Trial watch: Naked and vectored DNA-based anticancer vaccines

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Abbreviations: AFP, α-fetoprotein; APC, antigen-presenting cell; CDR, complementarity-determining region; CEA, carcinoembryonic antigen; CIN, cervical intraepithelial neoplasia; CTLA4, cytotoxic T lymphocyte protein 4; DAMP, damage-associated molecular pattern; DC, dendritic cell; FDA, Food and Drug Administration; GM-CSF, granulocyte macrophage colony-stimulating factor; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus; IL, interleukin; OS, overall survival; OVA, ovalbumin; PAP, prostate acid phosphatase; SCGB2A2, secretoglobin, family 2A, member 2; SOX2, SRY (sex determining region Y)-box 2; T, brachury homolog; TAA, tumor-associated antigen; TLR, Toll-like receptor; TRA, tumor rejection antigen; Treg, regulatory T cell; WT1, Wilms tumor 1.

One type of anticancer vaccine relies on the administration of DNA constructs encoding one or multiple tumor-associated antigens (TAAs). The ultimate objective of these preparations, which can be naked or vectored by non-pathogenic viruses, bacteria or yeast cells, is to drive the synthesis of TAAs in the context of an immunostimulatory milieu, resulting in the (re-)elicitation of a tumor-targeting immune response. In spite of encouraging preclinical results, the clinical efficacy of DNA-based vaccines employed as standalone immunotherapeutic interventions in cancer patients appears to be limited. Thus, efforts are currently being devoted to the development of combinatorial regimens that allow DNA-based anticancer vaccines to elicit clinically relevant immune responses. Here, we discuss recent advances in the preclinical and clinical development of this therapeutic paradigm.

Introduction

During the last 2 decades, several approaches have been conceived to (re-)activate a therapeutically relevant immune response against malignant cells, including dendritic cell (DC)-, peptide- and DNA-based vaccines.1-8 The goal of all such strategies is to endow host antigen-presenting cells (APCs) with the capacity to prime a robust and specific, cellular immune response against one or several tumor-associated antigens (TAAs).9,12 In the context of DC-based vaccination, this is achieved as circulating monocytes are collected from cancer patients, expanded ex vivo in the presence of a source of TAAs and appropriate maturation stimuli, and eventually re-infused (to the same individual).13-15 Peptide-based vaccination involves the direct administration to cancer patients of recombinant full-length TAAs or peptide thereof, near to invariably in conjunction with potent immunostimulatory agents commonly referred to as adjuvants.16-21 Finally, DNA-based vaccines consist of circularized DNA constructs encoding one or several TAAs, which are delivered to cancer patients as naked plasmids or within appropriate vectors.7,22-25 Vectored DNA-based vaccines should be conceptually differentiated from oncolytic viruses, be they natural or genetically manipulated, as well as from other forms of viral-based anticancer gene therapy, for at least 2 reasons. First, oncolytic viruses, as well as other vectors for gene therapy, target cancer cells, whereas TAA-coding constructs are taken up and expressed by non-malignant cells including APCs, myocytes and epithelial cells (depending on the specific vaccine and administration route).26-28 Second, while oncolytic virotherapy and the delivery of specific gene products to cancer cells aim at provoking their demise (ideally, but not invariably, accompanied by the elicitation of an immune response), DNA-based vaccines...
mediated antiangiogenic effects solely through the immune system.5,9,29

