# Therapeutic cancer vaccines for pediatric malignancies: advances, challenges, and emerging technologies

**Hannah E. Olsen, Geoffrey M. Lynn, Pablo A. Valdes, Christian D. Cerecedo Lopez, Andrew S. Ishizuka, Omar Arnaout[©], W. Linda Bi, Pier Paolo Peruzzi, E. Antonio Chiocca, Gregory K. Friedman[†], and Joshua D. Bernstock[†©]**

*Department of Neurosurgery, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA (H.E.O., P.A.V., C.D.C.L., O.A., W.L.B., P.P.P., E.A.C., J.D.B.); Avidea Technologies, Inc., Baltimore, Maryland, USA (G.M.L., A.S.I., J.D.B.); Department of Neurosurgery, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts, USA (P.A.V., J.D.B.); Division of Pediatric Hematology and Oncology, Department of Pediatrics, University of Alabama at Birmingham, Birmingham, Alabama, USA (G.K.F.); Department of Neurosurgery, University of Alabama at Birmingham, Birmingham, Alabama, USA (G.K.F.)*

[†]*These authors jointly supervised this work.*

**Corresponding Author:** Joshua D. Bernstock, MD, PhD, MPH, Department of Neurosurgery, Harvard Medical School, Brigham and Women's Hospital, Boston Children's Hospital Hale Building, 60 Fenwood Road, Boston, MA 02115, USA (jbernstock@bwh.harvard.edu).

## Abstract

Though outcomes for pediatric cancer patients have significantly improved over the past several decades, too many children still experience poor outcomes and survivors suffer lifelong, debilitating late effects after conventional chemotherapy, radiation, and surgical treatment. Consequently, there has been a renewed focus on developing novel targeted therapies to improve survival outcomes. Cancer vaccines are a promising type of immunotherapy that leverage the immune system to mediate targeted, tumor-specific killing through recognition of tumor antigens, thereby minimizing off-target toxicity. As such, cancer vaccines are orthogonal to conventional cancer treatments and can therefore be used alone or in combination with other therapeutic modalities to maximize efficacy. To date, cancer vaccination has remained largely understudied in the pediatric population. In this review, we discuss the different types of tumor antigens and vaccine technologies (dendritic cells, peptides, nucleic acids, and viral vectors) evaluated in clinical trials, with a focus on those used in children. We conclude with perspectives on how advances in combination therapies, tumor antigen (eg, neoantigen) selection, and vaccine platform optimization can be translated into clinical practice to improve outcomes for children with cancer.

Cancer continues to be a major cause of morbidity and mortality in children and is the second leading cause of death before adolescence.[1] The prognosis of pediatric cancer has markedly improved in recent years, with the average overall survival (OS) of pediatric cancers rising from 58% in 1975 to 83% in 2014.[2] Therapies for pediatric cancer, however, often cause significant toxicity that leads to lifelong disability.[3,4] Additionally, many children will develop aggressive malignancies refractory to maximal medical and surgical management and ultimately experience dismal outcomes.[5] Central nervous system (CNS) malignancies are among the most aggressive of pediatric cancers and are notoriously difficult to manage.[6,7] Decades of research into tumor biology and clinical studies evaluating chemotherapy, radiation, and surgical resection-based approaches have had limited success in improving survival outcomes.[6,8] The current standard of care for pediatric high-grade gliomas (HGGs), which represent approximately 10% of all pediatric CNS tumors, comprises surgical resection followed by concomitant radiotherapy and chemotherapy (ie, temozolomide) with a median OS of 10–18 months.[9–11] Highly

targeted agents with more favorable toxicity profiles and improved therapeutic efficacy are urgently needed to improve the quality of life and long-term outcomes of children with cancer.[12]

Immunotherapy harnesses the ability of the immune system to combat infection and neoplasia and has emerged as a promising treatment modality for many pediatric and adult malignancies.[12,13] Cancer immunotherapy can be broadly defined as any therapy that leverages autologous or engineered immune cells to mediate tumor killing and, as such, encompasses a variety of treatments with diverse compositions and mechanisms of action.[14,15] Examples of successful immunotherapies include antibodies that block immunosuppressive pathways, such as pembrolizumab, a PD-1 immune checkpoint inhibitor that has gained approval for treating a myriad of solid tumors; talimogene laherparepvec, an oncolytic virus approved for treating melanoma; and, more recently, tisagenlecleucel—a chimeric antigen receptor (CAR) T-cell therapy approved for treating pediatric acute lymphoblastic leukemia.[16–18]

Our understanding of tumor immunology has grown in tandem with technical improvements in vaccine development, leading to a renewed focus on vaccination as cancer therapeutic.[15,19–21] Prophylactic vaccination against microorganisms (eg, smallpox, polio, and influenza) is a highly effective method of preventing life-threatening infections.[22] Vaccination relies on exposing patients to the target microorganism or a structural fragment (ie, antigen) to generate an immune response that protects against future infection.[23] Similarly, therapeutic cancer vaccines can induce immune cells, particularly cytotoxic CD8+ T cells, to become activated, expanded, and licensed to mediate tumor-specific killing through recognition of tumor antigens.[24] As tumor cells demonstrate much greater homology with healthy tissue than infectious microorganisms, the crux of successful cancer vaccine construction lies in safeguarding healthy tissue while inducing targeted immunity against tumor antigens preferentially expressed by tumor cells.[20,21]

Tumor antigen selection is critical to the success of any cancer vaccine. The tumor antigen should be highly expressed and have a high affinity for binding major histocompatibility complex (MHC) molecules, which are key factors for ensuring that the antigen is adequately presented to enable immune cell recognition and killing.[25,26] Additionally, the length and number of antigens must be considered to maximize the breadth of both CD8+ and CD4+ T-cell responses, which each have unique requirements for antigen recognition: CD8+ T cells recognize peptides of 8–11 amino acids in length presented in MHC-I, whereas CD4+ T cells recognize peptides of 12–15 amino acids in length bound to MHC-II.[27,28] Several different classes of tumor antigens exist that can meet these criteria. Here we discuss the unique advantages and challenges associated with each class of tumor antigens.

Tumor-associated antigens (TAAs) are native proteins that are quantitatively overexpressed by tumor cells.[20,29] The advantage of TAAs is that they tend to be upregulated (ie, highly expressed) by certain tumor types and are thus conserved targets for vaccination.[29] Though the majority of vaccine studies have evaluated TAAs, this class of antigen faces a number of limitations. A key challenge is that TAA-reactive T cells can be removed by central tolerance, leaving only T cells with low affinity for tumor antigen recognition.[30] Additionally, there is a possible risk of damage to healthy tissue; although off-target toxicity has not yet been reported in vaccine studies, CAR T cells targeting certain TAAs have resulted in severe, dose-limiting toxicities.[31,32]

In contrast to TAAs, tumor-specific antigens (TSAs)—also known as neoantigens, are non-autologous proteins (ie, mutated proteins) arising from tumoral genetic instability.[33] TSAs provide the advantages that they are not expressed by healthy cells and are not subject to central tolerance. As compared with TAAs, TSAs generate more targeted and higher affinity T cells, thus providing potentially more effective treatment with a lower risk of autoimmunity.[34] While several hotspot mutations have been identified leading to commonly occurring TSAs for certain tumor types[35,36] as well as shared frameshift mutations occurring in microsatellite unstable tumors,[37] most TSAs are highly variant between individuals.[38,39] Thus, off-the-shelf approaches for targeting TSAs may not be practical for most patients and will instead require patient-specific identification and selection of TSAs for use in personalized cancer vaccines.[40,41] Fortunately, with the advent and increasing availability of high-throughput molecular and genomic profiling, TSAs have become practicable targets for cancer vaccination.[42,43]

The feasibility and safety of TSA-directed vaccination have been demonstrated in adult melanoma trials in which a TSA-directed vaccine alone or in conjunction with checkpoint blockade therapy yielded a robust clinical response.[44] Importantly, TSA-directed vaccination has also shown some efficacy against glioblastoma (GBM), despite this tumor's relatively low mutation load and immune-privileged environment.[45,46] Thus, these early trials provide compelling support for the use of TSA-directed vaccination in the pediatric cancer population, particularly for treating CNS malignancies.

In this review, we discuss the different classes of cancer vaccines and antigen targets while emphasizing their application in pediatric oncology. Vaccine classes are divided according to their composition and include cellular[47] (eg, dendritic cells[48]), peptide,[49] nucleic acid[50] (DNA or RNA), and viral vector-based.[15,51] Each has unique advantages and drawbacks as summarized in Table 1. As the majority of vaccination studies have been performed in adults, the utility and efficacy of this approach for pediatric malignancies, which can differ markedly from their adult counterparts in terms of molecular characteristics, histology, mutational burden, and neoantigen profile, has yet to be determined.[52–54] We provide an overview of past and current challenges faced in vaccine development and conclude by highlighting emerging technologies that overcome historic challenges and therefore have greater promise for treating childhood malignancies.

