Recognizing self from not-self and vice versa is the central paradigm of immunity. If a tissue/cell is of self-origin, the correct response of the immune system should be tolerance, and, if it is not-self, the appropriate response should be rejection. In oncology, it has proved very difficult to persuade the immune system to recognize tumour cells as not-self. Many attempts to stimulate the immune system to reject tumours, especially melanoma, have been made, using various immunotherapy protocols. The clinical results have been disappointing to date, despite the induction of high levels of antitumour T lymphocytes [1,2]. In organ transplantation and in autoimmune diseases, however, the strategy is the opposite, in order to prevent the immune system from rejecting organ transplants, or from destroying normal tissues such as joints, kidneys and blood vessels. Here the results of clinical trials have been more gratifying.

A good deal of cross-fertilization has been seen between the two fields of immunostimulation/immunosuppression research in an attempt to decipher the crucial mechanisms whereby rejection or tolerance predictably occurs. Although major histocompatibility complex presentation of antigenic peptides results in T-cell receptor activation, another concerted mechanism, called costimulation, is needed to complete T-cell activation. In this field, two major discoveries have been made. First, the costimulatory T-cell molecule CD28 was discovered and designated as a critical costimulatory receptor [3]. Secondly, its ligands B7.1 (CD80) and B7.2 (CD86), expressed on B cells and also on antigen presenting cells and tumour cells, were identified [4]. In contrast to the CD28/B7 system, however, which serves to costimulate T cells, it was found that some T cells can use B7-dependent pathways to negatively regulate T-cell activation and effector function. These have been termed T regulatory cells (reviewed in [5]). T regulatory cells express a CD4+CD25+ phenotype, and, more importantly, they express the anticytotoxic T lymphocyte-associated antigen 4 (CTLA-4) molecule on their cell surfaces [6]. Like CD28, CTLA-4 also binds to B7.1/B7.2, but with a higher affinity than CD28, with ligation serving to block T-cell activation. Hence, it is currently considered that CTLA-4 plays a major role in protecting the organism against autoimmunity [5].

This finding has inspired researchers to try to use this property to block T-cell activation in autoimmune diseases and in organ transplantation. A soluble form of CTLA-4 was designed by joining its extracellular domain to an immunoglobulin tail, CTLA4-Ig. This construct has been shown to promote the long-term survival of pancreas xenografts in mice [7].

In contrast to cyclosporine, which indiscriminately inhibits T cells, CTLA4-Ig selectively blocks the costimulatory signal. A randomized phase III study in antitumour necrosis factor refractory rheumatoid arthritis patients, comparing the CTLA4-Ig ‘Abatacept’ to a placebo, has yielded impressive clinical benefits [8].

Considering the important role of CTLA-4 in blocking T-cell activation, one might consider whether abrogating its influence could result in more efficient antitumour immunity. It has recently been proposed that CD4+CD25high lymphocytes – expressing the transduction factor foxp3 – are responsible for the lack of efficacy associated with tumour infiltrating lymphocytes commonly found in melanoma metastases [9]. Moreover, it has been demonstrated that interleukin-2, which is still used in the treatment of melanoma, increases the number of T regulatory cells in vivo [10]. The proof of concept was made in a murine model: administration of anti-CTLA-4 with granulocyte/macrophage-colony stimulating factor resulted in the eradication of 80% of established B16 melanoma tumours, and this was accompanied by depigmentation [11]. Thus, this important experiment strongly suggested that abrogating CTLA-4 signalling increases antimelanoma immunity, but, at the same time, these augmented effector cells appear capable of mediating autoimmunity against normal skin melanocytes, resulting in a situation resembling vitiligo. This finding has paved the way for the clinical use of anti-CTLA-4 in patients with melanoma. Fully humanized monoclonal antibodies against CTLA-4 have been used either alone [12,13] or in combination with specific peptide vaccines in stage IV melanoma patients [14,15]. Objective clinical responses, sometimes impressive in their nature, have been recorded. Two groups have reported greater clinical efficacy in cases in which autoimmune side effects were concomitantly observed [13,14], although this phenomenon was less evident in a report from a third group [15].

One is left concluding that the efficacy of immune rejection of melanoma, brought about by anti-CTLA-4 treatment, may be at the expense of collateral auto
immune disorders. The use of anti-CTLA-4 antibody in patients with melanoma has thus far yielded very promising results that need to be carefully analysed. In the present issue of *Melanoma Research*, Jeffrey S. Weber, from the University of California at Los Angeles, reviews the experimental background and the clinical results of anti-CTLA-4-based therapy in the setting of melanoma [16].

References

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(On behalf of the Editors.)