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Immunotherapy of autoimmunity and cancer: the penalty for success

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Abstract

Advances in our understanding of autoimmunity and tumour immunity have led to improvements in immunotherapy for these diseases. Ironically, effective tumour immunity requires the induction of the same responses that underlie autoimmunity, whereas autoimmunity is driven by dysregulation of the same mechanisms that are involved in host defence and immune surveillance. Therefore, as we manipulate the immune system to treat cancer or autoimmunity, we inevitably unbalance the vital mechanisms that regulate self tolerance and antimicrobial resistance. This Science and Society article aims to dissect the conundrum that is inherent to the concept of immunotherapy and highlights the need for new and more specific therapeutic approaches.

The development of cancer and autoimmunity can be seen as a failure of the immune system to control tumour cell growth and to regulate autoreactive responses, respectively. The ability to reprogramme the immune system so that it will maintain homeostasis without the need for continuous treatment is the holy grail of therapies for these diseases. Conventional therapies for autoimmunity and cancer rely primarily on broad-spectrum suppressive regimens. The serious side effects of prolonged chemotherapy for the treatment of cancer or the harsh immuno-suppressive regimens for the treatment of autoimmune disease are well-known and have driven the continuing quest for more specific and less toxic therapies.

The immune system is finely balanced to distinguish foreign from self antigens. The process of thymic (central) tolerance eliminates high-affinity self-antigen-specific T cells, as well as those that fail to recognize self antigens entirely, and spares T cells that recognize self antigens with intermediate affinity. Because the naive immune repertoire is positively selected on self antigens, self recognition is hard-wired in the system and this blurs the boundaries between autoimmunity and immunity. Normally, peripheral tolerance keeps potentially autoreactive lymphocytes in check because recirculating lymphocytes are exposed to tissue antigens under non-inflammatory conditions, which results in a tolerant, anergic state. However, in the presence of stimuli that provide danger signals, such as infection and tissue damage, self tolerance can be broken and autoimmune disease may ensue. Conversely, a repertoire that is

DATABASES

Entrez Genome Project: <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene>

cD20 | cD52 | cTLA4 | erBB2 | IL-2 | IL-2 α | vLA4

OMIM: <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM>

Graves' disease | multiple sclerosis | myasthenia gravis | pemphigus vulgaris | type 1 diabetes

FURTHER INFORMATION

Rachel R. Caspi's homepage: <http://www.nei.nih.gov/intramural/imm-reg.asp>

Medpage Today: <http://www.medpagetoday.com/Gastroenterology/InflammatoryBowelDisease/tb/3478>

Securities and Exchange Commission file (Biogen Idec Inc):

<http://www.sec.gov/Archives/edgar/data/875045/000095013508005223/b714958ke8vk.htm>

depleted of self-reactive cells may fail to provide effective recognition of growing cancers that express altered self antigens.

Similarly, autoimmunity and host anti-microbial immunity are inextricably linked, as effector responses that cause inflammatory tissue damage are the same ones that mediate effective host defence. Therefore, immunotherapeutic regimens that target common pathways of the immune system inevitably elicit both desirable and undesirable consequences. Strategies to eliminate cancer cells by breaking tolerance to self antigens can result in autoimmunity; conversely, suppressing immune function to inhibit autoimmune responses can compromise resistance to infection and allow for the development of malignancy^{1–5}.

Approaches to therapy, both in cancer and in autoimmunity, can broadly be divided into the antigen-specific and the antigen-non-specific (BOX 1). Each has its advantages and its drawbacks, which affect the choice of therapy.

Box 1

Antigen-specific versus antigen-non-specific immunotherapy approaches

In theory, antigen-specific approaches are the ideal way to modulate immune responses, as they are intended to specifically target the cells that are involved in the pathogenic process. However, in cancer immunotherapy, the antigens that are targeted by such approaches are often expressed by both cancer cells and healthy tissues. These include the antigens that are related to melanin and its metabolism, such as gp100, MART1 (melanoma antigen recognized by autologous T cells 1), TRP1 (tyrosinase-related protein 1) and TRP2, which are common to melanoma cells and normal melanocytes. Antigen-specific approaches for many autoimmune diseases are hampered by the fact that the antigens that are the targets of autoimmune reactions have not yet been identified. Moreover, the target antigens can change over time through a process known as epitope spreading.

