Cost and response criteria are the new challenges

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Although the concept of using immunotherapy to target an immune response against tumors is not new, this treatment modality is only now beginning to realize its full potential. Here, we take a look at the role of immunotherapy in cancer and some of the most exciting areas of clinical development (Figure 1).

The immune system and cancer

The immune system functions by recognizing signals (antigens) on the surface of invading organisms as "nonself" and mounting a response that ultimately leads to the death of these organisms. Because tumors are made up of our own cells they often don't display these signals and are therefore more or less tolerated by the body. When tumors do display unusual proteins on their surface that could be recognized as nonself, they are able to actively subvert the subsequent immune response.[1] Indeed, the property of immune evasion has now been added to the list of cancer hallmarks – the key features defined by Weinberg and Hanahan that allow a cell to become malignant.[2]

It has become clear that there are several ways in which tumors achieve a state of immune tolerance. Several of these mechanisms have been targeted for novel therapies and have resulted in the establishment of durable antitumor immune responses that are known as immunotherapies.

Targeting the immune system for cancer therapy

Most cancer therapies use drugs to directly kill tumor cells, but immunotherapy is a less direct approach that involves finding a way to stimulate a patient's immune system or to use components of the immune system to mount an immune response that will kill tumor cells. This can be done actively, by training the immune system to recognize tumor cells as targets to be destroyed, through the use of a vaccine or by preventing the tumor from suppressing a pre-existing antitumor immune response. Or it can be done passively, bypassing the patient's immune system and directly administering immune effector cells that have been engineered to target the tumor cells. Passive immunotherapy includes the use of monoclonal antibodies and adoptive cell therapy.[3]

Passive immunotherapy

Monoclonal antibodies

When the B cells of the immune system encounter a foreign antigen, they rapidly divide to form an army of clones that produce monoclonal antibodies (mAbs). These mAbs bind to their target antigen and initiate a range of immune responses that ultimately lead to the destruction of whatever is displaying the antigen. They have significant therapeutic potential thanks to their ability to seek out and destroy foreign cells, and were famously dubbed "magic bullets" by the German scientist Paul Ehrlich. Indeed, they represent the biggest success story for immunotherapy – the 3 top-selling cancer drugs in 2012 were mAbs.[4]

Although mAbs have been labeled as passive immunotherapy, there is mounting evidence that they have an active role in boosting the host antitumor immune response. They function as anticancer agents by targeting cancer cells for destruction by the immune system through antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), by inducing programmed cell death, or by blocking key signaling pathways involved in tumor cell growth and proliferation.[5,6]

A major limitation to mAb efficacy is their large size and limited functionality and, as such, researchers are working on ways to improve these. This includes the addition of sugar molecules (glycoengineering), which affects function and antigen binding; the use of smaller antibody fragments, which improves tumor penetration; and the generation of bispecific and trifunctional mAbs, which are able to target multiple antigens and can bind both tumor cells and immune effec-

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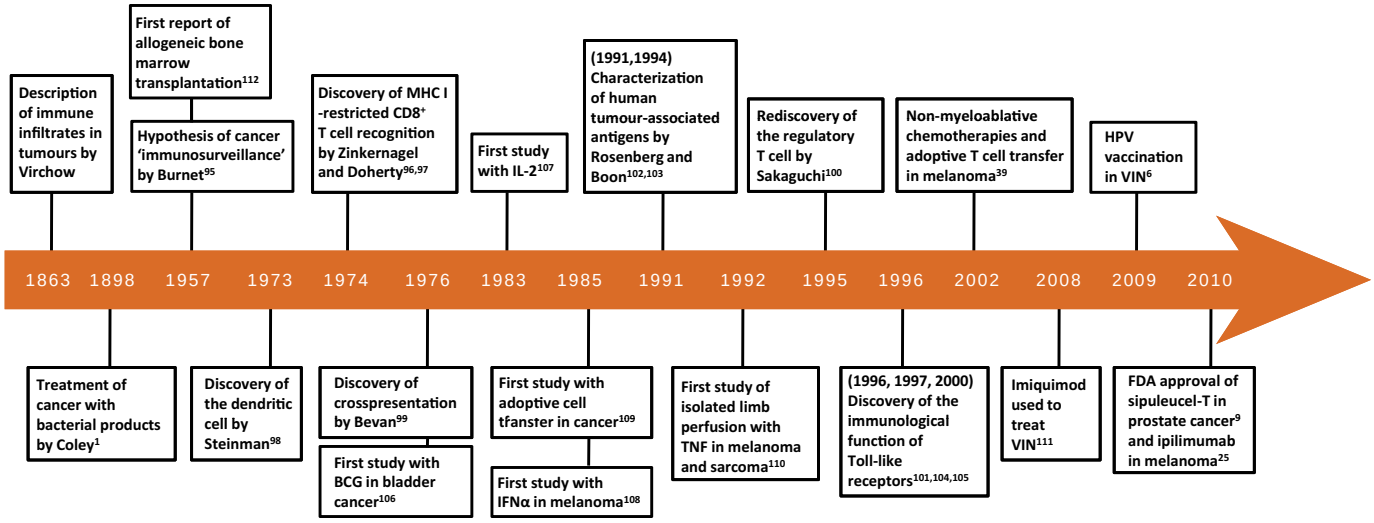