The delivery of naked constructs via the intramuscular route (along with an innocuous electric impulse that provokes the electroporation of myocytes and tissue-resident APCs) is the form of DNA-based anticancer vaccination currently preferred in clinical settings.30 Indeed, although promising results have been obtained with viral, bacterial and eukaryotic vectors, each of these approaches is associated with obstacles that have not yet been completely overcome.31-35 Viral vectors generally ensure increased transduction rates, yet are susceptible to neutralization by natural antibodies (elicited by packaging proteins), are relatively expensive, are not always compatible with the insertion of a large transgene, and are not completely devoid of risks of insertional mutagenesis.36-39 Along similar lines, the development of prokaryotic and eukaryotic (yeast) vectors is not sufficiently advanced for clinical applications.7,22-24 Nonetheless, both of these vectors stand out as promising alternatives to their viral counterparts for at least 2 reasons. First, they are compatible with oral administration.40-42 Second, they both have been shown to elicit potent mucosal immune responses,43-45 which are superior to intramuscular ones, possibly owing to endogenous immunostimulatory factors that trigger Toll-like receptor (TLR) signaling (such as bacterial lipopolysaccharide).46-50 As an alternative to electroporation, DNA-based vaccines can be delivered via the transdermal route, by gene gun,51,52 jet injection,53,54 and tattooing.55,56 None of these delivery methods, however, appears to be superior to electroporation which has been associated with elevated transfection rates,57-59 a minimal extent of tissue injury that exerts immunostimulatory effects (upon the release of damage-associated molecular patterns, DAMPs),46-50 and no significant toxicities.22,24

The target of DNA-based vaccines obviously determines their efficacy as well as their toxicity, a notion that we discussed in previous Trial Watches dealing with this and other TAA-specific active immunotherapies against cancer.9,63,64 One important obstacle against clinical efficiency is indeed represented by the emergence of so-called antigen-loss tumor variants, i.e., malignant cells that do not express the TAA targeted by the vaccine, and—under the selective pressure imposed by vaccine-elicited immunity—emerge and progressively substitute their TAA-expressing counterparts.65-68 Ultimately, this process is responsible for the formation of neoplastic lesions that are completely insensitive to vaccination. Vaccines simultaneously targeting 2 or more TAAs, or targeting so-called tumor rejection antigens (TRAs), i.e., antigens that are critically required for the survival of malignant cells, may partially circumvent this issue.69-74 However, the number of TRAs that are selectively expressed by neoplastic cells, i.e., not by their non-transformed counterparts or by other healthy tissues) is limited.69,75-77 In addition, progressive tumors often establish potent immunosuppressive networks that limit the efficacy of DNA-based vaccines and several other forms of immunotherapy.78-84 These immunosuppressive circuitries operate both locally and systemically and generally develop along with natural tumor progression, although the presence of an accrued immune reaction, such as that elicited by TAA-targeting vaccines, is expected to accelerate this process.85,86 The emergence of antigen-loss tumor variants and/or the establishment of local and systemic immunosuppression explains why—in spite of promising preclinical results—most DNA-based anticancer vaccines are not efficient in patients when employed as standalone immunotherapeutic interventions.5,9,25,87

As it stands, no DNA-based vaccine is currently approved for use in cancer patients by the US Food and Drug Administration (FDA) or equivalent agencies worldwide. On the contrary, at least 3 preparations of this type are licensed for use in dogs.88-92 Interestingly, one of the DNA-based vaccines approved for veterinary use relies on a xenogenous TAA, i.e., human tyrosinase.91 This said, it seems unlikely that xenogenous TAAs may always be superior to their endogenous counterparts at eliciting therapeutically relevant immune responses.

Along the lines of our Trial Watch series,93,94 here we discuss recent preclinical, translational and clinical advances in the development of DNA-based vaccines for oncological indications.

Update on the development of DNA-based anticancer vaccines

Completed clinical studies

Since the submission of our latest Trial Watch dealing with this topic (March 2014),5 the results of 4 clinical studies assessing the clinical profile of DNA-based anticancer vaccines have been published in international, peer-reviewed scientific journals (source http://www.ncbi.nlm.nih.gov/pubmed), and preliminary data from 3 additional studies have been presented at the American Society of Clinical Oncology (ASCO) annual meeting (source http://meetinglibrary.asco.org/).

