Biomarkers, February 2008; 13(1): 1–26

informa
healthcare

Serum soluble interleukin 2 receptor α in human cancer of adults and children: a review

E. BIEN & A. BALCERSKA

Department of Pediatrics, Hematology, Oncology and Endocrinology, Medical University of Gdansk, Poland

Abstract
Cancer growth and development is associated with the stimulation of the innate immune system, including enhanced interleukin 2 receptor (IL-2R) expression in immune cells and its shedding into the circulation in a soluble form of sIL-2Rα. In most haematological malignancies, including different types of leukaemias and lymphomas, sIL-2Rα has been found to be released directly from the surface of neoplastic cells thus reflecting the tumour bulk, turnover and activity. Several studies have proved that not only lymphoid cancer cells, but also some non-lymphoid cancer cells, express IL-2R on their surface. They include malignant melanoma and carcinomas of the kidney, head and neck, oesophagus and lung. It is suggested that in most malignant solid tumours, elevated levels of sIL-2Rα are likely to be the product of normal peripheral mononuclear cells activated in response to the neoplasm's growth or that they are released from activated lymphoid cells infiltrating neoplastic tissues. This latter hypothesis has been proved by discovering the high expression of CD25 on the cell surface of most of these cells. Although the precise source and biological role of sIL-2Rα has not been clarified definitively, pretreatment serum levels of sIL-2Rα have been shown to reflect the activity, advancement and biological aggressiveness of many types of cancer in adults and children as well as to correlate with prognosis and overall survival. The possibility of enriching the diagnostic tools of oncologists with a new biochemical marker of activity of neoplasms resulted in numerous studies and reports concerning the clinical usefulness of sIL-2Rα measurements in adult and, less frequently, in paediatric malignancies. This article presents the actual knowledge concerning the structure, source and biological function of sIL-2Rα in patients with haematological and non-haematological malignancies. The authors review the published data on clinical applicability of soluble IL-2Rα determination in terms of diagnostics, prognosis and treatment monitoring of particular types of malignant disorders both in adults and in children. They also provide an insight into the clinical usefulness of sIL-2Rα-blocking antibodies in patients with cancer, and in those who reject organ transplants, develop graft-versus-host disease after allogeneic bone marrow transplantation and are affected with autoimmune disorders.

Keywords: *Membrane-bound interleukin-2 receptor, soluble interleukin-2 receptor α, CD25, lymphoproliferative disorders, malignant solid tumours, tumour marker, diagnostics, prognosis, treatment monitoring, anti-CD25 immunotherapy, adults, children*

(Received 2 February 2007; accepted 11 September 2007)

Correspondence: Ewa Bien, Department of Pediatrics, Hematology, Oncology and Endocrinology, Medical University of Gdansk, 7 Debinki Street, 80-211 Gdansk, Poland. E-mail: ebien@amg.gda.pl

ISSN 1354-750X print/ISSN 1366-5804 online
DOI: 10.1080/13547500701674063

Introduction

Interactions between the immune system and malignant cells play an important role in tumorigenesis (Smyth et al. 2001, Diefenbach & Raulet 2002, Igney & Krammer 2002, Dranoff 2003). The role of the immune system in fighting cancer has been verified in the laboratory as well as with clinical experiments (de Pillis et al. 2006). Through the mathematical modelling of tumour growth, the presence of an immune component has been shown to be essential for producing clinically observed phenomena such as tumour dormancy, oscillations in tumour size and spontaneous tumour regression (Dalgleish & O'Byrne 2002). Anti-tumour responses of the immune system in cancer patients are generally attributed to the activation of tumour-specific T cells, both CD4+ and CD8+ (Houghton et al. 2001, Garcia-Lora et al. 2003, Nelson 2004, Disis & Lyerly 2005, Kaufman & Jedd 2006). There is also evidence that the presence of tumour-infiltrating T cells is associated with a favourable prognosis in several types of cancer (Trentin et al. 1994, Diefenbach & Raulet 2002, Pages et al. 2005). The activation of T cells is a highly regulated process commonly provoked by the expression of transformation-associated antigens on the cell membranes of neoplastic cells (Diefenbach & Raulet 2002, Rivoltini et al. 2002, Dranoff 2003).

Failure of the immune system to early detect and reject transformed cells may lead to cancer development and uncontrollable proliferation (Igney & Krammer 2002). It is well known that the growing neoplasm takes advantage of some regulative mechanisms of the host to assure it has optimal growth conditions. Indeed, in many instances tumours can reappear, become resistant to therapy and escape the host immune response (Dunn et al. 2002, Igney & Krammer 2002, Poggi & Raffaella 2006).

Some immunological phenomena may promote tumour growth, acting to block anti-neoplastic functions of the activated effector cells (Beatty & Paterson 2000, Chouaib et al. 2002, Poggi & Raffaella 2006). It has been proven on a cellular and molecular level that tumour cells can escape immune-mediated control by several mechanisms that lead to subversion of the anti-cancer response (Beatty & Paterson 2000, Chouaib et al. 2002, Dunn et al. 2002, Rivoltini et al. 2002, Garcia-Lora et al. 2003). These mechanisms include: (1) alteration of the expressions of classical and non-classical human leukocyte antigens and/or loss of tumour-associated antigens (TAA); (2) loss of co-stimulatory molecules, which are essential in inducing a powerful immune response; (3) the production of cytokines, which are strongly immunosuppressive; and (4) induction of anergy or clonal deletion or suppressor cells (Poggi & Raffaella 2006).

One of the basic phenomena responsible for tumour escape from immune-mediated surveillance is shedding of TAA. It is well known that most of the cells physiologically shed antigens bound to their cell membranes and release them into the circulation. This most probably reflects their physiological activity, proliferation and turnover. In the organism suffering from cancer the intensity of TAA shedding by neoplastic cells may correlate with the tumour stage, bulk and aggressiveness (Heaney & Golde 1996, 1998, Dunn et al. 2002).

Numerous TAA have been identified that can be recognized by T cells and thus exert specific anti-tumour immune response (Houghton et al. 2001, Rosenberg 2001, Smyth et al. 2001). The possibility of detecting and measuring of TAA released by normal or neoplastic cells into the body fluids has gained much interest lately.

Among many antigens associated directly and indirectly with tumour growth the soluble counterparts of cytokine receptors seem to play special pathophysiological roles. Some authors suggest that soluble receptors are the by-products of the membrane-bound receptor downregulation and they need not have intrinsic biological functions. Other models assume that soluble receptors are able to modify the biological response to their ligand, usually by competing for the ligand with the membrane-bound receptors (Rubin et al. 1986, Dummer et al. 1992, Murakami 2004). In some other instances soluble receptors may act as binding proteins to inhibit the fast degradation of the ligand (e.g. hormones). Several types of soluble receptors may affect signal transduction of the membrane-associated receptor by binding the ligand in the bloodstream and subsequently activating intracellular signalling of the cell-bound receptor. In this model, the soluble receptor–ligand complex can provide ligand sensitivity to cells that do not express the complete receptor (i.e. do not express the ligand-binding subunit). Some evidence exists that several types of soluble receptors may be able to associate with one of the subunits of the membrane-bound receptor only when the second non-binding subunit is synthesized in the same cell (Heaney & Golde 1998, Witkowska 2005).

Of course, several other models of soluble and membrane-bound receptor interrelationships may exist. It is also likely that many soluble receptors have more than one activity depending on the concentrations of ligand and soluble receptor and on the cellular context of the interaction. Nevertheless, many studies have shown that interleukin 2 receptor (IL-2R) and the soluble form of its alpha subunit (sIL-2Rα) are of special significance both in physiological and also several pathological phenomena (Waldmann 2002, 2007). Because many diseases of immune, neoplastic and inflammatory origin are associated with increased sIL-2Rα, it is possible that soluble receptors may be playing a part in the manifestation and severity of disease (Murakami 2004, Witkowska 2005). Some authors suggest that disease-related immunosuppression may be mediated by the increased concentration of sIL-2Rα, especially when its suppressive effect can be overcome with increased concentrations of IL-2 or can be abrogated if sIL-2R is removed by immunoabsorption or blocked with selective antibodies (Heaney & Golde 1998, Sabbioni et al. 2000, Warlé et al. 2003a, Mehta et al. 2004).

Interleukin 2 and the cell surface-bound IL-2 receptor

IL-2 was discovered as a T-cell proliferative factor purified from cultured phytohaemagglutinin-stimulated peripheral blood mononuclear cell (Morgan et al. 1976). IL-2 is a single polypeptide of molecular weight 15.5 kDa, 133 amino acid residues long. IL-2 is a globular protein containing two sets of a-helical domains, lying at right angles to each other. These a-helical regions are involved in the binding to the receptor, and indeed this helical motif is found in many other cytokines, involved in binding to their respective receptors (Waldmann 2002, Church 2003).

IL-2 is produced mainly by activated CD4+ T cells, although the expression of IL-2 by naive CD8+ T cells and dendritic and thymic cells has also been reported (Morris & Waldmann 2000, Fehniger et al. 2002, Nelson 2004). The cytokine is considered a potent immunomodulator playing an important role in both the activation and maintenance of an immune response. This cytokine activates numerous key cells in the immune system, acting as an autocrine factor driving the expansion of

antigen-specific T cells, and as a paracrine factor influencing the activity of a number of other cells including B cells, natural killer (NK) cells, lymphokine-activated killer (LAK) cells, neutrophils, monocytes and γ/δT cells (Cassell et al. 2002, Waldmann 2002, Church 2003, Bayer et al. 2005). Recent work, however, has uncovered an unexpected function of IL-2, which appears crucial to maintaining peripheral tolerance by supporting the survival and function of CD25+CD4+ regulatory T cells (Malek & Bayer 2004, Fehervari et al. 2006).

The ability of IL-2 to stimulate NK cell and CD8+ T-cell lysis of tumour targets resulted in much clinical interest in IL-2 as an anti-neoplastic biological agent (Rosenberg 2000, 2001, Cassel et al. 2002, Fehniger et al. 2002, Waldmann 2002). A recombinant human IL-2 analogue has been approved for the treatment of metastatic melanoma and metastatic renal cell carcinoma, yielding an overall objective response rate of approximately 15% (Atkins et al. 2000, Fisher et al. 2000).

To exert its biological effect, IL-2 must interact with its specific receptor (IL-2R). Among the other growth factor receptors the cell surface-bound IL-2R has a unique structure. It is composed of at least three distinct glycopeptide subunits called α (IL-2Rα), β (IL-2Rβ) and γ (IL-2Rγ) chains (Waldmann 1991, 2002, Murakami 2004).

The α chain also termed the light chain and CD25 (previously known as Tac antigen) is a protein of 55 kDa. Its primary structure shows no homology with any other known protein receptors. IL-2Rα lacks structural features characteristic for members of the immunoglobulin superfamily and does not belong to the cytokine receptor superfamily. It is composed of 251 amino acids including a signal peptide of 21 amino acids. Three parts of the α receptor: extramembrane, intramembrane and intracellular are composed of 219, 19 and 13 amino acids, respectively (Waldmann 1991, 2002, Nelson 2004, Murakami 2004). This intracellular domain is too short to act as an important site for signal transduction, and lacks any known consensus sequence for intracellular signalling. However, there is conserved sequence homology between humans and murine α subunits, indicating a possible important role (Anderson et al. 1995, Church 2003).

The β chain called also the heavy chain (IL-2Rβ, CD122), is a protein weighting 75 kDa (p75). The full-length IL-2Rβ contains 551 amino acids with a signalling peptide of the NH_2-terminal 26 amino acids within the structure. The extramembrane part of the β chain comprises 214 amino acids, intramembrane (membrane-spanning) – 25 and intracellular (cytoplasmic), the biggest one – 286. The latter part of the IL-2Rβ has been divided into three distinct subregions designated as the 'serine-rich' region (responsible for the mitotic signal transduction), the 'proline-rich' region and the 'acidic' region responsible for its physical association with a *src*-family protein tyrosine kinase following IL-2 stimulation. It has been shown that the β chain is shared by both the IL-2 and the IL-15 receptors (Bamford et al. 1994, Morris & Waldmann 2000, Nelson 2004).

