Advancing Cancer Vaccines to the Forefront of Immunotherapy

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Summary

- Therapeutic cancer vaccines aim to induce tumor-specific immune response
- Translation of preclinical and early clinical successes into improved clinical outcome of cancer patients is suboptimal
- Optimization efforts of cancer vaccine design focus on choice of tumor antigen, delivery method, and adjuvant
- Emerging trends favor personalized vaccines and combination therapies with immune checkpoint inhibitors

Introduction

Therapeutic cancer vaccines offer conceptually interesting approach of directing the immune system to specifically recognize and eliminate tumor cells, with the potential to significantly extend the current repertoire of available cancer immunotherapies. However, despite initial enthusiasm and promising early clinical evidence, the number of approved therapeutic cancer vaccines remains limited and their clinical efficacy as monotherapy has been modest (Hollingsworth and Jansen 2019). Challenges for therapeutic cancer vaccines include highly variable patient anti-tumor responses, low immunogenicity of tumor antigens, and the immunosuppressive tumor microenvironment (Hollingsworth and Jansen 2019). Therefore, recent optimization efforts focus on cancer vaccine composition to improve immunogenicity and on the inclusion of immunomodulating agents (Maeng and Berzofsky 2019). In addition, technological advances, such as genome sequencing to identify tumor (neo)antigens, machine learning for their computational prediction and validation (Smith, Selitsky et al. 2019) and novel bioengineering methods for cancer vaccine formulation (Goldberg 2019, Vermaelen 2019, Briquez, Hauert et al. 2020) are currently reshaping the field and hold the promise for generating clinically efficacious cancer vaccines. Our increasing knowledge on the complexity of tumor immunobiology allows for rational selections of therapeutic partners with synergistic potential in a clinical setting.

In this paper, we will discuss emerging trends in cancer vaccine design and analyze key translational aspects for the clinical utilization of cancer vaccines in the fast-evolving field of cancer immunotherapy.

Mechanisms of cancer vaccine anti-tumor effects

The ultimate goal of cancer immunotherapy is to elicit tumor-specific immune responses and tumor cell destruction, followed by long-lasting immunological memory to prevent disease recurrence. Cancer vaccines can achieve this through several steps (**Figure 1**), initiated by the presence of immunogenic tumor antigen(s) either delivered through the vaccine formulation or released directly from the tumor tissue due to oncolytic agent-induced tumor cell lysis (Szczepanski, Tenstad et al. 2014, Sveinbjornsson, Camilio et al. 2017). Tumor antigens are taken up and processed by resident dendritic cells (DCs) that subsequently migrate to the draining lymph nodes to (cross)-present the antigens to naïve CD4 and CD8 T cells. Such primed and activated T cells perform their respective functions: tumor antigen-specific CD8 T cells are recruited into the proximate and distant tumor sites to elicit their cytotoxic effector functions, inducing tumor cell death and subsequent release of antigens together with Danger Associated Molecular Patterns (DAMPs), that can further strengthen anti-tumor immune responses. The activated CD4 T cells support the generation of effector and central memory CD8 T cells and promote humoral anti-tumor responses, contributing to long-term anti-tumor protection. Additionally, tumor cell death can increase the production of pro-inflammatory

cytokines and chemokines, which in turn promotes the maturation of tumor-associated DCs and increases the influx of natural killer (NK) cells and M1-type macrophages, while reducing number and / or pro-tumoral activity of immunosuppressive M2-type macrophages, myeloid-derived suppressor cells (MDSCs), and regulatory T cells (Tregs) (for review see (Bommareddy, Shettigar et al. 2018, Sheen and Fiering 2019)).

