Cancer immunotherapy making headway

Harnessing the immune system to more effectively fight diseases has long been adopted and recently made great strides in cancer treatment. The promise of more specific, less toxic anti-tumour response through immunotherapy and vaccination compared to conventional therapeutics in cancer piqued the interest of researchers and led to the development of innovative approaches. One approach has been the use of checkpoint inhibitors that eliminate the 'brakes' on the immune system that can prevent immune cells from attacking cancer cells. Another approach is adoptive cell therapy, which involves the use of immune cells that are re-engineered to better recognize cancer cells and attack them. Cancer vaccines have also been adopted and involve the recognition of tumour antigens as 'non-self', ultimately stimulating the immune system to mount an effective anti-tumour response. However, a series of clinical trials have highlighted the need for caution and selectivity in their use due to the risks associated with autoimmunity and off-target toxicity. We asked experts in the field of immunotherapy and vaccine development to offer their opinion on new and existing therapeutics, as well as the challenges and successes in clinical use. In particular, they discuss the use of innovative materials in vaccine development and how they can enhance the potency and safety of vaccines. Moreover, they also discuss the innovative approaches in the use of adoptive cell therapies and dendritic cell vaccines that have been employed to generate anti-tumour immunity by activating tumour-specific lymphocytes. Other innovative approaches such as the generation of an immune-response against multiple tumour antigens by DNA demethylation agents are also discussed as well as the recent clinical trials that highlight the promise of immunotherapy in treating cancer.

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Published online: 23 May 2018
https://doi.org/10.1038/s41563-018-0091-8

Material aid for vaccines

Darrell Irvine provides an overview of the recent advances in materials science that have enabled the use of innovative natural and synthetic compounds in vaccine development capable of regulating the potency and safety of new vaccines progressing towards the clinic.

Effective vaccines have been a critical part of modern public health since the early twentieth century, and have helped to eradicate smallpox — and will probably eradicate polio as well — while dramatically lowering the global burden of dozens of other infectious diseases. However, efforts are still ongoing to develop fully effective vaccine strategies for many pathogens that establish chronic infections (for example, HIV, malaria, tuberculosis), and emerging/recurrent viruses such as pandemic flu, Ebola and Zika virus present new threats to be addressed. In addition, tolerogenic vaccines are envisioned to deal with immune responses against biologic drugs, autoimmune disorders and transplant rejection. Therapeutically, there is a resurgent interest in vaccines against cancer, especially vaccines that target so-called neoantigens, mutations in tumour proteins that can be safely recognized as non-self by the immune system. New technologies have often had an important role in modern vaccine development, and materials-based approaches to vaccine adjuvants and vaccine delivery are playing a key role in addressing these challenges. Importantly, a number of promising technologies are moving out of the lab and into the clinic to address the outstanding challenges noted above.

The majority of new vaccines in development for infectious diseases are 'subunit' vaccines, which include a well-defined protein or polysaccharide antigen derived from the pathogen that is the target for protective antibodies or, in some cases, T cell responses.

These antigens must be combined with adjuvants, materials that stimulate the immune system to promote recognition of the antigen and mount an effective immune response. Over the past 20 years, a broad set of innate immune receptors have been defined that allow immune cells to sense specific molecular signatures of microbes. These include, for example, Toll-like receptors (TLRs) that recognize bacterial lipopolysaccharides, viral RNA and DNA, and fungal polysaccharides. Ligands for TLRs have long been considered attractive vaccine adjuvant candidates, because they are single molecular agents acting on defined pathways. However, the potency of these compounds in triggering inflammatory pathways is a double-edged sword, as overstimulation at the injection site or leakage of these compounds into the systemic circulation can lead to side effects such as flu-like symptoms that are unacceptable for prophylactic vaccines. Recently several materials chemistry innovations have been demonstrated that illustrate clever ways to harness these promising compounds. Novartis developed a series of small molecule immune potentiators (SMIPs), a library of compounds that precisely stimulate chosen TLRs. As small molecules, many of these agents had unfavourable pharmacokinetics (for example, rapid dissemination into the blood following injection). To overcome this limitation, these immunomodulators were conjugated with phosphate linkers that undergo a high-affinity ligand exchange reaction with the surface of one of the most common licensed adjuvants, aluminium hydroxide (alum). By binding to alum, the compounds were prevented from leaking into the blood and were instead ferried primarily to lymph nodes by innate immune cells, leading to inflammation focused only in the draining lymph node — exactly where it is needed in a vaccine[1]. This approach has shown excellent results in non-human primates, an important animal model for human vaccine development. Novartis sold their vaccine portfolio to GSK, one of the world's other major vaccine manufacturers, and GSK is continuing to move these novel adjuvants forward toward clinical testing. A second promising approach is to conjugate TLR agonists to polymers that self-assemble into particulates of an appropriate size to carry them to lymph nodes from an injection site. This strategy was shown to greatly enhance the potency and safety of a small molecule TLR adjuvant in mouse models[2], and is now being moved toward clinical testing by Avidea Technologies.