**Table 1.** A Focused Comparison of the Different Classes of Cancer Vaccinations

| Vaccination Class | Advantages | Disadvantages |
|---|---|---|
| Dendritic cell (DC) | • Clinical efficacy established (eg, Sipuleucel-T)<br>• Greater control over DC activation and phenotype through ex vivo manipulation | • High cost, labor-intensive manufacturing to process patient samples ex vivo |
| Peptide | • Synthetic and rapidly manufacturable using automated equipment<br>• Most modular, enabling immune programming through adjuvant selection<br>• Low toxicity, low risk for biocontamination | • Weakly immunogenic unless adequately formulated with immunostimulant (adjuvant) in nanoparticles<br>• Limited number of antigens compared with nucleic acid and viral approaches |
| Nucleic acid (DNA/RNA) | • Rapid manufacturing using primarily automated equipment<br>• RNA has inherent innate immune (adjuvant) activity, shown to lead to robust T-cell responses | • DNA weakly induces T-cell immunity<br>• T-cell responses with RNA have been variable and depend on delivery platform and route of injection |
| Viral vectors | • Most potent vaccines for inducing T-cell immunity<br>• Viruses with large genomes can accommodate many antigens and other encoded therapies | • Anti-vector immunity limits the number of injections that can be given to patients<br>• Use of cell-based expression systems leads to higher costs, potential biocontaminants |

## Vaccination Types

### Dendritic Cell Vaccines

Dendritic cells (DCs) are "professional" antigen-presenting cells (APCs) that are specialized for processing and presenting antigens for priming CD4+ and CD8+ T cells and producing cytokines that drive expansion and differentiation of T-cell responses.[55] Thus, DCs act as a bridge between innate and adaptive immunity.[20,56,57] For use as cellular vaccines, autologous DCs are isolated via apheresis, matured using immunostimulatory agents (eg, filgrastim), and loaded with an antigen before reinjection into the patient via the intradermal, intravenous, intranodal, or subcutaneous route.[58,59] The advantage of isolating and manipulating DCs ex vivo is that antigen loading and activation can be performed under controlled conditions. Advances in gene-editing technologies including viral transduction, RNA interference, and CRISPR/Cas9 have greatly expanded scientists' ability to engineer DCs to optimally perform a host of antitumoral functions.[60] In addition, DC vaccines are often paired with adjuvants, such as imiquimod, interleukin-2, or KLH, which may be provided in the DC cultures or concomitantly delivered to increase the magnitude and duration of the antitumor response.[61] Limitations of DC-based vaccines include the labor-intensive and costly cell isolation/enrichment and ex vivo stimulation process[62], potentially weak responses due to insufficient cell numbers or inadequate cell activation or phenotype; and/or T-cell inactivation from an immunosuppressive tumor environment.[63] Despite these challenges, it is notable that the first cancer vaccine to receive Food and Drug Administration approval is the DC vaccine sipuleucel-T (Provenge) for prostate cancer.[64]

Based on data from phase I/II trials, DC-based vaccination appears to be well tolerated with minimal toxicity in children with a diverse spectrum of malignancies and pretreatment conditions.[57,65–67] Table 2 provides a summary of DC-based vaccine trials in children. Of note, most of these trials used autologous whole tumor lysate as antigenic material. Despite the non-randomized format of early-phase safety studies, several pediatric trials of DC-based vaccines have reported improvement in clinical outcomes, albeit transient, which directly correlated with the degree of cytotoxic T lymphocyte (CTL) response as compared to historical controls. However, it should be noted that all patients eventually progressed on therapy. A phase II trial investigating an autologous tumor lysate-pulsed DC vaccine in children with metastatic or relapsed sarcomas demonstrated a 12% increase in OS in the DC-based vaccine group compared to children receiving standard of care chemotherapy. Five-year OS of patients in the Ewing sarcoma/rhabdomyosarcoma subgroup was an unprecedented 77%[68] compared with 30–50% as per historical controls.[69–71] Infusion of autologous DCs and CTLs has also been shown to eradicate the minimal residual disease in children with acute myeloid leukemia following chemotherapy.[72] A study evaluating an autologous tumor lysate-pulsed DC vaccine in 45 children with relapsed malignant brain tumors demonstrated efficacy.[57] Median OS for relapsed HGG, GBM, and anaplastic astrocytoma patients was 13.5, 12.2, and 18.4 months, respectively, with the authors noting that HGG and atypical teratoid–rhabdoid tumor appeared to respond more favorably as compared to medulloblastoma/primitive neuro-ectodermal tumor and ependymoma. A follow-up phase IIb trial is currently ongoing (EudraCT 2009-018228-14). Benitez-Ribas recently performed a phase I study of a DC vaccine pulsed with autologous tumor cell-lines lysate as the antigen administered intradermally with KLH as the adjuvant, which is used as a source of CD4+ T-cell (helper) epitopes to augment the response, in 9 patients with newly diagnosed diffuse midline glioma (DMG) (formerly termed "diffuse intrinsic pontine glioma" or "DIPG"), a highly aggressive and universally fatal subgroup of pediatric HGG.[73] A specific antitumor response was observed in 8 patients as identified by immunologic studies in peripheral blood mononuclear cells. Cerebrospinal fluid (CSF) analyses showed anti-DMG specific T lymphocytes in 2 patients. Though the

**Table 2.**  Trials of DC-Based Vaccines in Pediatric Patients

| NCT | Study Phase | Tumor Type | Vaccine composition | | Outcomes | Reference |
|---|---|---|---|---|---|---|
| | | | Antigen | Adjuvant | | |
| *CNS* | | | | | | |
| n/a | I | Recurrent brain tumors | Autologous RNA-pulsed DCs | None | PR (1/7), SD (2/7) | Caruso et al., 2004[65] |
| n/a | I | Relapsed malignant glioma | Autologous tumor peptide-pulsed DCs | None | RD patients (6): PR (1), SD (1) / CR patients (6): CCR 3 years (2) | Rutkowski et al., 2004[74] |
| n/a | Not specified | Recurrent malignant brain tumors | Autologous whole tumor lysate-pulsed DCs | Imiquimod | OS: HGG: 13.5 m GBM: 12.2 m AA: 18.4 | Ardon et al., 2010[57] |
| NCT00107185 | I | Newly diagnosed or recurrent HGG | Autologous whole tumor lysate-pulsed DCs | None | PR (1/3), SD (2/3) | Lasky et al., 2013[75] |
| NCT02840123 | I | New diagnosed DIPG | Autologous DCs pulsed with allogeneic tumor lysate | None | No data | Benitez-Ribas et al., 2018[73] |
| *Solid tumor* | | | | | | |
| NCT00405327 | II | Relapsed solid tumors | Autologous tumor peptide-pulsed DCs | KLH | PR (1/15), SD (5/15) | Geiger et al., 2001[66] |
| | II | Recurrent alveolar rhabdomyosarcoma and Ewing sarcoma | Autologous tumor peptide (breakpoint region of fusion protein)-pulsed DCs | IL-2 | PD (15/15) | Dagher et al., 2002[76] |
| n/a | Not specified | Advanced solid extra-cranial tumors | Autologous tumor lysate-pulsed DCs | KLH | SC-treated patients (14): - CR patients (5): CCR (4), SD (1) - PR patient (1): PD (1) - PD patients (8): MR (1), SD (1) IN-treated patients (8): - CR patients (4): CCR (3), PD (1) - PD patients (4): PD (4 | Dohnal et al., 2007[77] |
| NCT00001566 | II | Metastatic or recurrent Ewing sarcoma and alveolar rhabdomyosarcoma | Autologous tumor peptide (translocation breakpoint)-pulsed DCs | IL-2 | CR (17/30), PR (11/30), PD (2/30) | Mackall et al., 2008[78] |
| n/a | Not specified | Refractory Ewing sarcoma, synovial sarcoma, neuroblastoma | Autologous tumor lysate-pulsed DCs | KLH | CR (1/5), SD -> PD (2/5), PD (1/5) | Suminoe et al., 2009[79] |
| n/a | I | Relapsed osteosarcoma | Autologous tumor lysate-pulsed DCs | KLH, IL-2 | No evidence of tumor regression | Himoudi et al., 2012[80] |
| NCT01241162 | I | Relapsed/refractory solid tumors neuroblastoma and sarcoma | Autologous tumor peptide (MAGE-A1, MAGE-A3, and NY-ESO-1 derived)-pulsed DCs | Imiquimod | CR (1/10), SD (1/10) | Krishnadas et al., 2015[81] |

**Table 2.** Continued

| NCT | Study Phase | Tumor Type | Vaccine composition — Antigen | Vaccine composition — Adjuvant | Outcomes | Reference |
|---|---|---|---|---|---|---|
| NCT00923351 | I/II | Metastatic and relapsed high-risk sarcomas | Autologous tumor lysate-pulsed DCs | KLH, IL-7 | OS: -Overall 51% -ES/RMS: 63% | Merchant et al., 2016[68] |
| *Hematological* | | | | | | |
| n/a | Not specified | AML | Autologous DCs and cytokine-induced killer cells | IL-2 | CR (20/22), PD (2/22) | Bai et al., 2015[72] |
| n/a | Case report | Relapsed ALL | Allogeneic WT-1-pulsed DCs | OK-432 | Relapse 14 months following treatment | Saito et al., 2015[67] |
| NCT00923910 | I/II | Post-HSCT relapsed ALL, AML, HL | Allogeneic WT-1-pulsed DCs | KLH | PD (5/5) | Shah et al., 2016[82] |

AA, anaplastic astrocytoma; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CNS, central nervous system; CR, complete response; ES, Ewing sarcoma; GBM, glioblastoma multiforme; HGG, high-grade glioma; HL, Hodgkin's lymphoma; HSCT, hematopoietic stem cell transplantation; IN, intranodal; KLH, Keyhole limpet hemocyanin; MR, mixed response; PD, progressive disease; PR, partial response; OS, overall survival; RD, residual disease; RMS, rhabdomyosarcoma; SC, subcutaneous; SD, stable disease; WT-1, Wilms' tumor 1.

authors have not yet reported clinical outcomes data, the vaccine was well tolerated and no dose-limiting toxicities were observed.

In summary, DC-based vaccination appears to be well tolerated and effective for inducing T-cell immunity in pediatric cancers, though additional studies will be needed to fully understand the potential of these therapies for the pediatric population.