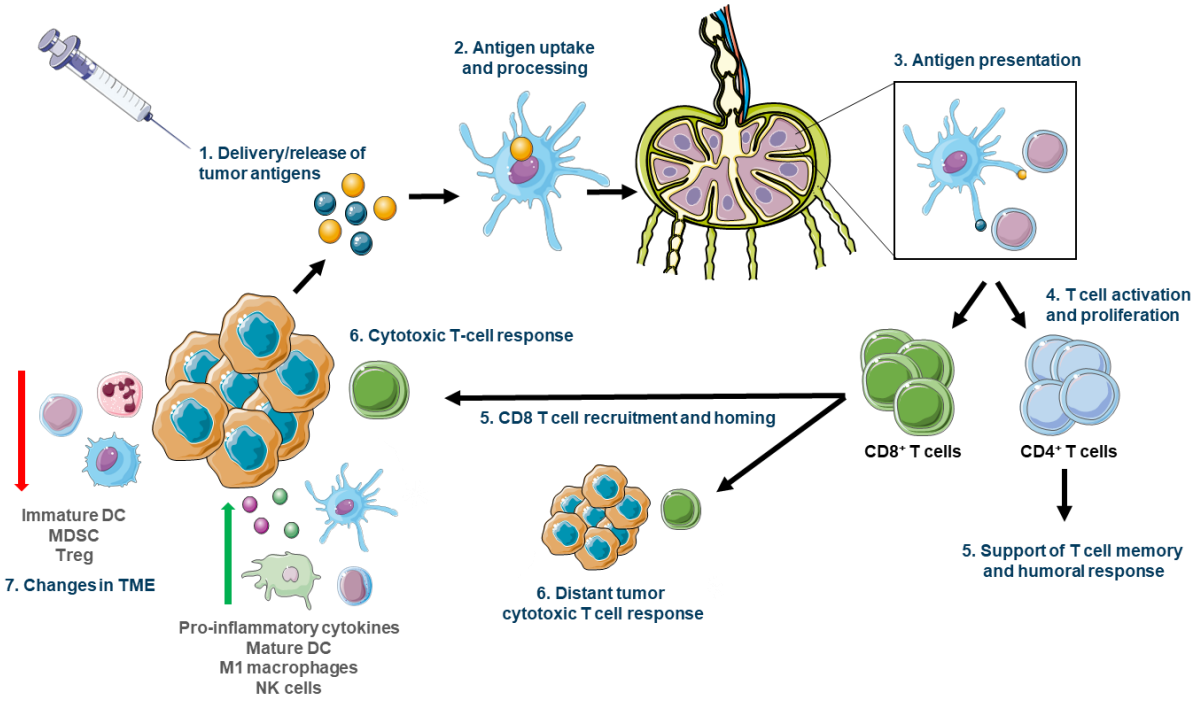

Figure 1 Mechanisms of cancer vaccine anti-tumor effects
Cancer vaccines induce anti-tumor immune responses by providing tumor antigens which trigger a cascade of immune cell activation, leading to local and distant tumor cell destruction, generation of long-term anti-tumor memory, and modulation of tumor microenvironment (Detailed explanation in the text; illustration made with Servier Medical Art tool).

Developmental landscape of cancer vaccines

The analysis of developmental efforts in this class of anti-cancer therapies (Jul2015-Jul2020) showed an active developmental landscape with 15 vaccines in preclinical phase of development (**Figure 2A**) and more than 400 active (ongoing or planned) early phase clinical trials investigating cancer vaccines (**Figure 2B**). This is in contrast to the number of active later stage (Phase III) trials (**Figure 2B**). This can be explained by a substantially lower success rate of clinical phase transition for cancer vaccines observed between Phase II and III (27%). In comparison, for the whole group of anti-cancer biologics, where cancer vaccines are included, this number reaches 40% (**Figure 2C**). Also, the number of approved cancer vaccines is limited: only three vaccines reached broad / global market authorization, each approved for a single cancer indication: sipuleucel-T (Provenge®) approved for treatment of metastatic hormone refractory prostate cancer, talimogene laherparepvec (Imlygec®) approved for treatment of metastatic melanoma, and the bacillus Calmette-Guerin (BCG) vaccine, approved for the treatment of in situ bladder carcinoma.

