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DRUG DISCOVERY

Harnessing the immune system to combat cancer

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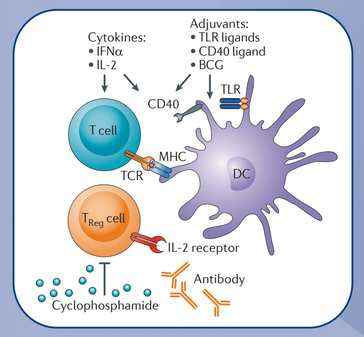
Efforts to harness the immune system to treat cancer date back more than a century, but progress was slow for decades. However, the recent clinical success of several anticancer immunotherapies has provided a boost to the field. Approaches to induce an antitumour immune response (see centre image) can be broadly subdivided into non-antigen-specific or antigen-specific categories. Non-antigen-specific strategies include nonspecific immune stimulation and inhibition of 'immune checkpoint' interactions, whereas antigen-specific strategies include adoptive cell transfer of autologous cancer-specific T cells and various therapeutic vaccination approaches.

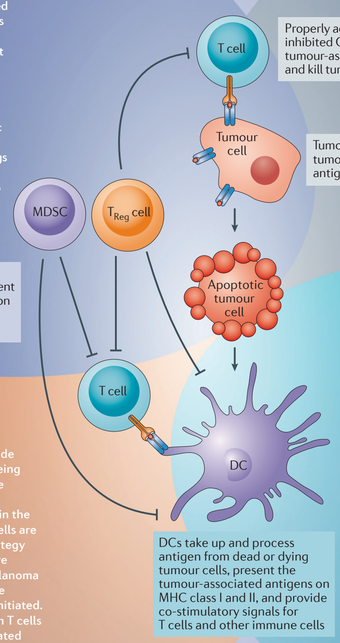
Examples of anticancer therapeutics in both broad categories — such as the immune checkpoint inhibitor ipilimumab and the therapeutic vaccine sipuleucel-T — have recently received regulatory approval, and several other agents are in clinical trials (see table). Such trials are faced with challenges such as selection of optimal methods of evaluation, as those developed for typical anticancer chemotherapies may not be well suited to immunotherapies. Nevertheless, recent encouraging clinical results, as well as the unexpected finding of a positive interaction between immunotherapy and chemotherapy, may herald a new era for anticancer immunotherapy.



Nonspecific immune stimulation

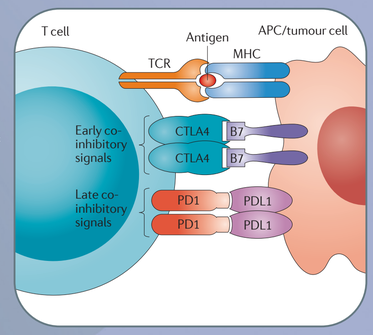
Nonspecific immune stimulation can be achieved with agents that stimulate immune effector cells such as T cells and APCs (for example, DCs), or inhibit and/or deplete immunoregulatory cells such as T_{Reg} cells. Effector T cells can be stimulated with cytokines such as IL-2 and IFNα, which are both approved for the treatment of melanoma and renal cell carcinoma. Durable complete remissions after IL-2 treatment of melanoma patients have been observed in selected patients. However, given the need for prolonged use and associated toxicity of these cytokines, they are not commonly used. Approaches that aim to provide full APC activation use adjuvants such as TLR ligands. The TLR7 agonist imiquimod is approved for the treatment of basal cell carcinoma. The adjuvant BCG has been approved as a standard therapy for local instillation in bladder cancer. Antibody-based approaches targeting the co-stimulatory receptor CD40 are in development. T_{Reg} cells can be depleted by targeting the IL-2 receptor with the anti-CD25 (IL-2 receptor α-chain) antibody daclizumab, the recombinant IL-2–diphtheria toxin conjugate denileukin diftitox or low-dose treatment with the chemotherapeutic cyclophosphamide. However, the lack of specificity of these approaches poses a significant challenge. Other cytotoxic chemotherapeutics and targeted anticancer drugs can have immune-stimulating effects by inducing immunogenic cell death, depleting suppressive immune cells, disrupting inhibitory pathways or sensitizing tumour cells to T cell-induced cell death. Novel innovative treatment schedules that fully exploit the immunogenic properties of these drugs need to be further developed.