The γ subunit of the IL-2R (p64, CD132) is composed of the 22 amino acid signal sequence and 347 amino acids making up the mature form of IL-2Rγ. Within this chain, regions of 232, 29 and 86 amino acids in length constitute the extracellular, membrane-spanning and cytoplasmic regions, respectively. The extracellular domain contains several unique motifs that are present in other cytokine receptors including those for IL-3, IL-4, IL-6, IL-7, IL-9, IL-13, IL-15, granulocyte-macrophage colony-stimulating factor (GM-CSF), G-CSF, prolactin, growth hormone and erythropoietin. This

indicates that IL-2Rγ belongs to the cytokine receptor superfamily. It is suggested that IL-2Rγ is required for the receptor-mediated internalization of IL-2 (Leonard et al. 1994, Murakami 2004, Nelson 2004).

Since each subunit of membrane-bound IL-2R is able to bind the ligand independently with either low (IL-2Rα) or intermediate (IL-2Rβ and γ) affinity, different combinations of the α, β and γ chains form the three different classes of IL-2 receptor (Cassel et al. 2002, Murakami 2004, Nelson 2004). It has been shown that the high-affinity receptor for IL-2 consists of all three subunits combined non-covalently and the presence of the α chain is necessary for the high-affinity IL-2R formation (Gutgsell & Malek 1994, Cassel et al. 2002). Although resting as well as mature activated B and T lymphocytes, monocytes, large granular lymphocytes (LGL) and NK cells constitutively express the β and γ chains, the α chain is rapidly induced and expressed only after mononuclear cell activation. Except for a minor subset of NK cells, non-stimulated peripheral blood lymphocytes do not express measurable levels of high-affinity receptors. The majority of NK cells, neutrophils and resting or IL-2-stimulated monocytes express only intermediate-affinity receptors. Monocytes stimulated with proinflammatory cytokines do express high-affinity receptors, but at levels far lower than NK cells or activated T cells (Cassel et al. 2002).

It seems significant that the β and γ subunits are the components of other interleukin receptors. The γ chain has been called the common receptor γ as it is present in at least seven other cytokine receptors (Leonard et al. 1994). The β subunit constitutes a part of the IL-15 receptor, the IL-15 molecule being very similar to the IL-2 system (Bamford et al. 1994, Morris & Waldmann 2000, Nelson 2004). This sharing of receptors is responsible for the redundancy in their functions well known in the cytokine network. It also helps to explain the finding that in IL-2 gene knockout mice the immune system can still function with only slight disruption (Church 2003).

The α subunit of the IL-2 receptor

The studies of the human IL-2Rα have been markedly facilitated by the identification of the monoclonal anti-receptor peptide antibody, termed anti-Tac, by Uchiyama et al. (1981). Utilizing this antibody it was shown that most resting T cells, B cells or monocytes in the circulation do not display the α subunit. It has been demonstrated that less than 5% of freshly isolated, non-stimulated human peripheral blood T cells react with anti-p55 antibodies. However, upon activation with different antigens or mitogens, the IL-2Rα become expressed within 4–8 h and reach a peak of 30 000–60 000 sites per cell approximately 48–96 h following activation (Waldmann 2002, 2007). The number of IL-2Rα declines progressively by 80–90% after 10–21 days following activation which is paralleled by a decline in an mRNA transcription for the CD25 peptide. Also the proliferative rate of cells follows and parallels the rise and fall in IL-2Rα expression (Rubin et al. 1985).

As it has been stated previously, the participation of the α subunit is necessary for the forming of the high-affinity receptor (Gutgsel &Malek 1994, Cassel et al. 2002). This is of great importance since only such receptors assure the optimal response of immunocompetent cells to the very small concentrations of IL-2. Cells expressing only β and γ chains can be stimulated, but only at very high concentrations of IL-2 and the biological significance of this is unclear. The ligand is thought to bind to the α and β subunits first, followed by heterodimerization of the αβγ chains to activate the

intracellular downstream signalling mechanisms (Church 2003). Furthermore, it has been demonstrated by Eicher and Waldmann (1998) that IL-2Rα on one cell can augment the IL-2 signalling by presenting IL-2 to the IL-2Rβ/γ on another cell. These findings suggest that the magnitude and duration of IL-2Rα expression may reflect the magnitude of clone expansion and the resultant immune responses. This phenomenon is of great importance in proper functioning of all the immunological processes depending on IL-2. This may explain in part the diminished immunocompetence in patients with decreased IL-2 production or the impairment of IL-2Rα expression and function on effector cells (Burton & Kay 1994, Roifman 2000).

In humans with neoplastic disease, IL-2Rα is expressed both on normal activated lymphocytes and monocytes and on the proportion of non-stimulated malignant cells. Specifically, virtually all patients with human T-cell lymphotropic virus-1 (HTLV-1)-associated adult T-cell leukaemia (ATL) and hairy cell leukaemia (HCL) constitutively express very large amounts of IL-2Rα on their cell surfaces (Ambrosetti et al. 1993b, Horiuchi et al. 1997, Waldmann 2002). The CD25 peptide has also been demonstrated on some leukaemic cells, including B-cell chronic lymphoblastic leukaemia (B-CLL) and acute lymphoblastic leukaemia (ALL) (Burton & Kay 1994, Nakase et al. 1994a,b) and chronic myeloproliferative diseases (Panteli et al. 2005). Atypical cells of most malignant lymphomas, both Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL), express the CD25 antigen in a great proportion of cases (Tesch et al. 1993, Nakase et al. 1994a, Waldmann 2002, 2007). Although the precise biological role of IL-2Rα expression in these malignant disorders is not clear, it may be involved in stimulating proliferation of the neoplastic cells (Nakase et al. 1994b, Waldmann 2002, 2007). Several studies have proved, however, that not only the lymphoid cancer cells, but also that some non-lymphoid cancer cells, express IL-2R. They include malignant melanoma, renal cell carcinoma, head and neck, oesophageal and lung and, most probably, colorectal cancers (Rimoldi et al. 1993, Yano et al. 1996, Wang et al. 2000, Tartour et al. 2001, Huang 2002).

IL-2 receptor – soluble form of its alpha subunit (sIL-2Rα)

In addition to the membrane-bound form of the IL-2Rα, a soluble form of this receptor (sIL-2Rα) was found to be released spontaneously in the culture supernatants of *in vitro* cultured T cells after stimulation with lectins and mitogens. Rubin et al. have proven that the soluble form of the α chain is smaller than its membrane counterpart (45 vs. 55 kDa), but it keeps the ability to bind IL-2 efficiently (Rubin et al. 1985, 1986). An enzyme-linked immunosorbent assay (ELISA) with the use of two non-competitive murine anti-human IL-2Rα antibodies (anti-Tac and 7G7/B6) has enabled the detection and quantification of the released soluble form of the CD25 molecule (Waldmann 1991, 2007). Nowadays there are several commercially available ELISA kits for soluble IL-2Rα measurements in body fluids with simple and not work-consuming methodology.

sIL-2Rα has been shown to be present in the serum and other body fluids of healthy individuals and its level (approximately 100–500 U ml^{-1}; 1 IU = 3.3 pg) reflects the activation of innate immunological responses occurring under physiological stimuli (Rubin et al. 1985). The release of soluble CD25 is proportional to its cell surface expression (Junghans & Waldmann 1996). It is excreted and catabolized by the

kidneys and has a serum half-life of 0.62 h. In renal failure the serum level of sIL-2Rα is increased due to its decreased catabolism (Morris & Waldmann 2000).

Komp et al. were the first to report that serum sIL-2Rα levels in healthy children were much higher than in adults and that they significantly increased with age (Komp et al. 1988). This phenomenon was later confirmed by others (Fujita et al. 2005, Bien et al. 2006). No important sex-related differences in sIL-2Rα levels were stated (Sadeghi et al. 2005). Moreover the plasma levels of sIL-2Rα did not differ significantly between nocturnal sleep and nocturnal wakefulness. There were also no significant diurnal variations for levels of the receptor in the study of Haack et al. (2004).

Increased serum levels of sIL-2Rα in non-cancerous disorders

Elevated serum levels of sIL-2Rα have been found in a variety of autoimmune and inflammatory diseases (Table I). They include rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, systemic sclerosis, myasthenia gravis, aplastic anaemia, Crohn's disease, celiac disease, sarcoidosis, non-infectious uveitis, toxic epidermal necrolysis, tropical spastic paraparesis, Bell's palsy, asthma and many others (Heaney & Golde 1996, 1998, Dejica 2001, Correia et al. 2002, Romaldini et al. 2002, Yilmaz et al. 2002, Grutters et al. 2003, Lis & Brzezinska-Wcislo 2003, Gustot et al. 2005, Witkowska 2005, Kuuliala et al. 2005, 2006, Can et al. 2006, Fukushima et al. 2007). Soluble IL-2Rα has also been shown to increase in most viral and bacterial infections (including chronic hepatitis B and C, febrile neutropenia, pneumonia, brucellosis, Lyme disease and latent tuberculosis (Fawcett et al. 1993, Soker et al. 2001, Matsuno et al. 2003, Makis et al. 2005, Shitrit et al. 2006, Xiao et al. 2006). Daily monitoring during the early course after liver transplantation has demonstrated the clinical relevance of serum sIL-2Rα as an early marker of acute liver graft rejection (Warlé et al. 2003b). It has also been shown to correlate with the severity of graft-versus-host disease following bone marrow transplantation (Kami et al. 2000). sIL-2Rα has proven to be an extremely important and valuable marker of the course of Langerhans cell histiocytosis in children (Ishii et al. 2006).

In these above-mentioned situations, the reason for having increased circulating sIL-2R is uncertain and may represent a non-specific response to inflammation or stress. In some instances serial determination of the receptor may be useful in the monitoring of disease severity and also in predicting and following of the response to anti-inflammatory therapies (Fawcett et al. 1993, Warlé et al. 2003a,b).

Soluble IL-2Rα as a marker of neoplastic diseases

The biological mechanisms underlying the increase of sIL-2Rα in serum and other body fluids in the course of malignant processes have not been defined clearly. It has been shown that in most neoplastic haematological conditions, especially in ATL and HCL, sIL-2Rα is released by neoplastic cells constitutively expressing CD25 antigen on their membrane (Ambrosetti et al. 1993b, Arun et al. 2000, Zhang et al. 2006). Thus the serum level of sIL-2Rα in most lymphoproliferative has been suggested to reflect directly the burden of the malignant transformed cells and the disease activity. In these situations sIL-2Rα may act as a true neoplastic marker. In patients with solid tumours the biological source and role of sIL-2Rα is more complex. The expression of

Table I. Disorders associated with the increased serum soluble interleukin (IL)-2 receptor α concentrations.

Autoimmune diseases	Neoplasia	Allograft rejection	Infections	Other
Aplastic anaemia	*Leukaemias*:	Renal	Brucellosis	*Drugs*
Asthma	Acute myelocytic	Liver	Chronic	*In vivo* IL-2
Behçet's syndrome	leukaemia	Cardiac	hepatitis B	administration
Bell's palsy	Adult T-cell leukaemia/	Bone	and C Febrile	*In vivo* G-CSF
Bipolar disorder	lymphoma	marrow	neutropenia	administration
Celiac disease	Chronic lymphocytic		HIV/AIDS	General
Crohn's disease	leukaemia		Infectious	anaesthesia
Giant cell arteritis	Chronic myelocytic		mononucleosis	*End-stage renal*
Idiopathic	leukaemia		Lyme disease	*disease*
thrombocytopenic	Hairy cell leukaemia		Pneumonia	*Veno-occlusive*
purpura	Acute lymphoblastic		Pulmonary	*disease*
Juvenile rheumatoid	leukaemia		tuberculosis	*Graft-versus-host*
arthritis	*Lymphomas:*		*Rubella*	*disease*
Kawasaki disease	Anaplastic large-cell		Sepsis	*Langerhans cell*
Multiple sclerosis	lymphoma			*histiocytosis*
Myasthenia gravis	Cutaneous T-cell lymphoma			*Burns*
Nephrotic syndrome	Mycosis fungoides			
Non-infectious uveitis	Non-Hodgkin's lymphomas			
Polymalgia rheumatica	(B cell)			
Rheumatoid arthritis	Hodgkin's lymphoma			
Sarcoidosis	Peripheral T-cell			
Scleroderma	lymphomas			
Systemic sclerosis	Multiple myeloma			
Sjögren's syndrome	*Malignant solid tumours:*			
Systemic lupus	Malignant melanoma			
erythmatosus	Soft tissue sarcomas			
Vasculitis	Head and neck cancer			
Wegerner's	Nasopharyngeal carcinoma			
granulomatosis	Breast cancer			
Toxic epidermal	Carcinomas of the lungs			
necrolysis	Cancer of the oesophagus,			
Tropical spastic	pancreas, stomach			
paraparesis	Renal cell cancer			
	Hepatocellular carcinoma			
	Ovarian cancer			
	Colorectal cancer			
	Childhood neoplasia:			
	Acute lymphoblastic			
	leukaemia			
	Hodgkin's and			
	non-Hodgkin's lymphomas			
	Wilms' tumour			
	Sarcomas of bone and			
	soft tissues			
	Haemophagocytic–histiocytic			
	syndrome			