FIGURE 1 A history of cancer immunotherapy, showing immunological discoveries and important clinical trials.[10]
Abbreviations: BCG, bacille Calmette–Guérin; IFNα, interferon-α; IL-2, interleukin-2; MHC, major histocompatibility complex; TNF, tumour necrosis factor; VIN, vulvar intraepithelial neoplasia.

tor cells simultaneously. The most advanced are conjugated antibodies, in which the antibody is joined to either radioactive chemicals (radioimmunoconjugates), toxins (immunotoxins), or cytotoxic drugs (antibody-drug conjugates). Currently, there are 4 conjugated antibodies that have been approved by the Food and Drug Administration (Table 1).[5,6]

Adoptive cell therapy

ACT involves the collection of immune cells (most commonly the T cells) from a patient, the manipulation of those cells outside of the body (to increase their number or enhance their activity), and then the reinfusion of the cells back into the patient. These immune cells can be collected from the tumor environment (eg, tumor-infiltrating lymphocytes [TILs]) or from the blood supply surrounding the tumor. In the treatment of melanoma, TILs taken from surgically resected tumors, expanded, and then readministered to patients, produced objective responses in 50%-70% of patients and complete regression in 40% patients.[6-9]

ACT faces a number of drawbacks, including that it is costly and time consuming, and there are also safety issues because patients have to undergo harsh preconditioning regimens to allow the T cells to survive but that put the patients at risk of opportunistic infections.[10]

T cells also feature prominently in many of the experimental immunotherapies that are currently being developed. For example, researchers are attempting to reprogram stem cells to act as cancer-targeted T cells, a strategy that has met with significant success in preclinical models.

Active immunotherapy

The limitation of passive immunotherapy approaches is that they are temporary and don't train the immune system to recognize tumors, which means that patients usually require prolonged or repeated treatment. In addition, they don't address the immunosuppressive mechanisms mounted by the tumor. Active immunotherapies aim to do both of those things.

Vaccines

Anticancer vaccines represent to many the holy grail of cancer immunotherapy. There are 2 distinct types of cancer vaccine – the prophylactic, which aim to prevent cancers from occurring, and the therapeutic, which aim to treat pre-existing cancers. Preventative vaccination requires identification of the causative agent of a tumor, which is challenging as there may be several causative agents; however, a few preventative vaccines for viral-associated tumors have had significant success, such as the human papillomavirus vaccine that helps prevent cervical cancer.[3,7] Therapeutic vaccines, have proven much more elusive and a string of failures bred significant skepticism about them. Finally, in 2010, persistence paid off and the first therapeutic vaccine was approved by the FDA: sipuleucel-T for the treatment of metastatic, castration-resistant prostate cancer. Approval was based on the results of the IMPACT (Immunotherapy Prostate Adenocarcinoma Treatment) trial in which the therapy improved overall survival (OS) by 4.1 months and reduced the risk of death by 22%, compared with placebo.[6,11]

