

## Advances in interleukin 2 receptor targeted treatment

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### Abstract

**T cell activation and cellular immune responses are modulated by interleukin 2 (IL2) through binding to its corresponding cell surface receptor. Three forms of the receptor are recognised based on IL2 binding affinity. The high affinity receptor is a heterotrimer composed of  $\alpha$ ,  $\beta$ , and  $\gamma_c$ -polypeptide chains. The 55 kDa  $\alpha$ -chain also known as the Tac (T cell activation) antigen or CD-25 is a unique subunit of the high affinity IL2 receptor (IL2R $\alpha$ ). Resting T cells express few IL2R $\alpha$ , however, when activated, the expression of IL2R $\alpha$  rapidly increases. The IL2R $\alpha$  is shed from the cell surface and is measurable in the serum as a 45 kDa soluble form (s-Tac or s-IL2R $\alpha$ ). Serum concentrations of s-Tac can be used as a surrogate marker for T cell activation and IL2R $\alpha$  expression. IL2R $\alpha$  is over expressed by T cells in a number of autoimmune diseases, allograft rejection and a variety of lymphoid neoplasms. IL2 induced proliferation of T cells can be inhibited by the murine monoclonal antibody (anti-Tac) directed against the  $\alpha$ -chain of the IL2R. Through molecular engineering, murine anti-Tac has been humanised reducing its immunogenicity without changing its specificity. Humanised anti-Tac (HAT) has been shown to reduce the incidence of renal and cardiac allograft rejection as well as decrease the severity of graft versus host disease in patients undergoing HLA matched allogeneic bone marrow transplantation. IL2R $\alpha$  targeted treatment with radioimmunoconjugates of anti-Tac and immunotoxins has shown promise in the treatment of CD25 expressing lymphomas.**

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In 1976, Morgan *et al* described an activity in the supernatants of cultured PHA stimulated peripheral blood mononuclear cells they termed T cell growth factor (TCGF) that was capable of stimulating the growth of bone marrow derived T lymphocytes.<sup>1</sup> Shortly thereafter, it was discovered that TCGF was required for the indefinite culture of cytolytic T cells *in vitro*.<sup>2</sup> In 1983, Taniguchi and coworkers using expression cloning isolated the cDNA for TCGF.<sup>3</sup> In recognition of its broad pleiotrophic activities, TCGF was subsequently renamed interleukin 2 (IL2).<sup>4</sup> It is a 153 aminoacid polypeptide with a 20 aminoacid signal sequence and a cysteine disulphide bridge. IL2 is a potent immunomodula-

tor whose major function is the activation of various cells of the immune system including helper T cells, cytotoxic T cells, B cells, NK cells and macrophages.

IL2 mediates its biological effects through binding to its corresponding cell surface receptor. There are three recognised IL2 receptors (IL2R): a high affinity ( $K_d = 10^{-11}$  M) receptor, an intermediate affinity ( $K_d = 10^{-9}$  M) receptor and a low affinity ( $K_d = 10^{-8}$  M) receptor.<sup>5</sup> These receptors are composed of up to three glycopeptide subunits: a 251 aminoacid 55 kDa  $\alpha$ -chain (CD25),<sup>6,7</sup> a 75 kDa  $\beta$ -chain (CD122)<sup>8</sup> and a 64 kDa  $\gamma_c$ -chain (CD132).<sup>9</sup> The  $\beta$ - and  $\gamma_c$ -chains share significant homology with other members of the class I cytokine receptor family, however, the separate  $\alpha$ -chains of the IL2R and the IL15R form a separate unique class. The high affinity receptor is a trimer consisting of an  $\alpha$ -,  $\beta$ - and  $\gamma_c$ -chain.<sup>10</sup> The intermediate affinity receptor is a dimer composed of a  $\beta$ - and a  $\gamma_c$ -chain, and the low affinity receptor appears to be a monomeric  $\alpha$ -subunit. The  $\gamma_c$ -subunit seems to be constitutively expressed on most lymphoid cells, but the expression of the  $\alpha$ - and  $\beta$ -chains are more tightly regulated. The various polypeptide subunits perform different functions. The  $\alpha$ -subunit mediates binding of IL2 and upregulates receptor sensitivity to IL2, the  $\beta$ -subunit also plays a part in binding of ligand, both the  $\beta$ - and  $\gamma_c$ -subunits mediate internalisation and signal transduction through the JAK 1 and 3 kinase pathways.<sup>11,12</sup> The IL2R and the IL15 receptor share a common  $\beta$ -chain, whereas the  $\gamma_c$ -subunit is shared among the IL2, IL4, IL7, IL9 and IL15 receptors.<sup>13</sup> Other surface molecules have been found to be associated with the IL2R including ICAM-1 (CD54) and MHC class I molecules.

