sub-Saharan Africa, and to a lesser extent the southeastern United States. The retrovirus HTLV-I is clearly associated with this disease and appears to play a major role in its pathogenesis.[20] Patients with ATL have serum antibodies to HTLV-I and the monoclonal integration of this retrovirus in their circulating malignant cells. Frank ATL generally has its onset in adulthood, 20 to 30 years following initial

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infection with HTLV-I. Principal clinical features include moderate lymphadenopathy, hepatosplenomegaly, and skin, central nervous system, and pulmonary involvement[21,22]; the occurrence of hypercalcemia is characteristic of ATL. Patients with acute ATL manifest a striking degree of immunosuppression and develop opportunistic infections such as *Pneumocystis* pneumonia and cryptococcal meningitis. The experiences of several clinical oncology groups using combination chemotherapy regimens in patients with this disease have been disappointing. In most chemotherapy series, overall mortality is approximately 50% within 5 months. No conventional treatment program appears successful in inducing long-term disease-free survival in ATL patients.

In our clinical trial, we wished to exploit the observation that the normal resting cells of patients with ATL do not display IL-2R$\alpha$, whereas the malignant T cells display 10,000 to 35,000 IL-2R$\alpha$/cell that are identified by the anti-Tac monoclonal antibody.[17,18] Thus IL-2R–directed immunotherapy using anti-Tac could theoretically eliminate IL-2R$\alpha$–expressing leukemic cells while retaining the Tac-nonexpressing normal T cells and their precursors that express the antigen receptors required for normal T-cell–mediated immune responses. In our preliminary studies, we observed that anti-Tac induced a remission in some patients with ATL without associated toxicity.[19] In the present study, the 19 patients with ATL treated with anti-Tac had few untoward reactions related to the immunotherapy and in general did not have a reduction in normal formed elements of the blood. Seven of 19 treated patients had a transient mixed (1), partial (4), or complete (2) remission, with partial and complete remissions lasting from 2 to more than 36 months.

## MATERIALS AND METHODS

*Patient population.* Nineteen patients with histologically confirmed HTLV-I–associated ATL were studied (Table 1). Each of the patients manifested the following features: (1) a histologically confirmed diagnosis of leukemia or lymphoma of mature T cells with polymorphic indented or lobulated nuclei; (2) intense expression of the Tac antigen (IL-2R$\alpha$) on at least 10% of the patient's peripheral blood, lymph node, or dermal T cells; (3) antibodies to HTLV-I demonstrable in the serum; and (4) omission of cytotoxic chemotherapy and radiation therapy for at least 3 weeks before entry into the trial. Patients with or without previous chemotherapy were eligible for inclusion in this study; 10 patients had failed to respond to prior therapy. Patients with symptomatic central nervous system disease were excluded; however, patients with malignant cells demonstrable in the cerebrospinal fluid were included and received intrathecal methotrexate. The patients ranged in age from 24 to 62 years (mean, 41 years); demographic factors in the patient group are shown in Table 1. Ten patients were male and nine female, 17 were black, one was Hispanic, and one was of Japanese origin, and 10 were from the United States, four were from Jamaica, and one each was from Japan, Cuba, Trinidad, Haiti, and Guyana. Using the criteria of Kawano et al[23] and Yamaguchi et al,[24] 11 patients with ATL were in the acute or crisis stage, four manifested ATL lymphoma, and four had chronic ATL.

*Therapeutic study plan.* Anti-Tac was administered intravenously (IV) over a 2-hour period in 100 mL normal saline containing 5% albumin. In the basic study plan for the initial nine patients, 20 mg anti-Tac was administered IV on two occasions during the first week of therapy, followed by 40 mg on two occasions during the second week. For the subsequent 10 patients, to achieve rapid saturation of the IL-2R, the basic plan involved IV administration of 50 mg anti-Tac on two occasions for each of the first 2 weeks of therapy. Dosing schedules were modified slightly in some patients, and additional 20- or 50-mg doses were administered during subsequent weeks to maintain the saturation of the IL-2R with the anti-Tac monoclonal antibody. Furthermore, in such cases sufficient anti-Tac was administered to yield measurable levels of circulating antibody in the serum of the patient. As noted above, patients with malignant cells in the central nervous system received intrathecal methotrexate.