Bilusic and colleagues (National Cancer Institute, National Institutes of Health, Bethesda, MD, USA) ran a Phase I clinical trial to test the safety and efficacy of a heat-killed Saccharomyces cerevisiae strain genetically modified to express carcinoembryonic antigen (CEA), a TAA that is overexpressed by several epithelial cancers,95-97 in adult individuals with metastatic, CEA-expressing carcinomas (NCT00924092).33 Twenty-five patients were enrolled in the study and allocated to receive the vaccine (named GI-6207) s.c. every 2 weeks (we) for 3 months (mo) and then monthly thereafter. Vaccination was well tolerated, the most common toxicities being Grade 1/2 injection-site reactions. Five patients experienced disease stabilization for more than 3 mo (range 3.5-18 mo). Moreover, some subjects exhibited increased amounts of CEA-specific CD8+ T lymphocytes coupled to decreased levels of CD4+CD25+FOXP3+ regulatory T cells (Tregs) after vaccination.33

Butterfield and collaborators (University of Pittsburgh Cancer Institute, Pittsburgh, PA, USA) investigated the clinical profile of a prime-boost vaccination strategy relying on a pVAX1-based plasmid encoding full-length human α-fetoprotein (AFP), an oncofetal antigen frequently re-expressed by hepatocellular carcinoma (HCC),98 co-injected i.m. with a granulocyte macrophage colony-stimulating factor (GM-CSF)-coding plasmid...
(prime), followed by a single intramuscular administration of an AFP-coding adenovirus (boost) (NCT00093548). Two patients with AFP+ HCC were vaccinated, and neither of them experienced adverse side effects. Signs of immunization could be documented in both individuals, in spite of pre-existing adenovirus-specific antibodies, including an increased amount of AFP-targeting CD8+ T lymphocytes. Of note, tumors in both patients eventually recurred, one of which was after 18 mo and with an AFP+ lesion.

Tiriveedhi and co-workers (Washington University School of Medicine, St. Louis, MO, USA) investigated the safety and efficacy of a pING-based plasmid coding for the breast cancer-associated antigen secretoglobin, family 2A, member 2 (SCGB2A2, best known as mamoglobin A)103-106 administered i.m. (3 times, with at least 21-d interval between vaccinations) to subjects with SCGB2A2+ breast carcinoma (NCT00807781).107 Fourteen individuals out of 52 originally enrolled in the study could be vaccinated, none of whom experienced severe (Grade 3-4) toxicities. Common Grade 1-2 side effects included vaccine site tenderness (in 1 out of 14 vaccinated patients), rash (in 1 out of 14 vaccinated patients) and the precipitation of shingle episode (in 2 out of 14 vaccinated patients). Eight of these patients expressed HLA-A2, allowing for precise immunological monitoring. In these individuals, vaccination efficiently elicited SCGB2A2-specific CD8+ T lymphocytes that were cytotoxic, in vitro, against SCGB2A2+HLA-A2+ breast carcinoma cells. Moreover, vaccinated subjects experienced a statistically significant improvement in progression-free survival as compared to enrolled patients who could not be vaccinated.107

DiPaola et al. (Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA) tested a multimodal immunotherapeutic strategy relying on the sequential administration of a vaccinia virus co-encoding kallikrein-related peptidase 3 (KLK3, best known as prostate-specific antigen, PSA)108,109 and 3 immunostimulatory molecules (i.e., CD58, CD80, and intercellular adhesion molecule 1, ICAM1),110-111 a fowlpox virus modified with the same transgenes113 (both in combination with recombinant GM-CSF),114,116 and androgen ablation therapy, in prostate carcinoma patients with PSA progression but no visible metastasis (NCT00108732).117 These viral vectors were developed by Bavarian Nordic (Washington, DC, USA) under the names of PROSTVAC®-V/TRICOM and PROSTVAC®-F/TRICOM, respectively.118-122 Forty patients were vaccinated, 25 of which did not experience disease progression prior to androgen ablation therapy. Of 27 patients eligible for this therapeutic option, 20 achieved a complete response at 7-mo follow-up. Of note, no Grade 4 toxicities related to treatment were documented.117

