Cancer vaccines and immunotherapy

Said Dermime, Anne Armstrong, Robert E Hawkins and Peter L Stern

CRC Departments of Medical Oncology and Immunology, University of Manchester and Paterson Institute for Cancer Research, Christie Hospital NHS Trust, Manchester, UK

It is now clear that many human tumour antigens can be recognised by the immune system. These tumour antigens can be classified into several groups including cancer-testis, differentiation, tissue specific, over-expressed, and viral-associated antigens. In many cases, there is a known molecular basis of carcinogenesis which provides the explanation for the differentiated expression of these antigens in tumours compared with normal cells. Improved understanding of the biology of the immune response, particularly of immune recognition and activation of T-cells, allow better design of vaccines. Pre-clinical comparative studies allow evaluation of optimal vaccine strategies which can then be delivered to the clinic. Currently, a range of cancer vaccines are being tested including those using tumour cells, proteins, peptides, viral vectors, DNA or dendritic cells. Ultimately, this research should give rise to an entirely new modality of cancer treatments.

Interest in vaccinating against tumours dates back to the 1890s when the New York surgeon William B Coley successfully treated some patients with sarcoma using bacterial toxins. In 1909, Paul Ehrlich successfully carried out immunisation in animals with tumour cells and suggested that tumours occur at a high frequency in humans but are kept under control by the immune system. Whilst this may be simplistic, it is clear that many tumour cells can be distinguished from their corresponding normal cells by the existence of tumour antigens that can be recognised by the host immune system.

Recent developments in tumour biology and basic immunology have provided new insights to our understanding of how tumour cells and the immune system interact. Indeed, many animal studies have now established the critical importance of T-cells in mediating antitumour immunity. It is clear that, in man, the process of carcinogenesis generates many changes in tumour cell antigen expression which are potentially, or actually, recognized by host T-cells (human tumour antigens). A detailed knowledge of mechanisms of antigen recognition by T-cells (processed peptides in the context of MHC class I or II molecules), the
'Danger signals'

1. Damage/danger causing local cytokine release, activation of dendritic cells (DCs).

2. DC antigen processing and migration. T-cells recognize, through the T-cell receptor (TCR), a complex of an antigenic peptide (P) (e.g. derived from a viral protein) bound to an HLA glycoprotein (major histocompatibility complex (MHC) class I or II molecules) located on the surface of the APC antigen. HLA polymorphism increases the chances of an individual existing within a population that can express an HLA-peptide complex resulting in protection against a particular pathogen.

3. Processed peptide antigens presented by DC major histocompatibility complex HLA class I or class II molecules to CD8 or CD4 T-cells, respectively, in secondary lymphoid tissues with second signal provided by DC B7 (CD80) interaction with CD28 on the T-cells.

4. Expansion of clones with specific T-cell receptor (TCR) for HLA-peptide complex and delivery of effectors to target tissue. (Adapted with permission from Little AM, Stern PL. *Trends Mol Med* 1999; 5: 337-42.)

Fig. 1 Four steps to specific anti-T-cell responses.
process of T-cell priming and activation (antigen presenting cells, co-stimulatory molecules, local cytokine environment), has allowed for the development of new cancer immunotherapies (Fig. 1). In cancer, such responses may be suppressed or may not have been optimally activated or have driven selection of tumour escape mechanisms. The aim of current cancer vaccines is, therefore, to induce de novo or potentiate existing antitumour immunity that can destroy autologous cancer cells. This review outlines the relevance of cell-mediated immunity to tumours, the range of potential human tumour antigen targets, and the various means being applied to optimise their use in vaccines. Necessarily, there is also a requirement to assess and develop the means to monitor the desired immunological endpoints in relation to clinical outcome.