The criteria for response were as follows: (1) complete response, disappearance of all measurable and assessable disease lasting more than 1 month; (2) partial response, a 50% reduction of leukemic cell count and a 50% reduction in the size of measurable lesions and no increase in the size of any measurable or assessable lesion or appearance of a new lesion for 1 month; (3) mixed response, identical to partial response with the exception that there is the appearance of a new lesion within 1 month in a tissue other than that involved initially; (4) stable disease, less than partial response with no new lesions or less than a 25% increase in any measurable lesion; (5) progressive disease, at least 25% increase in leukemic cell count or an increase of 25% or greater in any measurable lesion. A systems-oriented microcomputer-based patient data management system was devised and implemented in which historical, clinical, and laboratory data were stored and manipulated for analysis (R.P.J. and T.A.W.).

Approval was obtained from the institutional review board for these studies. Informed consent was provided according to the Declaration of Helsinki.

*Production of anti-Tac monoclonal antibodies.* The anti-Tac monoclonal antibody was produced as described previously[19] by fusion of NS-1 mouse myeloma cells with spleen cells of mice that had been immunized with a cell line derived from an ATL patient. The antibody does not function in complement-dependent cytotoxicity with human plasma nor does it induce antibody-dependent cellular cytotoxicity (ADCC) with human mononuclear cells. However, anti-Tac blocks the interaction of IL-2 with the high-affinity receptors for this lymphokine. Large quantities of the monoclonal antibody were produced by inoculating hybridoma cells into the peritoneal cavity of BALB/c mice and then purifying the mouse IgG2a anti-Tac from the resulting ascites fluid by diethylaminoethyl cellulose chromatography. The purified antibody was dialyzed against saline, centrifuged, filtered, precipitated with 20% sodium sulfate, and finally diluted in saline at pH 7.4 to a concentration of 2 mg/mL. Each lot of the product was assayed by immunoelectrophoresis in agar plates using antisera to IgG2a, $IgG_1$, and IgM, as well as polyvalent antibodies to most mouse proteins. Lots greater than 98% pure as assessed by these analyses and by high-performance liquid chromatography and sodium dodecyl sulfate–polyacrylamide gel electrophoresis were used. The monoclonal antibody preparation was sterilized by passage through a 0.22-$\mu$m membrane filter (Millipore, Marlborough, MA) by the Pharmaceutical Development Section of the Clinical Center of the National Institutes of Health (NIH) and was shown to be nonpyrogenic and sterile by the Bureau of Biologics.

*Immunofluorescence analysis of cell surface phenotype.* The phenotype of the leukemic cell population was defined by indirect and direct immunofluorescence performed with mouse monoclonal antibodies using a fluorescence-activated cell-sorter as described previously.[19] Two antibodies (anti-Tac and 7G7/B6) that are directed toward different epitopes of IL-2R$\alpha$ were used to define the expression of this receptor subunit. Other monoclonal antibodies used include antibodies reacting with HLA-DR (Ia-1; Ortho,