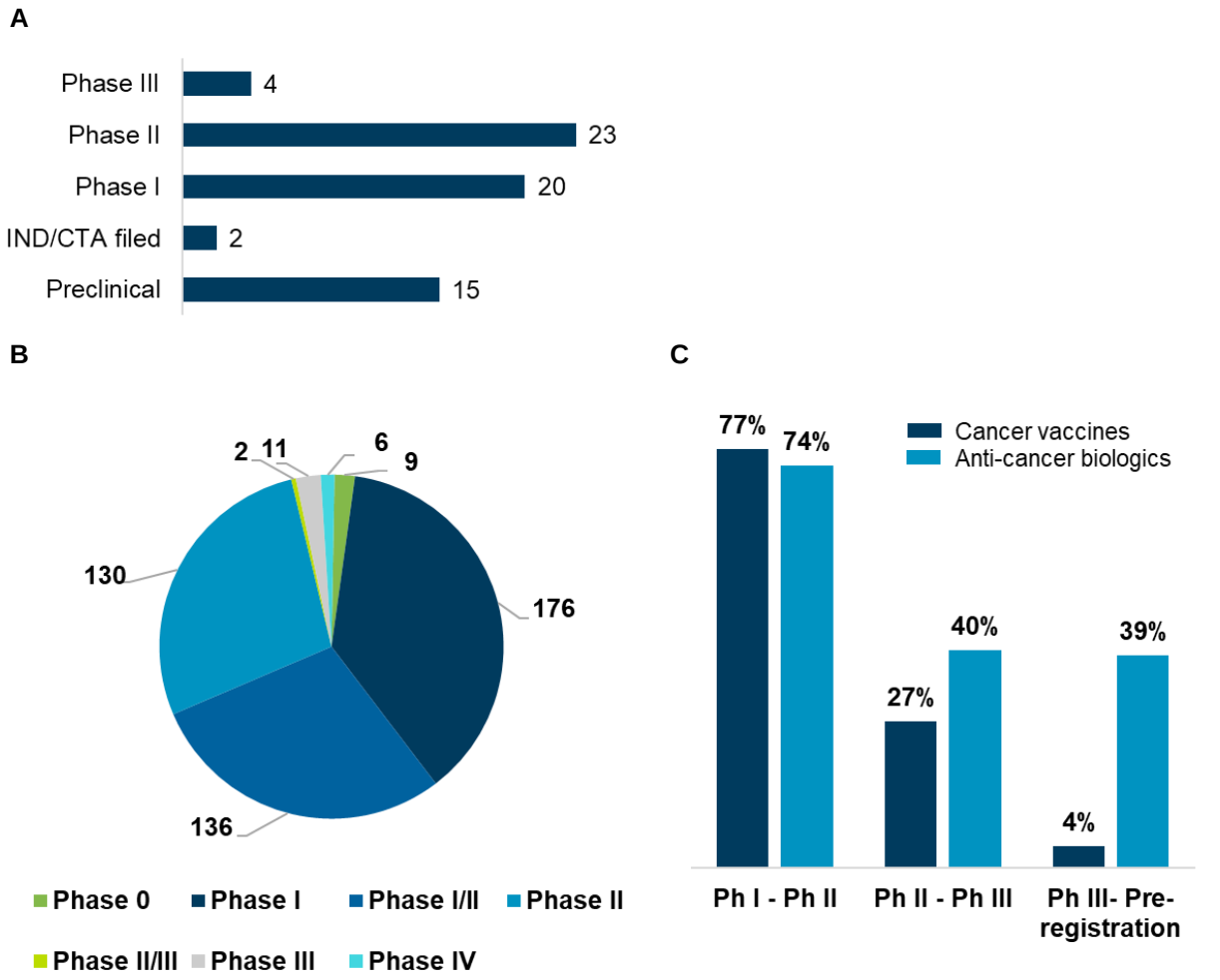

Figure 2 **Developmental landscape of cancer vaccines**: **A** Number of cancer vaccines per developmental stage (designation date from Jun2015). **B** Clinical trial landscape of cancer vaccines depicted as number of planned or ongoing clinical trials per phase, initiated between Jun2015 and Jun2020. **C** Success rate of clinical trial phase transition (%) for cancer vaccines and anti-cancer biologics (GlobalData, Jun2020)