Disis and colleagues (University of Washington, Seattle, WA, USA) tested the safety and immunogenicity of a DNA-based vaccine encoding the intracellular domain of erb-b2 receptor tyrosine kinase 2 (ERBB2, best known as HER2), which is overexpressed by a sizeable fraction of breast carcinomas,123,126 in individuals with HER2+ breast carcinoma (NCT00436254).127 Sixty-six patients with Stage III-IV breast carcinoma in remission were enrolled, 64 of which received 3 intradermal vaccine injections administered in combination with recombinant GM-CSF. Minimal toxicities were documented, and the patients who received an intermediate vaccine dose (100 μg/injection versus 10 and 500 μg/injection) were those exhibiting the highest incidence of immunological responders, the immune responses of longest duration and superior overall survival (OS). Interestingly, high doses were associated with increased DNA persistence at injection sites, but this corresponded to comparatively less robust and shorter immune responses.127 Possibly, this relates to the sequestration of antigen-specific CD8+ T lymphocytes at the vaccination site, which has previously been shown to prevent effective antitumor immune responses in preclinical models.128

Patel and collaborators (University of Nottingham, Nottingham, UK) investigated the clinical profile of a peculiar DNA-based anticancer vaccine encoding cytotoxic and helper T-cell epitopes from 2 melanoma-associated antigens (an immunotherapeutic paradigm developed by Scancell, Nottingham, UK, under the name of SCIB1), administered i.m. by electroporation to melanoma patients (NCT01138410).129 SCIB1 is a so-called “ImmunoBody”, i.e., a DNA-based vaccine in which TAA-derived epitopes are cloned within the complementarity-determining regions (CDRs) of a human antibody.130 In particular, SCIB1 codes from epitopes derived from premelanosome protein (PMEL, best known as gp100)131-133 and tyrosinase-related protein 2 (TRP2)134,135 within the CDRs of an IgG1 molecule. A total of 28 individuals with Stage III-IV melanoma were vaccinated (3 sequential vaccinations at 3 we intervals, then 2 additional vaccination at 3 and 6 mo), none of whom experienced dose-limiting toxicities. The most common side effect was pain at the injection site. Of 25 evaluable patients, 23 exhibited immunological responses to vaccination, and 1 achieved an objective clinical response. The study has not yet concluded although the OS times so far are encouraging.129

Singh and coworkers (National Cancer Institute, National Institutes of Health, Bethesda, MD, USA) assessed the safety and efficacy of a heat-killed S. cerevisiae strain genetically modified to express brachyury homolog (T) in subjects with advanced neoplasms (NCT01519817).136 T is a TAA implicated in both tumor progression and resistance to chemotherapy.137-141 Twenty-seven patients were enrolled and received escalating doses of the vaccine (named GI-6301) every 2 we for 7 injections and then bimonthly. No Grade 3-4 side effects related to vaccination were observed. Of 21 patients evaluable for immune responses, 7 exhibited T-specific CD8+ or CD4+ T lymphocytes. Moreover, treated patients with metastatic colon carcinoma experienced disease stabilization for 15 mo.

Preclinical and translational advances

Consistent efforts are being devoted to identify approaches that may endow TAA-targeting DNA-based vaccines with the ability to elicit robust and specific (and hence therapeutically relevant) immune responses in patients. This can be achieved by: (1) developing DNA constructs and vectors with improved specificity, transfection efficiency and/or immunostimulatory potential; (2) identifying novel TAAs/TRAs as vaccine targets; and (3) optimizing combinatorial immunochemotherapeutic regimens that

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significantly boost vaccine-elicited immune responses. All of these approaches have been investigated during the last 13 months with promising results.