membrane-bound IL-2Rα has been stated in the cell lines of some histological types of malignant solid neoplasms (Rimoldi et al. 1993, Yano et al. 1996, Wang et al. 2000, Tartour et al. 2001). It is suggested that elevated sIL-2Rα levels in body fluids of patients with most solid tumours reflect the augmented release of this receptor from

normal lymphoid cells activated in response to tumour growth. However, some authors postulate that increased levels of sIL-2Rα do not originate from activated peripheral blood mononuclear cells but are most probably released from activated lymphoid cells infiltrating neoplastic tissues (Trentin et al. 1994, Frydecka & Mazur 1996, Tartour et al. 2001, Sakata et al. 2002, Zhang et al. 2006). These cells have been shown to express CD25 on their surface (Trentin et al. 1994, Tartour et al. 2001, Sakata et al. 2002). In patients with advanced stages of mycosis fungoides the initial sIL-2Rα level was elevated and accompanied the increase in concentrations of acute-phase proteins and a decrease in their reactivity with Con A. This phenomenon was explained as the result of T-helper lymphocyte activation (Pawlaczyk & Sobieska 2006). On the other hand, in colorectal cancer patients it is unclear whether the presence of sIL-2Rα in the serum is solely due to T-cell activation. The study of Huang et al. (2002) suggested that there might be an additional source of serum sIL-2Rα other than T-cell upregulation. It might be released either from other immune cells or from tumour products.

Irrespective of whether sIL-2R expression is increased in response to a non-specific stimulus such as inflammation or results directly from release from proliferating tumour cells, it is important to consider that sIL-2R is likely to have intrinsic biological activity and may act as an immunosuppressant. Therefore many literature studies have been focused on the clinical applicability of sIL-2Rα as an indicator of neoplasm behaviour. In many types of human neoplastic disorders the pretreatment serum levels of sIL-2Rα have been shown to reflect the activity, advancement and biological aggressiveness of cancer as well as to correlate with prognosis and overall survival.

Significance of sIL-2Rα in diagnostics of adult malignancies

Lymphoproliferative disorders

Highly increased sIL-2Rα levels, compared with those in healthy people, have been reporteded at diagnosis of the majority of malignant disorders of adults, predominantly of lymphoproliferative origin (shown in Table I). They encompass HCL (Ambrosetti et al. 1993b, Arun et al. 2000), ATL (Zhang et al. 2006), HL and NHL (Ambrosetti et al. 1993a, Stasi et al. 1994, Viviani et al. 1998, Wakao et al. 2002, Goto et al. 2005, Nakase et al. 2005, Fabre-Guillevin et al. 2006), cutaneous T-cell lymphoma (CTCL) (Hassel et al. 2004), anaplastic large-cell lymphoma (ALCL) (Janik et al. 2004), acute lymphoblastic anaemia (ALL) (Moon et al. 2004, Lee et al. 2005, Nakase et al. 2005), chronic lymphoblastic leukaemia (CLL) (Hadj 2005), multiple myeloma (Kuku et al. 2005) and many others (Dummer et al. 1992, Burton & Kay 1994, Murakami 2004).

The highest reported levels of the serum sIL-2Rα were reported in adult patients with ATL and HCL (69000 and 48000 U ml^{-1}, respectively) (Ambrosetti et al. 1993b, Zhang et al. 2006). Similarly, the serum sIL-2Rα levels in patients with aggressive NHL have been reported to be more than 10 times higher than in healthy controls (Stasi et al. 1994). In the report of Viviani et al. (1998) baseline sIL-2R levels in 174 untreated patients with HL were significantly higher than in 65 healthy control subjects (1842 ± 129 U ml^{-1} vs. 420 ± 10 U ml^{-1}, $p < 0.0001$). Janik et al. (2004) have shown that serum sIL-2Rα levels were elevated in seven of nine patients with ALCL, mainly those positive for the anaplastic lymphoma kinase (*ALK*) gene.

Patients negative for ALK had normal serum sIL-2Rα levels and their tumours lacked CD25 expression.

Increased concentration of soluble IL-2Rα in cerebrospinal fluid (CSF) was also found a reliable marker indicating central nervous system (CNS) involvement in adult patients with ALL (Lee et al. 2005). The sIL2-Rα level of $>10\,\mathrm{U\,ml^{-1}}$ in conjunction with conventional cytology and the CSF leukocyte count might serve as an objective indicator of CNS involvement (displaying the sensitivity of 89.5% and the specificity of 89.6%). The study proved that the discrimination power of CSF sIL2-Rα for the presence of leukaemic blasts was better than that of CSF leukocyte counts. The other analyzed markers including: total protein, uric acid, glucose, aspartate aminotransferase and lactate dehydrogenase (LDH) were not significantly different in cytology (+) and cytology (−) samples.

Malignant solid tumours

In contrast to lymphoproliferative disorders, most malignant solid tumours are not usually associated with significantly increased serum level of sIL-2Rα at diagnosis unless when diagnosed in the generalized phase of disease (Lissoni et al. 1990, Nakase et al. 2005). Elevated mean pretreatment levels of the receptor have been reported in adult patients with malignant melanomas (Boyano et al. 2000), soft tissue sarcomas (Rutkowski et al. 2002) and carcinomas of the lungs (Kawashima et al. 2000, Sieminska 2004, Kaminska et al. 2006), pancreas (Kayhan et al. 2004), stomach (Murakami et al. 2002), kidney (Kallio et al. 2001), colon (Sakata et al. 2002), liver (Izzo et al. 1999, Parasole et al. 2001) and ovary (Frydecka et al. 1996, Sedlaczek et al. 2002) (Table I). In patients with primary or metastatic brain tumours serum levels of sIL-2R vary significantly, tending to be increased in the minority of cases (Yoshida & Morii 2000).

Nakase et al. (2005) have shown significantly higher sIL-2Rα levels both in haematological and non-haematological neoplasms compared with normal subjects. However, compared with solid malignancies, haematological neoplasms displayed a wide range of sIL-2Rα levels and extremely elevated values of the receptor were seen in certain cases. The authors suggested that sIL-2Rα levels might serve as one of the non-invasive markers for differential diagnosis between haematological and solid malignancy. Similar observations have been made by Bien et al. (2006) in children with leukaemias and lymphomas and malignant solid tumours.

Correlation of initial sIL-2Rα serum levels with the clinical stage and activity of neoplasms

Apart from the early and proper diagnosis of a neoplasm it is important to assess its clinical advancement and biological aggressiveness. This enables choice of the optimal treatment strategy for particular patients resulting in better outcome and survival rate. Unfortunately, the data on the clinical usefulness of sIL-2Rα as a marker of cancer stage are not unified.

The pretreatment serum levels of sIL-2Rα have been shown to reflect the tumour burden, activity and advancement of most neoplasms in adults. They comprised presumably lymphoproliferative disorders (mainly HL and NHL), but also several types of solid tumours: of ovary, colon, kidney, head and neck, stomach and malignant

melanoma (Lissoni et al. 1990, Ambrosetti et al. 1993a, Berghella et al. 1998, Viviani et al. 1998, Boyano et al. 2000, Kallio et al. 2001, Tartour et al. 2001, Sakata et al. 2002, Hassel et al. 2004).

Among patients with HL and NHL the presence of constitutional symptoms and bulky disease at diagnosis has been reported to be associated with poorer prognosis. Accordingly, highly elevated pretreatment levels of sIL-2Rα were observed in patients with advanced HL and NHL, displaying constitutional symptoms and/or bulky disease (Ambrosetti et al. 1993a, Pui et al. 1993). Hassel et al. (2004) demonstrated that serum sIL-2Rα correlated well with tumour burden in 41 patients with CTCL, which might be useful for disease monitoring during treatment.

In patients with malignant solid tumours the correlation of sIL-2Rα with stage depends on the type of cancer. The mean values of sIL-2Rα in patients with malignant melanoma were significantly higher in all stages than in normal controls; whereas in patients with renal cell cancer they increased with disease stage (Kallio et al. 2001, Goto et al. 2005). In contrast, there has been no correlation between initial serum sIL-2Rα concentration and the stage of breast cancer (Tesarova et al. 2000). Also in pancreatic adenocarcinoma and non-small-cell lung cancer the serum sIL-2Rα showed no association with tumour stage, histological grading and tumour size (Gansauge et al. 1998, Kaminska et al. 2006). Moreover, Gansauge et al. noted a trend toward lower sIL-2Rα concentration in patients with distant metastases, which was in opposition to most other studies.

Treatment monitoring with the serial serum sIL-2Rα measurements

Apart from the immediate diagnosis it is crucial to estimate the response to anti-tumour therapy. There have been several reports on the clinical significance of serial serum sIL-2Rα levels measurement during oncological therapy of some malignancies. However, the limitations of most of these studies are small groups of analyzed patients.

The significant correlation of sIL-2Rα levels with disease course and response to treatment has been shown in the majority of lymphoproliferative disorders, including HCL, ATL, ALL, HL and different types of NHL (Ambrosetti et al. 1993a,b, Stasi et al. 1994, Janik et al. 2004, Moon et al. 2004, Wakao et al. 2002, Zhang et al. 2006) as well as in some types of malignant solid tumours of adults. In the reports of Ambrosetti et al. (1993a) and Viviani et al. (1998) the highly elevated pretreatment serum levels of sIL-2Rα observed in adult patients with HL decreased significantly following good response to chemotherapy. However, the values of the receptor determined in the CR phase of disease were still much higher than these obtained after therapy termination and in the control group of healthy adults. The serum level of the sIL-2Rα was shown to return to normal range not before a year after stopping the treatment. After a median follow-up of 5 years, sIL-2R levels remained low in 114 patients in continuous CR, while they increased in nine out of 12 patients (75%) who relapsed. However, a temporary increase was also observed in six patients (5%) still in CR. Similarly, in the report of Vonderheid et al. (1998), 36 patients with advanced CTCL underwent serial measurements of sIL-2Rα levels during treatment with extracorporeal photopheresis and other modalities. The concentration of serum sIL-2Rα correlated well with the disease status and was more useful than LDH or Sézary cell count monitoring. In 14 newly diagnosed patients with multiple myeloma

Kuku et al. (2005) observed a significant reduction of the serum level of sIL-2Rα and several other proinflammatory cytokines (IL-1β, IL-6, IL-8, tumour necrosis factor (TNF)-α and C-reactive protein) after the VAD (vincristine–adriamycin–dexamethasone) chemotherapy. The authors concluded that analyzed mediators which were thought to play an important role in the pathogenesis of multiple myeloma were significantly suppressed by effective treatment. Also Janik et al. (2004) observed a significant decrease of serum sIL-2Rα levels in seven of nine patients with ALCL responding to chemotherapy and an increase in both patients developing tumour recurrence. An interesting report of Wakao et al. (2002) has proved the clinical usefulness of serial determinations of sIL-2Rα in predicting of the recurrence in patients with malignant lymphomas. In 13 relapsed patients logarithmic linear increases of sIL-2Rα were observed and they preceded the recurrence for over 10 months. In contrast, in 15 patients achieving and maintaining complete remission for more than 2 years, serum levels of sIL-2Rα were unchanged or decreased gradually. The authors concluded that serum sIL-2Rα is a better predictor of malignant lymphoma relapse than LDH and the international prognostic index.

The studies concerning clinical monitoring of serum sIL-2Rα during the course of solid tumours are not numerous and have many diverse conclusions. Frydecka et al. (1996b) has shown the usefulness of the serial measurements of serum sIL-2Rα levels in women with uterine and cervical cancer. Similarly, Boyano et al. (2000) reported that mean values of sIL-2Rα were significantly higher in patients with all stages of malignant melanoma than in normal controls and correlated with the disease progression. Statistical analysis showed that only sex, stage and sIL-2Rα value were the factors significantly associated with metastatic progression in melanoma patients. In contrast, Brunetti et al. (1999) and Lissoni et al. (1990) failed to prove any clinical use of serial determination of sIL-2Rα in patients with lung cancer and gastric, colorectal and breast cancer. Also, Tesarova et al. (2000) did not observe any influence of therapy administered to 31 women with different stages of breast cancer on the serum sIL-2Rα concentration.