## Peptide Vaccines

An alternative to loading DCs with antigenic material ex vivo is to vaccinate patients with peptide antigens that can be processed and presented by endogenous APCs, particularly DCs, that prime T-cell immunity in lymph nodes draining the sites of vaccination.[49] Peptide vaccines generally include one or more synthetic peptides comprising tumor antigens combined with immunostimulants ("adjuvants") that are used to enhance peptide antigen immunogenicity.[83,84] The length of peptide antigens is selected to maximize the breadth of the T-cell response and depends, in part, on the antigenic target. For TSAs, peptide antigens of 25 amino acids in length are typically used wherein the middle (15th amino acid) is the mutant (ie, tumor-specific) residue.[85,86] This length ensures that all 8–11 amino acid CD8+ T-cell epitopes and most 12–15 amino acid CD4+ T-cell epitopes including the mutant amino acid are represented in each sequence. A similar rationale is applied to TAAs, whereby protein antigens greater than 100 amino acids in length are produced as a pool of peptide fragments overlapping by 9–14 amino acids to ensure that most CD4+ and CD8+ T-cell epitopes are represented.[87,88] Finally, to maximize the breadth of T-cell responses, peptide vaccines typically composed of up to 20 unique peptide antigens, which is largely dictated by manufacturing and cost constraints.

Peptide vaccines are advantageous in that they can be produced rapidly, at relatively low cost, entirely by synthetic processes using automated equipment.[89,90] Additionally, peptide vaccines are among the most modular as they, unlike, other vaccine platforms (eg, viruses), have little to no inherent immunostimulatory properties and therefore enable the quality and magnitude of the immune response to be programmed based on the adjuvant(s) used.[91–93] A potential disadvantage of peptide-based vaccines is that they permit a lower antigen payload (~20 peptide antigens each of 25–35 amino acids in length) as compared with recombinant vaccine approaches (eg, viruses and nucleic acids) that can encode multiple protein antigens that are each several hundred amino acids in length.[94] However, more antigens are not necessarily better. The presence of multiple antigens can lead to competition that may diminish the response against any one specific antigen.[20,34] Additionally, T-cell responses directed against a single antigen can mediate durable tumor regression.[95,96] Thus, it is likely that the antigen payload of peptide-based therapeutic cancer vaccines, which typically comprise about 10–20 peptide antigens, is sufficient given appropriate antigen selection.[43,97]

Table 3 provides a summary of peptide-based vaccine trials in children. In the pediatric setting, several

**Table 3.** Trials of Peptide-Based Vaccines in Pediatric Patients

| NCT | Study Phase | Tumor Type | Vaccine Composition | | Outcomes | Reference |
|---|---|---|---|---|---|---|
| | | | Antigen | Adjuvant | | |
| *CNS* | | | | | | |
| NCT01130077 | I | High-risk gliomas | IL-13 receptor alpha 2, EphA2, survivin | Montanide ISA51, poly-ICLC | CR (2/24), PR (2/24), MR (1/24) SD (19/24) | Pollack et al., 2014[102] |
| NCT01130077 | I | Recurrent low-grade gliomas | IL-13 receptor alpha 2, EphA2, survivin | Montanide ISA51, poly-ICLC | PR (4/24), MR (1/24) SD (7/24) | Pollack et al., 2016[103] |
| NCT02960230 | I | DIPG, nonpontine DMG | H3.3K27M | Montanide ISA51, poly-ICLC | OS at 12 months DIPG 44%, nonpontine DMG 39% | Mueller et al., 2020[104] |
| *Solid tumor* | | | | | | |
| n/a | II | Rhabdomyosarcoma, osteosarcoma, liposarcoma, synovial sarcoma | WT-1 | Montanide ISA51 | CR (1/4), SD (1/4), PD (2/4) | Hashii et al., 2010[98] |
| n/a | I/II | Relapsed/refractory solid tumors | WT-1 | Montanide ISA51 | CR (5/9), MR (1/9), SD (1/9), PD (2/9) | Sawada et al., 2016[99] |
| n/a | Not specified | Solid tumors | WT-1 | OK-432 | No data | Hirabayashi et al., 2018[105] |
| n/a | I | Neuroblastoma | NY-ESO-1 | Montanide ISA51 | No data | Camisaschi et al., 2018[106] |
| n/a | I | Refractory solid tumors | KOC1, FOXM1, KIF20A | Incomplete Freund's adjuvant | SD (4/12), MR (2/12), PD (6/12) | Akazawa et al., 2019[107] |
| *Hematological* | | | | | | |
| n/a | II | ALL | WT-1 | Montanide ISA51 | PD (1/1) | Hashii et al., 2010[98] |
| n/a | II | ALL, AML | WT-1 | Montanide ISA51 | CR (2/3), PD (1/3) | Hashii et al., 2012[108] |
| n/a | I/II | ALL, AML, lymphoma | WT-1 | Montanide ISA51 | CR (4/4) | Sawada et al., 2016[99] |

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CNS, central nervous system; CR, complete response; DMG, diffuse midline gliomas; MR, mixed response; PD, progressive disease; poly-ICLC, polyinosinic–polycytidylic acid complexed with polylysine) and carboxymethylcellulose; PR, partial response; OS, overall survival; SD, stable disease; WT, Wilms' tumor 1.

early-phase studies have investigated Wilms' Tumor gene, WT-1, targeted peptide-based vaccines in children with solid and hematologic malignancies. In a study of 5 patients with various malignancies, Hashii et al.[98] found that intradermal vaccination with a single WT-1-derived short (9 amino acid) peptide antigen formulated in a water-in-oil emulsion-based adjuvant, Montanide ISA51, induced complete remission in one patient and a period of stable disease in another patient. However, clinical benefit was limited with 4 patients experiencing disease progression and/or death during the trial. In a larger study of 26 children and young adults less than 20 years old with relapsed solid and hematologic malignancies, no patients demonstrated a clinical response.[99] Limited efficacy with this approach may be due to the use of only a single short (minimal epitope) peptide antigen resulting in limited T-cell breadth, and/or use of an emulsion formulation that lacks immunostimulants (eg, Toll-like receptor agonists [TLRa]) needed for strong T-cell induction[100] and may instead promote T-cell exhaustion.[101]

Additional peptide vaccines targeting conserved tumor antigens have been tested in pediatric clinical studies. Kushner et al.[109] performed a phase I trial in which 15 children with high-risk neuroblastoma were administered a vaccine containing the immunological adjuvant OPT-821 and the neuroblastoma-associated antigens GD2 and GD3. Patients were also given β-glucan, a biologic response modifier that enhances the antitumor response.[110,111] No patients had dose-limiting toxicities and 12 patients demonstrated an antibody response against GD2 and/or GD3. Carcinoembryonic antigen glypican-3 (GPC3), a hepatic heparan sulfate proteoglycan expressed in many pediatric tumors such as hepatoblastoma, yolk-sac tumors, and Wilms' tumors, has also been piloted as a target for vaccination.[112,113] A phase I study of 18 pediatric patients with GPC3-expressing solid tumors found that vaccination with a single MHC-I matched GPC3-peptide formulated in a water-in-oil emulsion improved or maintained clinical status (CR + PR + SD) in 67% of patients,[114] despite using a suboptimal emulsion formulation, as discussed above.

Early peptide vaccine studies in pediatric CNS malignancies have been encouraging. Pollack et al.[102] investigated the safety and performance of a peptide vaccine targeting known glioma-associated antigens (IL-13Rα2, EphA2, and survivin) administered subcutaneously with polyinosinic–polycytidylic acid (poly[I:C]), a TLR-9 agonist, stabilized by poly(lysine) and carboxymethylcellulose (poly-ICLC) adjuvant in 26 children with newly diagnosed brainstem or non-brainstem gliomas. Five children had pseudoprogression, a transient increase in edema, and contrast enhancement secondary to a treatment-induced immune response that was followed by stabilization and/or regression.[115] Patients with pseudoprogression were successfully treated with dexamethasone and had a higher median survival (19.5 months vs 10.9 months). A phase I study of cytomegalovirus (CMV)-specific peptide vaccine in patients with recurrent medulloblastoma and malignant glioma is ongoing (NCT03299309) and is of interest given the noted expression of CMV proteins in such tumors.[116]

Peptide vaccines are also being studied in DMG. Ochs et al.[117] showed that vaccination with peptides derived from H3.3K27M (a unifying oncogenic mutation resulting in global methylation perturbation), and formulated in a water-in-oil emulsion administered subcutaneously, produced an effective, mutation-specific CD4+ and CD8+ T-cell-mediated immune response with antigen presentation on both MHC classes I and II in a humanized mouse model. Although they observed tumor regression in murine models, the experimental design consisted of DMG tumors in the flank rather than intracranially. This vaccine epitope is currently being tested in phase 1 clinical trial in combination with checkpoint inhibitors in children (NCT02960230).

While it is too early to quantify the potential of peptide-based vaccines for pediatric cancers, more advanced trials have been conducted in the adult population. Indeed, several phase III adult solid tumor trials have been conducted and have failed to show any clinical benefit.[118–120] While these results have dampened the initial enthusiasm for peptide-based vaccine approaches, recent mechanistic data suggest that suboptimal formulations may account, in part, for the observed weak efficacy and that formulating peptide antigens in nanoparticles that target endogenous DCs that promote T-cell immunity may be needed to improve efficacy.[121] Additionally, similarly to DC vaccines, peptide vaccines appear to perform optimally in patients with lower disease burden and when administered concomitantly with other treatment modalities like checkpoint inhibitors to allow for synergistic antitumor effects.[122]

In summary, peptide-based cancer vaccines can safely induce anticancer T-cell immunity in pediatric and adult populations; however, further studies are needed to understand how to optimize the composition (eg, delivery vehicle and adjuvant) and combination approaches with complementary therapeutic modalities to maximize T-cell responses and efficacy in children.