Less than 5% of normal circulating peripheral blood mononuclear cells express the IL2R $\alpha$  and then only at a very low level. The high affinity IL2R is not expressed on normal or unstimulated lymphocytes, but it is rapidly transcribed and expressed on activated T cells.<sup>14,15</sup> The 55 kDa  $\alpha$ -polypeptide (IL2R $\alpha$ ) of the high affinity receptor, also known as the Tac (T cell activation) antigen, or CD25 is enzymatically cleaved and shed from the surface of expressing cells.<sup>16</sup> It can be measured in the serum by ELISA assay as a 45 kDa monomer called soluble-Tac (s-Tac) or soluble-IL2 receptor (s-IL2R $\alpha$ ).<sup>17</sup> The release of s-Tac is proportional to its cell surface expression.<sup>18</sup> It is excreted and catabolised by the kidneys and has a serum half life ( $t_{1/2}$ ) of 0.62 hours. Serum values in normal healthy people range between 112–502 IU/ml (1 IU =

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3.3 picograms). The serum levels of s-Tac are increased in renal failure due to its decreased catabolism. Administration of exogenous IL2 will also increase serum s-Tac concentrations.<sup>19</sup>

Several murine monoclonal antibodies have been developed against the various subunits of the human IL2R and have been used for detection and diagnostic purposes as well as treatment. Included are anti-Tac (anti-CD25) that binds to an epitope on the  $\alpha$ -chain and inhibits the binding of IL2 to its receptor,<sup>6</sup> 7G7/B6 that binds to a separate epitope on the IL2R $\alpha$  and does not inhibit IL2 binding,<sup>20</sup> and Mik $\beta$ 1 that binds to the IL2R  $\beta$ -chain (CD122).<sup>21</sup> Anti-Tac, but not Mik $\beta$ 1 has been shown to inhibit IL2 induced proliferation of human T cells.<sup>22</sup> On the other hand, Mik $\beta$ 1 inhibits IL2 and IL15 binding on large granular lymphocytes and the activation of these cells that expresses the IL2R $\beta$ , but not the IL2R $\alpha$ . MIK $\beta$ 1 inhibits the action of IL15, but not IL2 on activated T cells that express the high affinity IL2 receptor. Anti-Tac and Mik $\beta$ 1 act synergistically to inhibit IL2 induced proliferation in T cells.<sup>23</sup>

The therapeutic use of murine monoclonal antibodies has been limited because of their immunogenicity and the rapid development of neutralising human antimouse antibodies (HAMA) in patients receiving them.<sup>24</sup> Furthermore the short in vivo survival of murine antibodies limits their use in chronic diseases. Major efforts have gone into developing molecular techniques for "humanising" these antibodies to reduce their immunogenicity. In humanised anti-Tac about 90% of the molecule (murine IgG<sub>2a</sub>) has been replaced with a human IgG<sub>1c</sub> sequence.<sup>25</sup> Humanised anti-Tac (HAT) has the advantages of a low incidence of induction of neutralising antibodies, a significantly prolonged serum half life ( $t_{1/2}$ ) of 20 days

compared with 40 hours for the murine antibody, and the ability to mediate antibody dependent cytotoxicity (ADCC) through its humanised Fc-domain.<sup>26</sup>

### IL2 receptor directed treatment in autoimmune disease

Little IL2R $\alpha$  is expressed on unstimulated T cells or is found as s-Tac in the serum of healthy people, however, significant increases in IL2R $\alpha$  are seen in the setting of autoimmune diseases, organ transplant rejection and in many T cell and B cell neoplasms (table 1). There are a large number of reports evaluating the use of serum s-Tac levels as a measure of disease activity in autoimmune diseases.<sup>27</sup> Investigators have attempted to follow the levels of s-Tac as an indicator of systemic lupus erythematosus (SLE) disease activity with mixed results.<sup>28-30</sup> In one study, patients with SLE exhibited greater lymphocyte activation having increased circulating CD25+ cells compared with normal controls, but the increased expression did not correlate with exacerbations of their lupus.<sup>31</sup>