**Table 1. Demographic and Clinical Features of ATL Patients**

| Patient No. | Type of ATL | Age/Sex/Race | sIL-2R (U/mL) | WBC/μL | Circulating IL-2R/Tac-Expressing Lymphocytes/μL | Antibodies to HTLV-I | Serum Ca | Abnormal Liver Function Tests |
|---|---|---|---|---|---|---|---|---|
| 1 | Acute | 39/F/B | 147,130 | 42,600 | 11,200 | + | 3.50 | + |
| 2 | Chronic | 28/M/B | 2,240 | 3,800 | 2,120 | + | 3.75 | + |
| 3 | Lymphoma | 25/M/B | 4,660 | 1,500 | <100 | + | 2.15 | + |
| 4 | Acute | 32/F/B | 2,200 | 20,700 | 12,930 | + | 2.35 | − |
| 5 | Acute | 62/M/B | 230,370 | 41,500 | 24,200 | + | 8.10 | + |
| 6 | Acute | 44/M/B | 87,710 | 12,700 | 1,600 | + | 4.35 | + |
| 7 | Acute | 41/M/B | 56,420 | 75,400 | 37,720 | + | 4.60 | + |
| 8 | Lymphoma | 57/F/A | 920 | 5,500 | 230 | + | 2.30 | − |
| 9 | Acute | 42/M/H | 60,170 | 102,800 | 50,600 | + | 4.40 | + |
| 10 | Acute | 58/F/B | 8,060 | 15,400 | 1,900 | + | 4.10 | − |
| 11 | Chronic | 40/M/B | 31,700 | 21,300 | 13,500 | + | 2.65 | + |
| 12 | Chronic | 55/M/B | 2,040 | 9,100 | 3,000 | + | 2.40 | − |
| 13 | Lymphoma | 53/M/B | 89,830 | 7,900 | 1,800 | + | 2.20 | − |
| 14 | Acute | 24/F/B | 31,580 | 32,100 | 12,700 | + | 3.90 | + |
| 15 | Acute | 42/F/B | 48,460 | 26,500 | 8,010 | + | 2.80 | − |
| 16 | Lymphoma | 34/M/B | 9,910 | 7,100 | <100 | + | 2.45 | + |
| 17 | Chronic | 41/F/B | 2,210 | 13,200 | 4,710 | + | 2.20 | − |
| 18 | Acute | 26/F/B | 158,130 | 177,000 | 152,900 | + | 3.80 | + |
| 19 | Acute | 60/F/B | 138,680 | 21,600 | 4,600 | + | 3.60 | + |

Abbreviations: B, black; H, Hispanic; A, Asian.

Raritan, NJ); human T-cell–associated antigens (CD2, CD3, CD4, CD5, and CD8; Ortho and Becton-Dickinson, Mountain View, CA); CD7 (3A1; a gift from Dr Barton Haynes); and CD45 and CD29 (Coulter Immunology, Hialeah, FL). The fluorescein isothiocyanate (FITC) antimouse IgG reagent was obtained from Coulter Immunology. Histograms for each cell type were integrated to determine the percentage of mononuclear cells that reacted with individual monoclonal antibodies. The absolute number of cells in the circulation per cubic millimeter expressing a particular antigen was determined from the product of (1) circulating white blood cell (WBC) count per cubic millimeter, (2) the proportion of these circulating WBCs that were mononuclear cells as determined by routine hematologic analysis, and (3) the proportion of these mononuclear cells that expressed the antigen under study as assessed by immunocytofluorography.

*Molecular genetic analysis of Tcr gene rearrangement and HTLV-I integration.* Analysis for clonal Tcr gene rearrangements and for HTLV-I integration were performed as described previously.[25,26] High–molecular-weight DNA was extracted from frozen cell suspensions containing approximately $10^8$ cells. DNA samples were digested with the restriction enzymes *Bam*HI, *Eco*RI, *Hin*dIII, or *Pst*I (International Biotechnologies, New Haven, CT, and New England Biolabs, Beverly, MA) and were size-fractionated on 0.5% to 0.9% agarose gels. They were transferred by the Southern blot technique to reinforced nitrocellulose paper (Schleicher and Schull, Keene, NH). Hybridization to randomly primed $^{32}$P-labeled DNA probes of the constant regions of the Tcr $\beta$ gene and the HTLV-I gene were performed, followed by washing at appropriate stringency and radioautography. Nonlymphoid control DNA was analyzed simultaneously to identify germline positions of the Tcr genes examined. The Tcr $\beta$ gene probe used was a 700-bp *Eco*RI fragment containing the mouse or human C$\beta$ region that recognizes both human C$\beta$ regions. The HTLV-I probe used was the 9-kb *Sac*I fragment containing the entire viral genome with the exception of the long terminal repeats (a gift from Dr Flossie Wong-Staal).

*Assay for antibodies to HTLV-I.* The sera of ATL patients were analyzed for antibodies to disrupted and inactivated HTLV-I using an enzyme-linked immunosorbent assay ([ELISA] Cellular Products, Buffalo, NY).