In cancer, two recent clinical trials reported results from the first personalized cancer vaccines targeting neoantigens, patient-specific cancer mutations. These and many encouraging preclinical studies have motivated new interest in strategies to develop therapeutic cancer vaccines, and several different materials-based technologies are in late preclinical/early clinical development with the specific goal of promoting T cell-based immunity required for cancer vaccines. The simplest form of neoantigen vaccines is based on the injection of synthetic peptide antigens, but these generally elicit weak immune responses. Several companies are developing new ways to enhance peptide vaccines: EVOQ Therapeutics is employing lipid nanodiscs that mimic lipoproteins for coformulation of peptides and adjuvant compounds[3]. Another start-up company, Vedantra Pharmaceuticals, is developing approaches to enhance peptide vaccines through polymeric conjugates that target antigens or adjuvant compounds to lymph nodes via reversible binding to albumin[4]. Recently, Novartis announced a partnership with the Wyss Institute and Harvard University to develop implantable and injectable scaffolds that carry antigens and immunostimulatory compounds to prime anti-tumor immunity, translating years of promising preclinical work from the laboratory of David Mooney at Harvard[5]. Thus, a diverse array of new technologies are being moved toward clinical testing for vaccine-based cancer immunotherapy.

Beyond peptide and protein-based vaccines, a major area of research is in the development of materials to deliver engineered RNA expressing antigens for therapeutic or prophylactic immunization. Here again there are many recent translational advances; too many to comprehensively mention here. BioNTech in Europe has carried out a pilot clinical trial intravenously administering mRNA vaccines formulated in lipid nanoparticles in cancer patients with the goal of targeting systemic dendritic cells[6]. Valera, a spin-off of Moderna focused on infectious diseases, has reported promising immunogenicity of mRNA-encoded influenza vaccines delivered by lipid nanoparticles in a phase I clinical trial[7]. CureVac has also developed mRNA vaccines, formulated as nanoparticles in complex with the cationic protein protamine, and recently reported induction of neutralizing antibody responses to a rabies vaccine in humans[8]. Novartis developed cationic nanoemulsions to deliver self-replicating RNAs for vaccination, and reported impressive immunogenicity in non-human primates at modest RNA doses[9]; GSK continues to develop this technology for human translation. Further enhancements in these nucleic acid platforms will be driven in part by improving the delivery materials used in these vaccines.

A final area of exciting recent advances is the development of tolerogenic vaccines that block unwanted immune responses. Selecta Biosciences has developed an approach employing biodegradable polylactide/poly(lactide-*co*-glycolide) nanoparticles carrying the immunosuppressive agent rapamycin, which can be co-administered with an antigen to promote tolerance to the latter molecule[10]. The company is currently in phase two clinical trials for a treatment to induce tolerance to recombinant uricase, an enzyme that is used to treat patients with gout but that is seen by the immune system as a foreign molecule. If successful, this system could provide a generic blueprint for promoting antigen-specific tolerance.