Immune recognition of human tumour cells

Animal models have demonstrated that, although humoral mechanisms may be relevant, it is T-cell-mediated immunity that is of critical importance in transplanted tumours. This has driven an effort to identify tumour antigens using human T-cells. T-cells recognise antigens on the cell surface of target cells as small peptides presented by class I or class II of the major histocompatibility complex (MHC) molecules (Fig. 1). CD8+ cytotoxic T-cells recognise short peptides derived from intracellular cytoplasmic proteins and presented at the cell surface by class I MHC molecules that are expressed by virtually all nucleated cells. In contrast, CD4+ helper T-cells recognise longer peptides derived from engulfed extracellular proteins and presented at the cell surface by class II MHC molecules by professional antigen presenting cells (APCs). APCs are central to the priming of T-cells by specific antigen in which dendritic cells (DCs) are the most potent stimulatory APCs. DCs exhibit several features which are necessary for the generation of T-cell-mediated antitumour immunity. They efficiently capture and take up antigens in peripheral tissues and transport these antigens to the primary and secondary lymphoid organs where they express high levels of MHC class I and II molecules that present the processed peptides to T-cells for the priming of antigen-specific responses. In addition, DCs express high levels of co-stimulatory molecules, that interact with receptors on T-cells, a second signal required to optimally activate antigen-specific T-cells. T-cell recognition results in interleukin 2 (IL-2, a cytokine necessary for T-cell growth) production by stimulated T-cells which, in turn, leads to T-cell proliferation and expansion. T-cells become tolerant (anergic) when they see antigens in the absence of this signal. To initiate the process of antigen presentation by the DCs, the antigen has to be present together with signals of tissue damage, the so-called ‘danger signals’. Stress proteins
such as heat shock proteins that chaperone tumour antigens can be regarded as a danger signal and available evidence suggests that heat shock proteins are an important source of antigen processed and presented by DCs under natural conditions\textsuperscript{10}.

According to the ‘immune surveillance’ hypothesis, expression of tumour antigens during neoplastic transformation should induce an immune response that can control tumour growth\textsuperscript{11}. However, evidence to support this can be demonstrated only in a fraction of tumours\textsuperscript{12}, and several mechanisms are thought to play important roles in tumour escape from the immune system. For instance, tumour cells can down-regulate or lose the expression of their MHC molecules resulting in inhibition of T-cell recognition\textsuperscript{13}. Lack of co-stimulatory molecules on tumours can prevent T-cell activation and lead to T-cell anergy in cancer patients\textsuperscript{14}. In addition, tumour cells may not be able to provide the danger signal necessary for optimal immune function\textsuperscript{9}. The local release of transforming growth factor (TGF-\textit{\textbeta}1) by progressor tumours can inhibit DC migration and reduce the ability of DC to mature into potent APC\textsuperscript{15}. Expression of Fas ligand molecules on tumour cells can interact with Fas receptors on T-cells resulting in induction of T cell death (apoptosis)\textsuperscript{16}. These various escape mechanisms contribute to the lack of effective antitumour immunity in patients, in spite of clear evidence of frequent recognition of a plethora of tumour antigens.

**Identification and classification of human tumour antigens**

Key studies established that autologous tumour-specific T-cells could be isolated from cancer patients and used to characterise the antigen recognised\textsuperscript{4}. In these studies, complementary cDNA libraries generated from tumour cells can be introduced into a target cell expressing an appropriate MHC molecule, and antitumour T-cells can be used to screen for the genes encoding the tumour antigens. Several other approaches can validate potential tumour antigen identification. An *in vitro* stimulation technique known as ‘reverse immunology’, can be used to generate T-cells that react against proteins known to be over-expressed in certain cancer cells. If cancer cells are recognised by these specific T-cells, then the selected protein may be a useful tumour antigen\textsuperscript{17}. Tumour antigens can also be discovered by investigating what peptides are eluted from the MHC molecules of tumour cells. Such eluted and concentrated peptides can be sequenced for identification and used to test their ability to generate T-cells\textsuperscript{18}. A third technique known as SEREX (serologic analysis of recombinant cDNA expression libraries) identifies tumour antigens recognised by patient antibodies\textsuperscript{19}. In this technique, proteins encoded by complementary cDNA libraries
from cancer cells are expressed in bacteria and sera from normal or cancer patients used to screen for tumour-specific antigens.

Tumour antigens recognised by human T cells fall into several general categories. Examples of well-defined tumour antigens from each category are presented in Table 1.