Optimization efforts of cancer vaccine design

The observed activity in preclinical and early clinical development of cancer vaccines suggests that there is remaining interest in the field for cancer vaccines and their potential to become an important addition to existing cancer (immuno-)therapies. Efforts are focusing on optimizing the technology and properties of different building blocks of cancer vaccine composition (**Figure 3**), which will impact the clinical efficacy.

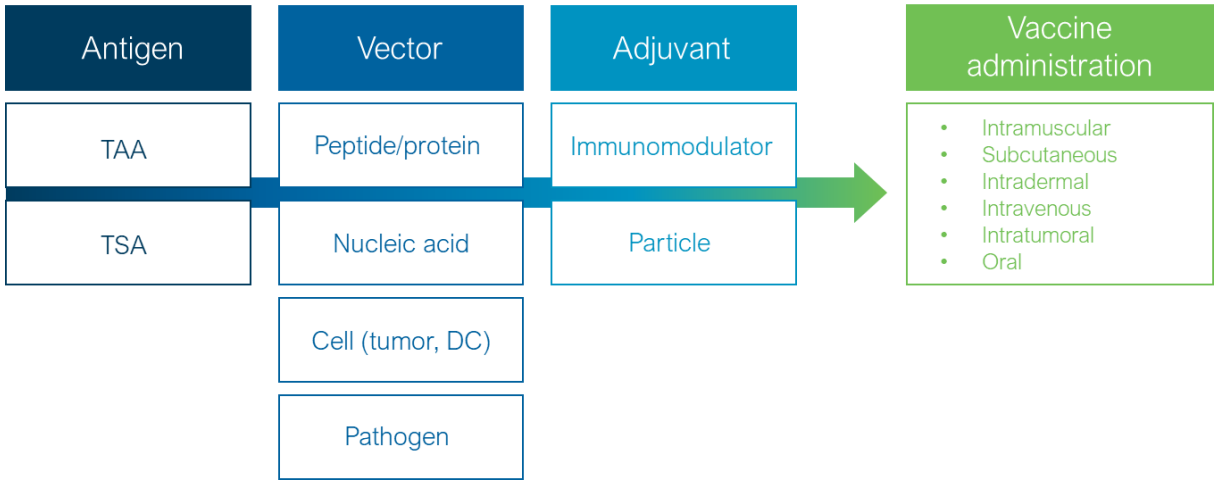

Figure 3 Cancer vaccine composition
Common components of a therapeutic cancer vaccine include: i) **antigen(s)**, which can be a tumor-associated antigen (TAA) or tumor-specific antigen (TSA); ii) **vector**, which delivers the antigen(s) as peptide/protein or a sequence encoded in nucleic acid (DNA, mRNA); the antigen can be also provided by intact or lysed autologous/allogeneic tumor cells, loaded into dendritic cells (DCs) or it can be delivered by pathogens, such as a bacterium or a virus; iii) **adjuvant**, which can be an immunomodulatory agent or a particle with dual function as immunomodulator and packaging vector. The components of a cancer vaccine, taken together, determine the most optimal **route of administration**.