## Nucleic Acid Vaccines

Nucleic acid vaccines utilize plasmid DNA or mRNA to express tumor antigens through transient transfection of muscle tissue or APCs (eg, DCs) following administration. Multiple genes can be incorporated into a single vector, and the nucleic acid can be modified to modulate expression and innate stimulation to augment the immune response.[65,123,124] Similar to peptide-based vaccines, nucleic acid vaccines enable lower costs and more rapid manufacturing as compared with cellular or viral vector-based vaccines, but, unlike peptides, still require the use of costly recombinant enzymes for production.[125] While early clinical studies in adult patients showed that DNA vaccines were sufficient in invoking a cellular and humoral immune response, there was little evidence of clinical benefit.[126] Indeed, recent preclinical data suggest that the platform and site of nucleic acid administration are critical to the capacity of such approaches to induce T-cell immunity.[127] Thus, numerous delivery approaches have been developed to improve antigen expression in APCs as a means to improve efficacy through the use of direct intra-lymph node injection, gene gun, electroporation, ultrasound, laser, liposome, microparticles, and/or nanoparticles.[128–131] Among the nucleic acid vaccine approaches, RNA lipoplexes appear to be one of the most promising and have shown the greatest capacity for inducing anticancer T-cell immunity.[127] Though additional optimization will be needed to balance

gene expression with innate stimulation that may lead to systemic toxicity and blunting of antigen expression, early data suggest that RNA-based vaccination approaches may eventually have a great therapeutic impact in pediatric cancers.

### Viral Vector Vaccines

Recombinant viral vectors, typically derived from the *Poxviridae*, *Adenoviridae*, and *Rhabdoviridae* families, are engineered to express tumor antigen transgenes and are among the most potent vaccine technologies for inducing T-cell immunity.[132–134] Viral vectors provide the advantages that they can encode a large number of antigens that can be expressed at high levels and rendered immunogenic through intrinsic innate immunostimulatory capacity of the virus. Viral vectors can be further engineered to maximize gene expression, target specific cell populations, and/or encode multiple additional therapeutic modalities.[135] Though viral vectors are easier to produce, purify, and store relative to more costly and labor-intensive cellular vaccines, like DC vaccines,[136] their dependence on recombinant technologies can result in higher costs than synthetic peptide-based vaccine approaches, and antibodies generated against the vector (antivector immunity) can limit their use to a single administration.[137]

PROSTVAC, a well-studied poxviral-based vaccine targeting prostate-specific antigen that also contains transgenes for T-cell co-stimulatory molecule expression, showed promise in an early-phase II double-blind randomized trial in metastatic castration-resistant prostate cancer; however, results from the subsequent phase III trial failed to show any survival improvement over placebo.[138,139] PROSTVAC in combination with the anti-CTLA-4 checkpoint inhibitor, ipilimumab, for metastatic castration-resistant prostate cancer has been proven safe in a phase I trial[140] and is currently being assessed in a randomized phase II trial (NCT02933255).

The vaccine TG4010, a modified vaccinia Ankara vector expressing MUC1 and IL-2, has been evaluated in combination with first-line chemotherapy for the treatment of patients with advanced-stage non-small-cell lung cancer and was found to improve progression-free survival at 6 months.[141] Though there are no current ongoing clinical trials, there are promising preclinical data to suggest that viral-based vaccines may be effective in brain tumors. Abdelaziz et al.[142] designed human cytomegalovirus (HCMV)-based vaccine expressing E6-derived peptide fused to HCMV proteins. Patient-derived GBM cells infected with these vectors efficiently stimulated E6-specific T cells. Additionally, a phase I dose escalation evaluating the safety of aglatimagene besadenovec (AdV-tk), an adenoviral vector expressing herpes virus thymidine kinase, followed by anti-herpetic prodrug in pediatric malignant glioma or recurrent ependymoma found the approach to be safe in combination with radiation therapy and temozolomide[143]; a subsequent phase II study is planned.

## Combination Immunotherapy

Therapeutic cancer vaccines principally mediate tumor clearance through the induction of cytotoxic T cells. However, cancers can evade T-cell recognition and killing by promoting an immunosuppressive environment, including through the expression of immune checkpoint molecules (eg, PD-L1) that directly inhibit T-cell killing. To overcome the immunosuppressive environment of tumors, vaccines that induce T-cell immunity should be used in combination with complementary therapies that reverse immune suppression. Indeed, many groups are starting to explore the potential of a combinatorial approach using vaccination to enhance the efficacy of other immunotherapy-based treatment modalities including checkpoint inhibitors, antiangiogenic agents, oncolytic viruses, and radiation.[19,144]

One of the most promising combination immunotherapies is the use of cancer vaccines with checkpoint inhibitors (eg, anti-PD-1/PD-L1 and anti-CTLA-4). Myriad preclinical studies have shown that cancer vaccines used in combination with checkpoint inhibitors lead to significantly improved efficacy as compared with either treatment used alone,[145] and now multiple clinical trials are ongoing evaluating this combination in patients.[19] Among the most promising studies thus far, a phase I trial found that a GM-CSF cell-based vaccine ("GVAX") in combination with ipilimumab, an anti-CTLA-4 antibody, enhanced the preexisting endogenous tumor-specific T-cell response compared to treatment with ipilimumab alone. Posttreatment expansion of the mesothelin-specific T-cell repertoire was associated with a significant improvement in OS in the combination arm, suggesting that the frequency of preexisting mesothelin-specific T cells are low and require a vaccine to induce larger pools of precursor T-cells.[146]

The use of viruses to modulate the tumor microenvironment and provide a more permissive environment for T-cell killing is another promising strategy that is gaining increasing attention. Accordingly, Koske et al.[147] demonstrated that combination treatment of Vesicular Stomatitis Virus-glycoprotein (VSV-GP), a chimeric VSV pseudotyped with GP of the lymphocytic choriomeningitis virus, followed by an ovalbumin peptide-loaded DC vaccine, significantly enhanced survival over either agent alone in a murine melanoma model. The authors found that this strategy alleviated local immune suppression in the tumor microenvironment by reducing regulatory T cells, activating tumor-infiltrating lymphocytes, and increasing inflammatory cytokines.

Though most combinatorial approaches have been tested in adults, there are a number of ongoing trials in the pediatric setting. A phase I trial using GVAX in combination with nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) for refractory neuroblastoma is ongoing (NCT04239040). Krishnadas et al. reported complete remission in a patient with relapsed stage 4 neuroblastoma after treatment with decitabine to upregulate cancer testis antigen expression,

followed by DC vaccine targeting the cancer testis antigens MAGE-A1, MAGE-A3, and NY-ESO. Additional phase I studies are underway to evaluate concomitant vaccination and radiation for pediatric HGG (NCT03615404, NCT02722512, and NCT00634231).

## Challenges and Emerging Technologies

While a variety of cancer vaccines have been evaluated in adult and pediatric patients, most have provided only modest efficacy. The shortcomings of prior vaccines may be in part due to weak immunogenicity of the vaccine leading to insufficient magnitude of CD8+ T-cell responses; inadequate, or loss, of expression of the tumor antigen, thereby enabling tumor cells to evade recognition; and/or, inability of vaccine-induced T cells to overcome the suppressive tumor microenvironment.[15,20,148] Recent advances in tumor antigen identification and selection algorithms are enabling more reliable antigen selection, and checkpoint inhibitors have proven effective for unleashing T cells to mediate tumor-specific killing. A key challenge remains the availability of vaccine technologies for reliably inducing high-magnitude CD8+ T-cell responses that correlate with immunotherapy efficacy.[15,20,148] Indeed, patients treated with a peptide-based vaccine comprising peptide neoantigens admixed with the immunostimulant polyICLC (Hiltonol) experienced limited benefit from therapy despite promising preclinical data.[85] Weak efficacy may be, in part, attributed to inadequate formulation of the peptide neoantigens (see below), though limitations in neoantigen prediction and selection cannot be ruled out as their validation is not possible in the absence of clear vaccine-mediated efficacy.

Toward improving peptide-based vaccine formulations for inducing CD8+ T-cell immunity, Lynn et al.[121] developed a vaccine platform based on peptide antigen–TLRa conjugates that are programmed to self-assemble into nanoparticles of an optimal size (~20 nm) for targeting lymph node resident DCs that promote T-cell immunity. Programmed self-assembly was developed to ensure formulation consistency for all possible antigens that can be generated from the human genome, thus enabling a universal approach for formulating tumor antigens. Importantly, improved formulation of tumor antigens, including neoantigens, with TLRa in self-assembling nanoparticles promoted improved uptake by and activation of APCs (eg, DCs) that was associated with enhanced immunogenicity and improved tumor clearance in 3 murine tumor models.[121] They also found that peptide physical form is a key determinant of CD8+ T-cell immunogenicity.

Specifically, they showed that hydrophilic, water-soluble peptide antigens are often non-immunogenic even when combined with potent immunostimulants, such as polyICLC, but that rendering such peptide antigens particulate significantly improves immunogenicity.[121] These data suggest that codelivery of peptide antigens with specific immunostimulants in nanoparticles will be key to the success of peptide-based cancer vaccines and

that self-assembling nanoparticles (eg, SNP-7/8a) offer an effective platform for achieving consistent nanoparticle formulations needed for reliable induction of CD8+ T cells.