**Table 1** Categories and examples of tumour-associated antigens recognised by human T-cells

<table>
<thead>
<tr>
<th>Category</th>
<th>Tumour antigens</th>
<th>Cancer expressing the antigen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer testis antigens</td>
<td>MAGE-1</td>
<td>(Melanoma, breast, head and neck, bladder, gastric and lung cancer)</td>
</tr>
<tr>
<td></td>
<td>MAGE-2</td>
<td></td>
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<tr>
<td></td>
<td>MAGE-3</td>
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<td></td>
<td>MAGE-12</td>
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<td>BAGE</td>
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<td>GAGE</td>
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<tr>
<td></td>
<td>NY-ESO-1</td>
<td></td>
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<tr>
<td>Differentiation antigens</td>
<td>Tyrosinase</td>
<td>*Melanoma</td>
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<tr>
<td></td>
<td>TRP-1</td>
<td></td>
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<tr>
<td></td>
<td>TRP-2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>gp100</td>
<td></td>
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<tr>
<td></td>
<td>MART-1</td>
<td></td>
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<tr>
<td></td>
<td>MC1R</td>
<td></td>
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<tr>
<td>Tumour specific antigens</td>
<td>Immunoglobulin B-cell NHL, MM</td>
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<tr>
<td></td>
<td>Idiotype</td>
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<tr>
<td></td>
<td>CDK4</td>
<td>Melanoma</td>
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<td></td>
<td>Caspase-8</td>
<td>Head and neck cancer</td>
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<td></td>
<td>β-Catenin</td>
<td>Melanoma</td>
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<td></td>
<td>CIA 0205</td>
<td>Bladder cancer</td>
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<tr>
<td></td>
<td>BCR/ABL</td>
<td>CML</td>
</tr>
<tr>
<td></td>
<td>Mutated p21/ras</td>
<td>Pancreatic, colon, lung cancer</td>
</tr>
<tr>
<td></td>
<td>Mutated p53</td>
<td>Colorectal, lung, bladder, head and neck cancer</td>
</tr>
<tr>
<td>Over-expressed self antigens</td>
<td>Proteinase 3</td>
<td>CML</td>
</tr>
<tr>
<td></td>
<td>WT 1</td>
<td>CML, ALL, AML</td>
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<tr>
<td></td>
<td>MUC-1</td>
<td>Breast adenocarcinoma</td>
</tr>
<tr>
<td></td>
<td>CEA</td>
<td>Colon, breast, pancreatic cancer</td>
</tr>
<tr>
<td></td>
<td>Normal p53</td>
<td>Breast, colon and other cancer</td>
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<tr>
<td></td>
<td>Her2/neu</td>
<td>Breast and ovary and lung</td>
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<td></td>
<td>PAP</td>
<td>Prostate cancer</td>
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<td></td>
<td>PSA</td>
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<tr>
<td></td>
<td>PSMA</td>
<td>Prostate cancer</td>
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<tr>
<td></td>
<td>α-Fetoprotein</td>
<td>Liver cancer</td>
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<tr>
<td></td>
<td>G250</td>
<td>Renal cell carcinoma</td>
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<tr>
<td>Viral antigens</td>
<td>HPV E6/E7</td>
<td>Cervical and penile cancer</td>
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<td></td>
<td>EBV LMP2a</td>
<td>EBV + Hodgkin's disease</td>
</tr>
<tr>
<td></td>
<td>HCV</td>
<td>Liver cancer</td>
</tr>
<tr>
<td></td>
<td>HHV-8</td>
<td>Kaposi sarcoma</td>
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</table>

*Some of these tumours express all of the tumour antigens in this category.*

NHL, non-Hodgkin’s lymphoma; MM, multiple myeloma; CML, chronic myeloid leukaemia; ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CEA, carcinoembryonic antigen; HPV, human papilloma virus, EBV, Epstein-Barr virus; HCV, hepatitis C virus; HHV, human herpes virus.
Cancer testis antigens

Cancer testis antigens are expressed in melanomas and several other tumours, but not in normal tissues except testis. This appears to be due to demethylation of the genes in testes and cancer cells. Since they are frequently expressed in different cancers, these antigens represent attractive targets for specific immunotherapy in cancer patients.

Differentiation antigens

These reflect the expression of normal products of a particular lineage which are associated with a particular point in differentiation and which might be found at relatively low concentration or on a small subset of cells. In cancer, the clonal expansion of the tumour and abnormal differentiation can provide a potential target for the immune system. There are several examples of such normal proteins controlling melanogenesis that are expressed on melanomas and also in normal melanocytes. Several peptides from these self antigens have been found to be targets for T-cells infiltrating tumours. Vaccination with these antigens can result in an immune response that may destroy normal tissues. T-cell-mediated vitiligo was demonstrated in melanoma patients after infusion with MART-1 specific CD8+ T-cell clones providing direct evidence that antigen-specific immunotherapy with such antigens can target not only antigen-positive tumour cells in vivo but also normal tissues expressing the tumour antigen20.

Tumour-specific antigens

These are unique antigens specific for each individual tumour. They represent normal proteins that contain mutations or gene fusions that result in the generation of unique proteins. They potentially provide ideal targets for vaccination since the immune response generated will be specific and is unlikely to cause damage to normal tissues.