1. Antigen selection

The first, and probably the most important step in designing a cancer vaccine, is selection of antigen(s). As depicted in **Figure 4**, there are two major groups of tumor antigens – tumor-associated antigens (TAAs) and tumor-specific antigens (TSAs). These two classes of tumor antigens differ in their specificity for tumor tissue, which is one of the main factors influencing vaccine safety and efficacy. Other differences between these two antigen classes are in terms of immunogenicity, which determines vaccine efficacy, and universality, which has consequences for the degree of broadness for patient / tumor application. Immunogenicity of the antigen is a core vaccine property, which determines the strength of the signal that is provided to the immune system and the type of immune response that can be expected. TAAs have a higher potential to induce mainly antibody-mediated immune response with lower anti-

	Category	Antigens	Relevant cancers	Tumor specificity	Immunogenicity	Universality
TAA	Cancer testis antigens	MAGEA1-4, NY-ESO-1, CT83, PRAME, SSX2	Bladder, breast, lung, melanoma, myeloma, ovaries, liver, prostate, esophagus	Intermediate	Intermediate	High
TAA	Differentiation- or lineage-specific antigens	Gp100, MART1, PSA, PSMA, CD19, tyrosinase	Melanoma, prostate, lymphoma	Variable	Low	
TAA	Overexpressed antigens	EGFR, Her2, CEA, mesothelin, MUC1, cyclin B1, EPHA2, survivin, telomerase	Colon, breast, bladder, cervix, lung, pancreas, prostate, ovaries, glioblastoma			
TSA	Oncoviral antigens	HPV, HBV, EBV	Cervix, liver, esophagus, Hodgkin lymphoma	High	High	High (for specific cancer types)
TSA	SNV neoantigens	Patient- and tumor-dependent			High	Low
TSA	INDEL frameshift neoantigens	TP53, ARID1A, PTEN, KMT2D, KMT2C	Sporadic gastric and colon cancer with MSI, renal cell carcinoma		Intermediate	Intermediate
TSA	Fusion protein neoantigens	FGFR3, ETV6-NTRK3	Bladder, breast, AML, ALL, CML, sarcomas		Intermediate	Intermediate

Figure 4 Characterization of tumor antigens (Turajlic, Litchfield et al. 2017, Finn 2018, Thomas, Al-Khadairi et al. 2018, Smith, Selitsky et al. 2019). Abbreviations: SNV: Single nucleotide variation; INDEL: Insertion and deletion; MAGEA 1-4: Melanoma-associated antigen 1-4; NY-ESO-1: Cancer/testis antigen 1; CT83:Cancer/testis antigen 83; PRAME: Preferentially expressed antigen in melanoma; SSX2: Cancer/testis antigen 2; gp100: glycoprotein 100; MART1: Melan-A protein and Melanoma Antigen 1; PSA: Prostate-specific antigen; PSMA: Prostate-specific membrane antigen; EGFR: Endothelial growth factor receptor; Her2: Human epidermal growth factor receptor 2; CEA: Carcinoembryonic antigen; MUC1: Mucin 1; HPV: Human papilloma virus; HBV: Hepatitis B virus; EBV: Epstein-Barr virus; TP53: Tumor protein 53; ARID1A: Human epidermal growth factor receptor 2; PTEN: Phosphatase and tensin homolog; FGFR3: Fibroblast growth factor; ETV6-NTRK3: Ets-leukemia virus-neurotrophic tropomyosin-related kinase fusion protein; AML: Acute myeloblastic leukemia; ALL: Acute lymphoblastic leukemia; CML: Chronic myelocytic leukemia