The immunogenicity of DNA-based anticancer vaccines has been successfully ameliorated by altering the sequence of TAAs targeted by vaccination in several ways, including random shuffling (which allowed for the generation of one construct with superior efficacy as compared to several other containing the same sequences arranged in a different manner),\(^{142}\) the removal of epitopes that elicit IL-10-producing, immunosuppressive T\(_{\text{H}}\)2 cells (as demonstrated in a vaccine targeting insulin-like growth factor binding protein 2, IGFBP2),\(^{143}\) and the fusion of the TAA-coding sequence with sequences encoding portions of cytotoxic T lymphocyte protein 4 (CTLA4),\(^{144}\) possibly because of the development of endogenous CTLA4-targeting antibodies (which may boost immune responses similar to their recombinant, FDA-approved counterpart ipilimumab).\(^{145-148}\) In addition, encouraging results have recently been obtained by delivering DNA-based vaccines within novel vectors including (but not limited to): a Semliki Forest virus-derived vector co-encoding GM-CSF, as demonstrated by targeting survivin and chorionic gonadotropin, β polypeptide (CGB) in a murine model of melanoma;\(^{149}\) an integrating plasmid based on the PiggBac system, as shown by targeting transgenic enhanced green fluorescent protein (eGFP) in mice;\(^{150}\) heat-killed \(P\) Richtia \(p\) toris, as proved by targeting an human papillomavirus (HPV)-16 antigen in a mouse model of cervical carcinoma prevention;\(^{151}\) attenuated \(L\)isteria \(m\) onocyogenes, as demonstrated by targeting CD24 in a murine model of transplantable HCC;\(^{152}\) living \(L\)actococcus \(l\)actis, as shown by targeting HPV-16 E7 in a mouse model of cervical cancer;\(^{153}\) a chitosan-based nanodelivery system, as proved by targeting E7 in mice receiving E7-expressing TC-1 cancer cells;\(^{154}\) and perhaps synthetic “pathogen-like” nanoparticles that preferentially target Langerhans cells, although immunological responses were not assessed in this study.\(^{154}\)

In an alternative approach, various molecules that (at least hypothetically) may serve as adjuvants to boost the ability of DNA-based anticancer vaccines to elicit robust immune responses have been identified. These molecules include (but are not limited to): IL-15, as demonstrated by targeting a viral protein in \(H\)IV\(^{15-16}\) vs. wild-type mice;\(^{155}\) the DAMPs\(^{61,156,157}\) IL-33 and high mobility group nucleosomal binding domain 1 (HMGN1), as shown by targeting the exogenous TAA ovalbumin (OVA) in mice receiving OVA-expressing EG7 cells or HPV-16 E7 in mice administered with TC-1 cells, respectively;\(^{158,159}\) the co-stimulatory receptor CD40, as proved in murine models of anticancer vaccination directed against tumor protein 53 (TP53, best known as p53) and gp100;\(^{160}\) the FDA-approved TLR7/TLR8 mixed agonist imiquimod, as demonstrated by targeting HPV-16 E7 in a murine model of cervical carcinoma;\(^{161}\) and the FDA-approved immunomodulatory drug lenalidomide,\(^{162,163}\) as shown in a model of DNA-based vaccination against murine lymphoma.\(^{164}\)