TABLE 1 Immunotherapies approved by Food and Drug Administration

Agent/active ingredient (brand name/s)	Year approved	Sponsor	Type of immunotherapy, how it works
Interferon-α (Roferon, Intron-A)	1986	Merck, Roche	Cytokine, stimulates immune system
Bacillus Calmette-Guerrin (Tice)	1990	Merck	Virus, inactivated form of the tuberculosis virus, serves as an immunomodulator
Interleukin-2 (Proleukin)	1992	Prometheus	Cytokine, stimulates immune system
Sargramostim (Leukine)	1992	Sanofi Aventis	Recombinant GM-CSF, stimulates immune system
Rituximab (Rituxan)	1997	Genentech	Naked mAb, CD20-targeting mAb
Trastuzumab (Herceptin)	1998	Genentech	Naked mAb, HER2-targeting mAb
Denileukin diftitox (Ontak)	1999	Eisai	Toxin-cytokine fusion, interleukin-2 fused to diphtheria toxin
Alemtuzumab (Campath)	2001	Genzyme	Naked antibody, CD52-targeting mAb
90-yttrium ibritumomab tiuxetan (Zevalin)	2002	Spectrum	Conjugated antibody, CD20-targeting mAb conjugated to radioactive isotope
131-iodine tositumomab (Bexxar)	2003	GlaxoSmithKline	Conjugated antibody, CD20-targeting mAb conjugated to radioactive isotope
Bevacizumab (Avastin)	2004	Genentech	Naked antibody, VEGF-targeting mAb
Cetuximab (Erbitux)	2004	Bristol-Myers Squibb	Naked antibody, EGFR-targeting mAb
Panitumumab (Vectibix)	2006	Amgen	Naked antibody, EGFR-targeting mAb
Ofatumumab (Arzerra)	2009	GlaxoSmithKline	Naked antibody, CD20-targeting mAb
Sipuleucel-T (Provenge)	2010	Dendreon	Vaccine, DCs loaded with a prostate cancer antigen
Ipilimumab (Yervoy)	2011	Bristol-Myers Squibb	Checkpoint inhibitor, CTLA-4-targeting mAb
Brentuximab vedotin (Adcetris)	2011	Seattle Genetics	Naked antibody, CD30-targeting mAb
Pertuzumab (Perjeta)	2012	Genentech	Naked antibody, HER2-targeting mAb
Ado-trastuzumab emtansine (Kadcyla)	2013	Genentech	Conjugated antibody, HER2-targeting mAb conjugated to a cytotoxic agent

Abbreviations: CTLA-4, cytotoxic T-lymphocyte antigen 4; DCs, dendritic cells; EGFR, epidermal growth factor receptor; GM-CSF, granulocyte macrophage colony-stimulating factor; HER2, human epidermal growth factor receptor 2; MAGE-A3, melanoma-associated antigen 3; mAb, monoclonal antibody; VEGF, vascular endothelial growth factor.

Therapeutic vaccines are designed to immunize a patient against a specific target antigen expressed on the surface of cancer cells (Figure 2). The antigen is delivered using a vector; most commonly a viral vector is used, but dendritic cell (DC)-based vaccines that use DCs to present antigens to immune effector cells are also being evaluated. Other common strategies include peptide vaccines, which use short amino acid stretches of the target protein antigen and are easier to produce.[1] Messenger RNA-based vaccines are also in the clinic for treatment of prostate and lung cancer (phase 1/2; NCT01915524, NCT01817738) and have the advantage of not requiring a vehicle for delivery to cells and may prove safer because they don't contain viral elements. Researchers are also investigating the potential of stem-cell based vaccines, which target the rapidly proliferating progenitor cells from which tumors develop.[6–8] A range of vaccines are in late-stage clinical testing in a host of different cancer types (Table 2).

Checkpoint inhibition

In many cases, an antitumor immune response is mounted and immune cells are found within the tumor and its microenvironment, yet tumor growth persists. Researchers are thus investing significant time and resources in understanding how tumors are able to fly under the radar of this established immune response. It is in this area that one of the most significant recent discoveries in the field of cancer immunotherapy has been made: the discovery of immune checkpoints.

