Principles of cancer immunotherapy

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Introduction

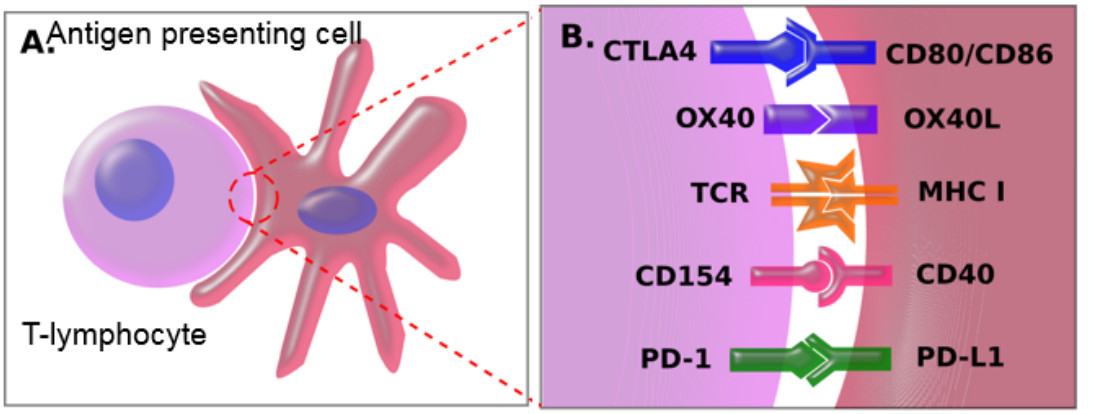
Cancer immunotherapy has a long history, but has rapidly developed since 2010. The goals of cancer immunotherapy are to kill or control cancer cells by activating, or reactivating the immune system.

The immune system

Our immune systems have evolved to a complex system involving innate and adaptive immune systems. Innate immunity starts with physical barriers (skin, mucus), and involves non-specific defences from immune cells such as neutrophils and natural killer cells. The adaptive immune system has evolved from innate immune cells, which include B-cells that produce antibodies, and is governed by lymphocytes, primarily alpha/beta, which include CD4+ helper, CD8+ killer and FOXP3+ regulatory T-cells.

The adaptive immune system is most relevant in managing the immune system, addressing viral infections, and has evolved to be the most important part of the immune system in terms of controlling and eliminating cancer.

Adaptive immune cells recognise other cells via antigen presentation. A small peptide fragment of a native, viral or cancer protein (the antigen or epitope) is “presented” on a cell surface complex made of proteins called the major histocompatibility complex (MHC). These epitopes are then recognised by proteins (e.g. the T-cell receptor, TCR) on the surface of individual T- or B-cell lymphocytes (Figure A). The repertoire of human T-cells and B-cells can recognise up to 109 individual patterns. The outcome of antigen presentation and recognition is determined by the balance of interactions between pairs of immune checkpoint costimulatory molecules (e.g. CTLA4-CD80, OX40-OX30L, CD154-CD40, PD1-PDL1; Figure B below).



Controlling the immune system: immune checkpoints

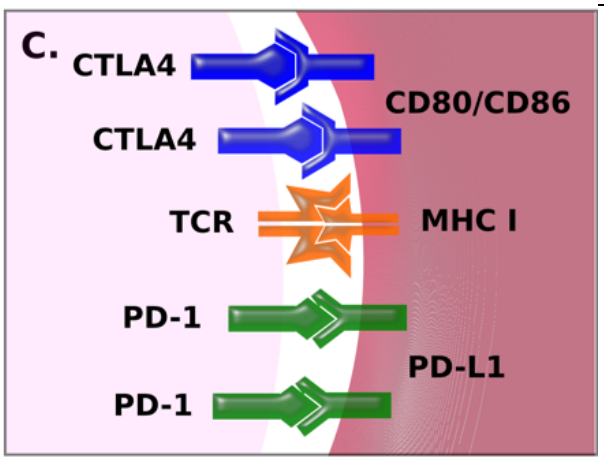
Uncontrolled immune activation leads to autoimmune diseases like ulcerative colitis, dermatitis and interstitial pneumonitis. The activity of the immune system is modulated and carefully controlled by costimulatory molecules called immune checkpoints. When antigen recognition occurs, a committee of other molecules interact on the surface of the immune cell and the target cell to determine the balance of the interaction. If the signals are largely positive, the immune cell activates and is primed to attack the antigen presented by the target cell. However if the balance of signals is negative, then the immune cell can become inactivated, sometimes permanently, and the antigen is accepted as a normal/self antigen (Figure B). Immune checkpoints of relevance to cancer include CTLA4, PD1 and PDL1 (see above).