Over-expressed ‘self’ antigens

These are normal ‘self’ proteins that are expressed constitutively in tumour cells. Two major factors have to be taken into consideration when using this type of antigen in vaccination: the possibility of induction of auto-immunity as well as the existence of immunological tolerance (anergy), which may make successful vaccination impossible.
Viral antigens

Some human malignancies are strongly associated with viruses. Viral proteins expressed on tumour cells can serve as specific targets for immune attack. Vaccines containing this type of antigen are highly likely to be immunogenic as they are foreign antigens. Elimination of these infectious agents may also be a strategy to help prevent cancer.

Vaccination with tumour antigens

The identification of human tumour antigens has made possible innovative approaches to antigen-specific vaccination. Several aim to combine selected tumour antigens and appropriate routes for delivering these antigens to the immune system in an attempt to optimise vaccination in humans.

Tumour cell-based vaccines

Whole tumour cells have been used to vaccinate humans with cancer. The fact that tumour itself is not able to induce an adequate immune response in patients in the first place, led to attempts to overcome such unresponsiveness by introduction of cytokine genes or co-stimulatory molecules, into the genome of the vaccine tumour cells. This should create micro-environmental conditions that prevent anergy and allows tumour destruction to take place. One important cytokine is the granulocyte macrophage colony-stimulating factor (GM-CSF) which is known to contribute to the maturation of DCs, which in turn enhances antigen presentation in vivo. The use of patient’s autologous tumour cells transfected with GM-CSF as a vaccine has been explored in phase I/II human clinical trials for melanoma, renal carcinoma, and prostate cancer. These trials have shown some success in generating specific immune responses against tumours. However, production of such vaccine is rather labour-intensive, slow, and logistically difficult. Allogeneic tumour cell vaccination offers an alternative approach in which cell lines derived from the tumour type that is the target of therapy can be established in vitro, genetically modified, and used as a single reagent. Several clinical trials have been carried out with different allogeneic tumour types transduced with different cytokine genes. A recent phase I clinical trial treated 14 patients with pancreatic cancer with escalating doses of allogeneic GM-CSF-secreting pancreatic tumour cell vaccine followed by adjuvant radiation and chemotherapy. No toxicity was recorded and, in 3 patients given the highest dose, there was
an increased delayed-type hypersensitivity (DTH) response to autologous tumour cells. Interestingly, these 3 patients were disease-free at least 25 months after diagnosis.

**Peptide-based vaccines**

Effective peptide vaccination depends on the *in vivo* loading of empty MHC molecules on professional APC expressing co-stimulatory molecules. A peptide-based vaccine that contains several T-cell epitopes, covering a wide range of MHC types, is likely to be successful in inducing polyclonal T-cell responses. Peptide vaccination for a number of tumours is being tested in clinical trials. Two phase I/II trials carried out in patients with metastatic melanoma\textsuperscript{25,26} using peptides derived from gp100 and MAGE-3 and resulted in specific immunity and/or clinical responses in a significant number of patients. Phase I/II trials have also been performed in patients with cervical cancer using two HPV16 E7 HLA-A2 binding peptides and a pan-MHC class II helper peptide\textsuperscript{27,28}. The clinical responses observed in these trials were linked to T-cells against the helper peptide and not to the HPV16 derived peptides.

**Recombinant virus-based vaccines**

Tumour antigen vaccines can be delivered by recombinant viral vectors. One advantage of the use of such viral vectors is their intrinsic ability to initiate immune responses, with inflammatory reactions occurring as a result of the viral infection creating the danger signal necessary for immune activation. An ideal viral vector should be safe and should not introduce an anti-vector immune response to allow for boosting antitumour specific responses. Recombinant viruses (review by Bonnet *et al*\textsuperscript{29}) such as vaccinia viruses, herpes simplex viruses, adenoviruses, adeno-associated viruses, retroviruses and avipox viruses have been used in animal tumour models and based on their encouraging results, human clinical trials have been initiated. These trials have demonstrated that recombinant viruses are safe in humans, and can break immune tolerance against self and/or weakly immunogenic tumour antigens. A phase I clinical trial with a vaccinia virus vector encoding the CEA (rV-CEA) antigen was carried out in patients with advanced colorectal cancer\textsuperscript{30}. Although anti-CEA specific T-cell responses could be generated, no significant antitumour effect was observed. One main reason for the lack of a clinical efficacy in these trials may be attributed to the prior exposure of the patients to the vaccinia virus. Reduced vaccine delivery as a result of memory responses to viral antigens following repeated doses of the vaccine could reduce the effect of
boosting. To avoid possible immunisation to the virus vectors, avipox virus vectors have been developed, as humans have not previously been exposed to these viruses and they cannot replicate in human tissues. A phase I clinical trial with recombinant avipox virus vector encoding the CEA antigen (avipox-CEA) was carried out in patients with advanced carcinoma. Again, although a significant increase in the number of anti-CEA specific T-cell precursors was recorded in most patients, no true objective antitumour effects were seen. Alternative promising approaches include prime-boost schedules with different vaccine vehicles. Recently, a phase I clinical trial has indicated that the combination of rV-CEA and avipox-CEA in a diversified prime and boost protocol was superior to the reverse order in the generation of anti-CEA specific T-cells responses.