*Assay for mouse Ig.* Murine IgG2a anti-Tac levels in the sera of patients were assayed with an ELISA technique using affinity-purified goat antimouse immunoglobulin absorbed onto polyvinyl plates at 100 ng/well and washed.[19] Bound murine anti-Tac was detected with a goat antimouse immunoglobulin conjugated with alkaline phosphatase (Sigma, St Louis, MO) and compared with a standard curve of anti-Tac antibody.

*Assay for human antimouse anti-Tac antibody.* The serum used in all assays was separated from peripheral blood and stored at −20°C until used. For detection of human antimouse antibodies (HAMA), the technique described by Schroff et al[27] was used, with the exception that anti-Tac was used in lieu of the T101 antibody. Serum antiglobulin levels for a given patient were considered meaningfully increased when the antiglobulin level after therapy was greater than twice that in the sample obtained before administration of the mouse monoclonal antibody.

## RESULTS

*Patient characteristics.* Nineteen patients with histologically confirmed HTLV-I–associated ATL were treated with IV administered anti-Tac (Table 1). Four patients had lymphoma-type ATL without circulating malignant cells; the peripheral blood WBC count in the remaining 15 patients before therapy ranged from 3,800 to 177,000/μL (geometric mean, 26,000). Patients with ATL had pretherapy serum soluble IL-2R (sIL-2R$\alpha$) levels of 920 to 230,370 U/mL (mean, 55,744), whereas the upper limit of the normal is 502 U/mL (mean, 238).[28] T-Cell leukemic populations were confirmed to be monoclonal by molecular genetic analysis of the rearrangement of genes encoding the Tcr $\beta$ chain. Southern blot analysis of the Tcr $\beta$ receptor gene rearrangement using a radiolabeled probe that hybridizes with the constant region of the Tcr $\beta$ chain showed a band that was not present in germline tissues, a hallmark of a clonally expanded population of T lymphocytes (Fig 1). Furthermore, Southern blot analysis of HTLV-I proviral integra-

tion in *Pst* I and *Eco*RI digests of DNA obtained from the patients defined the clonal integration of HTLV-I proviruses. Clinically, nine patients manifested involvement of the skin. Twelve were hypercalcemic, with a serum calcium level in these cases ranging from 2.65 to 8.1 mmol/L (normal range, 2.05 to 2.5 mmol/L). Mild to moderate liver function abnormalities were demonstrable in 12 of 19 cases.

Using flow cytometric phenotypic analyses of circulating mononuclear cells, we demonstrated that in 13 of 15 cases with leukemia, the predominant mononuclear cell population expressed the $CD3^+$, $CD4^+/CD8^-$, $CD25^+$ phenotype; phenotypes in the two remaining cases were $CD3^+$, $CD4^-/CD8^-$, $CD25^+$ and $CD3^-$, $CD4^+/CD8^-$, $CD25^+$. Circulating mononuclear cells of the patients showed intense expression of the Tac antigen on a relatively homogeneous cell population manifesting high fluorescence intensity (Fig 2). It appears that all of the circulating malignant cells expressed the Tac antigen. Although a small proportion of normal peripheral blood mononuclear cells manifest low-level Tac expression, the pattern observed within the leukemic population is quite distinct from that observed in normal individuals in terms of the homogeneity and intensity of Tac antigen expression (Fig 2). In the 15 leukemic cases, the abnormal cell population did not react with a CD7 (3A1) monoclonal antibody, which reacts with normal T-cell precursors and with at least 70% of normal mature $T_3$ lymphocytes.

*Response of ATL patients to treatment with anti-Tac monoclonal antibodies.* The initial basic protocol for anti-Tac therapy involved the administration of 20 mg anti-Tac on two occasions during the first week and 40 mg anti-Tac on two occasions during the second week of therapy for each patient (Table 2). After the second week of therapy, additional doses of 20 or 50 mg anti-Tac were administered to patients who had made an initial clinical response to anti-Tac therapy. It was noted that from 40 to 100 mg anti-Tac had to be administered to the patients to saturate the IL-2R$\alpha$ expressed by tumor cells. The IL-2Rs on leukemic cells were deemed to be saturated by the infused monoclonal antibody when the cells manifested the following three features: (1) reaction with FITC antimouse IgG; (2) reaction with FITC-labeled 7G7/B6 (an antibody that reacts with IL-2R$\alpha$ but does not cross-block with anti-Tac); and (3) no binding in direct immunofluorescence analysis with FITC-labeled anti-Tac, since the target antigen was blocked by in