Altogether these examples illustrate much promise in the use of new materials and materials chemistries to control the biodistribution, mechanisms of action, safety and potency of new vaccines. Clinical success of these technologies will pave the way for further development of such innovative approaches and provide important new information about the impact of materials-based vaccine strategies in humans. ❐

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Published online: 23 May 2018
https://doi.org/10.1038/s41563-018-0089-2

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Dendritic cells in cancer immunotherapy

Camille M. Le Gall, Jorieke Weiden, Loek J. Eggermont and Carl G. Figdor provide an overview of immunotherapeutics for cancer treatment that harness dendritic cells, their challenges in clinical use, and approaches employed to enhance their recruitment and activation to promote effective anti-tumour immunity.

Immunotherapy has revolutionized cancer treatment in the past two decades. Immune checkpoint inhibitors that relieve inhibitory signalling pathways in T cells have successfully proven that durable anti-tumour immune responses can be elicited in vivo. These T cells are instrumental as they can recognize and eliminate cancerous cells. Despite these advances, still a large proportion of patients are not responsive to immune checkpoint blockade therapy, mainly owing to low tumour-specific T cell counts, poor T cell infiltration in the tumour or T cell exhaustion. To increase T cell numbers and functionality, patients require de novo generation of T cells rather than mere rescue. This can be achieved by harnessing the key coordinators of immune responses: dendritic cells (DCs). DCs are specialized in taking up tumour antigens and in priming different subsets of antigen-specific T cells. Cytotoxic, or $CD8^+$ T cells, directly attack the tumour cells whereas helper, or $CD4^+$ T cells, are crucial in supporting $CD8^+$ T cell function and antibody production. As such, DCs are able to initiate de novo anti-tumour responses and are an essential target in our ongoing effort to improve anti-tumour immunity.

Current clinical DC-based strategies make use of patients' own DCs to generate therapeutic vaccines. DC vaccination requires induction of DC maturation to elicit potent T cell effector and memory immune responses. DCs are harvested from patients, maturated ex vivo using adjuvants, loaded with tumour antigens and injected back into the patients (Fig. 1). After injection, DCs present tumour antigens to tumour-specific T cells, resulting in T cell activation and expansion. As of 2010, sipuleucel-T (Provenge) is the first FDA approved DC vaccine for prostate cancer patients[1]. DC vaccination has been demonstrated safe for treatment of different cancer types[2], and was shown to elicit durable T cell responses in clinical trials[3]. This approach has been shown especially efficient in eliciting primary T cells in patients treated with naturally occurring DC subsets[4].

Although DC vaccination based on ex vivo loading of antigens has been instrumental in demonstrating the feasibility of harnessing DCs to induce potent anti-tumour immune responses, this strategy faces several challenges. Many patients develop de novo T cell responses but often this does not result in significant improvement of the subsequent clinical response. One factor explaining this could be the transition of DCs from an in vitro to an in vivo immunosuppressive environment, altering DC viability and functionality, and jeopardizing their ability to prime T cells. Another more practical hurdle is that the ex vivo DC culture procedure is expensive and time-consuming, and requires dedicated infrastructures, hindering its wide-spread clinical use. Finally, DC vaccines are a patient-derived cell-based therapy. It is hence problematic to ensure the quality of the product, as it strongly depends on the patient's immune system exhaustion level. However, many efforts are put into tackling these issues to create more effective DC vaccines. As these immunotherapies gradually enter the clinic, patients at an earlier cancer stage with a less exhausted immune system will be enrolled in trials, for which a larger benefit of DC vaccination is expected.