Cancer immunosurveillance and immunoevasion

Every cancer that becomes clinically detectable and relevant has survived elimination by the immune system. As soon as tiny cancers form, the aberrant proteins they express from mutated genes generate so-called “neoantigens” that can be recognised by the immune system by antigen presentation, targeting the aberrant cell for destruction.

Cancers are edited by this process, and may be eliminated at this point; so called immunosurveillance. Some cancers can enter a state of equilibrium with the immune system, and though present, remain clinically undetectable and irrelevant. If this balance is then later disturbed, for example by immunosuppression caused by age, illness or iatrogenic causes, the cancer can escape and evade immune control.

Cancer immunotherapies attempt to redress these escape mechanisms at many points, but a key mechanism for cancer cells to evade the immune system seems to be via negative immune checkpoint signalling (Figure C).



Spectrum of cancer immunotherapy

Cancer immunotherapies can be categorised by whether:

- they actively stimulate the immune system, or passively alter immune system signalling or cell populations, and,
- the treatment is targeted at a specific, known antigenic target, or is non-specifically stimulating the immune system.

	Active		
Non-specific	Bacillus Calmette-Guerin (BCG) Cytokines Oncolytic viruses	Cancer vaccines Oncogenic virus vaccines CAR-T-cells	**Specific**
	Lymphokine-activated killer cells Tumour-infiltrating lymphocytes (TILs)	Monoclonal antibodies Radioimmunotherapy Ex vivo expanded antigen-specific T-cells **Immune checkpoint inhibitors**	
	Passive		

(adapted from Davis et al., 2000)

Active non-specific cancer immunotherapy

- Bacillus Calmette-Guerin (BCG) is one of the most commonly used and earliest discovered cancer immune therapies. This live attenuated strain of *Mycobacterium tuberculosis* is instilled intravesically to reduce recurrence of debulked non-muscle invasive bladder cancer. The mechanism of action is a non-specific inflammatory reaction; side effects can include dysuria and other lower urinary tract symptoms.
- Immunostimulatory cytokines such as interferon-alpha and interleukin-2 were previously mainstay treatments of metastatic renal-cell carcinoma and melanoma. Interferon-alpha was used as adjuvant therapy in resected high-risk melanoma, though the survival advantage was debatable. Interleukin-2 is still used in some countries in a limited highly restricted patient population. Treatment requires ICU admission due to severe systemic inflammatory responses and hypotension. A proportion of patients who took IL2 have experienced long-term remission of their cancer.
- Oncolytic viruses such as T-VEC (talimogene laherparepvec) and CAVATAK® (Coxsackievirus A21) are attenuated or modified viruses that can be injected directly into tumour masses or administered intravenously. Infection of tumour cells is associated with activation of an immune response, that in some patients can even spread to other, uninjected tumour sites (the “abscopal” effect). Many viruses are being explored, but none are yet in routine clinical practice.

Active specific cancer immunotherapy

- Cancer vaccines have been trialled in many different formats, but all attempt to direct the immune system to recognise particular antigens that are then hoped to cause recognition and elimination of the cancer. Cancer vaccines can target a single peptide, a protein, or autologous or allogenic cancer cells. Unfortunately most of these vaccines have failed to improve patient outcomes. Sipeleucel-T is an allogeneic vaccine using prostate cancer cell lines that has a modest effect in prostate cancer, but is not available in Australia.
- Oncogenic virus vaccines are the most common and important form of cancer immunotherapy. Vaccines that prevent infection by the hepatitis B virus (causing hepatocellular carcinoma) or the human papillomavirus (causing cervical, anal, penile and some head and neck cancers) are internationally and numerically the most effective and most cost-effective cancer immunotherapies available.
- CAR-T-cells are autologous patient derived T-cells, that have been genetically modified to display cancer cell recognition molecules on their cell surface. In isolated cases these have generated extraordinary responses (e.g. CD19+ paediatric B-ALL) but with considerable toxicity.