Another promising peptide-based vaccine approach for ensuring codelivery of tumor antigens and immunostimulants in nanoparticles for inducing T-cell immunity is the use of synthetic high-density lipoprotein nanodiscs, which can be coupled with immunostimulatory CpG oligonucleotides and tumor antigen peptides. Kuai et al.[149] recently reported that the use of this nanocarrier technology in a murine colon adenocarcinoma model generated a robust neoantigen-specific CD8+ T-cell response resulting in complete inhibition of tumor growth; additionally, concomitant vaccination with dual PD-1 and CTLA-4 blockade led to complete tumor regression in approximately 90% of mice.

Though many next-generation vaccine technologies have been focused on solid tumors, innovation in biomaterials science has also made considerable progress in the setting of hematologic malignancies. Shah et al.[150] developed a macroporous cryogel composed of cross-linked polyethylene glycol and alginate scaffolding with entrapped TLR-9a cytosine–guanosine oligodeoxynucleotide and GM-CSF immunostimulants. Prophylactic administration of this vaccine with either WT-1 antigen or tumor cell lysate in a mouse model of AML elicited a potent CTL response and prevented engraftment of malignant cells in the bone marrow. Combinatorial administration of the vaccine with standard chemotherapeutic agents eradicated established AML and generated transferable protective T-cell immunity.

In addition to the type of vaccine used, the route of administration and vaccine schedule will likely require optimization in the clinical setting to achieve maximal benefit for patients. Accordingly, while most vaccines are administered by the intramuscular or subcutaneous routes, mounting evidence suggests that vaccination by the intravenous route may be favorable for promoting T-cell-mediated immunity independent of the vaccination platform used.[127,151]

A final consideration is how to integrate cancer vaccines into a complex treatment regimen comprising chemotherapy, radiotherapy, and immunotherapy, which may not always have synergistic effects. Indeed, many cancer patients require corticosteroid therapy at different points throughout treatment for various reasons (eg, tumor/treatment-related edema, pain relief, appetite stimulation).[152] However, there is growing evidence to suggest that the immunosuppressive nature of these drugs, due in large part to their effects on T-cell apoptosis, may reduce the efficacy of therapeutic approaches that rely on stimulating a robust anticancer immune response.[153,154] Wong et al.[155] found that dexamethasone treatment in adult patients with recurrent GBM profoundly decreased the efficacy of radiation and chemotherapy, leading to lower OS. Pitter et al.[156] found similar results in a retrospective analysis of GBM patient cohorts, which showed dexamethasone-induced antiproliferative effects conferred protection from radiotherapy- and chemotherapy-induced genotoxic stress. In a phase I study of H3.3K27M peptide vaccination in pediatric patients with DMG and DIPG, Mueller et al.[104] found

a negative association between dexamethasone administration and the longitudinal expansion of vaccine-reactive CD8^{+} T cells. Though, while immunosuppressive chemotherapy agents can have deleterious effects on cancer vaccine efficacy, certain chemotherapy regimens, particularly those that promote immunogenic cell death or selective depletion of suppressor cells (eg, regulatory T cells or myeloid-derived suppressor cells), have been shown to enhance vaccine efficacy.[157,158] Therefore, further research will be needed to fully delineate the impact and optimal regimen of chemotherapies, including corticosteroids, on cancer vaccination efficacy.

## Conclusions

The ability of checkpoint inhibitors and adoptive cell therapies to mediate durable regression of certain advanced cancers provides clinical proof-of-concept that tumor antigen-specific T cells can mediate tumor clearance and improve patient outcomes. These observations have fueled a resurgence in efforts to advance therapeutic cancer vaccines for priming and/or expanding tumor antigen-specific T-cell responses in patients for use alone or in combination with other therapies. Despite their immense promise, however, therapeutic cancer vaccines have only shown modest benefit in a small cohort of primarily adult patients in early-stage trials. While many challenges remain, the emergence of improved vaccine technologies for inducing T-cell immunity, as well as refined tools for tumor antigen selection, provide optimism that next-generation therapeutic cancer vaccines may effectively overcome historic limitations. Additionally, combination immunotherapies, including vaccines combined with checkpoint inhibitors, oncolytic viruses, certain chemotherapeutics,[159] and/or radiation, are emerging as effective approaches for reversing immune suppression within the tumor and augmenting vaccine efficacy.

Finally, it should be noted that vaccines and other immunotherapies that are safe but fail to demonstrate efficacy in adults with advanced cancers should not be ruled out for evaluation in pediatric populations. Adults are less responsive to vaccines due to thymic atrophy, whereas younger patients are more responsive to immunotherapies and are therefore more likely to mount an effective T-cell response to therapeutic cancer vaccines. Despite this general recognition, most novel immunotherapies are evaluated in adult populations, and treatments that fail in adults are often not advanced to testing in children. However, the small number of early-phase studies that have been conducted with pediatric patients has shown great promise in terms of safety, feasibility, and ability to generate an immunologic response. Though objective clinical response rates are low, advances in antigen design, adjuvant therapy, and combinatorial approaches may drastically change the landscape of immunotherapy in pediatric cancer.

In summary, given the tremendous potential of therapeutic cancer vaccines and their higher likelihood of success in pediatric populations, cancer vaccines and combination therapies should be rigorously investigated as potentially life-saving treatments for children with advanced malignancies refractory to conventional approaches.

## Keywords

checkpoint inhibitors | experimental therapeutics | immunotherapy | pediatric cancer | vaccination

**Conflicts of interest statement.** G.M.L. and A.S.I. are listed as inventors on patents describing polymer-based vaccines. G.M.L., J.D.B., and A.S.I. are employees/consultants of Avidea Technologies, Inc., which is commercializing polymer-based drug delivery technologies for immunotherapeutic applications. J.D.B. has an equity position in Treovir LLC and is a member of the POCKiT Diagnostics Board of Scientific Advisors.

## References

1. Murphy SL, Xu J, Kochanek KD, Arias E. Mortality in the United States, 2017. *NCHS Data Brief*. 2018 (328):1–8.

2. Jemal A, Ward EM, Johnson CJ, et al. Annual report to the nation on the status of cancer, 1975–2014, featuring survival. *J Natl Cancer Inst*. 2017;109(9):1–22.

3. Diller L, Chow EJ, Gurney JG, et al. Chronic disease in the childhood cancer survivor study cohort: a review of published findings. *J Clin Oncol*. 2009;27(14):2339–2355.

4. Bhattacharya D, Pomeroy SL, Pomeranz Krummel DA, Sengupta S. Epigenetics and survivorship in pediatric brain tumor patients. *J Neurooncol*. 2020;150(1):77–83.

5. Smith MA, Seibel NL, Altekruse SF, et al. Outcomes for children and adolescents with cancer: challenges for the twenty-first century. *J Clin Oncol*. 2010;28(15):2625–2634.

6. Karajannis M, Allen JC, Newcomb EW. Treatment of pediatric brain tumors. *J Cell Physiol*. 2008;217(3):584–589.

7. Gajjar A, Pfister SM, Taylor MD, Gilbertson RJ. Molecular insights into pediatric brain tumors have the potential to transform therapy. *Clin Cancer Res*. 2014;20(22):5630–5640.

8. Turner CD, Rey-Casserly C, Liptak CC, Chordas C. Late effects of therapy for pediatric brain tumor survivors. *J Child Neurol.* 2009;24(11):1455–1463.

9. Cohen KJ, Pollack IF, Zhou T, et al. Temozolomide in the treatment of high-grade gliomas in children: a report from the Children's Oncology Group. *Neuro Oncol.* 2011;13(3):317–323.

10. Jakacki RI, Cohen KJ, Buxton A, et al. Phase 2 study of concurrent radiotherapy and temozolomide followed by temozolomide and lomustine in the treatment of children with high-grade glioma: a report of the Children's Oncology Group ACNS0423 study. *Neuro Oncol.* 2016;18(10):1442–1450.

11. Guerra-García P, Marshall LV, Cockle JV, et al. Challenging the indiscriminate use of temozolomide in pediatric high-grade gliomas: a review of past, current, and emerging therapies. *Pediatr Blood Cancer.* 2020;67(1):e28011.

12. Foster JB, Madsen PJ, Hegde M, et al. Immunotherapy for pediatric brain tumors: past and present. *Neuro Oncol.* 2019;21(10):1226–1238.

13. Ring EK, Markert JM, Gillespie GY, Friedman GK. Checkpoint proteins in pediatric brain and extracranial solid tumors: opportunities for immunotherapy. *Clin Cancer Res.* 2017;23(2):342–350.

14. Zhang H, Chen J. Current status and future directions of cancer immunotherapy. *J Cancer.* 2018;9(10):1773–1781.

15. Wang SS, Bandopadhayay P, Jenkins MR. Towards immunotherapy for pediatric brain tumors. *Trends Immunol.* 2019;40(8):748–761.

16. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med.* 2018;379(21):2040–2051.

17. Andtbacka RH, Ross M, Puzanov I, et al. Patterns of clinical response with talimogene laherparepvec (T-VEC) in patients with melanoma treated in the OPTiM Phase III clinical trial. *Ann Surg Oncol.* 2016;23(13):4169–4177.

18. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med.* 2017;377(26):2531–2544.

19. Mougel A, Terme M, Tanchot C. Therapeutic cancer vaccine and combinations with antiangiogenic therapies and immune checkpoint blockade. *Front Immunol.* 2019;10:467.

20. Sampson JH, Mitchell DA. Vaccination strategies for neuro-oncology. *Neuro Oncol.* 2015;17(suppl 7):vii15–vii25.

21. Hollingsworth RE, Jansen K. Turning the corner on therapeutic cancer vaccines. *NPJ Vaccines.* 2019;4:7.

22. Plotkin SA. Correlates of protection induced by vaccination. *Clin Vaccine Immunol.* 2010;17(7):1055–1065.

23. Pulendran B, Ahmed R. Immunological mechanisms of vaccination. *Nat Immunol.* 2011;12(6):509–517.

24. Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. *Immunity.* 2013;39(1):1–10.