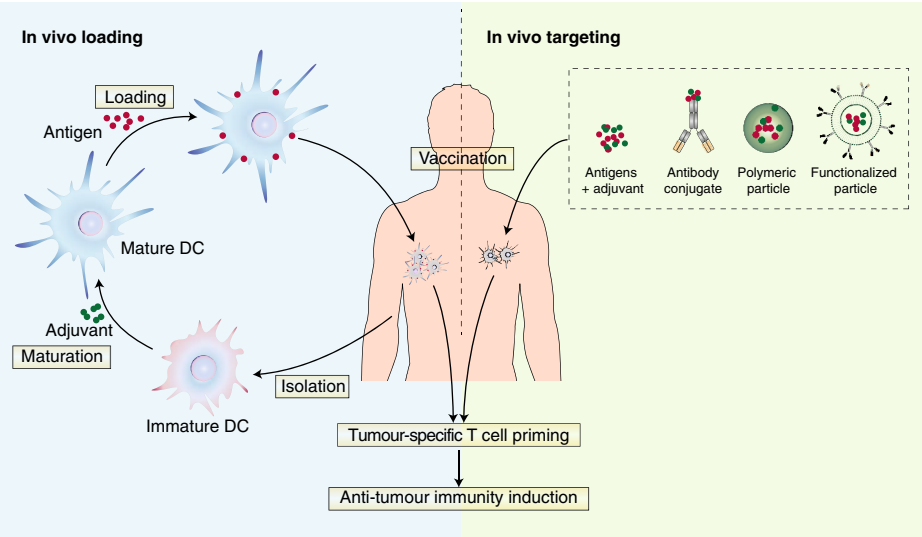

Fig. 1 | DC-based cancer vaccination strategies. Inducing anti-tumour immune responses by dendritic cells (DCs) activation, DC-based cancer vaccines aim to stimulate anti-cancer immunity in patients by harnessing the capacity of DCs to activate tumour-specific T cells. This can be done by infusing patients with ex vivo antigen loaded DCs (left) or by targeting antigens and adjuvants directly to DCs in vivo (right).

A promising development in DC immunotherapy is the generation of off-the-shelf vaccines. To circumvent the laborious preparation and variable quality associated with ex vivo prepared cell-based vaccines, DCs can be directly targeted to trigger their maturation (Fig. 1). In vivo DC activation requires the delivery of tumour antigens along with adjuvants to induce immunity rather than tolerance[5,6]. The first strategies towards in vivo DC vaccination were based on simply injecting peptides and adjuvants. This longstanding strategy has generally been inefficient for cancer treatment. Challenges such as stability, induction of tolerance, poor immunogenicity and transience of immune responses limit the efficacy of peptide-based cancer vaccines. To improve on this, pioneering studies by Steinman and colleagues successfully demonstrated that tumour-specific T cells responses can be elicited using antibodies against DC-specific surface receptors to direct antigens to DCs[5]. Alternatively, encapsulation strategies have been developed to increase the

circulatory stability and half-life of antigens. Recent advances in the nanotechnology field led to a surge of nanomaterials with potential biomedical application, leading to application of liposomes, PLGA nanoparticles, synthetic scaffolds and carbon nanotubes as delivery systems. These particles enable targeting of DCs by exploiting their unique capacity to take up particulates. Importantly, such approaches also enable co-delivery of antigens together with adjuvants to the same target cells, which was found to promote strong DC maturation. Particle composition, size and charge are highly correlated to its circulatory half-life and dictate uptake by specific cell types. Harnessing the different physicochemical properties of biocompatible materials allows for selective targeting of specific DC subtypes. A recent study by Sahin and colleagues describes an efficient mRNA-encapsulating liposome vaccine[7]. Owing to their charge and composition, these liposomes are preferentially targeted to the spleen, efficiently activating different types of DCs and thereby eliciting durable anti-tumour T cell responses. Antigen and adjuvant can also be directed to the same target cells using antibody conjugates, which can be easily generated thanks to advances in antibody engineering. These developments can be applied to functionalize carrier nanomaterials with antibodies targeting DCs for cell-specific immunogenic cargo delivery. Another strategy to enhance efficacy of DC activation uses macroscopic three-dimensional scaffolds to recruit DCs towards a site with high doses of antigen and adjuvant[8].