tumor efficacy. In contrast, TSAs have more potential to trigger immune response similar to anti-viral immune responses against foreign antigens, and are mediated mainly through CD8 cytotoxic cells (Nisis, D, A new wave of cancer vaccines, ASCO 2020). However, even high immunogenicity, reflected in the right strength and type of signal provided by the neoantigen, does not ensure effective tumor destruction. This is also determined by the biologic relevance of the target antigen, i.e. its importance in the tumor developmental hierarchy. Certain clonal alterations are present in all tumor cells and form the phylogenetic “trunk” of the tumor developmental tree. Subclonal alterations represent “branches” of the phylogenetic “trunk” and are present only in some subclones occurring later during tumor evolution (Amirouchene-Angelozzi, Swanton et al. 2017). If the vaccine utilizes neoantigen(s) that are present only on later developmental branches with potentially lower relevance to tumor growth, leaving earlier “ancestral” tumor clones untouched, the vaccine will not eliminate all tumor cells (Nisis, D, A new wave of cancer vaccines, ASCO 2020). Ideally, utilized (neo)antigens should also be indispensable for cancer cell to maintain its phenotype, as seen e.g. with HPV E6 and E7 oncoproteins (Pal and Kundu 2019). Their biological importance prevents cancer cells from down-regulation of such antigen expression, a common mechanism used by tumor cells to escape immune surveillance.

2. Cancer vaccine vector

The choice of a vector to deliver tumor antigen(s) has a significant influence on the accessibility of the antigens for antigen presentation and subsequent immune responses, but also has more practical consequences for vaccine production, such as feasibility of (large-scale) manufacturing. Importantly, the immunomodulatory properties of the vector itself can contribute to the overall immunogenicity of the vaccine. From different perspectives, nucleic acids have several benefits as antigen vectors (**Table 1**). First, they can harbor multiple tumor epitopes, which can increase the chance of inducing tumor antigen-specific CD8 T cell responses. Second, sequences for different adjuvants and immunomodulatory molecules can be encoded in such vectors to further boost immune responses. And lastly, nucleic acids have the ability to induce innate immune responses as they are sensed through signaling molecules, such as stimulator of interferon genes (STING) and toll-like receptors (TLRs). Optimization efforts of nucleic acid vectors are focusing on improving both delivery efficiency of DNA- or mRNA-based vaccines and their stability (**Table 1**). Different vectors and delivery platforms are also being combined in the efforts to provide targeted and enhanced antigen delivery. An example of such a combinatory approach translated into the clinic is an orally administered cancer vaccine against Vascular endothelial growth factor receptor 2 (VEGFR-2), which encodes antigen sequences in a DNA vector encapsulated in attenuated *Salmonella* bacterium, showing increased antigen-specific CD8 T-cell responses in patients with glioblastoma (NCT03750071; Wick, W. et al., 2020).

Table 1 Cancer vaccine vectors

Vector	Advantages	Disadvantages	Optimization
Nucleic acid (DNA, mRNA) Ref: Lopes, Feola et al. 2019, Gomez-Aguado, Rodriguez-Castejon et al. 2020	• Encoding multiple antigens and immunomodulatory molecules • Stability, safety, price • Innate immune responses through sensing molecules (PAMP and DAMP signals)	• Low transfection and translation efficiency due to limited penetration through extra- and intracellular membranes • mRNA stability against hydrolases and RNases	• Delivery methods, e.g. gene gun, DNA tattooing, electroporation • Packaging/ encapsulation in nanoparticles to prevent endosomal degradation • Length, codon optimization, chemical modifications
DC Ref: Perez and De Palma 2019	• Personalized delivery platform • Presence of antigens directly in antigen-presenting cell	• Heterogeneity in *ex vivo* differentiation • Suboptimal migratory capacity • Low antigen-presentation • Costs and labor demanding	• Addition of Notch-activating stromal cells FLT3L to induce anti-tumor phenotypes of conventional type 1 DCs • Gene editing (CRISPR/Cas9, RNAi)
Tumor cell Ref: Schijns, Pretto et al. 2015	• Broad repertoire of tumor antigens • Personalized vaccine (autologous tumor cells)	• Low immunogenicity	• Combination with antigen chaperones (HSP70), gp96-IgG fusion protein, or cytokines to increase DC maturation (GM-CSF)
Bacteria/virus Ref: Hollingsworth and Jansen 2019	• High immunogenicity (PAMP signals) • Genetic manipulation (expression of cytokines, co-stimulatory molecules) • Feasibility of production	• Immune response against vector • Risk of undesired infection	• Heterologous prime-boost strategy (alternating vector) • RNA viruses above DNA viruses • Attenuated strains
Peptide/Protein Ref: Maeng and Berzofsky 2019	• Delivery of epitopes of interest (T-cell epitopes) • Feasibility of production	• Low/moderate immunogenicity • Delivery to the effector side • HLA-restricted	• Epitope enhancement (amino-acid modifications) and length modifications (synthetic long peptides) • Packaging/encapsulation in DCs or nanoparticles • Combination of several peptides to increase coverage