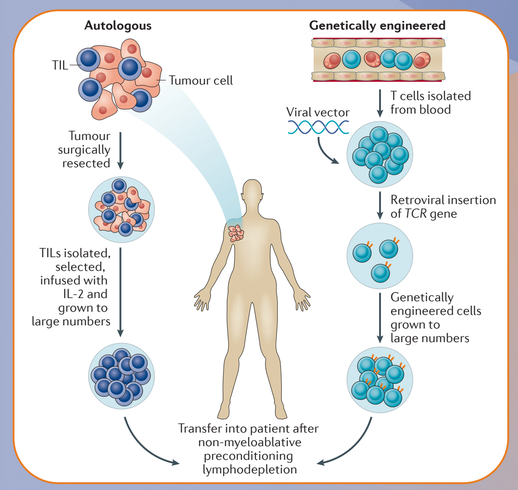
The induction of antitumour immunity



Immune checkpoint blockade

Several immune-inhibiting mechanisms that normally prevent collateral damage to tissues from an ongoing immune response can also help cancer cells evade the immune system. The figure shows the interaction between a T cell and an APC or tumour cell, detailing receptor interactions that downmodulate the activation of T cells that recognize antigen presented on MHC molecules. Blocking such immune checkpoints results in enhanced, nonspecific T cell activation and/or T cell survival. CTLA4–B7 interactions are important during the induction phase of the T cell response, whereas PD1–PDL1 interactions seem to have the most prominent role during the effector phase of the T cell response. The CTLA4-blocking antibody ipilimumab has recently been approved for treating patients with metastatic melanoma. Clinical trials that investigate antibodies targeting other immune checkpoint molecules such as PD1 or PDL1 are underway. Immune checkpoint-blocking approaches are not patient-tailored, which makes them less laborious and potentially less costly than cellular vaccines or adoptive cell transfer. However, the lack of specificity of immune activation means there is a risk of autoimmune side effects.



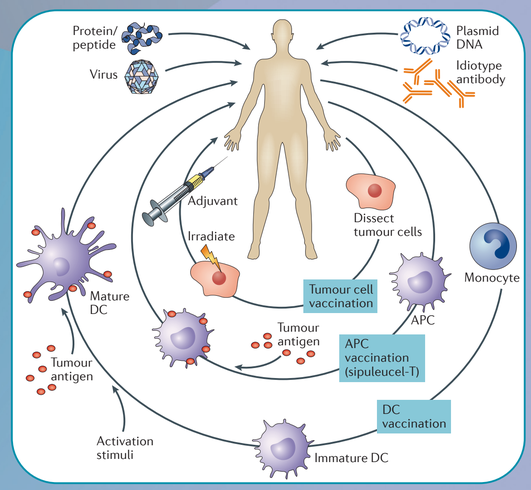


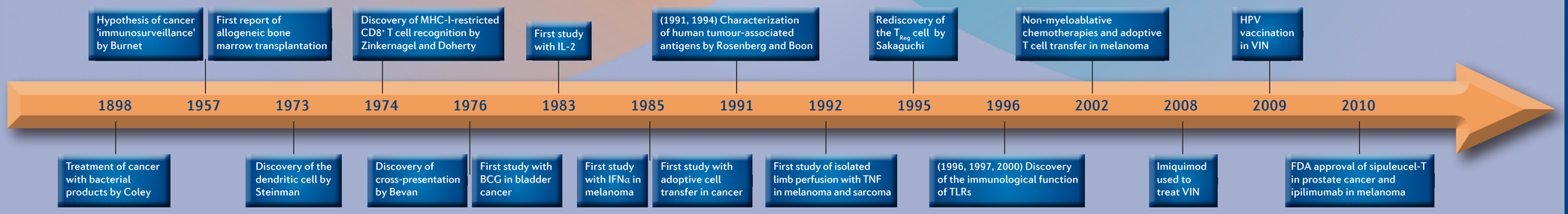
Adoptive cell transfer

Antigen-specific effector cells can be taken out of the patient, selected and expanded *ex vivo*, and then re-infused into the patient, obviating the need to provide antigens or activate APCs. Two main approaches are being explored. In the first approach, T cells that reside in the tumour are cultured from tumour resection specimens (mainly explored for melanoma) and expanded *ex vivo* in the presence of IL-2. When enough of these polyclonal T cells are obtained, they are re-infused into the patient. This strategy was improved by combining it with a non-myeloablative preconditioning chemotherapy regime. In selected melanoma patients encouraging durable complete responses were achieved and randomized multicentre trials are being initiated. However, at present it is only possible to obtain enough T cells in a minority of patients. The second strategy uses isolated peripheral blood T cells that are genetically engineered to express tumour-antigen-specific TCRs and then re-administered to the patient. This strategy has the advantage that enough T cells can be obtained for infusion in all patients, but a potential drawback is that the TCRs that are transfected into the T cells have a limited antigen-specificity repertoire.