In vivo DC targeting for cancer vaccination generated high expectations and was found to be successful in multiple pre-clinical studies. However, few clinical studies have been conveyed to date, as large scale GMP production of nanomaterials is notoriously difficult, time intensive and technically challenging[9]. As DC targeted vaccines are being developed, several immunological questions still need to be answered. For instance, although extensive work on immune checkpoint blockade has shed light on molecular mechanisms of $CD8^+$ T cell function, substantial lack of knowledge persists on $CD4^+$ T cell programming by DCs, and on the mechanisms explaining the diverse $CD4^+$ functions in anti-tumour immunity. DCs are a highly heterogeneous population, but subsets can be discriminated based on the expression pattern of specific surface proteins such as C-type lectins or chemokine receptors. For instance, plasmacytoid DCs, specialized in production of inflammatory cytokines crucial for T cell activation, specifically express BDCA-2, whereas CLEC9A expression is restricted to DCs highly specialized in $CD8^+$ T cell priming. Such receptors embody interesting molecular targets for directing cancer vaccines. It should be emphasized that not only the DC subset, but also the downstream signalling pathways elicited by receptor internalization, are crucial for the nature of immune responses following vaccination[10].

As our understanding of DC biology increases, mechanisms underlying the generation of durable cancer-specific immune responses are being unravelled. We expect that this knowledge will be applied for designing effective off-the-shelf therapies applicable to man. We foresee that future DC targeting vaccines will focus on combinations of (patient-specific) tumour antigens and adjuvants co-delivered by functionalized nanomaterials. Moreover, combining vaccines to target several DC subsets, such as plasmacytoid DCs and CLEC9A-expressing DCs, will be a valuable strategy to elicit potent and durable $CD8^+$ and $CD4^+$ T cell responses. Such vaccines could be further potentiated by combining them with immune checkpoint blockade agents, to remove immunosuppressive signals that newly generated T cells will have to face in the tumour microenvironment. These developments will contribute to establishing long-lasting clinical responses in patients treated with DC targeting cancer vaccines. ❐

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Published online: 23 May 2018
https://doi.org/10.1038/s41563-018-0093-6

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Adoptive T cell cancer therapy

Tumour heterogeneity and off-target toxicity are current challenges of cancer immunotherapy. Karine Dzhandzhugazyan, Per Guldberg and Alexei Kirkin discuss how epigenetic induction of tumour antigens in antigen-presenting cells may form the basis for multi-target therapies.

The idea of engaging the patient's own immune system to fight cancer has a long history, but it is only during the past decade that this field has experienced significant progress. Two main types of cancer immunotherapy have been shown to be capable of inducing durable clinical responses in several malignancies: immune checkpoint blockade and adoptive cell therapy. Currently the most widely available and successful approach is to use immune checkpoint inhibitors (ICIs), which are monoclonal antibodies directed against negative regulators of the immune response, including the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) receptor and the programmed death 1 (PD-1) receptor and its ligand PD-L1. Phase III clinical trials of CTLA-4, PD-1 and PD-L1 inhibitors as single-agent treatment have demonstrated improved overall and disease-free survival, forming the basis for the recent regulatory approval of these drugs as standard therapy for solid cancers[1]. It is generally accepted that the main mechanism of ICIs is to boost a pre-existing immune response against cancer cells, and that the main immunological targets are 'neoantigens' present in the cancer cells as a result of somatic mutations[2]. Many patients treated with ICIs experience immune-related adverse effects, usually autoimmune

manifestations in the skin, gut, liver, lung and endocrine glands, which can be severe and potentially fatal.

The second type of cancer immunotherapy, adoptive cell therapy, encompasses a variety of approaches relying on the ex vivo activation of the patient's own immune cells to better recognize and kill cancer cells when transferred back to the patient. One of the first successful approaches in this field was the use of tumour infiltrating lymphocytes (TILs), which involves the bulk ex vivo expansion of lymphocytes isolated from tumour biopsy tissue[3]. This approach showed a high clinical response rate in a selected group of melanoma patients (up to 24% complete tumour regression), but requires the transfer of large numbers of effector cells (up to 10^{11} cells), as well as prior lymphodepletion chemotherapy. In addition, it has proven difficult to expand TILs into sufficient quantities for malignancies other than melanoma, which significantly restricts the application of this technology. A more recent development is the transfection of ex vivo activated and expanded T cells with a chimaeric antigen receptor (CAR) consisting of a fragment of an antibody with specificity to a defined antigen (most often CD19 expressed on differentiated B cells and B-cell malignancies) fused with a fragment of the T-cell receptor (TCR)[4]. This so-called CAR-T technology has shown high response rates in patients with B-cell acute lymphoblastic leukemia, whereas attempts to treat patients with solid tumours using other targets are still in their infancy. Another genetic modification of T cells involves transfection with a TCR with specificity for a defined tumour antigen, which can be used for treatment of various cancers, including solid tumours[3]. Despite significant clinical response rates demonstrated for certain cancer types, this treatment should be used with extreme caution due to the risk of severe off-target toxicities, possibly related to the use of an affinity-enhanced TCR[5].