**DNA-based vaccines**

Direct vaccination with DNA encoding a tumour antigen has the advantage of simplicity and low cost of production. Such immunisation can induce both humoral and T-cell mediated immunity as the whole antigen is being delivered. DNA vaccines encoding weakly immunogenic antigens can be improved by vaccination with DNA encoding a protein antigen fused to a cytokine such as GM-CSF or the constant region of a foreign immunoglobulin, or a known highly immunogenic carrier protein such as fragment C (FrC) of tetanus toxin. The use of these ‘adjuvant-like’ elements has been shown to improve vaccine efficacy in experimental animals, and they are now being evaluated in human clinical trials. A phase I clinical trial using DNA encoding the variable fragment of B-cell lymphoma idiotype was carried out in 7 patients with low grade non-Hodgkin’s lymphoma. Escalating doses of the vaccine given intramuscularly did not result in muscle damage or anti-DNA antibodies, with the exception of minor redness in the skin and muscle ache. However, no anti-idiotypic specific immune response could be detected in these patients. The use of the idiotypic DNA without an adjuvant and the fact that these patients were immunosuppressed prior to vaccination may have contributed to such unresponsiveness. A further phase I/II clinical trial in remission patients with non-Hodgkin’s lymphoma is being conducted at this centre with escalating doses of vaccine incorporating the idiotypic scFv encoding DNA fused to the gene of FrC of tetanus toxin.

**Dendritic cells vaccines**

Several strategies have been used to load DCs with tumour antigens including peptides, proteins, tumour cell lysates or tumour-derived
RNA. Other strategies include DCs transfected with viral vectors expressing tumour antigens or fused with the whole tumour cells. The demonstration that immunisation of animals with DC-based vaccines can lead to rejection of established tumours, and the fact that functional DCs can be generated in vitro in large quantities from cancer patients, have made DCs an attractive vehicle to be used in human clinical trials. Hsu et al vaccinated 4 B-cell lymphoma patients with autologous DC-pulsed ex vivo with idiotypic protein. Patients received 3-4 infusions of the DC-protein together with subcutaneous soluble protein. No significant side-effects were recorded and all patients developed an anti-idiotypic immune response. Three patients had either partial or total regression of the disease. A phase I/II clinical trial of DC-based vaccine was carried out in patients with prostate cancer using DCs loaded with PSMA peptides given once every 6 weeks. In addition to induction of anti-PSMA specific T-cell activity, the numbers of the DCs given correlated with the duration of the immune response, with the majority of the patients (58%) still responding at the end of the follow-up period. In a clinical study of 16 patients with advanced melanoma, DCs were pulsed with either tumour lysate or peptides derived from (MART-1, gp100, MAGE-1 or MAGE-3) antigens in conjunction with KLH as a CD4+ helper and immunological tracer antigen. A peptide-specific DTH response was induced in 11/16 patients and 5/16 patients had objective responses with regression of metastases in several organs. One of the most interesting clinical trials was recently reported by Kugler et al in 17 patients with advanced renal cell carcinoma. In this trial, the tumour cells were fused with normal allogeneic donor DCs and were given as subcutaneous injections over several months. A 41% response rate (with 4 patients showing a prolonged complete response) was recorded. Interestingly, 65% of patients developed DTH reactions and CD8+ T-cells were shown to migrate to the site of vaccination in which T-cells clones with specificity to the MUC-1 antigen could be isolated. The rational behind the use of such vaccines is the ability of the tumour-allogeneic DC hybrid to stimulate CD4+ helper allo-reactive T-cells to release cytokines. These cytokines can contribute to activation and proliferation of tumour-specific CD8+ cytotoxic T-cells which then lyse tumour targets.