Checkpoint proteins essentially function as the on–off switch on cytotoxic T cells (the killing cells of the immune system). Switching these cells on and off is a 2-step process that requires the interaction of the T-cell receptor

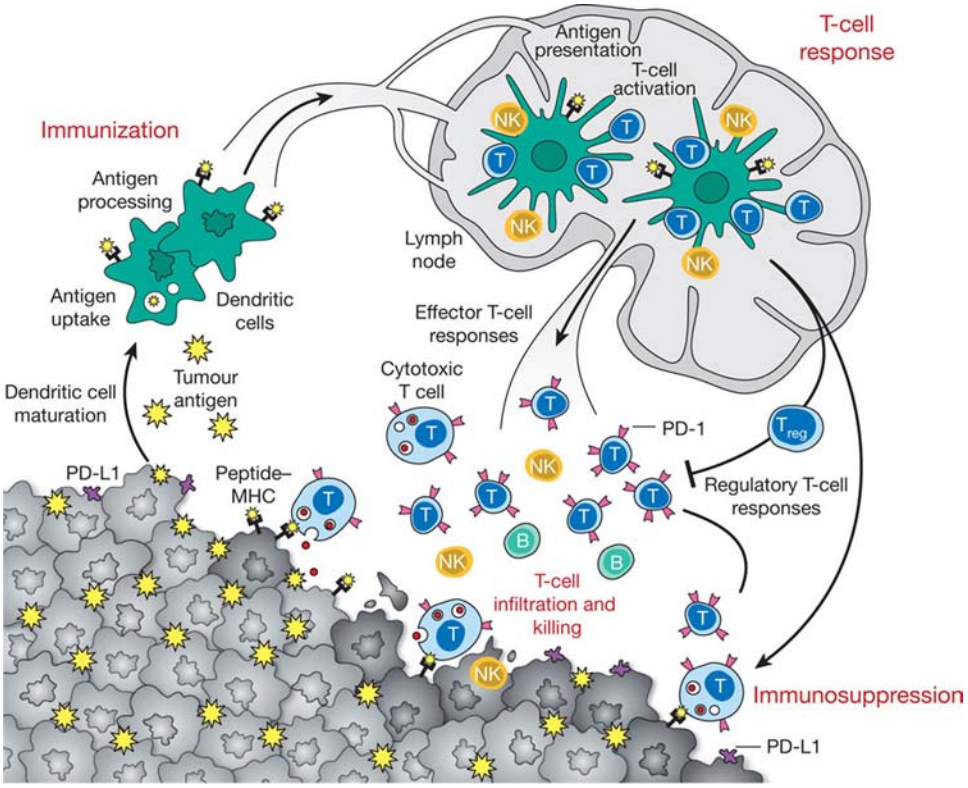

FIGURE 2 Generation and regulation of antitumor immunity.[3]
Abbreviations: MHC, major histocompatibility complex; PD-1, programmed death protein 1.

with a target cell, and then a secondary signal that determines if the T cell will be switched on or off. The checkpoint proteins are responsible for this secondary signal (called a coregulatory signal) and thus can be either stimulatory or inhibitory. It was discovered that one of the main ways in which cancer cells suppress the antitumor immune response is by hijacking the checkpoint proteins – ramping up production of inhibitory molecules and suppressing production of stimulatory molecules – thus allowing them to effectively switch off cytotoxic T cells.[6,8,12]

The checkpoint protein that has garnered the most attention is cytotoxic T lymphocyte antigen-4 (CTLA-4) and an antibody targeting CTLA-4, ipilimumab, was approved by the FDA in 2011 for the treatment of melanoma. Clinical trials demonstrated that 45% of patients treated with ipilimumab are alive after 1 year, 24% after 2 years, and some patients experienced durable clinical benefit that lasted longer than 4.5 years.[13]

A number of other checkpoint proteins are also being examined. The programmed death 1 (PD-1) receptor and its ligands PD-L1 and PD-L2 are part of the same family of coregulatory molecules as CTLA-4. A number of PD-1 and PD-L1/L2-targeting agents are in clinical development, the most advanced being nivolumab (BMS-936558). Others include pidlizumab, lambrolizumab, BMS-936559, MPDL3280A, and AMP-224, which are all in phase 1 or 2 trials in a variety of tumor types.