Prognostic value of the pretreatment sIL-2Rα serum levels

Data on the significance of pretreatment sIL-2Rα as a prognostic marker in cancers of adults are controversial. Lissoni et al. (1990) did not show any correlation between the initial sIL-2Rα level and subsequent course and outcome in adult patients with cancer of lungs, larynx, bronchi, stomach and breast. Also, the study of Parasole et al. (2001) did not confirm any predictive value of sIL-2Rα in hepatocellular cancer (HCC) patients. Pretreatment determination of this marker did not appear superior to the CLIP score used in practice for staging of HCC.

In contrast, several other studies emphasize the prognostic value of sIL-2Rα determination as regards the risk of neoplasm relapse or chance for long-term survival. Furthermore, in patients with malignant melanoma (Boyano et al. 2000, Ottaiano et al. 2006), head and neck cancer (Tartour et al. 2001), nasopharyngeal carcinoma (Wu et al. 1998) and NHL (Vonderheid et al. 1998, Goto et al. 2005) sIL-2Rα was proved to be the most precise marker associated with prognosis of local and distant recurrence. In the report of Kawashima et al. (2000) elevated preoperative serum sIL-2Rα concentration in patients with operable non-small-cell lung cancer was shown to reflect the occurrence of intrapulmonary metastases with over 87% sensitivity.

Similarly, Tartour et al. (2001) found that high sIL-2Rα concentrations at time of diagnosis were highly correlated with a shorter survival and higher risk of metastasis development within a 3-year follow-up in a cohort of 234 patients with head and neck squamous cell carcinoma. Thus, the authors suggested that serum sIL-2Rα could be employed in head and neck cancers as an independent prognostic marker. Also, Ottaiano et al. (2006) proved that sIL-2Rα could be an independent prognostic factor in patients with malignant melanoma. High initial values of the receptor or values increasing up to or more than 600 U ml^{-1} during follow-up were associated with higher Breslow tumour thickness, progression of the tumour and significantly lower 5-year disease-free survival rate.

Similarly, in adult patients with HL initial serum levels of sIL-2Rα correlated with subsequent disease course. The risk of HL recurrence in patients with a pretreatment sIL-2Rα level exceeding 1500 U ml^{-1} was 16.4% while in those with sIL-2Rα $<$1500 U ml^{-1} it was only 1.5% (Ambrosetti et al. 1993a). Viviani et al. (1998) observed that the pretreatment values of sIL-2Rα may be an indication of disease outcome similar to other conventional prognostic factors, such as number of involved sites, presence of B symptoms and extranodal extent. The study of Arun et al. (2000) showed that sIL-2R levels increase only in patients with HCL who go on to relapse. sIL-2Rα levels doubled a mean of 17.1 months (range 4–36 months) before absolute granulocyte count decreased by 50%. Thus, rising serum sIL-2Rα level identified those with an increased risk of relapse who needed more frequent observation than patients who maintained a sIL-2Rα level.

Significant correlation among high initial levels of sIL-2Rα and shorter overall survival were reported in both malignant solid tumours (Tartour et al. 2001, Huang et al. 2002, Ottaiano et al. 2006) and lymphoproliferative disorders (Ambrosetti et al. 1993a, Goto et al. 2005, Schütt et al. 2005). The usefulness of sIL-2Rα to prognosticate the probability of overall survival (OS) has been proved particularly in patients with HL and NHL. In 113 patients with previously untreated aggressive NHL high serum sIL-2Rα levels at onset (2000 U ml^{-1} and over) were associated with significantly lower survival rates than low sIL-2Rα levels (5-year OS of 24% vs. 74%). In addition, the initial sIL-2Rα concentration was shown to be a useful biomarker for selecting appropriate treatment when used in combination with the International Prognostic Index. The patients in the high-risk group and those with high sIL-2Rα in the low intermediate/high intermediate risk group had significantly lower survival rates than the patients in the low-risk group and those with low sIL-2Rα in the low intermediate/high intermediate risk group (Goto et al. 2005). In patients with multiple myeloma treated with thalidomide in combination with dexamethasone, the serum level of sIL-2R appeared to be a predictive factor for response rate and for survival (Schütt et al. 2005).

Clinical significance of sIL-2Rα in malignant disorders occurring in childhood

Neoplastic disease of childhood comprises a broad spectrum of malignant disorders characterized by multiple histopathological, clinical and biological features, very different from those in adults. Reports concerning clinical usefulness of sIL-2Rα in neoplasms typical for paediatric age are not numerous and predominantly focus only on the analysis of the pretreatment CD25 level (Pui et al. 1987, 1988, 1989, 1993,

Bodey et al. 1996, Bien et al. 2006, 2007). Types of childhood neoplasia associated with elevated sIL-2Rα are presented in Table I.

Pui et al. are the authors who have studied the problem of sIL-2Rα in children with various types of malignancies most extensively (1987, 1988, 1989, 1993). They showed that serum levels of sIL-2Rα at diagnosis in children with ALL, NHL and HL were highly elevated and exceeded those of the control group. However, Komp et al. (1988) questioned the results of Pui et al. obtained in children with NHL (1987) because of the improperly matched control group. Komp et al. (1988) were the first to show that serum sIL-2Rα levels in healthy children were much higher than in adults and that they significantly changed with age with highest levels observed in infants and young children. Based on the sIL-2Rα measurements in sera of 122 healthy children aged from 0 (umbilical blood) to 15 years, Komp et al. estimated the reference ranges for sIL-2Rα in particular age series. This report is of great clinical importance since it implies the necessity to create the age-adjusted control group or to express each obtained sIL-2Rα value as a multiplication of the upper limit of the reference range assessed for a particular age of the patient (Fujita et al. 2005, Bien et al. 2006).

The only studies concerning the usefulness of sIL-2Rα in paediatric malignant solid tumours come from Pui et al. (1993), Bodey et al. (1996) and Bien et al. (2006, 2007). The study of Pui et al. considered children diagnosed with Wilms' tumour and sarcomas of bone and soft tissues as well as children with HL. The values of sIL-2Rα obtained in particular types of neoplasms were not compared with the control group of healthy children but only between the localized and disseminated phases of cancer. The report showed clearly different behaviour of solid paediatric tumours and HL which probably resulted from distinct cell biology of these malignancies. Bien at al. (2007) suggested that sIL-2Rα could be a useful diagnostic marker since the median pretreatment serum levels of the receptor as well as the rates of elevated sIL-2Rα values in 18 children with Wilms' tumour and soft tissue sarcomas exceeded significantly the results obtained in healthy controls.

Pui et al. also investigated the prognostic significance of sIL-2Rα levels determined at diagnosis of some lymphoproliferative disorders. Among children with HL (Pui et al. 1989, 1993), NHL (Pui et al. 1987) and ALL (Pui et al. 1988), they showed a correlation between pretreatment sIL-2Rα concentrations and the rate of overall survival. Multivariate analysis performed in children with NHL proved that serum level of sIL-2Rα had a significantly higher predictive value than LDH concentration and disease stage. Thus, the authors suggested the determination of sIL-2Rα to be implemented in diagnostic and prognostic protocols for HL in children. Similarly, Viviani et al. (1998) stated that pretreatment sIL-2Rα levels in children with HL were significantly associated with the presence of constitutional symptoms. Bien et al. (2006) observed significantly higher sIL-2R levels in advanced stages of solid tumours and malignant lymphomas and in children with HL and NHL with general symptoms and bulky disease presentation. However, in a cohort of 344 newly diagnosed children with ALL multivariate analyses showed no correlation of the receptor with age, sex, race, leukocyte count, blasts count, LDH level, liver and spleen sizes, FAB classification and CNS involvement (Pui et al. 1988).

To the best of our knowledge there have been only two published studies concerning the usefulness of sIL-2Rα monitoring in children with cancer. Komp et al. (1989) reported that chemotherapy applied to nine children with haemophagocytic–histiocytic syndrome resulted in dramatic reduction of extremely high pretreatment

sIL-2Rα levels towards the normal range established for each particular age of patients at the time of examinations. The limitation of this report was the small number of patients included in the study and the fact that not all children were examined at all stages of disease. Probably the first report on the role of serial serum CD25 antigen monitoring in children with solid malignancies (including Wilms' tumour and soft tissue sarcomas) has been published recently in *Biomarkers* (Bien et al. 2007). In this study it was found that good response to anti-tumour therapy was paralleled with significant decline of pretreatment sIL-2Rα levels and decrease of its elevated rates. Thus, the authors suggested that sIL-2Rα serial measurements might be of some value in both diagnostics and treatment monitoring in childhood Wilms' tumour and sarcomas. This statement may be of special interest as these tumours lack any specific biochemical markers able to supplement the diagnostic and prognostic methods used in everyday oncological practice.

IL-2Rα as a target for immunotherapy

The rationale for targeting the α subunit of the IL-2 receptor

Immunotherapy of cancer has always been a very attractive fourth-modality therapeutic approach. The identification of tumour antigens has offered new perspectives and provided new opportunities for more accurate immunotherapy for cancer (Rosenberg et al. 2004, de Pillis et al. 2006, Volkland et al. 2007). Immunotherapy falls into three main categories: immune response modifiers, vaccines and monoclonal antibodies. The monoclonal antibodies are currently being developed to target specific cancer antigens. Since they are able to distinguish between normal and cancer cells, they may be used both in cancer diagnostics and treatment (Chouaib et al. 2002, Hadj 2005, Qu et al. 2005).

As mentioned above, in 1981 Uchiyama and co-workers discovered and produced the monoclonal antibody, termed anti-Tac, directed toward the α subunit of the IL-2 receptor. This antibody (later termed anti-CD25) played a crucial role in the understanding of the significance of the IL-2/IL-2R system in the physiological and abnormal immune responses (Uchiyama et al. 1981). IL-2Rα has been shown to be an exceptionally valuable target for immunotherapy because, physiologically, it is not expressed by resting T and B cells, and only 5% of the circulating lymphocytes express IL-2Rα at a very low level. The remaining mature T and B lymphocytes start to express the α subunit only after stimulation with cytokines, e.g. IL-1, IL-6 and TNF (Waldmann 1991, 2002, 2007, Church 2003). However, in several disorders the α subunit of the IL-2 receptor has been shown to be expressed on the cell surface. They include organ-allograft rejection, T cell-mediated autoimmune diseases and certain haematological malignancies. In particular, ATL, HCL, acute and chronic granulocytic leukaemia, HL and CTCL have been shown to be constitutively expressing the α subunit on their cellular surface. In contrast, in certain T cell-mediated diseases, such as transplant rejection or autoimmune diseases, the α subunit of the IL-2 receptor is expressed as a result of T-cell activation, which occurs predominantly in the area of the pathology, for example the synovial fluid in rheumatoid arthritis (Waldmann 1991, 2007, Linares et al. 2004, Nelson 2004, Witkowska 2005).

These observations provided the scientific rationale for the initiation of therapeutic studies with the anti-IL-2Rα monoclonal antibody (Waldmann 2002, 2007). Such IL-2Rα directed agents could theoretically eliminate CD25-expressing leukaemic cells

or activated T cells and their precursors involved in other disease states and in allograft rejection, while retaining the CD25 negative, normal T cells. It is suggested that the application of specific anti-IL-2α receptor antibodies in these diseases will cause maximum damage to the pathogenic cells with minimal side-effects to other non-α subunit expressing cells.

Specific anti-IL-2α receptor antibodies

The initial discovery of the α subunit of the receptor complex was by the development of a murine monoclonal antibody against activated T cells and this was named anti-Tac (Uchiyama et al. 1981). Since this, many adaptations have been made to the basic structure of anti-Tac in an attempt to improve its efficacy. Initial clinical uses of the unmodified murine anti-Tac were hampered by the problem that mouse antibodies were strongly immunogenic in humans. In the vast majority of clinical studies their usefulness was limited because they induced an immune response that neutralized their therapeutic effect (Qu et al. 2005, Tsurushita et al. 2005).