One of the major limitations of the above immunotherapies is the restriction of target antigens, particularly for CAR-T and TCR-transfected cells. In general, these approaches are effective only in situations where the target antigen is homogeneously expressed among tumour cells, such as the consistent expression of CD19 across B-cell malignancies. The majority of tumours, however, display a high degree of intra-tumour heterogeneity of target antigen expression[6], which may lead to the immunological escape of tumour cell variants (Fig. 1a)[4]. One approach to overcome this limitation would be to broadly target tumour specific antigens — for example, cancer/testis (CT) antigens — one of the first discovered families of shared human cancer antigens recognized by cytotoxic T lymphocytes[7]. These >100 antigens are widely expressed in cancer cells, but not in normal tissues except for germline cells of the testis, where they are not recognized by the immune system due to the lack of expression of major histocompatibility complex (MHC) molecules. Mono-antigen therapy using TCR-transfected cells specific against one member of this family, NY-ESO-1, demonstrated high efficacy (61% response) in the treatment of synovial cell carcinoma, where this antigen is expressed by 80% of tumours[8]. In the

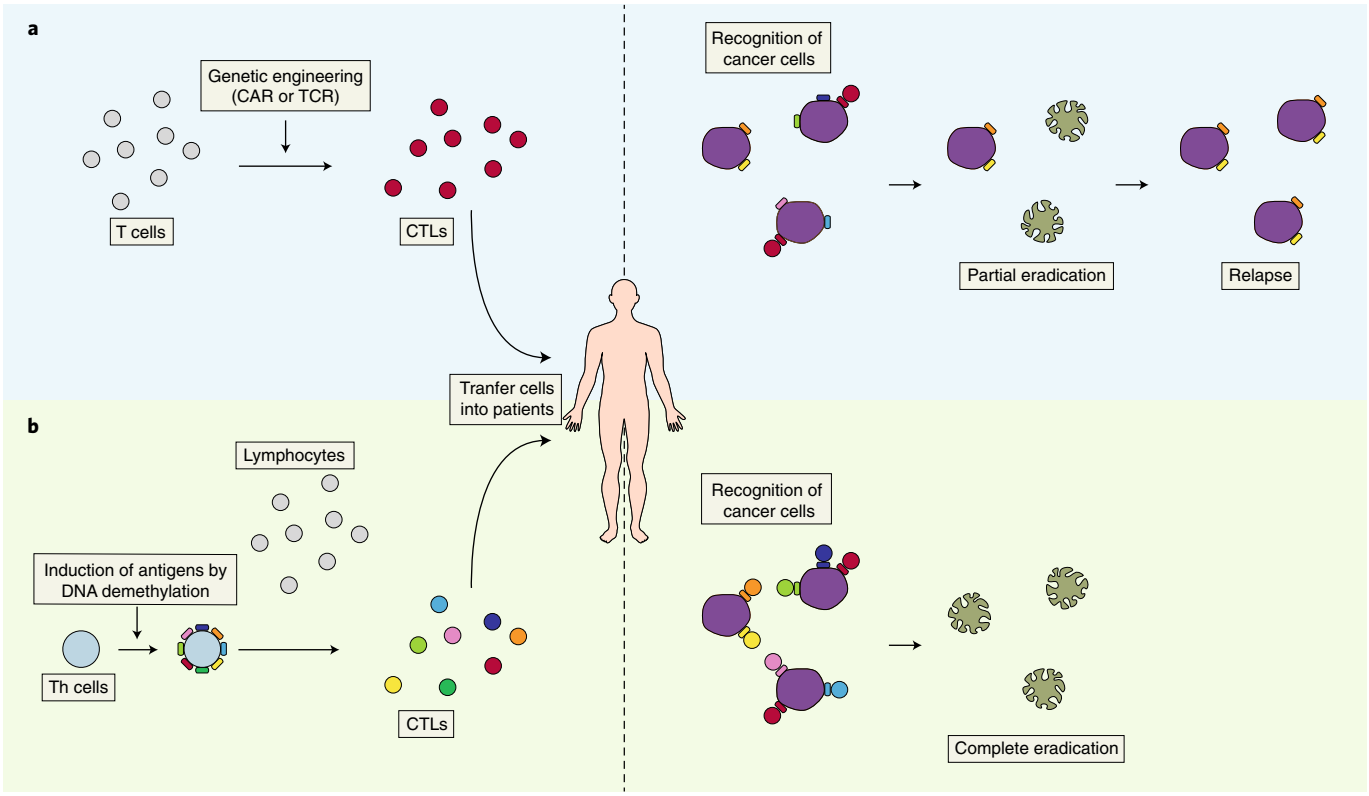

Fig. 1 | Current approaches to generating mono- or multi-antigen-directed immune responses for treatment of cancer. a, Genetic engineering of patient-derived T cells by transfection with a CAR or a TCR generates an immune response against a single tumour-associated antigen. Only cancer cells presenting this antigen will be killed by the effector cells, increasing the risk of tumour recurrence. **b**, Induction of multiple tumour-associated antigens by chemically induced DNA demethylation in antigen-presenting T helper (Th) cells can be used to generate an immune response against multiple antigens, with a greater potential for complete tumour eradication.

majority of other cancer types, however, CT antigens are more heterogeneously expressed, pointing to the need for multi-antigen targeting.

