Targeting Human IL-2 Receptors for Diagnosis and Therapy (43765)

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Abstract. **The high-affinity interleukin-2 receptor (IL-2R) is a multichain receptor with at least three IL-2 binding chains: IL-2Rα (55 kDa) bound by the monoclonal antibody anti-Tac, IL-2Rβ (75 kDa) and IL-2Rγ (64 kDa). The IL-2Rα also exists as a naturally occurring soluble molecule (sIL-2Rα). We target the IL-2R for immune intervention since resting normal cells do not express the high-affinity IL-2R, whereas this receptor is on some cells in certain lymphoid neoplasias, select autoimmune disorders, and in individuals rejecting organ allografts. Treatments have included unmodified murine anti-Tac and radioisotopes conjugated to murine anti-Tac. Our emerging understanding of the IL-2R system continues to open possibilities for more specific immune intervention.** [P.S.E.B.M. 1994, Vol 206]

Recent advances in the understanding of the human immune response over the past 20 years have moved our knowledge from the first morphologic definition of distinct lineages of lymphocytes to the current time, when the molecular cloning of the genes involved in the immune response has become commonplace. In part, these advances have been the result of the development of hybridoma-derived monoclonal antibody techniques. The development of monoclonal antibody technology by Kohler and Milstein (1) revolutionized the practice of medicine and led to the use of monoclonal antibodies for radioimmunoassays, enzyme-linked immunosorbent assays, immunocytopathology, and flow cytometric analyses for *in vitro* diagnosis and *in vivo* for the diagnosis and therapy of human disease. In the treatment of human disease, monoclonal antibodies have been used *in vivo* for the treatment of cancer and for the modulation of the immune response in autoimmune disorders, for suppression of the immune response in allograft rejection episodes and in situations where a foreign allograft attacks an immunocompromised host, the so-called graft versus host disease or GVHD (2). Dr. Thomas A. Waldmann's laboratory and my own have been collaborating in conducting studies using monoclonal antibodies directed against the human receptor for interleukin-2 (IL-2) for both diagnosis and therapy.

The transition from resting to activated lymphocytes which follows the engagement of specific cell surface receptors on T cells and B cells by exogenous antigen is associated with the synthesis and secretion of a variety of polypeptide hormones (lymphokines) of low molecular weight including IL-2. These hormones stimulate the growth and differentiation of cells through interaction with specific, high-affinity cell surface receptors for these lymphokines.

Recent evidence has shown that these cellular interleukin-2 receptors (IL-2R) are composed of at least three chains p55 (α), p75 (β), and p64 (γ) (5–8). These molecules are involved in binding IL-2 with high (p55, p75, and p64 combined), intermediate (p75 and p64), or low (p55 alone) affinity (3–6). Other molecules including CD54 (ICAM-1) and HLA Class I antigens have also been associated with the human IL-2R (7–9). The IL-2Rα or Tac protein is not expressed on normal resting lymphocytes but is rapidly synthesized and expressed on the cell surface of activated T cells, B cells, and monocytes.

The IL-2Rα (Tac protein) chain is recognized by the murine monoclonal antibody anti-Tac (10) and the IL-2Rβ chain by the murine monoclonal antibody Mikβ1 (11). The murine anti-Tac, an IgG_{2b} of κ light chain type does not fix human complement and will not mediate antibody-dependent cellular cytotoxicity.

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However, the monoclonal anti-Tac does inhibit binding of IL-2 to the Tac protein. The murine monoclonal antibody 7G7/B6 binds to the IL-2Rα at a different site than anti-Tac (12). In addition to being expressed on cell surfaces, the IL-2Rα was the first cytokine receptor to be identified in a naturally occurring soluble form *in vitro* and *in vivo* (13). This observation suggested that measurement of soluble IL-2Rα might be useful in monitoring immunologic activation occurring in disease states such as cancer, infectious diseases, autoimmune disorders, and allograft rejection episodes (14, 15). The enzyme linked immunoassay for soluble IL-2Rα is commercially available. Soluble IL-2Rα has been studied in more than 17 neoplastic diseases, 10 "autoimmune" disorders, five organ allograft conditions, 10 infectious diseases, four renal disorders, and five neurologic conditions. In terms of neoplasia, certain T cell, B cell, monocytic, and even granulocytic leukemias express the Tac antigen on their surface (15). Specifically, virtually all of the malignant cells of patients with the human T cell leukemia virus Type 1 (HTLV-1) associated adult T cell leukemia express the Tac antigen.

This distinct form of T cell leukemia (ATL) is a leukemia of mature T cells with a tendency for the malignant cells to infiltrate the skin (16). There is often an associated hypercalcemia and invariably a profound immunodeficiency state. Cases of ATL cluster geographically where infection with HTLV-1 is endemic, including the southwest of Japan, the Caribbean basin, sub-Saharan Africa, and the southeastern United States. HTLV-1 is a retrovirus that is the etiologic agent for ATL. The virus produces a protein termed *tax* which increases the transcription of several host genes including the IL-2Rα (Tac protein) gene. This presumably accounts for the fact that the HTLV-1 infected malignant ATL cells constitutively express large amounts of the IL-2Rα on their surface. The serum and urine of patients with ATL also contain large amounts of soluble Tac protein (17, 18) and the serum levels can be followed as a guide for responsiveness to therapy. We have examined the levels of soluble Tac protein in the sera of 50 patients with ATL (38 Japanese and 12 American), eight otherwise healthy HTLV-1 infected individuals, and 17 normal controls. The mean value for ATL patients, 16,461 U/ml (1 U = 3.3 pg), was elevated relative to normal controls, 238 U/ml, with none of the patient values falling within the 95% confidence limits of normal ($P \leq 0.0001$). The mean value for the otherwise healthy HTLV-1 infected individuals was also significantly different than normals ($P = 0.03$). In our hands, the measurement of soluble IL-2Rα has been extremely valuable in monitoring ATL patients during therapy (18).

The scientific rationale for therapeutic trials of anti-Tac therapy for ATL, therefore, rests with the observation that the malignant cells, but not resting normal cells, express large amounts of the IL-2Rα or Tac antigen. We have treated ATL patients with unmodified murine anti-Tac, *Pseudomonas* exotoxin-conjugated murine anti-Tac, and isotope emitting chelates of murine anti-Tac. Since the report of the nine initial treated patients (19), we have treated a total of 19 patients with unmodified murine anti-Tac. None of the treated patients experienced any untoward reactions. Of the nineteen, seven had remissions, four of these partial, one mixed and two complete, with partial and complete remissions lasting from 9 weeks to more than 3 yr. In October 1990, we initiated trials of [^{90}Y]chelated murine monoclonal antibody in patients with the ATL. In addition to the [^{90}Y]labeled antibody which is therapeutic due to emission of a β-particle, some patients also received the γ-ray emitting [^{111}In] labeled anti-Tac for the purpose of scanning to determine tumor burden and the distribution of labeled anti-Tac. Ten of 15 patients treated underwent a partial (eight patients) or complete (two patients) remission following ^{90}Y anti-Tac therapy. Future studies will utilize β- and α-emitting radioisotopes conjugated to murine and humanized anti-Tac and these isotopes conjugated to murine and humanized Mikβ1.

The clinical applications of anti-IL-2 receptor directed therapies will also include "autoimmune" disorders, neurologic disorders such as HTLV-1-associated myelopathy/tropical spastic paraparesis, and organ allograft rejection episodes.

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