To overcome these problems, genetic engineering has created chimeric and humanized forms of the murine anti-Tac antibody. These reagents have maintained the exquisite specificity and affinity to the tumour antigens but with reduced immunogenicity and toxicity in humans. Currently, two marketed specific anti-IL-2αR antibodies exist, called basiliximab and daclizumab. Basiliximab (Simulect®) is a chimeric monoclonal antibody produced by recombinant DNA techniques from a mouse myeloma cell line, in which 75% of the sequence has been humanized. Daclizumab (Zenapax®) is a humanized monoclonal antibody with approximately 90% of the murine sequence replaced by human sequences. The two antibodies are administered on different dose schedules because of their different pharmacokinetic profiles (Pascual et al. 2001, Church 2003, van Gelder et al. 2004).

Further adaptations have been made to the anti-IL-2R antibodies to increase their utility in treatment of particular diseases. These include the creation of the radiolabelled anti-CD25 constructs and immunotoxin-linked conjugates (Qu et al. 2005). Both α- and β-emitting radioisotopes have been attached to the antibody, including bismuth-212 and yttrium-90. The radiolabelled antibodies can penetrate a tissue area, and despite binding to only one cell, the emitting radiation can work over a distance of several cell diameters, eliminating surrounding cells at the same time. They also do not need to be internalized into the cell, unlike the immunotoxin antibody conjugates. These structures have in essence part of a toxic protein, such as diphtheria or *Pseudomonas* toxin, attached to the antibody, which then delivers this cytotoxic agent to the target cell. An alternate approach is the use of natural ligands of cells, such as IL-2, linked to toxins, such as diphtheria toxin, ricin toxin and *Pseudomonas* toxin, to target the IL-2 receptor and selectively kill IL-2 receptor-bearing cells (Linares et al. 2004).

Clinical effectiveness of the IL-2Rα targeted therapy

The administration of the humanized or chimeric forms of anti-IL-2Rα antibody proved to be of special value in the treatment of many T cell-mediated disorders including organ-allograft rejection, graft-versus-host disease in bone marrow recipients, several T cell-mediated autoimmune disorders and haematological malignancies.

Anti-IL-2 receptors – both daclizumab and basiliximab – have been proved effective in reducing the rate of acute rejection in kidney transplantation and also in improving both the rate of graft and patient survival. Daclizumab was also of value as an induction immunosuppression in immunologically high-risk kidney transplant patients compared with normally low-risk patients (Swiatecka-Urban 2003, Jirasiritham et al. 2004, Tsurushita et al. 2005). Clinical use of anti–IL-2R antibodies has also contributed to the substantial reduction of acute liver and cardiac allograft rejection episodes both in children and adults (Lietz et al. 2003, Orr et al. 2005). Administration of the anti-CD25 antibodies also proved effective in decreasing the severity of graft-versus-host disease in patients undergoing HLA-matched allogeneic bone marrow transplantation (Morris & Waldmann 2000, Przepiorka et al. 2000, Waldmann 2002, 2007). In addition to the effectiveness of anti-IL-2Rα antibodies in the prevention of organ-allograft rejection, it was shown that they are of value in the treatment of several T cell-mediated autoimmune disorders. In particular, daclizumab provided effective therapy for patients with non-infectious uveitis who were able to be weaned off their systemic immunosuppressive medications (Nussenblatt et al. 2003). Furthermore, patients with multiple sclerosis failing β-interferon therapy demonstrated a 78% reduction in the development of gadolinium-enhanced MRI lesions while on therapy with daclizumab (Bielekova et al. 2004). In addition, daclizumab seems to be a promising therapeutic option for patients with moderate aplastic anaemia and acquired pure red cell aplasia (Maciejewski et al. 2003, Sloand et al. 2006). Basiliximab has also been used successfully in the treatment of patients with severe psoriasis (Owen & Harrison 2000), epidermolysis bullosa acquisita (Haufs & Haneke 2001), severe chronic atopic dermatitis (Kagi & Heyer 2001) and several other inflammatory diseases (Church 2003).

IL-2R-targeted treatment of neoplasia

IL-2Rα-targeted treatment has shown promise in the treatment of several CD25-expressing human malignancies. The ability of anti-CD25 to block the binding of a specific cytokine growth factor (IL-2) to its receptor may inhibit the proliferation of the malignant cells over expressing IL-2Rα. As mentioned above, these cells originate from adult T-cell leukaemia/lymphoma, mycosis fungoides, peripheral T-cell lymphomas, HCL, Reed–Sternberg cells, anaplastic large-cell lymphoma and some B-cell neoplasms. The therapeutic trials of anti-CD25 started with ATL as the prototypical disease. ATL is an aggressive lymphoproliferative disorder caused by infection with the HTLV-1. The median survival for patients with acute form of ATL is very short with relatively few patients responding to chemotherapy or combination of interferon-alfa and zidovudine. Beginning in the 1980s, Waldmann and colleagues initiated a series of clinical trials with the use of monoclonal anti-CD25 antibodies as a therapeutic approach to ATL. The trials started with application of the unmodified murine anti-Tac; however, its efficacy appeared to be limited and led to the alternative approach of using this antibody as a carrier of cytotoxic agents such as toxins or radionuclides (Morris & Waldmann 2000, Waldmann 2007). The therapy with murine anti-Tac armed with the α-emitting isotope yttrium-90 and, more recently, ^{90}Y-labelled humanized anti-Tac (HAT) administered to patients with HTLV-I-associated ATL and the neurological disease, HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) was shown to produce remissions in over 50% of the

patients with ATL and 70% of patients with HL (O'Mahony et al. 2006, Fukushima et al. 2007, Waldmann 2007).

Other approaches to IL-2R-targeted treatment of cancer have been the use of ligand–toxin fusion proteins and immunotoxins (Volkland et al. 2007). DAB389IL-2 is a 58 kDa fusion protein engineered between the domains of diphtheria toxin and human IL-2 able to direct cytocidal activity to cells that express the IL2 receptor. In a clinical trial involving 35 patients with advanced treatment refractory CTCL and mycosis fungoides, DAB389IL2 produced a 37% response rate including 14% complete responses. A recent trial using a fusion protein of a truncated *Pseudomonas* exotoxin A and the Fv-fragment of anti-CD25 (LMB-2) showed promising early results in patients with IL-2Rα expressing lymphoid neoplasms including HCL, CLL, HL, CTCL and ATL (Morris & Waldmann 2000, Foss & Waldmann 2003, Waldmann 2007).

Future approaches under development include the use of HAT chelated to α-emitting radionuclides such as ^{212}Bi, ^{213}Bi or ^{211}At because of their more favourable radiobiological profiles. Combination of anti-IL-2R antibodies with other antibodies (anti-CD30) or with other modalities such as chemotherapy or other cytokines is also projected.

The field of receptor-targeted treatment is still in its infancy. No doubt with continued improvement of monoclonal antibody technology, refinements in linking toxins and radiopharmaceuticals to antibodies and ligands, the targeting of the IL-2R and other cytokine receptors holds great promise as treatment for a large number of diverse diseases. However, some issues should be taken into consideration. First, it was shown that only a fraction of receptors expressed in considerable amount in response to immune activation is associated with IL-2 (Taniguchi & Minami 1993). Therefore, anti-CD25 monoclonal antibodies must almost completely saturate CD25 before a significant inhibition of IL-2-mediated events can be expected. This would explain clinical data from a psoriasis trial in which incomplete saturation of CD25 by daclizumab as a consequence of more infrequent dosing led to relapses (Krueger et al. 2000). Another issue of anti-CD25 therapies is the presence of serum soluble CD25 (Mehta et al. 2004). sIL-2Rα measurements may be useful in the monitoring of patients treated with monoclonal antibodies against the IL-2 receptor, since a decrease in the serum level of sIL-2R has been found to parallel the reappearance of CD25-positive T lymphocytes (Warle et al. 2003a, Ter Meulen et al. 2004). On the other hand, soluble CD25 could absorb a portion of the antibody translating into the need for higher therapeutic doses. Lastly, one must remember that therapy with the use of anti-CD25 antibodies may still allow receptor stimulation by IL-2 through the intermediate affinity receptor complex assembly (Rickert et al. 2004).

Conclusions

Despite many studies and literature reports concerning the behaviour of sIL-2Rα in particular types of lymphoproliferative and solid neoplasms, the biological significance of high serum levels of this receptor has not been definitely established. Also, the precise source of sIL-2Rα in these conditions has not been defined clearly – increased shedding from tumour cells or lymphocytes activated by tumour growth have been postulated (Heaney & Golde 1996). Nevertheless, large amounts of circulating sIL-2Rα capable of binding IL-2 efficiently (Rubin et al. 1986, Dummer et al. 1992) may

result in impairment of IL-2-dependent functions, including anti-tumour response (Burton & Kay 1994). Diminished NK-cell activity in CTCL may also be explained by elevated levels of sIL-2Rα neutralizing IL-2 (Dummer et al. 1992). However, some investigators reported diminished production of both IL-2 and its high-affinity membrane receptor in activated lymphocytes isolated from patients with malignant gliomas, HL and ALL (Frydecka & Mazur 1996, Zhang et al. 2006). Also, elevated soluble receptor concentrations in the ascites of patients with ovarian cancer and in the serum of patients with breast cancer were found to correlate with a decreased number of infiltrating lymphocytes in the tumours which suggests that sIL-2Rα may depress an endogenous anti-tumour immune response (Sabbioni et al. 2000).

These observations may in part explain the phenomenon of highly increased sIL-2Rα in aggressive, advanced or metastatic malignancies. Although the reason and biological role of the increased concentrations of sIL-2Rα still need to be elucidated definitively, the clinical usefulness of soluble IL-2Rα determination in most human cancers is of special value and interest for oncologists.

References

Ambrosetti A, Nadali G, Vinante F, Carlini S, Veneri D, Todeschini G, Morosato L, Sabata de D, Chilosi M, Maggi E, Parronchi P, Romagnani S, Semenzato G, Perona G, Pizzolo G. 1993a. Serum levels of soluble interleukin-2 receptor in Hodgkin disease. Cancer 72:201–206.

Ambrosetti A, Nadali G, Vinante F, Ricetti MM, Todeschini G, Morosato L, de Sabata D, Bergamo Andreis IA, Chilosi M, Semenzato G, et al. 1993b. Soluble interleukin-2 receptor in hairy-cell leukemia: a reliable marker of disease. International Journal of Clinical & Laboratory Research 23:34–37.

Anderson DM, Kumaki S, Ahdieh M, Bertles J, Tometsko M, Loomis A, et al. 1995. Functional characterisation of the human interleukin-15 receptor alpha chain and close linkage of IL-15RA and IL-2RA genes. Journal of Biological Chemistry 270(29):862–869.

Arun B, Curti BD, Longo DL, Stevens D, Alvord WG, Gause BL, Watson T, Kopp WC, Janik JE. 2000. Elevations in serum soluble interleukin-2 receptor levels predict relapse in patients with hairy cell leukemia. Cancer Journal for Scientific American 6:21–24.

Atkins MB, Kunkel L, Sznol M, Rosenberg SA. 2000. High-dose recombinant interleukin-2 therapy in patients with metastatic melanoma: long-term survival update. Cancer Journal for Scientific American 6:11–14.

Bamford RN, Grant AJ, Burton JD, Peters C, Kurys G, et al. 1994. The interleukin (IL) 2 receptor beta chain is shared by IL-2 and a cytokine, provisionally designated IL-T, that stimulates T-cell proliferation and the induction of lymphokine-activated killer cells. Proceedings of the National Academy of Science USA 91:4940–4944.

Bayer AL, Yu A, Adeegbe D, Malek TR. 2005. Essential role for interleukin-2 for CD4(+)CD25(+) T regulatory cell development during the neonatal period. Journal of Experimental Medicine 201:769–777.

Beatty GL, Paterson Y. 2000. IFN-gamma can promote tumor evasion of the immune system in vivo by down-regulating cellular levels of an endogenous tumor antigen. Journal of Immunology 165:5502–5508.

Berghella AM, Pellegrini P, Del Beato T, Marini M, Tomei E, Adorno D, Casciani CU. 1998. The significance of an increase in soluble interleukin-2 receptor level in colorectal cancer and its biological regulating role in the physiological switching of the immune response cytokine network from TH1 to TH2 and back. Cancer Immunology & Immunotherapy 45:241–249.