A recent study demonstrated how an immune response against multiple CT antigens can be generated by inducing endogenous expression of these antigens in antigen-presenting cells (Fig. 1b)[9]. In normal cells, CT antigens are silenced by hypermethylation of the corresponding gene promoters, but can be reactivated with agents that demethylate DNA. A prerequisite for chemically inducing DNA demethylation in cells is that these cells proliferate; therefore, 'professional' antigen-presenting cells such as dendritic cells are not suitable for this purpose. Instead, T-helper cells were shown to be highly efficient as antigen-presenting cells for ex vivo immunization after induction of CT-antigen expression through chemical DNA demethylation, leading to the generation of polyclonal populations of CTLs with a high capacity for recognizing and killing cancer cells, but not normal cells[9]. In a phase I clinical trial of refractory (end-stage) glioblastoma, injection of cytotoxic cells led to durable tumour regression in three out of ten patients who lived long enough to receive the planned three injections of therapeutic cells[9]. Notably, relatively low numbers of cells ($<10^8$) were injected and with no prior lymphodepletion. Moreover, no treatment-related serious adverse effects were observed, which distinguishes this treatment modality from other types of immunotherapy. The lack of clinical response in the majority of patients should be viewed in the context of the very serious disease state of these patients, with highly aggressive and rapidly growing tumours.

Considering that CT antigens are expressed across many malignancies, it is tempting to speculate that targeting antigens induced by DNA demethylation may be a broadly applicable approach to cancer treatment. Future development of this technology should involve the combination with other types of immunotherapy, including ICIs, which could potentially increase the activity of the therapeutic cells by suppressing immune-inhibitory pathways. Furthermore, combination with systemic DNA-demethylating drugs, such as repeated low-dose administration of decitabine[10], could induce upregulation of CT antigens in cancer cells and thereby increase the efficacy of the immunological recognition by immune effector cells. ❐

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Published online: 23 May 2018
https://doi.org/10.1038/s41563-018-0094-5

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