During the last 13 months, several laboratories demonstrated the ability of novel DNA-based anticancer vaccines to elicit therapeutically relevant immune responses in mice. These vaccines target well known TAAs, such as HER2, glypican 3 (GPC3), which is generally overexpressed by HCC cells,\(^{165}\) and tyrosinase (TYR), which is selectively expressed by melanocytes,\(^{166}\) as well as proteins that were not considered as therapeutically targetable TAAs, including sequestosome 1 (SQSTM1), an autophagic adaptor with oncogenic functions,\(^{167}\) SRY (sex determining region \(Y\)) box 2 (SOX2), a transcription factor important for the maintenance of cancer stem cells,\(^{168}\) and CD248, a protein that is not expressed by malignant cells but by the tumor endothelium.\(^{169}\) Finally, recent efforts have been devoted to the characterization of the cellular and immunological mechanisms that may underlie the therapeutic efficacy of DNA-based anticancer vaccination. In this context, it has been shown that a DNA vaccine targeting Wilms tumor 1 (WT1) affords mice with complete protection against an otherwise lethal challenge with WT1-expressing mesothelioma cells as it elicits WT1-specific CD8\(^{+}\) T cells while reducing the amounts of immunosuppressive Tregs and myeloid-derived suppressor cells (MDSCs).\(^{170}\) Moreover, the failure of a CEA-targeting DNA vaccine to exert therapeutic activity against colorectal carcinoma cells has been associated with the ability of the latter to avoid the presentation of CEA to CEA-specific CD8\(^{+}\) T lymphocytes.

**Recently initiated clinical trials**

Since the submission of our latest Trial Watch dealing with this topic (March 2014),\(^{5}\) only 8 clinical trials have been initiated to test the safety and efficacy of DNA-based anticancer vaccines (source http://clinicaltrials.gov/). Seven of these studies are based on naked DNA constructs near to invariably administered \(i.m.\) by electroporation (NCT02139267; NCT02157051; NCT02163057; NCT02172911; NCT02204098; NCT02241369; NCT02348320). In addition, one trial relies on semi-allogenic human fibroblasts (MRC-5 cells) as vectors (NCT02211027). All these studies are Phase I or Phase II/III trials (Table 1).

Naked constructs encoding proteins from HPV strains that are causally associated with the development of head and neck cancer and cervical neoplasms\(^{171-173}\) are being tested in patients affected by these conditions. In particular, the safety and efficacy of a plasmid encoding the E6-E7 fusion protein from HPV-16 and -18 (developed by Inovio, Plymouth Meeting, PA, US, under the name of VGX-3100 SynCon\(^{6}\)) administered \(i.m.\) by electroporation together with an interleukin (IL)-12-coding construct (called INO-9012) and optionally combined with external beam radiation therapy, are being assessed in cohorts of head and neck squamous cell carcinoma (HNSCC) or cervical carcinoma patients (NCT02139267; NCT02172911). Another naked plasmid coding for HPV-16/18 E6-E7 (developed by Genexine, Gyeonggi-do, Republic of Korea, under the name of GX-188E) as well as for the immunostimulatory molecule \(fms\)-like tyrosine kinase-3 ligand (FLT3LG),\(^{174-176}\) administered \(i.m.\) by electroporation, is being tested as a standalone immunotherapeutic intervention in subjects with Grade III cervical intraepithelial neoplasia (CIN) (NCT02139267). Finally, the clinical profile of a naked DNA-based vaccine targeting non-disclosed antigens from HPV-6 (developed by Inovio under the name of...
INO-3106), administered i.m. by electroporation together with INO-9012, is being assessed in patients with HPV-6-associated aerodigestive malignancies, including HNSCC.177,178 (NCT02241369).

The safety and efficacy of a naked DNA construct encoding mammaglobin-A administered i.m. by electroporation, are being investigated in breast carcinoma patients undergoing neoadjuvant endocrine therapy (NCT02204098). A plasmid coding for various patient-specific tumor-derived epitopes is being tested as a single immunotherapeutic regimen in subjects with triple-negative (i.e., estrogen receptor-, progesterone receptor- and HER2-negative) breast carcinoma (NCT02348320). Along similar lines, the clinical profile of a naked DNA plasmid encoding various TAAs, including MDM2 proto-oncogene, E3 ubiquitin protein ligase (MDM2), SOX2, and Y box-binding protein 1 (YBX1),179-182 administered intradermally in combination with ligase (MDM2), SOX2, and Y box-binding protein 1 (YBX1),179-182 administered intradermally in combination with IL-12-coding plasmid and EBRT (NCT02172911).