25. Abelin JG, Keskin DB, Sarkizova S, et al. Mass spectrometry profiling of HLA-associated peptidomes in mono-allelic cells enables more accurate epitope prediction. *Immunity.* 2017;46(2):315–326.

26. McGranahan N, Furness AJ, Rosenthal R, et al. Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade. *Science.* 2016;351(6280):1463–1469.

27. Comber JD, Philip R. MHC class I antigen presentation and implications for developing a new generation of therapeutic vaccines. *Ther Adv Vaccines.* 2014;2(3):77–89.

28. Lundegaard C, Lund O, Nielsen M. Predictions versus high-throughput experiments in T-cell epitope discovery: competition or synergy? *Expert Rev Vaccines.* 2012;11(1):43–54.

29. Ilyas S, Yang JC. Landscape of tumor antigens in T cell immunotherapy. *J Immunol.* 2015;195(11):5117–5122.

30. Pedersen SR, Sørensen MR, Buus S, Christensen JP, Thomsen AR. Comparison of vaccine-induced effector CD8 T cell responses directed against self- and non-self-tumor antigens: implications for cancer immunotherapy. *J Immunol.* 2013;191(7):3955–3967.

31. Morgan RA, Yang JC, Kitano M, Dudley ME, Laurencot CM, Rosenberg SA. Case report of a serious adverse event following the administration of T cells transduced with a chimeric antigen receptor recognizing ERBB2. *Mol Ther.* 2010;18(4):843–851.

32. Parkhurst MR, Yang JC, Langan RC, et al. T cells targeting carcinoembryonic antigen can mediate regression of metastatic colorectal cancer but induce severe transient colitis. *Mol Ther.* 2011;19(3):620–626.

33. Castle JC, Kreiter S, Diekmann J, et al. Exploiting the mutanome for tumor vaccination. *Cancer Res.* 2012;72(5):1081–1091.

34. Zamora AE, Crawford JC, Thomas PG. Hitting the target: how T cells detect and eliminate tumors. *J Immunol.* 2018;200(2):392–399.

35. Tran E, Ahmadzadeh M, Lu YC, et al. Immunogenicity of somatic mutations in human gastrointestinal cancers. *Science.* 2015;350(6266):1387–1390.

36. Chang MT, Asthana S, Gao SP, et al. Identifying recurrent mutations in cancer reveals widespread lineage diversity and mutational specificity. *Nat Biotechnol.* 2016;34(2):155–163.

37. Roudko V, Bozkus CC, Orfanelli T, et al. Shared immunogenic polyepitope frameshift mutations in microsatellite unstable tumors. *Cell.* 2020;183(6):1634–1649 e1617.

38. Chen DS, Mellman I. Elements of cancer immunity and the cancer-immune set point. *Nature.* 2017;541(7637):321–330.

39. Ward JP, Gubin MM, Schreiber RD. The role of neoantigens in naturally occurring and therapeutically induced immune responses to cancer. *Adv Immunol.* 2016;130:25–74.

40. Kreiter S, Castle JC, Türeci O, Sahin U. Targeting the tumor mutanome for personalized vaccination therapy. *Oncoimmunology.* 2012;1(5):768–769.

41. Sensi M, Anichini A. Unique tumor antigens: evidence for immune control of genome integrity and immunogenic targets for T cell-mediated patient-specific immunotherapy. *Clin Cancer Res.* 2006;12(17):5023–5032.

42. Sahin U, Türeci Ö. Personalized vaccines for cancer immunotherapy. *Science.* 2018;359(6382):1355–1360.

43. Hu Z, Ott PA, Wu CJ. Towards personalized, tumour-specific, therapeutic vaccines for cancer. *Nat Rev Immunol.* 2018;18(3):168–182.

44. Carreno BM, Magrini V, Becker-Hapak M, et al. Cancer immunotherapy. A dendritic cell vaccine increases the breadth and diversity of melanoma neoantigen-specific T cells. *Science.* 2015;348(6236):803–808.

45. Keskin DB, Anandappa AJ, Sun J, et al. Neoantigen vaccine generates intratumoral T cell responses in phase Ib glioblastoma trial. *Nature.* 2019;565(7738):234–239.

46. Sampson JH, Gunn MD, Fecci PE, Ashley DM. Brain immunology and immunotherapy in brain tumours. *Nat Rev Cancer.* 2020;20(1):12–25.

47. Palucka K, Banchereau J. Dendritic-cell-based therapeutic cancer vaccines. *Immunity.* 2013;39(1):38–48.

48. Sabado RL, Balan S, Bhardwaj N. Dendritic cell-based immunotherapy. *Cell Res.* 2017;27(1):74–95.

49. Melief CJM. Smart delivery of vaccines. *Nat Mater.* 2018;17(6):482–483.

50. Deering RP, Kommareddy S, Ulmer JB, Brito LA, Geall AJ. Nucleic acid vaccines: prospects for non-viral delivery of mRNA vaccines. *Expert Opin Drug Deliv.* 2014;11(6):885–899.

51. Draper SJ, Heeney JL. Viruses as vaccine vectors for infectious diseases and cancer. *Nat Rev Microbiol.* 2010;8(1):62–73.

52. Paugh BS, Qu C, Jones C, et al. Integrated molecular genetic profiling of pediatric high-grade gliomas reveals key differences with the adult disease. *J Clin Oncol.* 2010;28(18):3061–3068.

53. Jones C, Karajannis MA, Jones DTW, et al. Pediatric high-grade glioma: biologically and clinically in need of new thinking. *Neuro Oncol.* 2017;19(2):153–161.

54. Gröbner SN, Worst BC, Weischenfeldt J, et al. The landscape of genomic alterations across childhood cancers. *Nature.* 2018;555(7696):321–327.

55. Steinman RM. Dendritic cells in vivo: a key target for a new vaccine science. *Immunity.* 2008;29(3):319–324.

56. Guo C, Manjili MH, Subjeck JR, Sarkar D, Fisher PB, Wang XY. Therapeutic cancer vaccines: past, present, and future. *Adv Cancer Res.* 2013;119:421–475.

57. Ardon H, De Vleeschouwer S, Van Calenbergh F, et al. Adjuvant dendritic cell-based tumour vaccination for children with malignant brain tumours. *Pediatr Blood Cancer.* 2010;54(4):519–525.

58. Banchereau J, Palucka AK. Dendritic cells as therapeutic vaccines against cancer. *Nat Rev Immunol.* 2005;5(4):296–306.

59. Tuyaerts S, Aerts JL, Corthals J, et al. Current approaches in dendritic cell generation and future implications for cancer immunotherapy. *Cancer Immunol Immunother.* 2007;56(10):1513–1537.

60. Perez CR, De Palma M. Engineering dendritic cell vaccines to improve cancer immunotherapy. *Nat Commun.* 2019;10(1):5408.

61. Vermaelen K. Vaccine strategies to improve anti-cancer cellular immune responses. *Front Immunol.* 2019;10:8.

62. Boudousquie C, Boand V, Lingre E, et al. Development and optimization of a GMP-Compliant manufacturing process for a personalized tumor lysate dendritic cell vaccine. *Vaccines (Basel).* 2020;8(1).

63. Kalinski P, Muthuswamy R, Urban J. Dendritic cells in cancer immunotherapy: vaccines and combination immunotherapies. *Expert Rev Vaccines.* 2013;12(3):285–295.

64. Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med.* 2010;363(5):411–422.

65. Caruso DA, Orme LM, Neale AM, et al. Results of a phase 1 study utilizing monocyte-derived dendritic cells pulsed with tumor RNA in children and young adults with brain cancer. *Neuro Oncol.* 2004;6(3):236–246.

66. Geiger JD, Hutchinson RJ, Hohenkirk LF, et al. Vaccination of pediatric solid tumor patients with tumor lysate-pulsed dendritic cells can expand specific T cells and mediate tumor regression. *Cancer Res.* 2001;61(23):8513–8519.

67. Saito S, Yanagisawa R, Yoshikawa K, et al. Safety and tolerability of allogeneic dendritic cell vaccination with induction of Wilms tumor 1-specific T cells in a pediatric donor and pediatric patient with relapsed leukemia: a case report and review of the literature. *Cytotherapy.* 2015;17(3):330–335.

68. Merchant MS, Bernstein D, Amoako M, et al. Adjuvant immunotherapy to improve outcome in high-risk pediatric sarcomas. *Clin Cancer Res.* 2016;22(13):3182–3191.

69. Carli M, Colombatti R, Oberlin O, et al. European intergroup studies (MMT4-89 and MMT4-91) on childhood metastatic rhabdomyosarcoma: final results and analysis of prognostic factors. *J Clin Oncol.* 2004;22(23):4787–4794.

70. Paulussen M, Ahrens S, Burdach S, et al. Primary metastatic (stage IV) Ewing tumor: survival analysis of 171 patients from the EICESS studies. European Intergroup Cooperative Ewing Sarcoma Studies. *Ann Oncol.* 1998;9(3):275–281.

71. Pappo AS, Anderson JR, Crist WM, et al. Survival after relapse in children and adolescents with rhabdomyosarcoma: a report from the Intergroup Rhabdomyosarcoma Study Group. *J Clin Oncol.* 1999;17(11):3487–3493.

72. Bai Y, Zheng JE, Wang N, et al. Effects of dendritic cell-activated and cytokine-induced killer cell therapy on 22 children with acute myeloid leukemia after chemotherapy. *J Huazhong Univ Sci Technolog Med Sci.* 2015;35(5):689–693.