Bielekova B, Richert N, Howard T, Blevins G, Markovic-Plese S, McCartin J, Frank AJ, Wurfel J, Ohayon J, Waldmann TA, McFarland HF, Martin R. 2004. Humanized anti–CD25 (daclizumab) inhibits disease activity in multiple sclerosis patients failing to respond to interferon beta. Proceedings of the National Academy of Science USA 101:8705–8708.

Bien E, Balcerska A, Ciesielski D. 2006. Diagnostic and prognostic significance of serum soluble interleukin 2 receptor in children with malignancies. Wiadomości Lekarskie 59:10–15.

Bien E, Balcerska A, Kuchta G. 2007. Serum level of soluble interleukin-2 receptor α correlates with the clinical course and activity of Wilms' tumour and soft tissue sarcomas in children. Biomarkers 12:203–213.

Bodey B, Psenko V, Lipsey AL, Kaiser HE. 1996. Soluble interleukin-2 receptors in sera of children with primary malignant neoplasms. Anticancer Research 16:219–224.

Boyano MD, Garcia-Vasquez MD, Lopez-Michelena T, Gardeazahal J, Bilbao J, Canavate ML, Galdeano AG, Izu R, Diaz-Ramon L, Raton JA, Diaz-Perez JL. 2000. Soluble interleukin-2 receptor, intercellular adhesion molecule-1 and interleukin-10 serum levels in patients with melanoma. British Journal of Cancer 83:847–852.

Brunetti G, Bossi A, Baiardi P, Jedrychowska I, Pozzi U, Bacchella L, Bernardo G. 1999. Soluble interleukin 2 receptor (sIL2R) in monitoring advanced lung cancer during chemotherapy. Lung Cancer 23:1–9.

Burton J, Kay NE. 1994. Does IL-2 receptor expression and secretion in chronic B-cell leukemia have a role in down-regulation of the immune system? Leukemia 8:92–96.

Can M, Yüksel B, Demirtaş S, Tomaç N. 2006. The effect of montelukast on soluble interleukin-2 receptor and tumor necrosis factor alpha in pediatric asthma. Allergy & Asthma Proceedings 27:383–386.

Cassell DJ, Choudhri S, Humphrey R, Martell RE, Reynolds T, Shanafelt AB. 2002. Therapeutic enhancement of IL-2 through molecular design. Current Pharmaceutical Design 8:2171–2183.

Chouaib S, Thiery J, Gati A, Guerra N, El Behi M, Dorothee G, Mami-Chouaib F, Bellet D, Caignard A. 2002. Tumor escape from killing: role of killer inhibitory receptors and acquisition of tumor resistance to cell death. Tissue Antigens 60:273–281.

Church AC. 2003. Clinical advances in therapies targeting the interleukin-2 receptor. QJM 96:91–102.

Correia O, Delgado L, Roujeau JC, Le Cleach L, Fleming-Torrinha JA. 2002. Soluble interleukin 2 receptor and interleukin 1alpha in toxic epidermal necrolysis: a comparative analysis of serum and blister fluid samples. Archives of Dermatology 138:29–32.

Dalgleish AG, O'Byrne KJ. 2002. Chronic immune activation and inflammation in the pathogenesis of AIDS and cancer. Advances in Cancer Research 84:231–276.

Dejica D. 2001. Serum soluble IL-2 receptor as a marker of lymphocyte activation in some autoimmune diseases. Effect of immunosuppressive therapy. Roumanian Archives of Microbiology and Immunology 60:183–201.

de Pillis LG, Gu W, Radunskay. AE. 2006. Mixed immunotherapy and chemotherapy of tumors: modeling, applications and biological interpretations. Journal of Theoretical Biology 238:841–862.

Diefenbach A, Raulet D. 2002. The innate immune response to tumors and its role in the induction of T-cell immunity. Immunological Reviews 188:9–21.

Disis ML, Lyerly HK. 2005. Global role of the immune system in identifying cancer initiation and limiting disease progression. Journal of Clinical Oncology 23:8923–8925.

Dranoff G. 2003. Coordinated tumor immunity. Journal of Clinical Investigation 111:1116–1118.

Dummer R, Posseckert G, Nestle F, Witzgall R, Burger M, Becker JC, Schäfer E, Wiede J, Sebald W, Burg G. 1992. Soluble interleukin-2 receptors inhibit interleukin 2-dependent proliferation and cytotoxicity: explanation for diminished natural killer cell activity in cutaneous T-cell lymphomas in vivo? Journal of Investigative Dermatology 98:50–54.

Dunn G, Bruce A, Ikeda H, Old L, Schreiber R. 2002. Cancer immunoediting: from immunosurveillance to tumor escape. Nature Immunology 3:991–998.

Eicher DM, Waldmann TA. 1998. IL-2α on one cell can present IL-2 to IL-2Rβ/γ_c on another cell to augment IL-2 signaling. Journal of Immunology 161:5430–5437.

Fabre-Guillevin E, Tabrizi R, Coulon V, Monnereau A, Eghbali H, Soubeyran I, Soubeyran P. 2006. Aggressive non-Hodgkin's lymphoma: concomitant evaluation of interleukin-2, soluble interleukin-2 receptor, interleukin-4, interleukin-6, interleukin-10 and correlation with outcome. Leukemia & Lymphoma 47:603–611.

Fawcett PT, Rose CD, Proujansky R, Gibney KM, Molloy DM, Doughty RA. 1993. Serial measurement of soluble interleukin 2 receptor levels: an early indicator of treatment response for Lyme disease. Journal of Rheumatology 20:996–998.

Fehervari Z, Yamaguchi T, Sakaguchi S. 2006. The dichotomous role of IL-2: tolerance versus immunity. Trends in Immunology 27:109–111.

Fehniger TA, Cooper MA, Caligiuri MA. 2002. Interleukin-2 and interleukin-15: immunotherapy for cancer. Cytokine & Growth Factor Reviews 13:169–183.

Fisher RI, Rosenberg SA, Fyfe G. 2000. Long-term survival update for high-dose recombinant interleukin-2 in patients with renal cell carcinoma. Cancer Journal for Scientific American 6:55–57.

Foss FM, Waldmann TA. 2003. Interleukin-2 receptor-directed therapies for cutaneous lymphomas. Hematology/Oncology Clinics of North America 17:1449–1458.

Frydecka I, Mazur G. 1996. Impaired CD25 expression and soluble CD25-IL-2Rα receptor release by anti-CD3 stimulated peripheral blood mononuclear cells in Hodgkin's disease patients. Archivum Immunologiae et Therapiae Experimentalis 44:127–130.

Frydecka I, Rusiecka M, Kuliczkowski K, Kornafel J. 1996. Serum soluble interleukin 2 receptor α and soluble CD8 levels in patients with gynecological malignancies undergoing radiotherapy. Archivum Immunologiae et Therapiae Experimentalis 44:123–126.

Fujita N, Okamoto Y, Gotoh Y, Yada Y, Suzuki Y, Ando T, Togari H, Nishida M. 2005. Serum evaluation of the balance between soluble interleukin-2 and interleukin-4 receptors. Cytokine 32:143–148.

Fukushima N, Nishiura Y, Nakamura T, Kohno S, Eguchi K. 2007. Blockade of IL-2 receptor suppresses HTLV-I and IFN-γ expression in patients with HTLV-I-associated myelopathy/tropical spastic paraparesis. Internal Medicine 46:347–351.

Gansauge E, Steinbach G, Gansauge S, et al. 1998. Prognostic significance of soluble interleukin-2 receptor in adenocarcinoma of the pancreas. Cancer Letters 134:193–199.

Garcia-Lora A, Algarra I, Garrido F. 2003. MHC class I antigen, immune surveillance and tumour immune escape. Journal of Cell Physiology 195:346–355.

Goto H, Tsurumi H, Takemura M, Ino-Shimomura Y, Kasahara S, Sawada M, Yamada T, Hara T, Fukuno K, Goto N, Okuno M, Takami T, Seishima M, Moriwaki H. 2005. Serum-soluble interleukin-2 receptor (sIL-2R) level determines clinical outcome in patients with aggressive non-Hodgkin's lymphoma: in combination with the International Prognostic Index. Journal of Cancer Research & Clinical Oncology 131:73–79.

Grutters JC, Fellrath JM, Mulder L, Janssen R, van den Bosch JM, van Velzen-Blad H. 2003. Serum soluble interleukin-2 receptor measurement in patients with sarcoidosis: a clinical evaluation. Chest 124: 186–195.

Gustot T, Lemmers A, Louis E, Nicaise C, Quertinmont E, Belaiche J, Roland S, Van Gossum A, Devière J, Franchimont D. 2005. Profile of soluble cytokine receptors in Crohn's disease. Gut 54:488–495.

Gutgsell NS, Malek TR. 1994. Formation of high affinity IL-2 receptors is dependent on a nonligand binding region of the (subunit. Journal of Immunology 153:3899–3907.

Haack M, Pollmächer T, Mullington JM. 2004. Diurnal and sleep-wake dependent variations of soluble TNF- and IL-2 receptors in healthy volunteers. Brain. Behavior & Immunity 18:361–367.

Hadj TA. 2005. Alemtuzumab for B-cell chronic lymphocytic leukemia. Issues in Emerging Health Technologies 66:1–4.

Hassel JC, Meier R, Joller-Jemelka H, Burg G, Dummer R. 2004. Serological immunomarkers in cutaneous T cell lymphoma. Dermatology 209:296–300.

Haufs MG, Haneke E. 2001. Epidermolysis bullosa acquisata treated with basiliximab, an interleukin-2 receptor antibody. Acta Dermato-Venereologica 81:72.

Heaney ML, Golde DW. 1996. Soluble cytokine receptors. Blood 87:847–857.

Heaney ML, Golde DW. 1998. Soluble receptors in human disease. Journal of Leukocyte Biology 64: 135–146.

Horiuchi S, Koyanagi Y, Yanaka Y, Waki M, Matsumoto A, Zhou YW, Yamamoto M, Yamamoto N. 1997. Altered interleukin-2 receptor α-chain is expressed in human T-cell leukaemia virus type-I-infected T-cell lines and human peripheral blood mononuclear cells of adult T-cell leukaemia patients through an alternative splicing mechanism. Immunology 91:28–34.

Houghton AN, Gold JS, Blachere NE. 2001. Immunity against cancer: lessons learned from melanoma. Current Opinions in Immunology 13:134–140.

Huang A, Quinn H, Glover C, Henderson DC, Allen-Mersh TG. 2002. The presence of interleukin-2 receptor alpha in the serum of colorectal cancer patients is unlikely to result only from T cell up-regulation. Cancer Immunology. Immunotherapy 51:53–57.

Igney FH, Krammer PH. 2002. Immune escape of tumors: apoptosis resistance and tumor counterattack. Journal of Leukocyte Biology 71:907–920.

Ishii R, Morimoto A, Ikushima S, Sugimoto T, Asami K, Bessho F, Kudo K, Tsunematu Y, Fujimoto J, Imashuku S. 2006. High serum values of soluble CD154, IL-2 receptor, RANKL and osteoprotegerin in Langerhans cell histiocytosis. Pediatric Blood & Cancer 47:194–199.

Izzo F, Cremona F, Delrio P, Leonardi E, Castello G, Pignata S, Daniele B, Curley SA. 1999. Soluble interleukin-2 receptor levels in hepatocellular cancer: a more sensitive marker than alfa fetoprotein. Annals of Surgical Oncology 6:178–185.

Janik JE, Morris JC, Pittaluga S, McDonald K, Raffeld M, Jaffe ES, Grant N, Gutierrez M, Waldmann TA, Wilson WH. 2004. Elevated serum-soluble interleukin-2 receptor levels in patients with anaplastic large cell lymphoma. Blood 104:3355–3357.

Jirasiritham S, Sumethkul V, Mavichak V, Lertsithichai P, Jirasiritham S. 2004. The role of anti-IL-2 receptor in high-risk kidney transplant patients. Transplant Proceedings 36:2110–2112.

Junghans RP, Waldmann TA. 1996. Metabolism of Tac (IL-2Ra): physiology of cell surface shedding and renal catabolism, and suppression of catabolism by antibody binding. Journal of Experimental Medicine 183:1587–1602.

Kagi MK, Heyer G. 2001. Efficacy of basiliximab, a chimeric anti-interleukin-2 receptor monoclonal antibody, in a patient with severe chronic atopic dermatitis. British Journal of Dermatology 145: 350–351.