Antigen-non-specific approaches are directed against cell-surface molecules, receptors or functions that are involved in common activation and effector pathways of the immune system. These include co-stimulatory and adhesion molecules, cytokines, such as interleukin-2, and cytokine receptors. Enhancement of these pathways to increase antitumour responses could in parallel cause undesirable responses and toxicity as a result of excess production of pro-inflammatory mediators. Conversely, inhibition of common activation and effector pathways to counteract autoimmunity could negatively affect desired immune responses that are involved in host defence.

The discussion in this Science and Society article is not intended to be an exhaustive review of immunological approaches to the treatment of autoimmunity and cancer. The tables in this article give some examples, and several excellent reviews have recently been published on the subject^{4,6–12}. Instead, I focus on the complications of selected therapeutic approaches that are supported by clinical data to make the point that, often, the more successful a therapy, the higher its penalty in terms of side effects. However, as immunotherapeutic options increase and develop, better knowledge of immune pathways is improving our ability to tread the narrow line between treatment efficacy and unacceptable collateral damage.

Cancer

Immune therapies for cancer attempt to harness and direct the immune mechanisms that eradicate tumours. Essentially they seek to break tolerance and elicit autoimmunity, by either antigen-non-specific or antigen-specific approaches. This notion encapsulates the main

limitation that is inherent to this approach and indicates the types of problem that are encountered as a result (TABLE 1).

Early approaches that were used to augment antitumour mechanisms in a tumour-bearing host included the administration of interleukin-2 (IL-2) and type I interferons (IFN α and IFN β)^{13, 14}. The main penalty of these treatments was high toxicity (for example, vascular leak syndrome with IL-2 treatment), and therefore these approaches had limited efficacy. They have been superseded by more sophisticated antigen-non-specific approaches that target cellular receptors, such as cytotoxic T-lymphocyte antigen 4 (CTLA4), IL-2 receptor α -chain (IL-2R α , also known as CD25), CD20 (also known as MS4A1), HER2 (human epidermal growth-factor receptor 2; also known as ERBB2 and NEU)^{5,7,15,16}, and by antigen-specific approaches that promote specific antitumour responses using self or differentiation antigens (TABLE 1). Examples of self tumour antigens include carcino-embryonic antigen in colon cancer, prostate antigen and melanoma antigens, such as MART1 (melanoma antigen recognized by autologous T cells 1) and gp100 (REFS^{12,17}). Despite lacking considerable toxicity, strategies that involve active vaccination against self tumour antigens using recombinant vaccinia viruses or tumour-antigen-loaded dendritic cells have been disappointing in terms of efficacy¹⁸. In some cases, antigen-specific and antigen-non-specific approaches can be combined — for example, antitumour vaccination can be combined with CTLA4 blockade¹⁹. CTLA4 is a co-inhibitory receptor that is constitutively expressed by regulatory T cells. Its expression is also induced on effector T cells following activation and leads to inhibition of their function. CTLA4 blockade eliminates regulatory T cells while increasing the expansion and activation of effector T cells, which together strongly enhance a patient's endogenous (or vaccine-induced) antitumour responses¹⁹.

Adoptive transfer approaches, which have shown some success but also considerable toxicity, rely on using patient-derived tumour-infiltrating lymphocytes (TILs) that are expanded *ex vivo* and transferred back into patients who have been rendered lymphopenic^{12,20}. This approach to cancer therapy has had favourable results in patients with melanoma (in about 50% of the cases), but its use is limited to patients with resectable tumours that have TILs that can be expanded *ex vivo* (FIG. 1). As lymphodepletion combined with adoptive transfer is a recent approach to cancer immunotherapy, the level of improvement to the long-term survival of treated patients is not yet clear.

The cardinal problem with all approaches that aim to augment the host immune response to cancer is that many tumour antigens that serve as key therapeutic targets are also expressed in normal tissues. Consequently targeting melanoma antigens (which are also melanocyte differentiation antigens) by active vaccination or by adoptive transfer of TILs often results in the development of the autoimmune disease vitiligo (see Glossary box). When the potency of the therapy was increased by pre-transfer lymphodepletion that allows for the subsequent marked expansion of the transferred cells²¹, or by treatment with the CTLA4-specific antibody, autoimmune side effects were also increased. Although vitiligo might be considered an acceptable side effect, patients can also experience an autoimmune reaction in the eye that closely mimics autoimmune uveitis²¹ (FIG. 2). This is probably because the iris, the retinal pigment epithelium and the choroid all contain melanin. Indeed, several uveitic diseases, including Vogt–Koyanagi–Harada (VKH) disease and sympathetic ophthalmia, involve responses to melanin-associated antigens and result in inflammation and depigmentation of the eye with a consequent loss of vision^{22,23}.