The metabolic enzyme indoleamine (2,3)-deoxygenase (IDO) is a different kind of checkpoint protein. It modulates T-cell activity by depleting the amino acid tryptophan that is essential for T-cell function. It has been found to be overexpressed by both tumor cells and tumor-infiltrating T cells. Several IDO inhibitors are in clinical trials, including indoximod (NewLink Genetics Corporation), in phase 2 trials of metastatic breast cancer (NCT01792050) and refractory metastatic prostate cancer in combination with sipuleucel-T (NCT01560923).

Challenges for the future

Nine hurdles facing the development of immunotherapy were recently outlined (Table 3).[14] Among the most significant are cost and lack of appropriate measurements of response. Cost is an issue both in the development of immunotherapies, which require a significant financial investment, and in administration of the final product. A complete treatment course of ipilimumab, for example, which consists of 4 infusions over a 3-month period, costs $120,000, and the cancer vaccine sipuleucel-T costs $93,000 for 3 infusions.

Oncologists typically evaluate a patient's response to cancer therapy by measuring the tumor area or volume using criteria such as RECIST (Response Evaluation Criteria in Solid Tumors) and modified World Health Organization criteria. However, although effective traditional therapies rapidly result in a reduction in tumor size, immunotherapies often have a delayed response, which may follow a period of apparent tumor growth (eg, 10%-20% of patients taking ipilimumab show an increase in tumor size after 3 months of treatment but subsequently go on to achieve tumor regression). As such, a challenge to the development of immunotherapy has been the need to develop alternative response criteria.[1,10]

Truly unlocking the full potential of immunotherapy will likely require combination regimens between multiple different types of immunotherapy or between immuno-

TABLE 2 Late-stage clinical trials in immunotherapies, as of 2013

Agent	Trial phase, cancer type, trial number	Manufacturer	Type of immunotherapy, how it works
AGS-003 (Arcelis)	Phase 3, metastatic RCC, NCT01582672	Argos Therapeutics	DC therapy, DCs loaded with patients messenger RNA
Algenpantucel (HyperAcute)	Phase 3, pancreatic, NCT01072981	NewLink Genetics	Vaccine, irradiated live combination of 2 human pancreatic cell lines that express the mouse enzyme α-1,3-galactosyl transferase
Allovectin-7	Phase 3, melanoma, NCT00395070	Vical/AnGes MC	Gene therapy, plasmid/lipid complex containing DNA encoding HLA-B7 and β2-microgluobulin
Biovax ID	Phase 3, NHL, NCT00091676	Biovest International/ National Cancer Institute	Vaccine, hybridoma-derived idiotype (B-cell antigen) vaccine, made from patients' tumor cells
IMA901	Phase 3, RCC, NCT01265901[a]	Immatics Biotechnologies	Vaccine, combination of multiple different tumor-associated peptides
Lucanix	Phase 3, NSCLC, NCT00676507	NovaRX	Vaccine, 4 NSCLC cell lines modified to block the secretion of TGF-β
MAGE-A3	Phase 3, melanoma (failed to demonstrate extended DFS) Phase 3, NSCLC (ongoing), NCT00480025	GlaxoSmithKline	Vaccine, targets MAGE-A3
Multikine	Phase 3, advanced head & neck, NCT01265849	CEL-SCI/Teva/Orient Europharma	Combination immunotherapy, combines passive and active immune components; mixture of cytokines including interleukins, interferons, and chemokines
Neuvax	Phase 3, breast, NCT01479244	Galena Biopharma	Vaccine, peptide derived from HER2 combined with GM-CSF
PROSTVAC	Phase 3, prostate, NCT01322490	Bavarian Nordic	Vaccine, sequentially dosed combination of *Vaccinia* and *Fowlpox* poxviruses that encode prostate-specific antigen and costimulatory molecules
Rindopepimut (CDX-110)	Phase 3, *EGFRvIII* mutation-positive brain cancer, NCT01480479	Celldex Therapeutics	Vaccine, *EGFRvIII* antigen combined with carrier protein
Stimuvax	Phase 3, NSCLC, NCT00409188	Oncothyreon/Merck	Vaccine, liposome vaccine against MUC-1
Talimogene laherparepvac (T-VEC)	Phase 3, melanoma, NCT00769704	Amgen	Virus, cancer cell-killing virus based on the *herpes simplex-1* virus
TG4010 (MVA-MUC-IL2)	Phase 3, NSCLC, NCT01383148	Transgene/Novartis	Vaccine, recombinant *Vaccinia* virus expressing the MUC-1 antigen and IL-2
Nivolumab (BMS-936558)	Phase 3; advanced melanoma, metastatic RCC, metastatic NSCLC; NCT01844505, NCT01668784, NCT01673867	Bristol-Myers Squibb	Checkpoint inhibitor, mAb targeting PD-1 protein
Tremelimumab	Phase 3; advanced melanoma (discontinued); ongoing phase 1 and 2 trials as combination therapy in melanoma, prostate cancer; NCT00702923, NCT01103635	MedImmune/Pfizer	Checkpoint inhibitor, mAb targeting CTLA-4
Elotuzumab	Phase 3, multiple myeloma, NCT01239797	Bristol-Myers Squibb/Abbott	Naked antibody, CD2-targeting mAb
Farletuzumab	Phase 3, ovarian, NCT00849667	Morphotek	Naked antibody, folate receptor-α-targeting mAb
Inotuzumab ozogamicin	Phase 3, acute lymphocytic leukemia, NCT01564784	Pfizer/UCB	Conjugated antibody, CD22-targeting mAb conjugated to a cytotoxic agent