Kallio JP, Tammela TL, Marttinen AT, Kellokumpu-Lehtinen PL. 2001. Soluble immunological parameters and early prognosis of renal cell cancer patients. Journal of Experimental Clinical Cancer Research 20:523–528.

Kami M, Matsumura T, Tanaka Y, Mikami Y, Miyakoshi S, Ueyama J, Morinaga S, Mori S, Machida U, Kanda Y, Chiba S, Sakamaki H, Hirai H, Muto Y. 2000. Serum levels of soluble interleukin-2 receptor after bone marrow transplantation: a true marker of acute graft-versus-host disease. Leukemia & Lymphoma 38:533–540.

Kaminska J, Kowalska M, Kotowicz B, Fuksiewicz M, Glogowski M, Wojcik E, Chechlinska M, Steffen J. 2006. Pretreatment serum levels of cytokines and cytokine receptors in patients with non-small cell lung cancer, and correlations with clinicopathological features and prognosis. M-CSF-an independent prognostic factor. Oncology 70:115–125.

Kaufman HL, Jedd D. 2006. Is tumor immunity the same thing as autoimmunity? Implications for cancer immunotherapy. Journal of Clinical Oncology 24:2230–2232.

Kawashima O, Kamiyoshihara M, Sakata S, Endo K, Saito R, Morishita Y. 2000. The clinicopathological significance of preoperative serum-soluble interleukin-2 receptor concentrations in operable non-small-cell lung cancer patients. Annals of Surgical Oncology 7:239–245.

Kayhan B, Kayhan B, Akdogan M. 2004. Can IL-2R alpha be a valuable marker along with CA 19-9 in the diagnosis of chronic pancreatitis and pancreatic cancer? International Journal of Biological Markers 19:196–202.

Komp DM, McNamara J, Buckley P. 1989. Elevated soluble interleukin-2 receptor in childhood hemophagocytic histiocytic syndromes. Blood 73:2128–2132.

Komp DM, Shapiro E, McNamara J. 1988. Soluble interleukin-2 receptor in childchood non-Hodgkin's lymphoma. Blood 71:1172–1174.

Krueger JG, Walters IB, Miyazawa M, Gilleaudeau P, Hakimi J, Light S, Sherr A, Gottlieb AB. 2000. Successful in vivo blockade of CD25 (high affinity interleukin 2 receptor) on T cells by administration of humanized anti-Tac antibody to patients with psoriasis. Journal of American Academy of Dermatology 43:48–458.

Kuku I, Bayraktar MR, Kaya E, Erkurt MA, Bayraktar N, Cikim K, Aydogdu I. 2005. Serum proinflammatory mediators at different periods of therapy in patients with multiple myeloma. Mediators of Inflammation 3:171–174.

Kuuliala A, Söderlin M, Kautiainen H, Repo H, Leirisalo-Repo M. 2005. Circulating soluble interleukin-2 receptor level predicts remission in very early reactive arthritis. Scandinavian Journal of Rheumatology 34:372–375.

Kuuliala A, Nissinen R, Kautiainen H, Repo H, Leirisalo-Repo M. 2006. Low circulating soluble interleukin 2 receptor level predicts rapid response in patients with refractory rheumatoid arthritis treated with infliximab. Annals of the Rheum Disease 65:26–29.

Lee W, Kim SJ, Lee S, Kim J, Kim M, Lim J, Kim Y, Cho B, Lee EJ, Han K. 2005. Significance of cerebrospinal fluid sIL-2R level as a marker of CNS involvement in acute lymphoblastic leukemia. Annals of Clinical & Laboratory Science 35:407–412.

Leonard WJ, Noguchi M, Russell SM, McBride OW. 1994. The molecular basis of X-linked severe combined immunodeficiency: the role of the interleukin-2 receptor gamma chain as a common gamma chain, gamma c. Immunological Reviews 138:61–86.

Lietz K, John R, Beniaminovitz A, Burke EM, Suciu-Foca N, Mancini DM, Edwards NM, Itescu S. 2003. Interleukin-2 receptor blockade in cardiac transplantation: influence of HLA-DR locus incompatibility on treatment efficacy. Transplantation 75:781–787.

Linares R, Pacheco JR, Good TA. 2004. Efficacy of different targeting agents in the photolysis of interleukin-2 receptor bearing cells. Journal of Photochemistry and Photobiology B. Biology 77:17–26.

Lis AD, Brzezinska-Wcislo LA. 2003. Soluble receptors of cytokines in sera of patients with systemic sclerosis – clinical correlation. Wiadomości Lekarskie 56:532–536.

Lissoni P, Barni S, Rovelli F, Viviani S, Maestrono GJM, Conti A, Tancini G. 1990. The biological significance of soluble interleukin-2 receptors in solid tumors. European Journal of Cancer 26:33–36.

Maciejewski JP, Sloand EM, Nunez O, Boss C, Young NS. 2003. Recombinant humanized anti-IL-2 receptor antibody (daclizumab) produces responses in patients with moderate aplastic anemia. Blood 102:3584–3586.

Makis AC, Galanakis E, Hatzimichael EC, Papadopoulou ZL, Siamopoulou A, Bourantas KL. 2005. Serum levels of soluble interleukin-2 receptor alpha (sIL-2Ralpha) as a predictor of outcome in brucellosis. Journal of Infections 51:206–210.

Malek TR, Bayer AL. 2004. Tolerance, not immunity, crucially depends on IL-2. Nature Reviews Immunology 4:665–674.

Matsuno O, Okubo F, Masutomo K, Yoshida F, Okubo T, Miyazaki E, Kumamoto T. 2003. Elevated concentrations of soluble IL-2 receptor in both bronchoalveolar lavage fluid and serum in a patient with BOOP. Tohoku Journal of Experimental Medicine 201:61–65.

Mehta R, Shah G, Adler W, Kittur D. 2004. Soluble interleukin 2 receptor (sIL-2R) levels in renal transplant recipients. Clinical Transplantation 18(Suppl. 12):67–71.

Moon Y, Kim Y, Kim M, Lim J, Kang CS, Kim WI, Shim SI, Chung NG, Park YH, Min WS, Han K. 2004. Plasma soluble interleukin-2 receptor (sIL-2R) levels in patients with acute leukemia. Annals of Clinical & Laboratory Science 34:410–415.

Morgan DA, Ruscetti FW, Gallo R. 1976. Selective in vitro growth of T-lymphocytes from normal human bone marrow. Science 193:1007–1009.

Morris JC, Waldmann TA. 2000. Advances in interleukin 2 receptor targeted treatment. Annals of the Rheumatic Diseases 59:i109–114.

Murakami S. 2004. Soluble interleukin-2 receptor in cancer. Frontiers in Bioscience 9:3085–3090.

Murakami S, Sakata H, Tsuji Y, Okubo K, Hamada S, Hirayama R. 2002. Serum soluble interleukin-2 receptor as a predictor of lymph node metastasis in early gastric cancer. Digestive Surgery 19:9–14.

Nakase K, Kita K, Nasu K, Ueda T, Tanaka I, Shirakawa S, Tsudo M. 1994a. Differential expression of interleukin-2 receptors (alpha and beta chain) in mature lymphoid neoplasms. American Journal of Hematology 46:179–183.

Nakase K, Kita K, Shirakawa S, Tanaka I, Tsudo M. 1994b. Induction of cell surface interleukin 2 receptor alpha chain expression on non-T lymphoid leukemia cells. Leukemia Research 18:855–859.

Nakase K, Tsuji K, Tamaki S, Tanigawa M, Ikeda T, Miyanishi E, Shiku H. 2005. Elevated levels of soluble interleukin-2 receptor in serum of patients with hematological or non-hematological malignancies. Cancer Detection & Prevention 29:256–259.

Nelson BH. 2004. IL-2, regulatory T cells, and tolerance. Journal of Immunology 172:3983–3988.

Nussenblatt RB, Thompson DJ, Li Z, Chan CC, Peterson JS, Robinson RR, Shames RS, Nagarajan S, Tang MT, Mailman M, Velez G, Roy C, Levy-Clarke GA, Suhler EB, Djalilian A, Sen HN, Al-Khatib S, Ursea R, Srivastava S, Bamji A, Mellow S, Sran P, Waldmann TA, Buggage RR. 2003. Humanized anti-interleukin-2 (IL-2) receptor alpha therapy: long-term results in uveitis patients and preliminary safety and activity data for establishing parameters for subcutaneous administration. Journal of Autoimmunity 21:283–293.

O'Mahony D, Morris JC, Carrasquillo JA, Le N, Paik CH, Whatley M, Pittaluga S, Fleisher TA, Lee C, Gao W, O'Hagan D, Brechbiel M, Waldmann TA, Janik JE. 2006. Phase I/II study of Yttrium-90 labeled humanized anti-Tac (HAT) monoclonal antibody and calcium DTPA in CD25-expressing malignancies. Journal of Nuclear Medicine 47:98P.

Orr DW, Portmann BC, Knisely AS, Stoll S, Rela M, Muiesan P, Bowles MJ, Heaton ND, O'Grady JG, Heneghan MA. 2005. Anti-interleukin 2 receptor antibodies and mycophenolate mofetil for treatment of steroid-resistant rejection in adult liver transplantation. Transplantation Proceedings 37:4373–4379.

Ottaiano A, Leonardi E, Simeone E, Ascierto PA, Scala S, Calemma R, Bryce J, Caraco C, Satriano RA, Gianfranco N, Franco R, Botti G, Castello G. 2006. Soluble interleukin-2 receptor in stage I-III melanoma. Cytokine 33:150–155.

Owen CM, Harrison PV. 2000. Successful treatment of severe psoriasis with basiliximab, an interleukin-2 receptor monoclonal antibody. Clinical & Experimental Dermatology 25:195–197.

Pages F, Berger A, Camus M, et al. 2005. Effector memory T cells, early metastasis, and survival in colorectal cancer. New England Journal of Medicine 353:2654–2666.

Panteli KE, Hatzimichael EC, Bouranta PK, Katsaraki A, Seferiadis K, Stebbing J, Bourantas KL. 2005. Serum interleukin (IL)-1, IL-2, sIL-2Ra, IL-6 and thrombopoietin levels in patients with chronic myeloproliferative diseases. British Journal of Haematology 130:709–715.

Parasole R, Izzo F, Perrone F, Pignata S, Galati MG, Leonardi E, Castiglione F, Orlando R, Castello G, Esposito G, Gallo C, Daniele B. 2001. Prognostic value of serum biological markers in patients with hepatocellular carcinoma. Clinical Cancer Research 7:3504–3509.

Pascual J, Marcén R, Ortuño J. 2001. Anti-interleukin-2 receptor antibodies: basiliximab and daclizumab. Nephrology Dialysis Transplantation 16:1756–1760.

Pawlaczyk M, Sobieska M. 2006. A correlation between acute phase proteins and cytokines in patients suffering from mycosis fungoides. Acta Dermatovenerologica Alpina Panonica Adriatica 15:107–112.

Poggi A, Raffaella M. 2006. Mechanisms of tumor escape: role of tumor microenvironment in inducing apoptosis of cytolytic effector cells. Archivum Immunologiae et Therapiae Experimentalis 54:323–333.

Przepiorka D, Kernan NA, Ippoliti C, Papadopoulos EB, Giralt S, Khouri I, Lu JG, Gajewski J, Durett A, Cleary K, Champlin R, Andersson BS, Light S. 2000. Daclizumab, a humanized anti-interleukin-2 receptor alpha chain antibody, for treatment of acute graft-versus-host disease. Blood 95:83–89.

Pui C-H, Ip SH, Kung P, Dodge RK, Berard CW, Crist WM, Murphy SB. 1987. High serum interleukin-2 receptor levels are related to advanced disease and a poor outcome in childhood non-Hodgkin's lymphoma. Blood 70:624–628.

Pui CH, Ip SH, Iflah S, Behm FG, Grose BH, Dodge RK, Crist WM, Furman WL, Murphy SB, Rivera GK. 1988. Serum interleukin 2 receptor levels in childhood acute lymphoblastic leukemia. Blood 71:1135–1137.

Pui CH, Ip SH, Thompson E, Wilimas J, Brown M, Dodge RK, Hoyos de RA, Berard CW, Crist WM. 1989. High serum interleukin-2 receptor levels correlate with a poor prognosis in children with Hodgkin's disease. Leukemia 3:481–484.

Pui CH, Hudson M, Luo X, Wilimas J, Evans W, Crist WM. 1993. Serum interleukin-2 receptor levels in Hodgkin disease and other solid tumors of childhood. Leukemia 7:1242–1244.