As for the clinical trials discussed in our previous Trial Watches file of DNA-based anticancer vaccines*, the safety and efficacy of a naked DNA construct encoding various TAAs, including MDM2 proto-oncogene, E3 ubiquitin protein ligase (MDM2), SOX2, and Y box-binding protein 1 (YBX1),179-182 administered intradermally in combination with ligase (MDM2), SOX2, and Y box-binding protein 1 (YBX1),179-182 administered intradermally in combination with IL-12-coding plasmid and EBRT (NCT02172911)

Abbreviations: CIN, cervical intraepithelial neoplasia; EBRT, external beam radiation therapy; GM-CSF, granulocyte macrophage colony-stimulating factor; HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus; IL-12, interleukin-12; i.m., intra musculum; TAA, tumor-associated antigen.

*Initiated after 2014, March 1st.

Table 1 Clinical trials recently started to evaluate the therapeutic profile of DNA-based anticancer vaccines*

| Indication(s) | Phase | Status | TAA(s) | Co-encoded molecule(s) | Co-therapy | Vector | Delivery | Ref. |
|---------------|-------|--------|--------|------------------------|------------|--------|----------|------|
| Breast carcinoma | I     | Not yet recruiting | Personalized epitopes | None | None | Naked plasmid | i.m. (electroporation) | NCT02348320 |
| Breast carcinoma | I     | Not yet recruiting | CDH3 ENG MDM2 SOX2 YBX1 | None | GM-CSF | Naked plasmid | Intradermal | NCT02157051 |
| Breast carcinoma | I     | Recruiting | SCGB2A2 | None | Endocrine therapy | Naked plasmid | i.m. (electroporation) | NCT02204098 |
| Cervical carcinoma | I/II  | Recruiting | HPV E6/E7 | None | IL-12-coding plasmid and EBRT | Naked plasmid | i.m. (electroporation) | NCT02139267 |
| HNSCC | I     | Not yet recruiting | Personalized epitopes | None | None | MRC-5 cells | Intradermal | NCT02211027 |
| HNSCC | I     | Recruiting | HPV-6 antigens | None | IL-12-coding plasmid | Naked plasmid | i.m. (electroporation) | NCT02241369 |
| HNSCC | I     | Recruiting | HPV-6 antigens | None | IL-12-coding plasmid | Naked plasmid | i.m. (electroporation) | NCT02163057 |

Co-therapy

Table 1 Clinical trials recently started to evaluate the therapeutic profile of DNA-based anticancer vaccines*
(source http://clinicaltrials.gov/). NCT01145508 (a Phase II study) is investigating the therapeutic profile of a vaccination strategy based on the sequential, subcutaneous administration of PROSTVAC-V/TRICOM and PROSTVAC-E/TRICOM, alone of combined with conventional chemotherapy, to subjects with metastatic, castration-resistant prostate carcinoma. So far, 10 individuals have been enrolled in the study, 8 of which effectively started treatment with either chemotherapy only (2 patients) or chemotherapy plus vaccination (6 patients). Only 3 patients completed the entire course of therapy (1 from the chemotherapy arm, 2 from the chemotherapy plus vaccination arm), owing to adverse effects, death or physician’s decision. The limited number of patients enrolled in the study, however, prevents concluding to what extent these toxicities truly relate to vaccination (source http://clinicaltrials.gov/).

Concluding Remarks

Accumulating preclinical and clinical evidence indicates that DNA-based anticancer vaccines are relatively ineffective when employed as standalone immunotherapeutic interventions. Along with the unprecedented clinical success recently obtained with metastatic, castration-resistant prostate carcinoma. So regrettably, the number of trials initiated during the last 13 months to test this immunotherapeutic paradigm. Nonetheless, we are positive that combining DNA-based anticancer vaccines with appropriate immunostimulants, be them checkpoint blockers, other immunomodulatory monoclonal antibodies, TLR agonists or cytokines, may pave the way to the development of next-generation combinatorial regimens with improved clinical efficacy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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