TABLE 2 (*continued*)

Agent	Trial phase, cancer type, trial number	Manufacturer	Type of immunotherapy, how it works
Naptumomab estafenatox	Phase 3, RCC, NCT00420888	Active Biotech	Conjugated antibody, 5T4-targeting mAb conjugated to the *Staphylococcal enterotoxin E* immunotoxin
Necitumumab	Phase 3, NSCLC, NCT00981058	Eli Lilly	Naked antibody, EGFR-targeting mAb
Obinutuzumab (GA-101)	Phase 3; hematologic malignancies; NCT00981058, NCT01059630, NCT01287741	Genentech	Naked antibody, CD20-targeting mAb
Onartuzumab (MetMab)	Phase 3; NSCLC, gastric; NCT01887886, NCT01662869	Genentech	Naked antibody, cMet receptor-targeting mAb
Racotumomab	Phase 3, NSCLC, NCT01460472	CIMAB/Laborotorio Elea SACIF	Naked antibody, GM3-targeting mAb
Ramucirumab	Phase 3; gastric, liver, breast, CRC, NSCLC; NCT01168973, NCT00703326, NCT00917384, NCT01140347, NCT01183780	Eli Lilly	Naked antibody, VEGFR-targeting mAb

Abbreviations: CTLA-4, cytotoxic T-lymphocyte antigen 4; DCs, dendritic cells; DFS, disease-free survival; EGFR, epidermal growth factor receptor; GM-CSF, granulocyte macrophage colony-stimulating factor; HER2, human epidermal growth factor receptor 2; IL-2, interleukin 2; MAGE-A3, melanoma-associated antigen 3; mAb, monoclonal antibody; MUC-1, mucin-1; NHL, non-Hodgkin lymphoma; NSCLC, non–small-cell lung cancer; PD-1, programmed-death 1; RCC, renal cell carcinoma; TGF, transforming growth factor; VEGF(R), vascular endothelial growth factor (receptor).
[a] Interim results expected early 2014, granted orphan drug designation by the Food and Drug Administration.

TABLE 3 Key hurdles in the development of cancer immunotherapy[a]

1. Limitations of animal models to predict efficacy in humans
2. Lengthy process to obtain approval for clinical trials
3. Complexity of cancer, immune response, mechanisms of tumor-induced immunotolerance
4. Limited availability of reagents for combination immunotherapy studies
5. Limited funding for translation of research into patients
6. Lack of biomarkers of efficacy
7. Current clinical response criteria inappropriate for assessment of immunotherapy
8. Lack of translational research for immunotherapy
9. Insufficient exchange of information critical to advancing the field

[a] Adapted from Fox et al.[14]

therapies and other treatments such as targeted agents or chemotherapy. This is reflected in the fact that numerous combination studies are already underway. Combinations incorporating immunotherapy have the potential to offer tumor control in both the short- and long-term and provide more durable, long-lasting effects.

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