Passive non-specific cancer immunotherapy

- Lymphokine-activated killer (LAK) cells and tumour-infiltrating lymphocytes (TILs) are autologous patient immune cells harvested from peripheral blood or tumour tissue and expanded *ex vivo*. TILs can be expanded substantially and then reinjected into patients. This has led to some responses in uncontrolled clinical trials.

Passive specific cancer immunotherapy

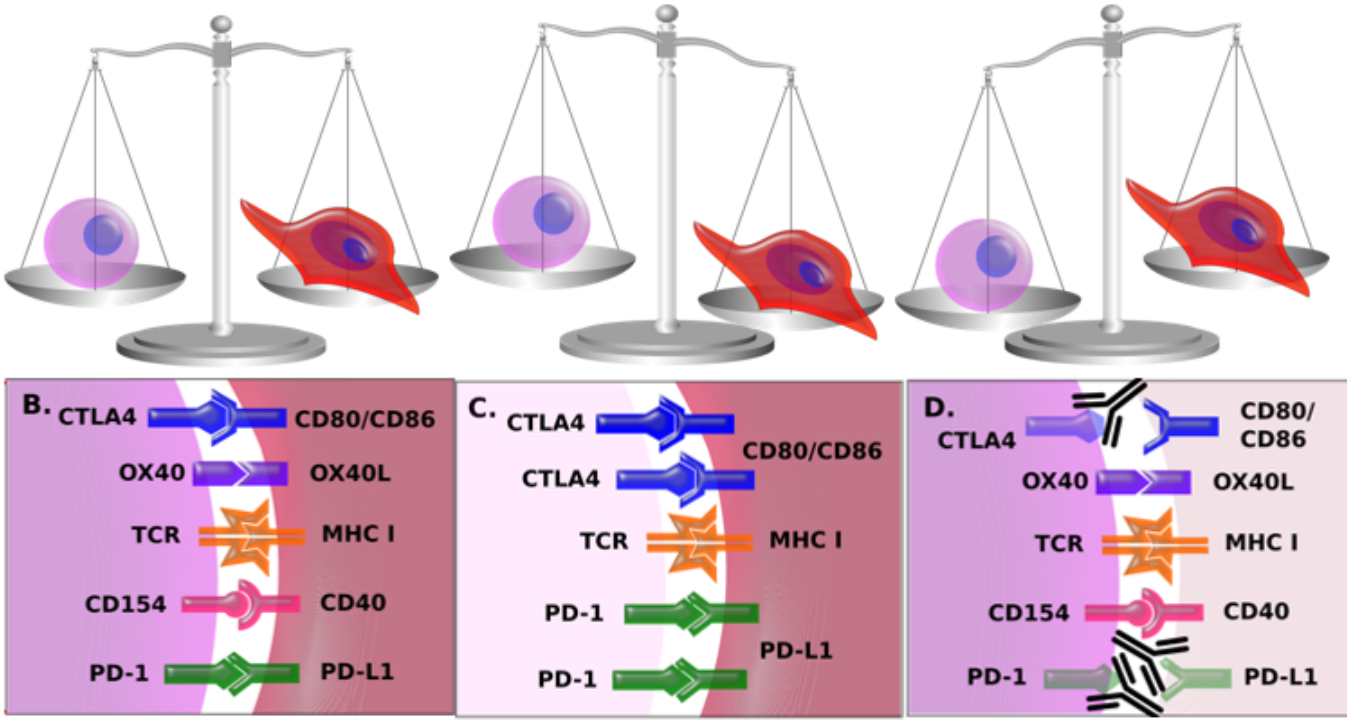
- Humanised monoclonal antibodies cause cancer cell death by a variety of mechanisms including direct action of antibody (receptor blockade or agonist activity, delivery of a drug or cytotoxic agent; e.g. Traztuzumab in HER2 positive breast cancer), complement dependant cytotoxicity, antibody-dependent cellular cytotoxicity (ADCC; e.g. rituximab). Radioimmunotherapy uses alpha-emitting radioisotopes (e.g. 177-lutetium) bound to antibodies to deliver radiotherapy specifically to tumour cell deposits.
- Antigen-specific T-cells can be expanded *ex vivo* in a similar fashion to TILs but have been specifically selected for individual antigens of interest to the patient's tumour.