Similar findings have been reported in patients with rheumatoid arthritis (RA) where serum or synovial fluid s-Tac levels were found to correlate with disease activity or response to treatment in some studies but not others.<sup>32-35</sup> In a study by Suenaga and colleagues, two of three patients with increased s-Tac (> 2 SD above normal) and joint findings suspicious for but not diagnostic of RA, developed frank RA when followed up for one year compared with 25% of patients with joint pain and normal s-Tac levels.<sup>36</sup> Increased s-IL2R $\alpha$  levels have been found to correlate with the systemic onset of juvenile rheumatoid arthritis (JRA) but not with onset of limited disease<sup>37</sup> and with activity of Sjögren's syndrome.<sup>38</sup> One report suggested that pleural effusions from RA could be differentiated from those of SLE based on the higher levels of s-Tac found in these effusions.<sup>39</sup> Soluble IL2R $\alpha$  levels have been found to be increased in Wegener's granulomatosis, vasculitis, polymyalgia rheumatica, giant cell arteritis, Kawasaki disease, and Behçet's syndrome

Experimental animal models of autoimmune uveitis<sup>40</sup> as well as uveitis patients demonstrate increased circulating T cells bearing large numbers of high affinity IL2 surface receptors. Ten patients with progressive chronic bilateral non-infectious sight threatening posterior and intermediate uveitis were weaned off of their systemic immunosuppression and treated with HAT 1mg/kg intravenously at two week intervals for 12 weeks, then at three week intervals for 12 weeks and finally at four week intervals to complete one year of treatment.<sup>41</sup> Eight of the 10 patients had improvement of their visual acuity and two patients had progressive deterioration. Six patients developed transient rashes during the treatment as the only potential toxicity and no patient developed neutralising antibodies to the HAT. Additional benefits of the IL2R targeted treatment were that after the patients were tapered off of systemic corticosteroids, there were improvements in blood pressure and serum cholesterol levels.

Table 1 Causes of increased serum soluble IL2R $\alpha$  (Tac) concentrations

<i>Allograft rejection</i>	<i>Neoplasia</i>
Bone marrow	Acute myelocytic leukaemia
Cardiac	Anaplastic large cell lymphoma
Liver	Adult T cell leukaemia/lymphoma
Renal	Chronic lymphocytic leukaemia
	Chronic myelocytic leukaemia
<i>Autoimmune disease</i>	Cutaneous T cell lymphoma/
Aplastic anaemia	Mycosis fungoides
Behçet's syndrome	Hairy cell leukaemia
Crohn's disease	Hodgkin's disease
Giant cell arteritis	Non-Hodgkin's lymphomas (B cell)
Juvenile rheumatoid arthritis	Peripheral T cell lymphomas
Kawasaki disease	
Multiple sclerosis	<i>Veno-occlusive disease</i>
Polymyalgia rheumatica	
Rheumatoid arthritis	
Sarcoidosis	
Scleroderma	
Sjögren's syndrome	
Systemic lupus erythematosus	
Vasculitis	
Wegener's granulomatosis	
<i>Drugs</i>	
In vivo IL2 administration	
<i>End stage renal disease</i>	
<i>Infections</i>	
HIV/AIDS	
Pulmonary tuberculosis	
Rubeola	
Infectious mononucleosis	
Sepsis	