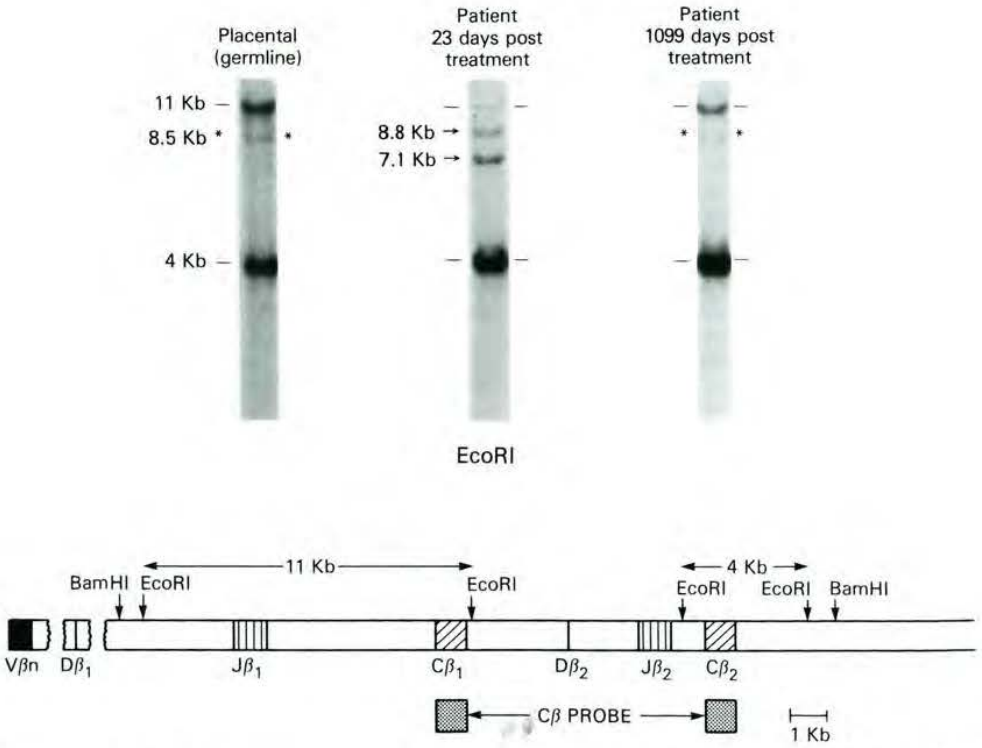


**Fig 1. Analysis of Tcr $\beta$ gene rearrangements to monitor anti-Tac monoclonal antibody treatment in patient no. 5 with ATL using a Tcr $\beta$ constant region probe (C$\beta$). The Tcr $\beta$ constant region genes are on four and 11-Kb *Eco*RI fragments in placental (germline) DNA as indicated (---). The 11-Kb band contains C$\beta$1, whereas C$\beta$2 is present in the 4-Kb band. *An artifactual band at 8.5 Kb that is a result of an incomplete digestion at a site 5′ of the C$\beta$2 locus. Digests of patient peripheral blood DNA during an active phase of the disease 23 days after initiation of therapy yielded a diminished 11-Kb band as well as two nongermline bands (→ that reflect a monoclonal Tcr $\beta$ pattern of gene rearrangement. This pattern indicates that both alleles for Tcr $\beta$ in the leukemic clone rearranged into C$\beta$1. Patient DNA obtained in remission 1,099 days following initiation of therapy did not express the two nongermline bands, thus confirming elimination of the circulating monoclonal population. In the schematic diagram of the germline arrangement of the Tcr $\beta$ chain gene, we indicate the locations of the *Bam*HI and *Eco*RI restriction endonuclease sites as well as the C$\beta$ regions recognized by the cDNA probe.**

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