73. Benitez-Ribas D, Cabezón R, Flórez-Grau G, et al. Immune response generated with the administration of autologous dendritic cells pulsed with an allogenic tumoral cell-lines lysate in patients with newly diagnosed diffuse intrinsic pontine glioma. *Front Oncol.* 2018;8:127.

74. Rutkowski S, De Vleeschouwer S, Kaempgen E, et al. Surgery and adjuvant dendritic cell-based tumour vaccination for patients with relapsed malignant glioma, a feasibility study. *Br J Cancer.* 2004;91(9):1656–1662.

75. Lasky JL 3rd, Panosyan EH, Plant A, et al. Autologous tumor lysate-pulsed dendritic cell immunotherapy for pediatric patients with newly diagnosed or recurrent high-grade gliomas. *Anticancer Res.* 2013;33(5):2047–2056.

76. Dagher R, Long LM, Read EJ, et al. Pilot trial of tumor-specific peptide vaccination and continuous infusion interleukin-2 in patients with recurrent Ewing sarcoma and alveolar rhabdomyosarcoma: an inter-institute NIH study. *Med Pediatr Oncol.* 2002;38(3):158–64.

77. Dohnal AM, Witt V, Hügel H, Holter W, Gadner H, Felzmann T. Phase I study of tumor Ag-loaded IL-12 secreting semi-mature DC for the treatment of pediatric cancer. *Cytotherapy.* 2007;9(8):755–770.

78. Mackall CL, Rhee EH, Read EJ, et al. A pilot study of consolidative immunotherapy in patients with high-risk pediatric sarcomas. *Clin Cancer Res.* 2008;14(15):4850–4858.

79. Suminoe A, Matsuzaki A, Hattori H, Koga Y, Hara T. Immunotherapy with autologous dendritic cells and tumor antigens for children with refractory malignant solid tumors. *Pediatr Transplant.* 2009;13(6):746–753.

80. Himoudi N, Wallace R, Parsley KL, et al. Lack of T-cell responses following autologous tumour lysate pulsed dendritic cell vaccination, in patients with relapsed osteosarcoma. *Clin Transl Oncol.* 2012;14(4):271–279.

81. Krishnadas DK, Shusterman S, Bai F, et al. A phase I trial combining decitabine/dendritic cell vaccine targeting MAGE-A1, MAGE-A3 and NY-ESO-1 for children with relapsed or therapy-refractory neuroblastoma and sarcoma. *Cancer Immunol Immunother.* 2015;64(10):1251–1260.

82. Shah NN, Loeb DM, Khuu H, et al. Induction of immune response after allogeneic Wilms' tumor 1 dendritic cell vaccination and donor lymphocyte infusion in patients with hematologic malignancies and post-transplantation relapse. *Biol Blood Marrow Transplant.* 2016;22(12):2149–2154.

83. Bezu L, Kepp O, Cerrato G, et al. Trial watch: peptide-based vaccines in anticancer therapy. *Oncoimmunology.* 2018;7(12):e1511506.

84. Dubensky TW Jr, Reed SG. Adjuvants for cancer vaccines. *Semin Immunol.* 2010;22(3):155–161.

85. Ott PA, Hu Z, Keskin DB, et al. An immunogenic personal neoantigen vaccine for patients with melanoma. *Nature.* 2017;547(7662):217–221.

86. Yadav M, Jhunjhunwala S, Phung QT, et al. Predicting immunogenic tumour mutations by combining mass spectrometry and exome sequencing. *Nature.* 2014;515(7528):572–576.

87. Sabbatini P, Tsuji T, Ferran L, et al. Phase I trial of overlapping long peptides from a tumor self-antigen and poly-ICLC shows rapid induction of integrated immune response in ovarian cancer patients. *Clin Cancer Res.* 2012;18(23):6497–6508.

88. Melief CJ, van der Burg SH. Immunotherapy of established (pre)malignant disease by synthetic long peptide vaccines. *Nat Rev Cancer.* 2008;8(5):351–360.

89. Slingluff CL Jr. The present and future of peptide vaccines for cancer: single or multiple, long or short, alone or in combination? *Cancer J.* 2011;17(5):343–350.

90. Calvo Tardón M, Allard M, Dutoit V, Dietrich PY, Walker PR. Peptides as cancer vaccines. *Curr Opin Pharmacol.* 2019;47:20–26.

91. Brito LA, O'Hagan DT. Designing and building the next generation of improved vaccine adjuvants. *J Control Release.* 2014;190:563–579.

92. Lynn GM, Laga R, Darrah PA, et al. In vivo characterization of the physicochemical properties of polymer-linked TLR agonists that enhance vaccine immunogenicity. *Nat Biotechnol.* 2015;33(11):1201–1210.

93. Lynn GM, Laga R, Jewell CM. Induction of anti-cancer T cell immunity by in situ vaccination using systemically administered nanomedicines. *Cancer Lett.* 2019;459:192–203.

94. Prow NA, Jimenez Martinez R, Hayball JD, Howley PM, Suhrbier A. Poxvirus-based vector systems and the potential for multi-valent and multi-pathogen vaccines. *Expert Rev Vaccines.* 2018;17(10):925–934.

95. Tran E, Turcotte S, Gros A, et al. Cancer immunotherapy based on mutation-specific CD4+ T cells in a patient with epithelial cancer. *Science.* 2014;344(6184):641–645.

96. Tran E, Robbins PF, Lu YC, et al. T-Cell transfer therapy targeting mutant KRAS in cancer. *N Engl J Med.* 2016;375(23):2255–2262.

97. Schneble E, Clifton GT, Hale DF, Peoples GE. Peptide-based cancer vaccine strategies and clinical results. *Methods Mol Biol.* 2016;1403:797–817.

98. Hashii Y, Sato E, Ohta H, Oka Y, Sugiyama H, Ozono K. WT1 peptide immunotherapy for cancer in children and young adults. *Pediatr Blood Cancer.* 2010;55(2):352–355.

99. Sawada A, Inoue M, Kondo O, et al. Feasibility of cancer immunotherapy with WT1 peptide vaccination for solid and hematological malignancies in children. *Pediatr Blood Cancer.* 2016;63(2):234–241.

100. Coffman RL, Sher A, Seder RA. Vaccine adjuvants: putting innate immunity to work. *Immunity.* 2010;33(4):492–503.

101. Hailemichael Y, Overwijk WW. Peptide-based anticancer vaccines: the making and unmaking of a T-cell graveyard. *Oncoimmunology.* 2013;2(7):e24743.

102. Pollack IF, Jakacki RI, Butterfield LH, et al. Antigen-specific immune responses and clinical outcome after vaccination with glioma-associated antigen peptides and polyinosinic-polycytidylic acid stabilized by lysine and carboxymethylcellulose in children with newly diagnosed malignant brainstem and nonbrainstem gliomas. *J Clin Oncol.* 2014;32(19):2050–2058.

103. Pollack IF, Jakacki RI, Butterfield LH, et al. Immune responses and outcome after vaccination with glioma-associated antigen peptides and poly-ICLC in a pilot study for pediatric recurrent low-grade gliomas. *Neuro Oncol.* 2016;18(8):1157–1168.

104. Mueller S, Taitt JM, Villanueva-Meyer JE, et al. Mass cytometry detects H3.3K27M-specific vaccine responses in diffuse midline glioma. *J Clin Invest.* 2020;130(12):6325–6337.

105. Hirabayashi K, Yanagisawa R, Saito S, et al. Feasibility and immune response of WT1 peptide vaccination in combination with OK-432 for paediatric solid tumors. *Anticancer Res.* 2018;38(4):2227–2234.

106. Camisaschi C, Renne SL, Beretta V, et al. Immune landscape and in vivo immunogenicity of NY-ESO-1 tumor antigen in advanced neuroblastoma patients. *BMC Cancer.* 2018;18(1):983.

107. Akazawa Y, Hosono A, Yoshikawa T, et al. Efficacy of the NCCV Cocktail-1 vaccine for refractory pediatric solid tumors: a phase I clinical trial. *Cancer Sci.* 2019;110(12):3650–3662.

108. Hashii Y, Sato-Miyashita E, Matsumura R, et al. WT1 peptide vaccination following allogeneic stem cell transplantation in pediatric leukemic patients with high risk for relapse: successful maintenance of durable remission. *Leukemia.* 2012;26(3):530–532.

109. Kushner BH, Cheung IY, Modak S, Kramer K, Ragupathi G, Cheung NK. Phase I trial of a bivalent gangliosides vaccine in combination with β-glucan for high-risk neuroblastoma in second or later remission. *Clin Cancer Res.* 2014;20(5):1375–1382.

110. Cheung NK, Modak S, Vickers A, Knuckles B. Orally administered beta-glucans enhance anti-tumor effects of monoclonal antibodies. *Cancer Immunol Immunother.* 2002;51(10):557–564.

111. Yan JL, van der Hoorn A, Larkin TJ, Boonzaier NR, Matys T, Price SJ. Extent of resection of peritumoral diffusion tensor imaging-detected abnormality as a predictor of survival in adult glioblastoma patients. *J Neurosurg.* 2017;126(1):234–241.

112. Filmus J. Glypicans in growth control and cancer. *Glycobiology.* 2001;11(3):19R–23R.

113. Kinoshita Y, Tanaka S, Souzaki R, et al. Glypican 3 expression in pediatric malignant solid tumors. *Eur J Pediatr Surg.* 2015;25(1):138–144.

114. Tsuchiya N, Hosono A, Yoshikawa T, et al. Phase I study of glypican-3-derived peptide vaccine therapy for patients with refractory pediatric solid tumors. *Oncoimmunology.* 2017;7(1):e1377872.