### IL2 receptor targeted treatment in organ transplantation

Serum concentrations of the soluble form of the IL2R $\alpha$  has been found to be increased in patients rejecting allografts and activated T cells play a major part in graft rejection.<sup>42</sup> In the United States two monoclonal anti-IL2R $\alpha$  antibodies have been clinically approved to prevent renal allograft rejection. Daclizumab (Zenapax, Hoffmann-LaRoche, Nutley, NJ) is the humanised monoclonal with approximately 90% of the murine sequence replaced by human sequences and basiliximab (Simulect, Novartis Pharma, East Hanover, NJ), a chimerical monoclonal antibody in which 75% of the sequence has been humanised.<sup>43 44</sup> The two antibodies are administered on different dose schedules because of their different pharmacokinetic profiles. Basiliximab is administered as a 20 mg intravenous dose two hours before transplant and again on the fourth postoperative day for a total of two doses. Daclizumab is approved to be administered intravenously at 1 mg/kg preoperatively and postoperatively at weeks 2, 4, 6, and 8 for a total of five doses. In a pilot study, 10 patients receiving living related renal allografts and two patients receiving cadaveric transplants were randomised to receive daclizumab 0.5 mg/kg or 1 mg/kg weekly, or 0.5 mg/kg or 1 mg/kg every two weeks beginning 12 hours before transplant for a total of five doses along with cyclosporine, corticosteroids and azathioprine.<sup>45</sup> None of the allograft recipients experienced an episode of rejection in the first year, compared with 7 of 17 (41%) historical controls. In a US multicentre Phase III randomised double blind placebo controlled study, 260 patients undergoing first cadaveric renal transplant were randomised to standard treatment with cyclosporine, azathioprine and corticosteroids, or this regimen plus daclizumab.<sup>46</sup> Of the 126 patient receiving daclizumab, 28 (22%) had a biopsy confirmed episode of rejection compared with 35% of 134 control patients receiving standard immunosuppression plus placebo ( $p = 0.03$ ). There was, however, no statistically significant difference in graft survival between the two treatment groups at one year (95% *v* 90%,  $p = 0.08$ ) and there was no difference with respect to adverse drug reactions, infectious complications or the incidence of cancer between the groups. In a second European multicentre Phase III randomised double blind placebo controlled study daclizumab was compared with placebo in 275 patients receiving a less intensive immunosuppressive regimen of cyclosporine and corticosteroids receiving their first cadaveric renal transplant.<sup>47</sup> At six months 28% of patients on the daclizumab arm had a biopsy confirmed episode of acute rejection compared with 47% of patients in the placebo arm ( $p = 0.001$ ). Patients on the daclizumab treatment arm had better graft function, reduced need for antithymocyte or antilymphocyte globulin, lower administered corticosteroid doses, a lower incidence of cytomegalovirus infections, a lower incidence of infectious deaths and a greater one year survival than patients on the placebo arm (99% *v* 94%,  $p =$

0.01). Randomised controlled clinical trials using basiliximab in renal transplantation have shown similar encouraging results.<sup>43</sup>

IL2R $\alpha$  receptor directed treatment has also been shown to improve the survival of other organ allografts. In a primate cardiac allograft model, the efficacy of HAT was compared with murine anti-Tac for the prevention of rejection.<sup>48</sup> Both monoclonal antibodies resulted in superior allograft survival compared with controls, however, HAT was less immunogenic and resulted in a better survival compared with the murine antibody. Recently, 55 patients undergoing first cardiac allograft were randomised to cyclosporine, mycophenolate mofetil and prednisone with or without daclizumab 1 mg/kg intravenously administered every two weeks for five doses.<sup>49</sup> Acute rejection occurred in 17 of 27 patients on standard immunosuppression and in 5 of 28 patients on the standard immunosuppression plus HAT treatment arm ( $p = 0.04$ ). In addition, the severity of the rejection episodes was reduced and the time to first episode of rejection was prolonged in the HAT treatment group. No increased toxicity or higher incidence of infection or cancer was seen in the HAT treatment arm.

Mixed results have been seen in trials using HAT for patients undergoing liver transplantation. In one study 28 patients undergoing a liver transplant were treated with prednisone, cyclosporine and HAT and no episodes of acute rejection were reported.<sup>50</sup> Recently, a pilot study was terminated after seven of seven patients developed rejection when treated with a regimen of corticosteroids, mycophenolate mofetil and daclizumab without cyclosporine or other calcineurin inhibitor compared with 36% of patients treated with corticosteroids, mycophenolate mofetil and a calcineurin inhibitor.<sup>51</sup> These investigators suggested the high rejection rate was the result of the absence of a calcineurin inhibitor in the immunosuppressive regimen and the lower than anticipated serum levels of daclizumab in hepatic transplant patients compared with renal transplant patients.

IL2 receptor targeted treatment is being evaluated for the prevention and treatment of graft versus host disease (GvHD). GvHD is the most frequent complication of allogeneic bone marrow transplantation occurring in 30–60% of HLA matched sibling transplants.<sup>52–54</sup> The incidence of GvHD is as high as 90% in matched unrelated donor transplants and the mortality of acute grade 4 GvHD approaches 100%.<sup>55</sup> GvHD is mediated by the reactivity of mature T cells in the donor marrow against recipient alloantigens.<sup>56 57</sup> Donor T cells stimulated by alloantigens secrete IL2 and express IL2R $\alpha$ .<sup>58</sup> Several studies have shown an association of soluble IL2R $\alpha$  levels and the activity of GvHD.<sup>59 60</sup> Serum soluble Tac levels increase at the time of engraftment and at the onset of acute and chronic GvHD.<sup>61</sup> The peak concentration of s-ILR $\alpha$  correlated with the severity of the GvHD and falls as the patients' GvHD resolves.<sup>62 63</sup> Prolonged increase in serum s-IL2R $\alpha$  is often followed by the development

of chronic GvHD. Patients with large increases of their s-IL2R $\alpha$  levels have a poorer survival compared with patients with mild increases. In contrast, other studies have found little predictive or diagnostic role for monitor of s-Tac as an indicator of GvHD. Sepsis, veno-occlusive disease and other conditions common in the bone marrow transplant setting other than GvHD can cause increase in the serum s-IL2R $\alpha$  levels.<sup>64</sup>