In a cohort of melanoma patients who received TILs plus IL-2 after a lymphocyte-depleting chemotherapeutic regimen, 5 out of 35 patients developed uveitis²¹. In two other reports, three cases of uveitis were recorded in patients who received antibodies that were specific for CTLA4 plus IL-2 with and without vaccination with gp100 (REFS^{24,25}). Usually melanoma-treatment-

associated uveitis responds well to local steroid therapy. However, in a recent example a patient received an aggressive treatment of immunoablation and transfer of melanoma-specific CD8⁺ T cells, and this resulted in the development of uveitis that mimicked the potentially blinding VKH disease (R. B. Nussenblatt, personal communication). Examination of fluid aspirate from the eye revealed the presence of activated TILs. In this case, uveitis was refractory to topical treatment, persisted after regression of the tumour, required continuous local and systemic therapy to control inflammation and resulted in a visual deficit. As this type of aggressive anti-tumour therapy becomes more readily available and possibly moves from the clinical trial to the clinical-treatment setting, some patients could be faced with the decision of whether to continue this particular anticancer therapy at the expense of their vision.

Uveitis is just one of the autoimmune ‘penalties’ that can accompany aggressive treatments such as adoptive TIL therapy and CTLA4-specific antibody therapy. In one study, of the 198 patients with melanoma who were treated with the CTLA4-specific antibody²⁶, 21% developed enterocolitis, five of whom developed an intestinal perforation or required a colectomy. The presence of autoimmune complications was associated with treatment success; the patients who developed autoimmunity were more likely to experience favourable responses against melanoma. Similar outcomes, in which severe autoimmunity was positively correlated with anticancer responses in malignant melanoma, ovarian cancer and renal cell carcinoma, were also reported by another study²⁷. However, in patients who had previously received a GM-CSF (granulocyte/macrophage colony-stimulating factor)-containing tumour vaccine, the autoimmune manifestations following CTLA4-specific antibody treatment were more moderate. It is possible that this was due to the concurrent stimulation of anti-tumour immunity by vaccination, which allowed for an anticancer effect to be achieved with a lower dose of the CTLA4-specific antibody, thereby reducing the severity of its off-target effects¹⁹. Similarly, a single injection of the CTLA4-specific antibody to patients with prostate cancer did not induce severe autoimmunity²⁸. So, more serious autoimmune complications tended to be related to a higher dose of the CTLA4-specific antibody.

Autoimmunity is not the only penalty of successful cancer treatment. Trastuzumab (Herceptin, Genentech, Inc.), a therapeutic monoclonal antibody that shows efficacy in the treatment of patients with breast cancer, has a high incidence of cardiotoxicity, which manifests as congestive heart failure in severe cases²⁹. This is because the HER2 breast-cancer antigen that is targeted by the therapeutic antibody is also expressed by heart-muscle cells^{15,16}. The risk of cardiomyopathy is higher in the patients who are being treated concurrently with anthracyclines, and some deaths have been recorded as a result of treatment²⁹. Therefore, cardiomyopathy is an important safety concern and can be a limiting factor in the use of trastuzumab in patients with breast cancer.

Autoimmunity

Coming in the wake of conventional immunosuppressive therapies (cortico-steroids, macrolides, antimetabolites and alkylating agents) is a host of new biological agents that target immune cells more selectively (TABLE 2). In contrast to cancer therapies, which aim to increase immune responses, antigen-non-specific immunotherapies for autoimmunity aim to inhibit common immune-cell activation and effector pathways, including those that are triggered by cytokines and cytokine receptors, as well as adhesion and co-stimulatory molecules. Antigen-specific therapies aim to eliminate, tolerize or regulate the effector lymphocytes that have escaped control mechanisms and that contribute to autoimmune tissue damage (BOX 1) (reviewed in REF. 4).