Immune checkpoint inhibitors

Recognising the importance of immune checkpoints for cancer immunoevasion, a rapidly increasing number of immune checkpoint inhibitors have been designed. Several of these are now in clinical practice; a panoply of agents is in clinical trials and early development.

Mechanism of action of immune checkpoint inhibitors

Manipulation of immune checkpoint signalling has focused on the negative regulatory molecules to date The molecular mechanism of action of checkpoint inhibitors is relatively straightforward; these antibodies block interaction of the checkpoint and its binding partner is physically interrupted by a tightly bound antibody (Figure below). When checkpoints are appropriately activated (left) then the immune system is in balance. If the tumour cell (red) increases checkpoint signalling (e.g. more CTLA4 or PDL1; centre) then the immune system is inhibited. Blocking antibodies (black) that block CTLA4 signalling, or PD1/PDL1 signalling can redress this balance (right) allowing the immune system to re-establish control of the cancer.



Current examples of immune checkpoint inhibitors

- Ipilimumab (Yervoy®) is the first-in-class checkpoint inhibitor, which blocks CTLA4, a negative regulatory checkpoint. When intracellular CTLA4 molecule is expressed on the surface of the T cell, binding of CTLA4 to B7 turns off T cell activation. Ipilimumab binds to CTLA4 and inhibit the binding of CTLA4 and B7. This means the T cell remains activated. The site of action for ipilimumab remains unclear, but likely helps expansion of the immune response both in tumours and in distant lymph nodes.
- Tremelimumab is another anti-CTLA-4 antibody that inhibits the CTLA4 checkpoint protein. The activities and side effects of these two antibodies appear similar.
- Pembrolizumab (Keytruda®) and nivolumab (Opdivo®) are anti-PD1-antibodies that block the binding of PD1 to PD-L1 and PD-L2. PD-L1 can be overexpressed on cancer cells, where it appears to be used by cancer cells to evade the immune system. The activities and side effects of these two antibodies appear similar.
- Atezolizumab, avelumab and durvalumab are anti-PD-L1-antibodies. They block the binding of PD-L1 to PD1. The activity and side effects of these PD-L1 antibodies seem relatively similar to each other, but would appear to be less potent and less toxic than anti-PD1 antibodies.
- Combinations of checkpoint inhibitors and combinations with other anticancer treatments are being vigorously studied. For example the combination of ipilimumab and nivolumab has shown more apparent benefit in patients with melanoma and renal cell carcinoma, at the price of much more common and severe side effects.

Side effects of checkpoint immunotherapy antibodies

The side effects of immune checkpoint antibodies are due to autoimmune over activation. Some side effects like diarrhoea and rash are relatively common, and though mostly mild and manageable, they can sometimes be life threatening.

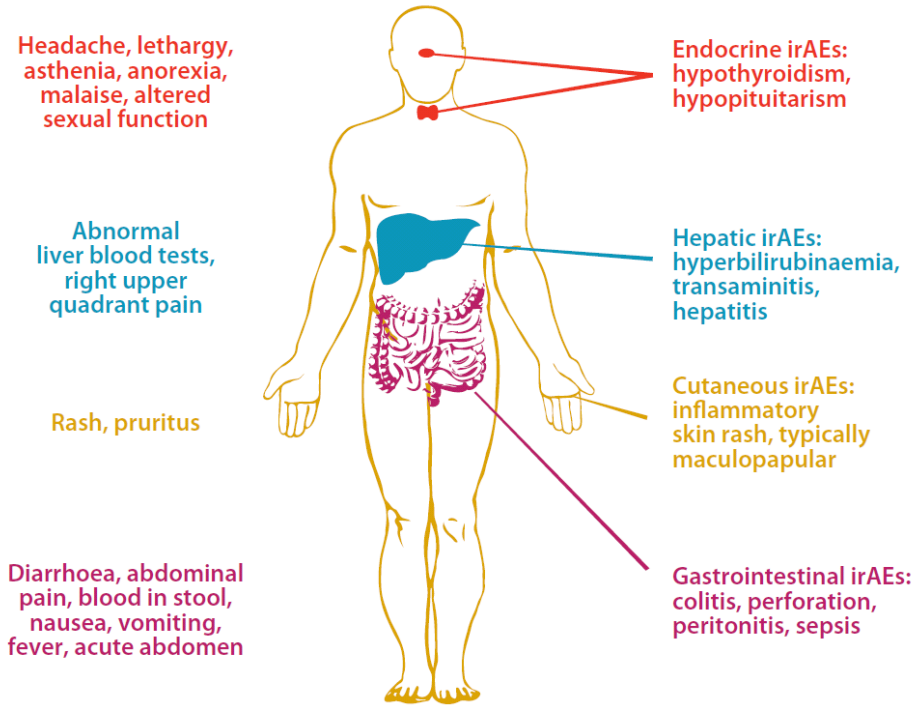
Checkpoint immunotherapy must be managed with caution, diligence and robust and routine communication between patients and their health carers.