GvHD is treated with corticosteroids and immunosuppressive agents, however, the use of anti-CD25 antibodies is receiving increasing attention as an adjunct to treatment or for patients who are resistant to corticosteroids. Prophylactic use of monoclonal antibodies to IL2R $\alpha$  reduces the incidence and severity of GvHD in murine models.<sup>65</sup> Early clinical trials, however, were disappointing. A study using a rat monoclonal antibody (LO-Tact-1) directed against IL2R $\alpha$  as prophylaxis for GvHD in 10 patients undergoing HLA matched sibling donor bone marrow transplant found it had no benefit in reducing the incidence of GvHD, the frequency of relapse or overall survival.<sup>66</sup> Studies using an IL2-*Pseudomonas* exotoxin A fusion protein or a *Pseudomonas* exotoxin A-anti-Tac Fv fragment have been shown to reduce circulating CD25+ T lymphocytes, reduce alloreactive T cells by 100-fold and decrease the incidence of GvHD in mice transplanted with allogeneic cells.<sup>67</sup>

Two recent studies suggest a benefit of humanised anti-Tac (daclizumab) for the treatment of GvHD. In a study of 20 patients with corticosteroid refractory acute GvHD who were treated with doses of daclizumab ranging from 0.5 mg/kg to 1.5 mg/kg, four complete and two partial responses were seen.<sup>68</sup> Toxicity was limited to chills and diaphoresis in one patient and no patient developed an antibody response to the humanised antibody. In a second study, 24 patients with advanced or corticosteroid refractory GvHD were treated with 1 mg/kg daclizumab on days 1, 8, 15, 22, 29.<sup>69</sup> Patients were evaluated for response of their GvHD on day 43. The complete response rate for this group of patients was 29% and the survival on day 120 was 29%. In the same study, a second cohort of 19 patients received daclizumab 1 mg/kg on a more intensive schedule (days 1, 4, 8, 15 and 22). The complete response rate on day 43 was 47% and survival on day 120 was 53%. No significant toxicity was seen in either cohort, but a reduction of serum s-IL2R $\alpha$  and circulating CD3+, CD25+ cells were noted. These laboratory changes were not predictive of outcome.

### IL2 receptor targeted treatment of neoplasia

The greatest expression of IL2R $\alpha$  and highest s-Tac levels are seen in the setting of T cell malignancies. This coupled with the ability of anti-Tac to block the binding of a specific cytokine growth factor (IL2) to its receptor, inhibiting proliferation of the malignant cell, make this an ideal target for specific monoclonal antibody treatment. Over expression of

IL2R $\alpha$  is seen on the cells of adult T cell leukaemia/lymphoma (ATL), mycosis fungoides, peripheral T cell lymphomas, hairy cell leukaemia, Reed-Sternberg cells (Hodgkin's disease), anaplastic large cell lymphoma and some B cell neoplasms.<sup>70</sup>

ATL has served as the prototypical disease for the therapeutic trials of anti-Tac. ATL is an aggressive lymphoproliferative disorder caused by infection with a novel human retrovirus: the human T cell lymphotropic virus type 1 (HTLV-1).<sup>71-72</sup> HTLV-1 infection is geographically clustered found primarily in the Caribbean basin, Western Africa and Southern Japan.<sup>73</sup> After infection, reverse transcription and integration of the virus into a host T cell genome, expression of the virally encoded 42 kD *tax* protein acts as a promiscuous transcriptional activator binding to the promoters of multiple families of genes, most notably the IL2, IL2R $\alpha$  and NF $\kappa$ B genes.<sup>74</sup> This results in increased gene expression and dysregulation of cell growth. About 5% of infected people will develop an aggressive form of T cell leukaemia or lymphoma<sup>75</sup> characterised by a CD3+, CD4+, CD25+ phenotype.<sup>76</sup> In its most aggressive form, ATL patients developed high circulating cell counts, severe hypercalcaemia, lytic bone lesions, skin and solid organ infiltration, liver failure, leukaemic leptomeningitis and profound immunosuppression. The median survival for patients with acute ATL is approximately five months.<sup>77</sup> Chemotherapy has had little impact on the disease with relatively few patient responses and a short duration of remission. Even the combination of interferon alfa and zidovudine (AZT), a treatment used throughout much of the world results in a median survival of only three months.<sup>78-79</sup>