Antigen-specific therapies

For many autoimmune diseases, the self antigens involved have yet to be identified. However, for diseases in which the antigens are known or good candidate antigens are available (such as myasthenia gravis³⁰, Graves' disease³¹, pemphigus vulgaris³², type I diabetes³³, multiple sclerosis³⁴ and various types of uveitis^{22,35–37}), antigen-specific therapy would seem to be the ideal approach. As experimental strategies for the induction of antigen-specific tolerance improve, feasibility of antigen-specific regulation comes within reach. Nevertheless, as a clinical approach, antigen-specific therapy is still in its infancy and there are serious concerns about introducing a disease-relevant antigen into an individual who is already sensitized to that antigen. Two highly publicized clinical trials in patients with multiple sclerosis, which used altered peptide ligands (APLs) that mimic myelin epitopes, were halted owing to hypersensitivity responses and disease exacerbation^{38,39}. By contrast, glatiramer acetate (Copaxone, Teva Pharmaceutical Industries Ltd), which is a random co-polymer of basic amino acids that was initially developed as a mimic of myelin basic protein, was approved by the US Food and Drug Administration (FDA) in 1996 for the treatment of relapsing-remitting multiple sclerosis. Glatiramer acetate was recently shown to also have immunoregulatory properties because it increased the numbers of regulatory T cells and modulated the function of antigen-presenting cells. Therefore, it might be useful in the treatment of not only multiple sclerosis but also other autoimmune diseases⁴⁰. Glatiramer acetate is currently the only FDA-approved antigen-specific treatment for an autoimmune disease. Serious side effects following its administration have not been reported, but its efficacy in controlling disease is limited⁴¹.

Antigen-non-specific therapies

Given the current state of knowledge, antigen-non-specific approaches that target common lymphocyte activation mechanisms are far more accessible.

Probably the best known and most widely used immunotherapy for rheumatoid arthritis is blockade of the pro-inflammatory cytokine tumour-necrosis factor (TNF) with TNF-specific antibodies or soluble TNF receptors. TNF blockade is now also used for psoriasis, Spondyloarthropathy and Crohn's disease. It was initially reported that TNF blockade in cultures of synovial tissue from inflamed joints reduced the production of many pro-inflammatory mediators, including IL-1, IL-6, GM-CSF and IL-8 (REF. 42). This effect of TNF blockade on inflammation is central for its efficacy, but also underpins its severe side effects, as these pro-inflammatory cytokines are important for an effective host immune response against microorganisms. Although TNF blockade has been a successful treatment for many patients, it can cause lethal reactivation of latent infections, most commonly tuberculosis. It can also increase the probability of developing lymphoma, especially when administered in conjunction with immunosuppressive treatments, such as methotrexate or corticosteroids^{3,9}. Paradoxically, despite decreasing arthritis, TNF blockade for prolonged periods can increase the onset of multiple sclerosis and possibly lupus and other autoimmune disorders^{43–45}, an outcome that may be related to the role of TNF in promoting the apoptosis of effector T cells⁴⁶.

Another highly effective (and highly publicized) biological agent is the monoclonal antibody that is specific for the T-cell adhesion molecule VLA4 (very late antigen 4; also known as $\alpha_4\beta_1$ -integrin), natalizumab (Tysabri, Biogen Idec, Inc. and Elan Corporation PLC). Natalizumab was approved in November 2004 for the treatment of relapsing-remitting multiple sclerosis because it reduced the frequency of disease exacerbation. VLA4 is an adhesion and tissue-homing molecule expressed by T cells that have previously been exposed to antigen and have effector function. Such T cells are thought to participate in the immunopathology of multiple sclerosis. Blockade of VLA4 prevents the entry of these T cells into the tissue in which they mediate immunopathology. However, inhibition of lymphocyte trafficking to the brain

also prevents the normal physiological process of immune surveillance. A Phase III clinical trial in patients with multiple sclerosis that was showing every sign of success was halted owing to the emergence of progressive multifocal leukoencephalopathy (PML) in some patients who were concurrently being treated with IFN β . This was caused by the reactivation of latent JC virus (a polyomavirus that is carried by 80% of the population) in the brains of these patients⁵. PML has previously been associated only with severe immunodeficiency states, including AIDS and chemotherapy. Because the number of affected cases was low compared with the clear benefit of the therapy, the drug is now back on the market, albeit with restrictions on its use. Nevertheless, two new cases of PML were reported in July 2008, one of them in a patient not taking other multiple sclerosis drugs (see [Medpage Today](#) and [Securities and Exchange Commission file](#)). So, for both TNF- and VLA4-specific antibody therapies, their potent ability to block harmful immune responses goes hand in hand with their potential to cause severe complications⁹.