Vaccination strategies

The goal of immunotherapeutic vaccination approaches is to 're-educate' endogenous T cells by presenting the tumour antigen in the context of appropriate APC activation stimuli. Tumour antigens can be administered in the form of synthetic proteins or peptides, or encoded by a plasmid DNA or virus. Viral vectors can also have direct oncolytic activity. For some B cell malignancies, idiotype antibodies have been explored as tumour-specific vaccines. An alternative approach that does not require the identification of tumour-specific antigens is the use of extracted, irradiated tumour cells that are re-administered to the patient. For all of the above, adjuvants such as TLR agonists or GM-CSF are required. Alternatively, APCs can be extracted from a patient's bloodstream, cultured and activated with cytokines or adjuvants, loaded with antigen *ex vivo*, and re-administered to the patient. The antigens can be selected well-known tumour antigens or derived from whole-tumour cells. The former strategy was followed for the development of sipuleucel-T for the treatment of prostate cancer. Alternatively, DCs (the professional APCs of the immune system) can be cultured from peripheral blood monocytes in the presence of IL-4 and GM-CSF, and activated and loaded with antigen *ex vivo*. Tailor-made vaccination approaches require complex production processes that are associated with substantial costs, and so far it has been challenging to achieve durable complete responses.





Examples of experimental and approved anticancer immunotherapies*

Drug (companies)	Formulation	Tumour type	Current phase of development
Immune checkpoint blockade			
Ipilimumab (Bristol-Myers Squibb)	CTLA4-blocking antibody	Melanoma	Approved
		Prostate cancer and NSCLC	Phase III
		Other tumours	Phase I–II
Tremelimumab (Pfizer)	CTLA4-blocking antibody	Melanoma	Phase III
		Other tumours	Phase I–II
MDX-1106 (Medarex/ Bristol-Myers Squibb)	PD1-blocking antibody	Melanoma, RCC and NSCLC	Phase II
CT-011 (CureTech)	PD1-blocking antibody	Melanoma and haematological malignancies	Phase II
MK-3475 (Merck)	PD1-blocking antibody	Solid tumours	Phase I
AMP-224 (Amplimmune/ GlaxoSmithKline)	PDL2–IgG1 fusion protein	Solid tumours	Phase I
Adoptive cell transfer			
Adoptive transfer with TILs	Polyclonal T cells against multiple tumour-associated antigens	Melanoma	Phase II
Adoptive transfer with TCR-transduced T cells	Monoclonal T cells with high-affinity TCR against single tumour-associated antigens	Melanoma	Phase I
Vaccination strategies			
Sipuleucel-T (Dendreon)	Autologous APC vaccine loaded with prostate acid phosphatase	Prostate cancer	Approved
DC-based vaccines	Autologous DCs loaded with tumour antigens	All cancer types	Phase I–III
MAGE-3 ASCI (GlaxoSmithKline)	MAGE-3 protein	NSCLC	Phase III
PROSTVAC (Bavarian Nordic)	Poxvirus-based PSA-targeted vaccine	Prostate cancer	Phase III
OncoVEX (BioVex)	Attenuated herpes simplex type 1 virus encoding human GM-CSF	Melanoma and HNSCC	Phase III
Idiotype antibodies	Patient-specific tumour-derived idiotype antibody plus GM-CSF	Follicular lymphoma	Phase III
Melanocyte protein PMEL	gp100 peptide vaccine in Montanide adjuvant combined with IL-2	Melanoma	Phase III
Nonspecific immune stimulation			
IL-2 (Novartis/ Prometheus)	Recombinant human IL-2	Melanoma and RCC	Approved for melanoma in some and for RCC in most countries
IFNα (Schering-Plough/ Hoffmann-La Roche)	Recombinant human IFNα	Melanoma and RCC	Approved for melanoma (adjuvant) and RCC in several countries
Cyclophosphamide	Low-dose preferentially depletes T_{Reg} cells	Several cancer types	Phase I–II
Daclizumab (Hoffman-La Roche)	Anti-CD25 (IL-2 receptor α-chain) antibody	Several cancer types	Phase I–II
Denileukin diftitox (Eisai)	Recombinant IL-2–diphtheria toxin conjugate	Several cancer types	Phase I–II
CP-870893 (Pfizer)	CD40 agonist monoclonal antibody	Solid tumours	Phase I
Imiquimod (Meda/ Graceway/iNova)	TLR7 agonist	Basal cell carcinoma, VIN and CIN	Approved for basal cell carcinoma; in Phase III for VIN and CIN
Resiquimod (Medicis Global Services Corporation)	TLR7 agonist alone or in combination with vaccines	Melanoma and T cell lymphoma	Phase I
CPG 7909 (Pfizer)	TLR9 agonist	Melanoma	Phase II
BCG	Intravesical administration of BCG as adjuvant	Urothelial cancer	Approved
'Immunogenic' chemotherapy and targeted agents	Classic chemotherapeutics	Several cancer types	Approved drugs but immunogenic potential not fully explored