PAMP: Pathogen-associated molecular pattern; DAMP: Danger-associated molecular pattern, FLT3L: FMS-like tyrosine kinase 3 ligand; DC(s): Dendritic cell(s); CRISP: Clustered regularly interspaced short palindromic repeat; RNAi: RNA interference; HSP70: Heat-shock protein 70; gp96IgG: Glycoprotein 96-immunoglobulin G; GM-CSF: Granulocyte-monocyte colony-stimulating factor; HLA: Human leukocyte antigen

3. Adjuvant

Many of the cancer vaccination strategies developed thus far have been hindered by unsuccessful induction of anti-tumor immune responses, despite the high immunogenicity of antigens used (Vermaelen 2019). One possible explanation for the failure of eliciting a proper immune response is the generation of such responses under immunosuppressive conditions in the tumor microenvironment and immune tolerance to some tumor antigens (Bowen, Svrivastava et al. 2018). Different adjuvants can facilitate or support processes needed for adequate immune responses at different stages of T cell activation and / or can modulate the tumor microenvironment:

- Antigen delivery and uptake: nanoparticles
- DC maturation and antigen presentation: cytokines (GM-CSF)
- T-cell activation: co-stimulatory molecules (CD70, CD40L, 4-1BB)
- T-cell activation: cytokines (IL-12)
- Modulation of the tumor microenvironment: TLR agonists, STING agonists

Major improvements have been achieved in bioengineering strategies for nanoparticle design, focusing on materials, architecture, and composition, with enhanced antigen-delivery capacities and immunogenic properties (Briquez, Hauert et al. 2020, Xi, Ye et al. 2020). Similarly, targeted delivery of immunostimulating cytokines and co-stimulatory molecules have been improved by encoding their sequence in nucleic acid vectors, where several components can be expressed simultaneously together with sequences for (neo)antigens. The latter has already been successfully applied in Phase II trial with stage III or IV unresectable melanoma patients, investigating an mRNA-based cancer vaccine encoding three immunomodulating molecules (CD40L, CD40, and TLR-4) and four melanoma antigens (tyrosinase, gp100, MAGE-A3, and MAGE-C2), electroporated into DCs (De Keersmaecker, Claerhout et al. 2020).

Combination with immune checkpoint inhibitors

Despite the efforts to improve efficacy, monotherapy with cancer vaccines has rarely been curative thus far. The increasing understanding of the mechanisms underlying different immunomodulatory drugs allows for rational combination of cancer vaccines with other treatment modalities.