Minimizing penalties, maximizing success

Is a more potent immunotherapy necessarily more destructive, or can we overcome the disadvantages? Because immunotherapy manipulates the fundamental components of the immune response that underlie not only pathological but also normal immune functions, penalty can probably never be separated entirely from success. However, despite the associated hazards, immunotherapy has already saved or improved the lives of millions of people. As we gain more experience, we are learning to use existing therapies in better ways (BOX 2) and developing treatments with better efficacy-to-toxicity ratios.

Box 2

Reducing treatment toxicity without sacrificing efficacy

Combine it

Using a combination of therapeutic agents might allow for a reduction in the dose of each individual drug to levels that are not toxic. Thus, the severe autoimmune side effects of treatment of cancer with a monoclonal antibody that is specific for cytotoxic T-lymphocyte antigen 4 (CTLA4) may be attenuated if it is used at lower doses and in combination with a vaccine (for example, containing melanoma antigen); this retains the desired increase in immune responses while allowing the dose and duration of treatment to be reduced¹⁹. Other examples of such combination approaches include the use of the CTLA4-immunoglobulin fusion protein abatacept (Orencia, Bristol-Myers Squibb) or the B-cell-depleting agent rituximab (Rituxan, Genentech, Inc. and Biogen Idec) in combination with the immunosuppressive drug methotrexate to treat rheumatoid arthritis that is resistant to drugs or tumour-necrosis factor (TNF) blockade. The effectiveness of the combination therapy is similar to that of TNF blockade alone but has fewer side effects⁵⁴.

Modify it

Early clinical trials using the CD3-specific mouse monoclonal antibody OKT3, which is designed to temporarily eliminate T cells, caused severe systemic toxicity owing to initial widespread T-cell activation and cytokine storm. The more recently developed humanized forms of CD3-specific antibody that have been designed so they do not bind to activating Fc receptors (referred to as hOKT3 γ 1 Ala-Ala and ChAglyCD3) have been better tolerated (albeit not free of side effects) and seem to be beneficial in early-onset type 1 diabetes^{48–49}.

Time it

Recent clinical trials that have been carried out in patients with rheumatoid arthritis in the Netherlands show that if patients are treated earlier in the disease process, they need fewer courses of TNF blockade for effective long-term remission. A shorter course of treatment is expected to reduce the side effects of therapy⁵⁵.

To minimize the unintended side effects of immunotherapy, we must develop more specific methods to target pathogenic cell populations, be they cancer cells or autoimmune lymphocytes. Systematic and rigorous studies are needed to define cancer target antigens that are minimally shared with normal tissues¹¹. One such candidate might be carcinoembryonic antigen, which is highly expressed in colon cancer cells but not in normal colonic tissue; another candidate could be mucin-1, a ubiquitous cell-surface antigen that is heavily glycosylated in normal cells but not in cancer cells, and therefore the two forms differ antigenically¹⁷. Conversely, in autoimmunity clinical experience is identifying therapies that have a more favourable efficacy-to-toxicity ratio for specific diseases. The CD20-specific antibody that depletes mature B cells, rituximab (Rituxan, Genentech, Inc. and Biogen Idec), is approved for the treatment of B-cell cancers and rheumatoid arthritis that is refractory to TNF blockade, and is used off-label in systemic lupus erythematosus. Cases of PML have been reported in patients who are being chronically treated with rituximab, especially those who are immunosuppressed. Surprisingly, in multiple sclerosis, which is considered to be a primarily T-cell-mediated disease, a single course of rituximab reduced inflammatory brain lesions and clinical relapses for 48 weeks⁴⁷. Similarly, treatment of patients with type 1 diabetes with a single course of CD3-specific antibody that has been humanized and rendered non-Fc-binding results in improvement of disease lasting at least 2 years, which suggests that its mechanism of action involves immune regulation rather than solely lymphocyte depletion^{48,49}. Two antibodies that target T cells, the CD52-specific antibody alemtuzumab (Campath-1H, Genzyme Corporation and Schering AG) and the CD25-specific antibody daclizumab (Zenapax, F. Hoffman–LaRoche Ltd), are in Phase III clinical trials and are producing promising results⁵⁰.

