1. INTRODUCTION

Interleukin-2 (IL-2) was first described as a T-cell growth factor (TCGF) in 1976 by Morgan et al. when it was noted that conditioned medium could support T-cell growth (1). IL-2 was later demonstrated to have no direct antitumor activity, but to mediate antitumor activity indirectly through the host immune response (2,3). The primary source of IL-2 is from an antigen-stimulated TH1-type CD4+ T cell and, to a lesser extent, from...
activated CD8+ cells (4). At least two external signals are required for T-cell activation, one through the T-cell receptor complex (TCR/CD3+), and the second from an accessory cell expressing B7, a ligand for the T-cell CD28+ receptor. It is encoded on chromosome 4q26-28 (5) and was first cloned in 1983 (6). IL-2 is a 15 kD protein consisting of two paired α helices bound by an interchain di-sulfide bond between cysteine residues at positions 58 and 105. IL-2 interacts with the T-cell IL-2 Rβγ heterodimer at the receptor, the structure of which is similar to that of IL-4 and GM-CSF (7).

The functional IL-2 receptor is composed of three subunits, IL-2Rα, IL-2Rβ, and IL-2Rγ. The IL-2Rα (CD25+) was the first subunit characterized and has a molecular weight of 55 kD (p55). It is a transmembrane protein with a large extracellular region, the only known function of which is to bind IL-2. It is upregulated by IL-2 and it may be part of a positive feedback loop for T-cell activation. IL-2Rα is a low affinity receptor ($K_d = 10^{-8} M$). It is thought that the IL-2 molecule first binds IL-2Rα, which then facilitates association with the IL-2Rβγ (8). Circulating levels of IL-2Rα have been found in some disease states but have no known functional role. IL-2Rβ (CD 122+) is a 70–75 kD protein (p70–75). This subunit has an intermediate binding affinity ($K_d = 10^{-9} M$) for IL-2. Finally, IL-2Rγ has a molecular weight of 64 kD (p64) and forms a heterodimer with IL-2Rβ. The resulting receptor, IL-2Rβγ, has an intermediate binding affinity ($K_d = 10^{-9} M$). The complex is critical for IL-2 internalization and induction of the proliferative signal. Both the IL-2Rβ and the IL-2Rγ chains are members of the Type I cytokine receptor family (9). The complete IL-2 receptor, the IL-2Rαβγ trimeric complex, has high affinity binding ($K_d = 10^{-11} M$) for IL-2, thus low levels of exogenous IL-2 can activate T cells. Within 15-30 min of IL-2 binding, the IL-2/IL-2Rαβγ complex undergoes endocytosis and degradation by lysozymes.

IL-2 stimulation induces dimerization of the cytoplasmic domains of IL-2Rβ and IL-2Rγ and aggregation of JAK 1 and JAK 3 that associates with them, respectively. This induces phosphorylation of the JAK kinases and subsequent activation of downstream STAT 5 and STAT 3 (10). The STAT 5 and STAT 3 proteins then migrate to the nucleus were they bind to IL-2 transcription factors.

2. BIOLOGICAL ACTIVITY OF RECOMBINANT IL-2

On May 5, 1992, high-dose IL-2 was approved by the Food and Drug Administration (FDA) for the treatment of metastatic renal cell cancer (RCC). The dose and schedule were based on the reported data from 255 patients treated with high-dose IL-2. Treatment consisted of 600,000 IU/kg IL-2 intravenously every 8 h for 14 doses over 5 d and was then repeated after a 9-d rest period (11).

The dose of IL-2 is expressed as international units (IU) as defined by the World Health Organization (WHO) (12). As a matter of reference, 6 IU are equivalent to 2 Roche units and to 1 Cetus unit, as described in early publications. A recent publication cautioned that this equivalence has been defined in vitro and may not apply when one attempts to achieve similar biologic effect in vitro (13). The gene was isolated and cloned in 1983 (6) and produced using recombinant technology in a genetically modified Escherichia coli (14). The recombinant form differs from the native protein in that it is nonglycosylated, by the lack of the N-terminal alanine and a serine substitution for cysteine at amino acid position 125. As currently produced, 1.1 mg of Chiron IL-2 is equivalent to 18 million ($18 \times 10^6$) IU (11).