Examples of immune related side effects include:

- Gastrointestinal immune-related side effects: colitis caused by checkpoint inhibitors can start innocuously as diarrhoea, but may progress to perforation and peritonitis.
- Dermatological immune-related side-effects: maculopapular rash often on the trunk; vitiligo can occur if an immune response against melanocyte antigens is generated.
- Endocrine immune-related side-effects: similar to postpartum autoimmune situations, thyroiditis and hypophysitis can occur with checkpoint inhibitors.
- Liver immune-related side-effects: hepatitis and pancreatitis can rarely occur.
- Respiratory immune-related side-effects: pneumonitis and sinusitis have been reported with checkpoint inhibitors.

Any illness in a patient treated with checkpoint inhibitors should have an autoimmune cause ruled out.

Immune-related side effects are also noteworthy for being slow in onset, usually only occurring after 1-2 doses are given, and may even occur after treatment has completed. They are also slow to resolve, so if steroid immunosuppression is required to control immune related side effects, this is usually titrated downwards over at least 4 up to 8 weeks.



Managing side-effects of immune checkpoint cancer immunotherapy

Side effects of cancer treatment in general are characterised by their grade, or intensity:

Grade	Symptoms	Management of side effect	Cancer treatment
1	Mild	Supportive	Continue
2	Troublesome	Targeted to reverse side-effect	Pause
3	Severe	Inpatient	Withhold, at least
4	Very severe	Intensive	Discontinue

Management of immune-related side effects of checkpoint antibodies is tailored to symptoms and graduated in response. For immune-related side effects this translates to supportive care and immunosuppression, as outlined in the following broad guidelines:

Grade	Symptoms	Management	Example
1	Mild	Supportive	Loperamide for diarrhoea; emollients and hydrocortisone cream for rash
2	Troublesome	Targeted	Oral prednisone 1mg/kg, weaning to zero slowly over 4 weeks
3	Severe	Inpatient	Intravenous methylprednisolone 2mg/kg x 3 days, then oral prednisone as above
4	Very severe	Intensive	Infliximab IV or oral mycophenolate mofetil, then corticosteroids

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Managing expectations of immune checkpoint cancer immunotherapy

- Checkpoint immune antibodies only help some patients. The dramatic and enduring benefits in a few patients of checkpoint inhibitors like ipilimumab, pembrolizumab and nivolumab provide great hope to patients and interest for clinicians, but it is clear that only a minority of patients experience these dramatic responses.
- Benefit can take a long time to be realised. Because checkpoint inhibitors are not direct anti-cancer agents in themselves, but rather work through activating the immune system. Like the onset of side effects, so too the declaration of benefits takes weeks or months. This can be a very stressful and difficult time for patients and their families, waiting and hoping.
- Stable disease is more common than response. While many patients do see shrinkage of their cancers it is more common that the cancer becomes stable in size. This is not a bad thing; patients can have long survival and good quality of life. But measuring success in terms of “response rate” will lead to disappointment.
- Many cancers do not respond to checkpoint inhibitors. It is still unclear who will and who will not benefit from checkpoint inhibitors. Melanoma, lung, kidney and bladder cancer patients have been the most studied to date. Colorectal cancer seemed unsuccessful but a small subgroup of patients has been identified that may benefit; likewise breast cancer (the triple-negative subgroup). Prostate cancer seems resistant to the CTLA4 and PD1 targeted drugs developed so far.
- Cancer patients taking checkpoint inhibitors must still receive excellent palliative care and end-of-life counselling. Despite anecdotes of cancer patients responding to single doses of nivolumab or pembrolizumab, many patients will continue to progress and die from their cancer. Robust and open communication is important to offer hope, but also to realistically plan for unwanted outcomes.