Preclinical animal models often do not predict the complications that are encountered in patients, but occasionally the complications that are implied by animal studies may not apply to humans. A case in point: 10 years ago Nussenblatt *et al.*⁵¹ adapted the CD25-specific antibody daclizumab, which had been successful in eliminating CD25-expressing leukaemias, for the treatment of autoimmune uveitis on the basis that activated uveitogenic effector T cells express CD25 (the α -chain of the IL-2R). However, studies have subsequently shown that mice and humans also have CD25-expressing IL-2-dependent regulatory T cells that are crucial for the control of autoimmunity, and mice that lack IL-2 develop severe autoimmunity owing to a regulatory T-cell defect⁵². If Nussenblatt *et al.* had been aware of the possibility of such dire consequences following blockade of CD25 on regulatory T cells by daclizumab, as implied by these subsequent studies, the trial may not have proceeded. Thankfully, however, the clinical pilot study was successful, allowing most patients to reduce or discontinue their conventional immunosuppressive medications. Daclizumab is now being developed for the treatment of uveitis and multiple sclerosis.

To expand our ability to evaluate treatment outcome, it will be important to identify new biomarkers. Such efforts are currently being carried out by members of the Biomarkers Consortium, which was launched on 5 November 2006. This initiative is a public–private partnership that includes government agencies, non-profit and pharmaceutical companies, and representatives of the public, including patient-advocacy organizations⁵³. Although we may never be able to eliminate the penalty for success completely, as our knowledge and experience progress, the balance of safety and efficacy will undoubtedly improve.

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Glossary

Altered peptide ligand, (APL)

A peptide analogue in which the key T-cell receptor contact residues are altered, leading to the induction of only a partial response by the T cells that are specific for the original agonist peptide. Some APLs may stimulate regulatory T cells without activating effector T cells

Crohn's disease

A form of chronic inflammatory bowel disease that can affect the entire gastrointestinal tract, but is most common in the colon and terminal ileum. It is characterized by transmural inflammation, narrowing of the gut lumen and granuloma formation, and is thought to result from an abnormal T-cell-mediated immune response to commensal bacteria

Epitope spreading

The *de novo* activation of autoreactive T cells by self antigens that have been released after B- or T-cell-mediated bystander damage

Psoriasis

A chronic skin disease that affects 1–2% of the population, in which the skin becomes inflamed, producing red, thickened areas with silvery scales, most often on the scalp, elbows, knees and lower back. Recent evidence points to a T-cell-mediated pathogenesis in genetically susceptible individuals, which results in inflammation and epidermal hyperplasia

Spondyloarthropathy

A group of inflammatory joint diseases that are associated with the MHC class I molecule HLA-B27. It is often associated with anterior uveitis

Sympathetic ophthalmia

Destructive uveitis in one eye (sympathizing) following a penetrating wound to the other. It is considered to be an autoimmune response to antigens that are released from the wounded eye

Vitiligo

A depigmenting disorder of the skin and hair that is caused by the destruction of melanocytes that produce cutaneous pigments

Vogt–Koyanagi–Harada disease

A serious and potentially blinding condition that also targets the melanin in the anterior and the posterior pole of the eye

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Figure 1. A simplified model of common immune responses following adoptive immunotherapy Tumour-infiltrating lymphocytes (TILs) are expanded *in vitro* in the presence of excised tumour cells and interleukin-2 (IL-2). CD8⁺ cytotoxic T lymphocytes (CTLs) are activated and expanded. These cells are then infused back into the patient, where they home not only to the tumour to mediate tumour regression, but also to healthy tissues that express melanin, such as the skin and eye, to cause autoimmune inflammation.

A Vitiligo

Before therapy

After therapy

B Uveitis

Figure 2. Severe vitiligo and uveitis induced by adoptive immunotherapy for melanoma

A | Extensive vitiligo in a patient who received cytoreductive therapy followed by infusion of autologous, *in vitro*-expanded CD8⁺ T cells. **B** | The images show the occurrence of uveitis in a patient with melanoma who was treated with monoclonal antibody that was specific for CTLA4 (cytotoxic T-lymphocyte antigen 4). The clinical picture is similar to that seen in patients who have been treated with cytoreductive therapy and tumour-infiltrating lymphocytes. The images are a slit-lamp photograph of the patient's left eye, showing inflammation and an irregular pupil (iris adheres to lens) (**Ba**) and a slit-lamp photograph of the right eye (after pupil dilation), showing iris pigment epithelium and fibrin (indicated by

arrows) that has adhered to the surface of the lens (**Bb**). Images are reproduced from REF. ¹² (**A**) and REF. ²⁵ (**B**).