*References for approved drugs are included under further reading.

Bavarian Nordic A/S
Bavarian Nordic A/S is a vaccine-focused biotechnology company developing and producing novel vaccines for the treatment and prevention of life-threatening diseases with a large unmet medical need. The company's pipeline targets cancer and infectious diseases, and includes ten development programs. The oncology pipeline is developed through the subsidiary BN ImmunoTherapeutics, located in Mountain View, California. The company's lead program is PROSTVAC®, a therapeutic vaccine candidate for treatment of advanced prostate cancer that is the subject of an ongoing pivotal Phase 3 trial and is being developed under a collaboration agreement with the National Cancer Institute. For more information, visit www.bavarian-nordic.com

Dendreon
Dendreon is a biotechnology company whose mission is to target cancer and transform lives through the discovery, development, commercialization and manufacturing of novel therapeutics. The company applies its expertise in antigen identification, engineering and cell processing to produce active cellular immunotherapy (ACI) product candidates designed to stimulate an immune response in a variety of tumor types. Dendreon's first product, PROVENGE® (sipuleucel-T), was approved by the U.S. Food and Drug Administration (FDA) in April 2010. Dendreon is exploring the application of additional ACI product candidates and small molecules for the potential treatment of a variety of cancers. Visit us at www.dendreon.com

Abbreviations

APC, antigen-presenting cell; BCG, bacille Calmette–Guérin; CIN, cervical intraepithelial neoplasia; CTL, cytotoxic T lymphocyte; CTLA4, cytotoxic T lymphocyte antigen 4; DC, dendritic cell; GM-CSF, granulocyte–macrophage colony-stimulating factor; HNSCC, head and neck squamous cell carcinoma; HPV, human papilloma virus; IFNα, interferon-α; IL-2, interleukin-2; MAGE-3, melanoma-associated antigen 3; MDSC, myeloid-derived suppressor cell; NSCLC, non-small-cell lung cancer; PD1, programmed cell death protein 1; PDL1, PD1 ligand 1; PSA, prostate-specific antigen; RCC, renal cell carcinoma; TCR, T cell receptor; TIL, tumour-infiltrating lymphocyte; TLR, Toll-like receptor; TNF, tumour necrosis factor; T_{Reg} cell, regulatory T cell; VIN, vulvar intraepithelial neoplasia.

Further Reading

Dunne, A., Marshall, N. A. & Mills, K. H. *Curr. Opin. Pharmacol.* **11**, 404–411 (2011).
Figdor, C. G. *et al. Nature Med.* **10**, 475–480 (2004).
Jacobs, J. F. *et al. Lancet Oncol.* **13**, e32–e42 (2012).
Kantoff, P. W. *et al. N. Engl. J. Med.* **363**, 411–422 (2010).
Lesterhuis, W. J., Haanen, J. B. & Punt, C. J. *Nature Rev. Drug Discov.* **10**, 591–600 (2011).
Robert, C. *et al. N. Engl. J. Med.* **364**, 2517–2526 (2011).
Rosenberg, S. A. *Nature Rev. Clin. Oncol.* **10**, 577–585 (2011).
Sharma, P. *et al. Nature Rev. Cancer* **11**, 805–812 (2011).
Topalian, S. L., Weiner, G. J. & Pardoll, D. M. *Clin. Oncol.* **29**, 4828–4836 (2011).
van Seters, M. *et al. N. Engl. J. Med.* **358**, 1465–1473 (2008).
Weber, J. *et al. Clin. Cancer Res.* **17**, 1664–1673 (2011).

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