Beginning in the 1980s, a series of clinical trials were initiated in the Metabolism Branch of the NCI by Waldmann and colleagues using monoclonal anti-Tac antibodies as a therapeutic approach to ATL. In the first trial, 19 patients with acute ATL were treated with unmodified murine anti-Tac.<sup>80</sup> Ten of the 18 patients had failed prior chemotherapy. Two patients achieved complete remissions, four had a partial response and one patient a mixed response. The duration of remissions ranged from nine weeks to more than three years. Toxicities included fever in two patients and transient pancytopenia in one patient. The short serum half life of murine anti-Tac and the development of human antimouse antibodies (HAMA) limited the usefulness of this approach. In a follow up phase I/II study, murine anti-Tac was armed with the  $\beta$  emitting isotope <sup>90</sup>Yttrium in an effort to enhance leukaemic cell killing.<sup>81</sup> Eighteen patients with ATL were treated with 5–15 mCi <sup>90</sup>Y labelled murine anti-Tac. Two complete and seven partial responses were seen in 16 evaluable patients. Toxicity was confined to the haematopoietic system, primarily granulocytopenia and thrombocytopenia. However, a significant number of patients developed HAMA titres limiting the ability to administer repeated doses of the antibody. With the approval and availability of

humanised anti-Tac (dacluzimab), the Metabolism Branch has pursued clinical trials using  $^{90}\text{Y}$  labelled HAT in ATL, other CD25 expressing T cell neoplasms and Hodgkin's disease. Recently we initiated a phase I/II trial of high dose (4–8 mg/kg) unmodified HAT as a treatment for patients with of ATL. End points for this study are dose limiting toxicity, the ability to achieve > 95% anti-Tac saturation of the IL2R $\alpha$  on circulating ATL cells or in lymphomatous tissue (lymph nodes, skin, etc) and tumour response. Future approaches under development are the use of HAT chelated to  $\alpha$  emitting radionuclides such as  $^{212}\text{Bi}$ ,  $^{213}\text{Bi}$  or  $^{211}\text{At}$  because of their more favourable radiobiological profiles, as well as the use of non-cross reactive antibodies such as high dose unmodified HAT in combination with low dose radioisotope armed humanised 7G7/B6 to block IL2 stimulation (HAT) and deliver a lethal dose of radioactivity to the malignant cells (radiolabelled 7G7/B6). Combination of anti-IL2R antibodies with other antibodies (anti-CD30) or with other modalities such as chemotherapy or other cytokines is also projected.

Other approaches to IL2R targeted treatment of cancer have been the use of ligand-toxin fusion proteins and immunotoxins. DAB $_{389}$ IL-2 is a 58 kDa fusion protein engineered between the enzymatic and translocation domains of diphtheria toxin (DT) and human IL2 that can be expressed in *Escherichia coli*.<sup>82</sup> This fusion protein is able to direct cytotoxic activity to cells that express the IL2 receptor. The toxin is unable to be taken up by other cells because it lacks the cell receptor binding domain. When bound to cells expressing the IL2R and internalised, the DT kills cells by catalysing the irreversible ADP-ribosylation of elongation factor-2 (EF-2) and subsequent inhibition of protein synthesis. It has been estimated that even one cytosolic molecule of DT is lethal to the cell.<sup>83</sup> In a clinical trial involving 35 patients with advanced treatment refractory cutaneous T cell lymphoma and mycosis fungoides, DAB $_{389}$ IL2 produced a 37% response rate including 14% complete responses.<sup>84</sup> Toxicities included fever/chills, hypotension, nausea/vomiting and liver enzyme abnormalities. A recent trial using a fusion protein of a truncated *Pseudomonas* exotoxin A and the Fv-fragment of anti-Tac (LMB-2) showed promising early results in patients with I-2R $\alpha$  expressing lymphoid neoplasms including hairy cell leukaemia and ATL.<sup>85</sup>

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 IL2R and other cytokine receptors holds great promise as treatment for a large number of diverse diseases.

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