Table 1
Immunotherapeutic approaches for the treatment of cancer

Approach	Principles and uses (examples)	Side effects and caveats	Refs
Triggering inflammation	A classic approach involves the administration of live BCG directly into tumours. It is used to treat bladder carcinoma and is being further developed using modern genetic engineering tools	Pneumonitis and/or hepatitis; renal or disseminated BCG infection	56
Cytokine therapy	An early approach involved the administration of IL-2 for the <i>in vivo</i> expansion of NK cells and T cells. Owing to high toxicity, this has been superseded by newer cellular immunotherapies. GM-CSF is used as an adjuvant in tumour vaccination	Systemic toxicity, such as vascular leak, following treatment with IL-2	14
Monoclonal antibody therapy	Administration of <i>ex vivo</i> -generated antibodies, such as CD25-specific antibody (daclizumab), to treat ATL; CD20-specific antibody (rituximab) to treat B-cell lymphoma; HER2-specific antibody (trastuzumab) to treat breast cancer; CTLA4-specific antibody (ipilimumab) to treat melanoma and renal cell carcinoma	Toxicity to normal tissues (trastuzumab); induction of severe autoimmunity (ipilimumab)	5·7·15·16
Cellular immunotherapy	Infusion of autologous or allogeneic stem cells (to treat haematopoietic malignancies) into patients who are partly or completely immunoablated; Infusion of tumour-specific lymphocytes (to treat melanoma and other solid tumours) into patients who are partly or completely immunoablated	Autoimmunity owing to off-target responses, including GVHD (in haematopoietic malignancies) and uveitis (in melanoma)	12
Antitumour vaccination	Administration of a tumour vaccine as a preparation of tumour antigens. For example: tumour antigens encoded in a viral vector with or without integrated adjuvant activity to boost T-cell or innate immune cell responses; tumour-antigen-loaded dendritic cells acting as carriers and APCs	Relatively few complications reported, but overall limited efficacy; potential for autoimmunity	18

APC, antigen-presenting cell; ATL, adult T-cell leukaemia; BCG, *Mycobacterium bovis* bacillus Calmette–Guérin; CTLA4, cytotoxic T-lymphocyte antigen 4; GM-CSF, granulocyte/macrophage colony-stimulating factor; GVHD, graft-versus-host disease; HER2, human epidermal growth-factor receptor 2.

Table 2
Immunotherapeutic approaches for the treatment of autoimmunity

Approach	Principles and uses (examples)	Side effects and caveats	Refs
Antigen-specific tolerance	Administration of antigen or antigen analogue in a tolerogenic form to promote anergy in pathogenic cells or elicit regulatory T cells	When unsuccessful, autoimmune symptoms can worsen	8·38·39
Cytokine therapy	Antagonism of pro-inflammatory cytokines, such as TNF and IL-1 to treat rheumatic and chronic febrile diseases Infusion of regulatory cytokines, such as IL-10, to treat psoriasis Infusion of IFN β (betaseron) to treat multiple sclerosis	Systemic and haematological toxicity (IL-10, betaseron); gastrointestinal and liver toxicity, myalgia (betaseron) Systemic toxicities related to inhibition of host defence	9·57
Targeting of particular cell populations	Infusion of CD3-specific antibody to reduce and/or modulate T cells Infusion of CD20-specific antibody to eliminate B cells Infusion of agonistic CD28-specific antibody to increase the numbers of regulatory T cells	Systemic toxicity in some cases of CD3-specific antibody and CD28-specific antibody treatment due to general T-cell activation	49·58·59
Immunoablation and reconstitution	Ablation of the immune system and reconstitution with autologous or allogeneic bone marrow to reprogramme the immune system	Acute autologous or allogeneic GVHD	6·10
Targeting common lymphocyte activation mechanisms	Blockade of co-stimulatory molecules, cytokine receptors or adhesion molecules using agents such as CTLA4-immunoglobulin fusion protein (abatacept), CD40-specific antibody, CD25-specific antibody (daclizumab) and VLA4-specific antibody (natalizumab)	Susceptibility to new infections or reactivation of latent infections that are related to the inhibition of host defence	5·7·54

CTLA4, cytotoxic T-lymphocyte antigen 4; GM-CSF, granulocyte/macrophage colony-stimulating factor; GVHD, graft-versus-host disease; IFN β , interferon- β ; TNF, tumour-necrosis factor; VLA4, very late antigen 4.