Qu Z, Griffiths GL, Wegener WA, Chang CH, Govindan SV, Horak ID, Hansen HJ, Goldenberg DM. 2005. Development of humanized antibodies as cancer therapeutics. Methods 36:84–95.

Rickert M, Boulanger MJ, Goriatcheva N, Garcia KC. 2004. Compensatory energetic mechanisms mediating the assembly of signaling complexes between interleukin-2 and its alpha, beta, and gamma(c) receptors. Journal of Molecular Biology 339:1115–1128.

Rimoldi D, Salvi S, Hartmann F, Schreyer M, Blum S, Zografos L, Plaisance S, Azzarone B, Carrel S. 1993. Expression of IL-2 receptors in human melanoma cells. Anticancer Research 13:555–564.

Rivoltini L, Carrabba M, Huber V, Castelli C, Novellino L, Dalerba P, Mortarini R, Arancia G, Anichini A, Fais S, Parmiani G. 2002. Immunity to cancer: attack and escape in T lymphocyte-tumor cell interaction. Immunological Reviews 188:97–113.

Roifman CM. 2000. Human IL-2 receptor alpha chain deficiency. Pediatric Research 48:6–11.

Romaldini CC, Barbieri D, Okay TS, Raiz R Jr, Cançado EL. 2002. Serum soluble interleukin-2 receptor, interleukin-6, and tumor necrosis factor-alpha levels in children with celiac disease: response to treatment. Journal of Pediatric Gastroenterology & Nutrition 35:513–517.

Rosenberg SA. 2000. Interleukin-2 and the development of immunotherapy for the treatment of patients with cancer. Cancer Journal from Scientific American 6:2–7.

Rosenberg SA. 2001. Progress in human tumour immunology and immunotherapy. Nature 411:380–384.

Rosenberg SA, Yang JC, Restifo NP. 2004. Cancer immunotherapy: moving beyond current vaccines. Nature Medicine 10:909–915.

Rubin LA, Kurman CC, Fritz ME, Biddison WE, Boutin B, Yarchoan R, Nelson D.L. 1985. Soluble interleukin 2 receptors are released from activated human lymphoid cells in vitro. Journal of Immunology 135:3172–3177.

Rubin LA, Jay G, Nelson DL. 1986. The released interleukin 2 receptor binds interleukin 2 efficiently. Journal of Immunology 137:3841–3844.

Rutkowski P, Kaminska J, Kowalska M, Ruka W, Steffen J. 2002. Cytokine serum levels in soft tissue sarcoma patients: correlations with clinico-pathological features and prognosis. International Journal of Cancer 100:463–471.

Sabbioni MEE, Siegrist HP, Bacchi M, et al. 2000. Association between immunity and prognostic factors in early stage breast cancer patients before adjuvant treatment. Breast Cancer Research & Treatment 59:279–287.

Sadeghi M, Daniel V, Naujokat C, Weimer R, Opelz G. 2005. Strikingly higher interleukin (IL)-1alpha, IL-1beta and soluble interleukin-1 receptor antagonist (sIL-1RA) but similar IL-2, sIL-2R, IL-3, IL-4, IL-6, sIL-6R, IL-10, tumour necrosis factor (TNF)-alpha, transforming growth factor (TGF)-beta and interferon IFN-gamma urine levels in healthy females compared to healthy males: protection against urinary tract injury? Clinical & Experimental Immunology 142:312–317.

Sakata H, Murakami S, Hirayama R. 2002. Serum soluble interleukin-2 receptor (IL-2R) and immunohistochemical staining of IL-2R/Tac antigen in colorectal cancer. International Journal of Clinical Oncology 7:312–317.

Schütt P, Ebeling P, Buttkereit U, Brandhorst D, Opalka B, Poser M, Müller S, Flasshove M, Moritz T, Seeber S, Nowrousian MR. 2005. Thalidomide in combination with dexamethasone for pretreated patients with multiple myeloma: serum level of soluble interleukin-2 receptor as a predictive factor for response rate and for survival. Annals of Hematology 84:594–600.

Sedlaczek P, Frydecka I, Gabryś M, Van Dalen A, Einarsson R, Harłozińska A. 2002. Comparative analysis of CA125, tissue polypeptide specific antigen, and soluble interleukin-2 receptor alpha levels in sera, cyst, and ascitic fluids from patients with ovarian carcinoma. Cancer 95:1886–1893.

Shitrit D, Izbicki G, Shitrit Bar-Gil A, Raz M, Sulkes J, Kramer MR. 2006. Role of soluble interleukin-2 receptor levels in patients with latent tuberculosis. Lung 184:21–24.

Sieminska A. 2004. The value of measuring the serum level of soluble interleukin-2 receptors in lung cancer patients. Polski Merkuriusz Lekarski 16:188–190.

Sloand EM, Scheinberg P, Maciejewski J, Young NS. 2006. Brief communication: successful treatment of pure red-cell aplasia with an anti-interleukin-2 receptor antibody (daclizumab). Annals of Internal Medicine 144:181–185.

Smyth MJ, Godfrey DI, Trapani JA. 2001. A fresh look at tumor immunosurveillance and immunotherapy. Nature Immunology 2:293–299.

Soker M, Colpan L, Ece A, Devecioglu C, Haspolat K. 2001. Serum levels of IL-1 beta, sIL-2R, IL-6, IL-8, and TNF-alpha in febrile children with cancer and neutropenia. Medical Oncology 18:51.

Stasi R, Zinzani PL, Galieni P, Lauta VM, Damasio E, Dispensa E, Dammacco F, Tura S, Papa G. 1994. Detection of soluble interleukin-2 receptor and interleukin-10 in the serum of patients with aggressive non-Hodgkin's lymphoma. Cancer 74:1792–1800.

Swiatecka-Urban A. 2003. Anti-interleukin-2 receptor antibodies for the prevention of rejection in pediatric renal transplant patients: current status. Paediatric Drugs 5:699–716.

Taniguchi T, Minami Y. 1993. The IL-2/IL-2 receptor system: a current overview. Cell 73:5–8.

Tartour E, Mosseri V, Jouffroy T, Deneux L, Jaulerry C, Brunin F, Fridman WH, Rodriguez J. 2001. Serum soluble interleukin-2 receptor concentrations as an independent prognostic marker in head and neck cancer. Lancet 357:1263–1264.

Tesch H, Günther A, Abts H, Jücker M, Klein S, Krueger GR, Diehl V. 1993. Expression of interleukin-2R alpha and interleukin-2R beta in Hodgkin's disease. American Journal of Pathology 142:1714–1720.

Ter Meulen CG, Jacobs CW, Wetzels JF, Klasen IS, Hilbrands LB, Hoitsma AJ. 2004. The fractional excretion of soluble interleukin-2 receptor-alpha is an excellent predictor of the interleukin-2 receptor-alpha status after treatment with daclizumab. Transplantation 77:281–286.

Tesarova P, Kvasnicka J, Umlaufova A, Homolkova H, Jirsa M, Tesar V. 2000. Soluble TNF and IL-2 receptors in patients with breast cancer. Medical Science Monitor 6:661–667.

Trentin L, Zambello R, Bulian P, Cerutti A, Milani A, Pirone E, Nitti D, Agostini C, Semenzato G. 1994. Functional role of IL-2 receptors on tumour-infiltrating lymphocytes. British Journal of Cancer 69:1046.

Tsurushita N, Hinton PR, Kumar S. 2005. Design of humanized antibodies: from anti-Tac to Zenapax. Methods 36:69–83.

Uchiyama T, Broder S, Waldmann TA. 1981. A monoclonal antibody (anti-Tac) reactive with activated and functionally mature human T cells. I. Production of anti-Tac monoclonal antibody and distribution of Tac (+) cells. Journal of Immunology 126:1393–1397.

Van Gelder T, Warlé M, ter Meulen RG. 2004. Anti-interleukin-2 receptor antibodies in transplantation: what is the basis for choice? Drugs 64:1737–1741.

Viviani S, Camerini E, Bonfante V, Santoro A, Balzarotti M, Fornier M, Devizzi L, Verderio P, Valagussa P, Bonadonna G. 1998. Soluble interleukin-2 receptors (sIL-2R) in Hodgkin's disease: outcome and clinical implications. British Journal of Cancer 77:992–997.

Volkland J, Lumsden J, Mølhøj M, Raum T, Hausmann S, Wissing S, Wissinger M, Hoffmann P, Sriskandarajah M, Kvesic M, Baeuerle PA, Pflanz S. 2007. A humanized monoclonal antibody against interleukin-2 that can inactivate the cytokine/receptor complex. Molecular Immunology 44:1743–1753.

Vonderheid EC, Zhang Q, Lessin SR, Polansky M, Abrams JT, Bigler RD, Wasik MA. 1998. Use of serum soluble interleukin-2 receptor levels to monitor the progression of cutaneous T-cell lymphoma. Journal of the American Academy of Dermatology 38:207.

Wakao D, Murohashi I, Tominaga K, Yoshida K, Kishimoto K, Yagasaki F, Itoh Y, Itoh K, Sakata T, Kawai N, Kayano H, Suzuki T, Matsuda A, Hirashima K, Bessho M. 2002. Serum thymidine kinase and soluble interleukin-2 receptor predict recurrence of malignant lymphoma. Annals of Hematology 81:140–146.

Waldmann TA. 1991. The interleukin-2 receptor. Journal of Biological Chemistry 266:2681–2684.

Waldmann TA. 2002. The IL2/IL 15 receptor systems: targets for immunotherapy. Journal of Clinical Immunology 22:51–56.

Waldmann TA. 2007. Anti-Tac (daclizumab, Zenapax) in the treatment of leukemia, autoimmune diseases, and in the prevention of allograft rejection: a 25-year personal odyssey. 2007. Journal of Clinical Immunology 27:1–18.

Wang LS, Chow KC, Li WY, Liu CC, Wu YC, Huang MH. 2000. Clinical significance of serum soluble interleukin 2 receptor-alpha in esophageal squamous cell carcinoma. Clinical Cancer Research 6:1445.

Warlé MC, Kwekkeboom J, Tilanus HW, Metselaar HJ. 2003a. Basiliximab interferes with the detection of soluble IL-2 receptor by the Immulite Immunoassay system. Journal of Immunological Methods 275:133–136.

Warlé MC, Metselaar HJ, Hop WCJ, Gyssens IC, Kap M, Kwekkeboom J, De Rave S, Zondervan PE, Ijzermans JNM, Tilanus HW, Bouma GJ. 2003b. Early differentiation between rejection and infection in liver transplant patients by serum and biliary cytokine patterns. Transplantation 75:146–151.

Witkowska AM. 2005. On the role of sIL-2R measurements in rheumatoid arthritis and cancers. Mediators of Inflammation 3:121–130.

Wu LJ, Chen KY, Chi KH, Chen SY, Liang MJ, Shiau CY, Wang LW, Liu YM, Chow KC, Yen SH. 1998. The significance of soluble interleukin-2 receptor in monitoring disease relapse in patients with nasopharyngeal cancer. Japanese Journal of Clinical Oncology 28:729.

Xiao P, Chen QF, Yang YL, Guo ZH, Chen H. 2006. Serum soluble interleukin-2 receptor levels in patients with chronic hepatitis B virus infection and its relation with anti-HBc. World Journal of Gastroenterology 12:482–484.

Yano T, Fukuyama Y, Yokoyama H, Yano T, Fukuyama Y, Yokoyama H, Takai E, Tanaka Y, Asoh H, Ichinose Y. 1996. Interleukin-2 receptors in pulmonary adenocarcinoma tissue. Lung Cancer 16:13–19.

Yilmaz M, Tarakcioglu M, Bayazit N, Namiduru M, Kanlikama M. 2002. Serum cytokine levels in Bell's palsy. Journal of Neurological Sciences 15:69–72.

Yoshida S, Morii K. 2000. Serum concentrations of soluble interleukin-2 receptor in patients with malignant brain tumors. Journal of Surgical Oncology 75:131–135.

Zhang Z, Zhang M, Garmestani K, Talanov VS, Plascjak PS, Beck B, Goldman C, Brechbiel MW, Waldmann TA. 2006. Effective treatment of a murine model of adult T-cell leukemia using 211At-7G7/B6 and its combination with unmodified anti-Tac (daclizumab) directed toward CD25. Blood 108:1007–1012.