115. Thust SC, van den Bent MJ, Smits M. Pseudoprogression of brain tumors. *J Magn Reson Imaging.* 2018;48(3):571–589.

116. Cobbs CS, Harkins L, Samanta M, et al. Human cytomegalovirus infection and expression in human malignant glioma. *Cancer Res.* 2002;62(12):3347–3350.

117. Ochs K, Ott M, Bunse T, et al. K27M-mutant histone-3 as a novel target for glioma immunotherapy. *Oncoimmunology.* 2017;6(7):e1328340.

118. Middleton G, Silcocks P, Cox T, et al. Gemcitabine and capecitabine with or without telomerase peptide vaccine GV1001 in patients with locally advanced or metastatic pancreatic cancer (TeloVac): an open-label, randomised, phase 3 trial. *Lancet Oncol.* 2014;15(8):829–840.

119. Mitchell P, Thatcher N, Socinski MA, et al. Tecemotide in unresectable stage III non-small-cell lung cancer in the phase III START study: updated overall survival and biomarker analyses. *Ann Oncol.* 2015;26(6):1134–1142.

120. Rini BI, Stenzl A, Zdrojowy R, et al. IMA901, a multipeptide cancer vaccine, plus sunitinib versus sunitinib alone, as first-line therapy for advanced or metastatic renal cell carcinoma (IMPRINT): a multicentre, open-label, randomised, controlled, phase 3 trial. *Lancet Oncol.* 2016;17(11):1599–1611.

121. Lynn GM, Sedlik C, Baharom F, et al. Peptide-TLR-7/8a conjugate vaccines chemically programmed for nanoparticle self-assembly enhance CD8 T-cell immunity to tumor antigens. *Nat Biotechnol.* 2020;38(3):320–332.

122. Crotty E, Downey K, Ferrerosa L, et al. Considerations when treating high-grade pediatric glioma patients with immunotherapy. *Expert Rev Neurother.* 2020;21(2):1–15.

123. Aurisicchio L, Ciliberto G. Genetic cancer vaccines: current status and perspectives. *Expert Opin Biol Ther.* 2012;12(8):1043–1058.

124. Sahin U, Derhovanessian E, Miller M, et al. Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer. *Nature.* 2017;547(7662):222–226.

125. Pardi N, Hogan MJ, Porter FW, Weissman D. mRNA vaccines—a new era in vaccinology. *Nat Rev Drug Discov.* 2018;17(4):261–279.

126. Tiptiri-Kourpeti A, Spyridopoulou K, Pappa A, Chlichlia K. DNA vaccines to attack cancer: strategies for improving immunogenicity and efficacy. *Pharmacol Ther.* 2016;165:32–49.

127. Kranz LM, Diken M, Haas H, et al. Systemic RNA delivery to dendritic cells exploits antiviral defence for cancer immunotherapy. *Nature.* 2016;534(7607):396–401.

128. Ribas A, Weber JS, Chmielowski B, et al. Intra-lymph node prime-boost vaccination against Melan A and tyrosinase for the treatment of metastatic melanoma: results of a phase 1 clinical trial. *Clin Cancer Res.* 2011;17(9):2987–2996.

129. Buchan S, Grønevik E, Mathiesen I, King CA, Stevenson FK, Rice J. Electroporation as a "prime/boost" strategy for naked DNA vaccination against a tumor antigen. *J Immunol.* 2005;174(10):6292–6298.

130. Greenland JR, Letvin NL. Chemical adjuvants for plasmid DNA vaccines. *Vaccine.* 2007;25(19):3731–3741.

131. Cui Z, Mumper RJ. Microparticles and nanoparticles as delivery systems for DNA vaccines. *Crit Rev Ther Drug Carrier Syst.* 2003;20(2–3):103–137.

132. Manikandan C, Kaushik A, Sen D. Viral vector: potential therapeutic for glioblastoma multiforme. *Cancer Gene Ther.* 2020;27(5):270–279.

133. Chiocca EA, Nassiri F, Wang J, Peruzzi P, Zadeh G. Viral and other therapies for recurrent glioblastoma: is a 24-month durable response unusual? *Neuro Oncol.* 2019;21(1):14–25.

134. Pol JG, Zhang L, Bridle BW, et al. Maraba virus as a potent oncolytic vaccine vector. *Mol Ther.* 2014;22(2):420–429.

135. Guo ZS, Lu B, Guo Z, et al. Vaccinia virus-mediated cancer immunotherapy: cancer vaccines and oncolytics. *J Immunother Cancer.* 2019;7(1):6.

136. Larocca C, Schlom J. Viral vector-based therapeutic cancer vaccines. *Cancer J.* 2011;17(5):359–371.

137. Iampietro MJ, Larocca RA, Provine NM, et al. Immunogenicity and cross-reactivity of rhesus adenoviral vectors. *J Virol.* 2018;92(11).

138. Kantoff PW, Schuetz TJ, Blumenstein BA, et al. Overall survival analysis of a phase II randomized controlled trial of a Poxviral-based PSA-targeted immunotherapy in metastatic castration-resistant prostate cancer. *J Clin Oncol.* 2010;28(7):1099–1105.

139. Gulley JL, Borre M, Vogelzang NJ, et al. Phase III trial of PROSTVAC in asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer. *J Clin Oncol.* 2019;37(13):1051–1061.

140. Madan RA, Mohebtash M, Arlen PM, et al. Ipilimumab and a poxviral vaccine targeting prostate-specific antigen in metastatic castration-resistant prostate cancer: a phase 1 dose-escalation trial. *Lancet Oncol.* 2012;13(5):501–508.

141. Quoix E, Ramlau R, Westeel V, et al. Therapeutic vaccination with TG4010 and first-line chemotherapy in advanced non-small-cell lung cancer: a controlled phase 2B trial. *Lancet Oncol.* 2011;12(12):1125–1133.

142. Abdelaziz MO, Ossmann S, Kaufmann AM, et al. Development of a human cytomegalovirus (HCMV)-based therapeutic cancer vaccine uncovers a previously unsuspected viral block of MHC Class I antigen presentation. *Front Immunol.* 2019;10:1776.

143. Kieran MW, Goumnerova L, Manley P, et al. Phase I study of gene-mediated cytotoxic immunotherapy with AdV-tk as adjuvant to surgery and radiation for pediatric malignant glioma and recurrent ependymoma. *Neuro Oncol.* 2019;21(4):537–546.

144. Totsch SK, Schlappi C, Kang KD, et al. Oncolytic herpes simplex virus immunotherapy for brain tumors: current pitfalls and emerging strategies to overcome therapeutic resistance. *Oncogene.* 2019;38(34):6159–6171.

145. Gatti-Mays ME, Redman JM, Collins JM, Bilusic M. Cancer vaccines: enhanced immunogenic modulation through therapeutic combinations. *Hum Vaccin Immunother.* 2017;13(11):2561–2574.

146. Le DT, Lutz E, Uram JN, et al. Evaluation of ipilimumab in combination with allogeneic pancreatic tumor cells transfected with a GM-CSF gene in previously treated pancreatic cancer. *J Immunother.* 2013;36(7):382–389.

147. Koske I, Rössler A, Pipperger L, et al. Oncolytic virotherapy enhances the efficacy of a cancer vaccine by modulating the tumor microenvironment. *Int J Cancer.* 2019;145(7):1958–1969.

148. Kwok D, Okada H. T-Cell based therapies for overcoming neuroanatomical and immunosuppressive challenges within the glioma microenvironment. *J Neurooncol.* 2020;147(2):281–295.

149. Kuai R, Ochyl LJ, Bahjat KS, Schwendeman A, Moon JJ. Designer vaccine nanodiscs for personalized cancer immunotherapy. *Nat Mater.* 2017;16(4):489–496.

150. Shah NJ, Najibi AJ, Shih TY, et al. A biomaterial-based vaccine eliciting durable tumour-specific responses against acute myeloid leukaemia. *Nat Biomed Eng.* 2020;4(1):40–51.

151. Baharom F, Ramirez-Valdez RA, Tobin KKS, et al. Intravenous nanoparticle vaccination generates stem-like TCF1+ neoantigen-specific CD8+ T cells. *Nat Immunol.* 2021;22(1):41–52.

152. Twycross R. The risks and benefits of corticosteroids in advanced cancer. *Drug Saf.* 1994;11(3):163–178.

153. Adhikaree J, Moreno-Vicente J, Kaur AP, Jackson AM, Patel PM. Resistance mechanisms and barriers to successful immunotherapy for treating glioblastoma. *Cells.* 2020;9(2):263.

154. Herold MJ, McPherson KG, Reichardt HM. Glucocorticoids in T cell apoptosis and function. *Cell Mol Life Sci.* 2006;63(1):60–72.

155. Wong ET, Lok E, Gautam S, Swanson KD. Dexamethasone exerts profound immunologic interference on treatment efficacy for recurrent glioblastoma. *Br J Cancer.* 2015;113(2):232–241.

156. Pitter KL, Tamagno I, Alikhanyan K, et al. Corticosteroids compromise survival in glioblastoma. *Brain.* 2016;139(Pt 5):1458–1471.

157. Welters MJ, van der Sluis TC, van Meir H, et al. Vaccination during myeloid cell depletion by cancer chemotherapy fosters robust T cell responses. *Sci Transl Med.* 2016;8(334):334ra352.

158. Zitvogel L, Galluzzi L, Smyth MJ, Kroemer G. Mechanism of action of conventional and targeted anticancer therapies: reinstating immunosurveillance. *Immunity.* 2013;39(1):74–88.

159. Pol JG, Atherton MJ, Stephenson KB, et al. Enhanced immunotherapeutic profile of oncolytic virus-based cancer vaccination using cyclophosphamide preconditioning. *J Immunother Cancer.* 2020;8(2).