**Evaluation and monitoring of vaccine-induced immunity**

Because it is still not yet clearly known which are the most important immune effectors induced after vaccination, both humoral and cellular immune responses should be measured. For an antibody response, an established standard technique – the enzyme-linked immunosorbent
assay (ELISA) – is the most reliable assay that can be used to look for antitumour activity. For T-cells, the frequency of tumour-specific T-cells is difficult to assess using standard assays. Two sensitive *in vitro* assays namely IFN-γ ELISpot and HLA-tetramers are being used\(^43\). Fresh peripheral blood mononuclear cells can be used directly in the assays. However, a single round of *in vitro* stimulation can be carried out in the case of weak responses\(^44\). The fact that HLA-tetramers detect both antigen-stimulated and naive T-cells and IFN-γ ELISpot only measures the number of memory and effector cells\(^43\) makes the latter a more appropriate and reliable technique for discriminating between naive and vaccine-induced T-cells. Finally, the *in vivo* assay DTH\(^45\) is being used in several clinical trials and DTH responses seem to correlate with clinical responses.

**Potentiating the immune response to tumour antigens**

Optimisation of techniques to produce optimally functional DCs *in vitro* is very important as many injections may be needed in order to break tolerance and sustain responses to poorly immunogenic tumour antigens. A recent clinical trial\(^46\) demonstrated that treatment of advanced cancer patients with flt3 ligand, a hematopoietic growth factor, expanded circulating DCs 20-fold *in vivo*.

Generation of sustained CD8\(^+\) cytotoxic T-cell responses with antitumour effect usually requires help from CD4\(^+\) helper T-cells\(^47\). The constant region of a foreign immunoglobulin\(^33\), or a known highly immunogenic carrier protein such as fragment C (FrC) of tetanus toxin\(^34\) and KLH as an immunological tracer antigen\(^42\), may be used as a CD4\(^+\) helper target.

Administration of DC activators and immunomodulating cytokines along with a DC-based vaccine may result in benefit. For example, *in vitro* activation of DCs with commercially available CD40 ligand or introduction of the gene encoding CD40 ligand into DCs should enhance the potency of a DC-based vaccine\(^49\). The gene encoding IL-12, a cytokine produced by activated DCs, may also be introduced into DCs. This should allow Th1 cell activation which, in turn, recruits CD8\(^+\) cytotoxic T-cell responses in addition to its enhancement of natural killer cell cytotoxicity\(^49\).

The method for antigen loading of DCs should be selected to suit an appropriate vaccine. Certainly, the incorporation of relatively more easily produced RNA or DNA may offer a viable alternative to peptide or protein and viral-based vaccines.

The route of DC administration can also be selected to induce a desirable humoral or cellular immune response. Antibody responses may
be important for antigens expressed at the cell surface of tumours, such as the idio
typic immunoglobulin in B-cell lymphomas, whereas T-cell responses are necessary for intracellular antigens such as bcr/abl in CML. The intradermal and intralymphatic routes can lead to Th1 cellular immunity whereas the intravenous route favours humoral immunity with antibody production.

Key points for clinical practice

1. Over 50% of patients diagnosed with cancer will ultimately die of their disease. Alternative modes of treatment are undoubtedly needed.

2. There is clear evidence that tumours are immunogenic; however, in patients who develop cancer, the immune response to most tumours is by definition insufficient.

3. The ideal tumour antigen is one that is tumour specific and expressed on all tumour cells; most currently identified tumour antigens are expressed to some degree on normal tissues.

4. Vaccination with tumour antigens that are not tumour specific carries the risk of induction of autoimmunity, the consequences will depend on the distribution of the cross-reacting antigen. Autoimmune responses to major organs (such as the heart) are potentially disastrous whereas induction of treatable diseases (such as diabetes in association with curative cancer therapy) may be acceptable.

5. Whilst safety issues are routinely addressed using patients for whom no conventional treatment is available, it is anticipated that vaccines will be most effective when given to patients with minimal disease.

6. A number of different types of cancer vaccines are being developed in preclinical and clinical studies. The optimal vaccine, route and immunisation schedule remain to be determined. It is as yet unclear if all tumour types will be able to be successfully treated with vaccine therapy. Immune escape strategies of tumours will not always be circumventable.

7. As our understanding of the immunological mechanisms underlying antitumour immunity increases, there is increasing hope that cancer vaccines will offer a valuable new mode of treatment.

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Tumour antigens in human cancer

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