To fully uncover the potential of combination therapies, cancer vaccines should be complementary and / or synergistic to existing types of (immuno-) therapy, such as immune checkpoint inhibitors (Zhao, Chen et al. 2019). Examples supporting the concept include impressive results from a Phase Ib clinical trial combining the oncolytic virus T-VEC with anti-programmed cell death protein (PD)-1 therapy, showing 62% overall response to combination therapy in comparison to 33% of anti-PD-1 treatment alone in patients with advanced melanoma (Ribas, Dummer et al. 2017). A more recent study using the combination of T-VEC and the anti-PD-1 antibody demonstrated that this approach can yield effective anti-tumor responses in patients with advanced and metastatic sarcoma, who have very limited treatment options (the overall objective response rate reached in the study was 35%) (Kelly, Antonescu et al. 2020). Importantly, in both studies, the combination therapy was associated with a manageable safety profile (10% and 20% of grade 3 treatment-related toxicity, respectively) (Ribas, Dummer et al. 2017, Kelly, Antonescu et al. 2020). An important factor in combining a cancer vaccine and an immune checkpoint inhibitor, is the right timing and context of treatment administration (J Clin Oncol 38: 2020 (suppl; abstract 2514). Tumors that are already infiltrated with CD8 T cells (so-called ‘hot’ tumors), with high mutational burden and related presence of neoantigens may (partially) benefit from immune checkpoint inhibitor monotherapy and addition of cancer vaccine would further boost the existing immune responses. However, patients with low immunogenic tumors (so-called ‘cold’ tumors) constitute a therapeutically challenging group, not responding to immune checkpoint inhibitors; in these patients, cancer vaccines may induce T cell infiltration, synergizing with concomitant or sequential treatment with an immune checkpoint inhibitor (Nisis, D., A new wave of cancer vaccines, ASCO 2020).

Such combination strategies have been applied in clinical trials, also in tumors with a low inherent immunogenic profile, such as glioblastoma (NCT03491683, J Clin Oncol 38: 2020 suppl; abstract 2514) or ovarian cancer (NCT03073525; J Clin Oncol 38: 2020 suppl; abstract 3002).

Conclusions and future perspectives

Unlike prophylactic vaccines against oncoviruses that have been successfully implemented in the clinic, such as vaccines against human papillomavirus (HPV) or hepatitis B virus (HBV), therapeutic cancer vaccines remain to prove their clinical potential. The reasons for the discrepancy between the concept and promising preclinical data, and their limited effect in the clinical setting can possibly be contributed to suboptimal choices made for different components of a vaccine and / or their combination. Such choices may result in low immunogenicity of these therapeutic vaccines and an inappropriate type of immune response (tolerance versus anti-tumor). Our increasing knowledge of tumor immunobiology and related requirements for inducing anti-tumor immune response against tumor antigens has been recently translated into novel approaches aiming to overcome previous limitations. Such approaches include e.g. selection of antigens based on their potential specificity for the tumor tissue and their immunogenicity, leading to the generation of personalized anti-cancer vaccines, and utilization of vectors, such as nucleic acids, which allow for delivering several (neo)antigens and potentially also adjuvants. Our analysis of the current developmental and clinical landscape showed regained interest in the concept of cancer vaccination. The results of ongoing trials are anticipated to confirm the potential of cancer vaccines to become established contributors to current cancer immunotherapies.

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Short author biography

Katka Franke, PhD, has more than 10 years' experience in the field of Immunology/Immuno-Oncology. After completing her PhD in Immunology at Vrije University in Amsterdam, she worked as junior-, and later as senior postdoctoral scientist at Sanquin Research in Amsterdam, where she coordinated and participated in several academic and industrial projects in the field of cancer immunotherapy. As consultant at CATO SMS, she is responsible for providing expert (immuno-)oncology advice and assists sponsors to shape their drug/clinical development plans, assuring successful launch of their product into the clinic. Email: katka.franke@cato-sms.com

Inka Pawlitzky, PhD, has over 12 years of oncology translational and drug development experience and heads the Oncology Drug Development Affairs team at CATO SMS. An immunologist by training (PhD Tufts Medical School, Boston), she completed postdoctoral fellowships (Max Planck Institute for Immunobiology and Epigenetics, and Netherlands Cancer Institute) investigating the regulation of DNA rearrangements and pluripotency mechanisms in tumorigenesis. As senior scientist at Leica Biosystems she gained expertise in companion diagnostics. Since 2017, Inka is responsible for providing expert consultancy services for innovative cancer therapies in terms of drug and clinical development planning and regulatory strategies, with particular emphasis on emerging immunotherapies. Email: inka.pawlitzky@cato-sms.com