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REVIEW

Prostate cancer vaccines: the long road to clinical application

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Abstract Cancer vaccines as a modality of immune-based cancer treatment offer the promise of a non-toxic and efficacious therapeutic alternative for patients. Emerging data suggest that response to vaccination largely depends on the magnitude of the type I immune response generated, epitope spreading and immunogenic modulation of the tumor. Moreover, accumulating evidence suggests that cancer vaccines will likely induce better results in patients with low tumor burden and less aggressive disease. To induce long-lasting clinical responses, vaccines will need to be combined with immunoregulatory agents to overcome tumor-related immune suppression. Immunotherapy, as a treatment modality for prostate cancer, has received significant attention in the past few years. The most intriguing characteristics that make prostate cancer a preferred target for immune-based treatments are (1) its relative indolence which allows sufficient time for the immune system to develop meaningful antitumor responses; (2) prostate tumor-associated antigens are mainly tissue-lineage antigens, and thus, antitumor responses will preferentially target prostate cancer cells. But, also in the event of eradication of normal prostate epithelium as a result of immune attack, this will have no clinical consequences because the prostate gland is not a vital organ; (3) the use of prostate-specific antigen for early detection of recurrent disease allows for the initiation of vaccine immunotherapy while tumor burden is still minimal. Finally, for improving clinical outcome further to increasing vaccine potency, it is imperative to recognize prognostic and predictive biomarkers of clinical benefit that may guide to select the therapeutic strategies for patients most likely to gain benefit.

Keywords Prostate cancer · Cancer vaccines · Immunomodulation · Epitope spreading · Cross-presentation · Biomarkers

Abbreviations

ADT	Androgen deprivation therapy
ANO7	Anoctamin 7
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
FDA	Food and Drug Administration
IFNγ	Interferon gamma
mCRPC	Metastatic castration-resistant prostate cancer
MUC1	Mucin 1
NK	Natural killer
NY-ESO-1	New York esophageal squamous cell carcinoma
OS	Overall survival
PAP	Prostatic acid phosphatase
PBMC	Peripheral blood mononuclear cells
PD-1	Programmed death 1 receptor
PFS	Progression-free survival
PSA	Prostate-specific antigen
PSCA	Prostate stem cell antigen
PSMA	Prostate-specific membrane antigen
RECIST	Response Evaluation Criteria in Solid Tumors
TAA	Tumor-associated antigen
TGFβ	Transforming growth factor beta

Introduction

The continuous interaction between various elements of the immune system and the developing autologous tumor

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has been extensively studied under the concept of immunoediting [1]. The latter comprises dynamic processes under and during which the immune system not only protects the host against cancer progression but also shapes the immunogenicity of the emerging tumors. Precise analyses and understanding of the various mechanisms underlying such dynamic processes have provided the justification for immune-based therapies for cancer. Single or combined immunotherapies have demonstrated remarkable clinical responses, unequivocally establishing a quite promising role for the immune system in cancer treatment. Nevertheless, long-lasting clinical responses have been observed only in a limited number of patients [2]. This poses a central challenge in increasing the success rates of immune-based treatments by identifying the ideal patient population to benefit from immunotherapies and how we can use information about their tumors for designing more effective treatments.

Immunotherapy is now an established treatment approach for prostate cancer, with multiple clinical trials demonstrating improvements in overall survival (OS) [3]. These studies include randomized controlled vaccination trials with sipuleucel-T (the first FDA-approved vaccine) and another with a recombinant virus-based vaccine, PROSTVAC-VF, both of which rely on stimulating the immune system to target prostate proteins [3]. Although traditional treatments for prostate cancer lack specificity and mostly focussed on androgen deprivation and chemotherapy, immunotherapeutic approaches rely on activating the hosts' immune lymphocytes to specifically attack prostate cancer cells and generate tumor-specific memory [4, 5]. At this point, we should mention the complex dynamics which exist between traditional antineoplastic treatments and their positive effects on the immune system by stimulation of the antigenicity of malignant cells, their immunogenicity, or their susceptibility to immune attack [6]. Thus, chemotherapy or androgen deprivation in prostate cancer may act as immune modulators, further increasing the potency of therapeutic vaccines. Moreover, immune checkpoint-blockade strategies have been shown to boost endogenous antitumor immunity by dampening tumor-induced suppressor signaling [7]. Ipilimumab, a human monoclonal antibody, inhibits suppressive signals in T cells by binding to CTLA4 receptors and in this way blocking their interaction with B7. This FDA-approved immune checkpoint inhibitor has shown encouraging results when combined with PROSTVAC-VF in clinical trials in patients with advanced prostate cancer [8]. An intensified antitumor immune response will ultimately result in more efficient lysis of the autologous tumor. During the process of tumor cell killing by activated cytotoxic effectors, dendritic cells (DC) may expand the antitumor T cell response via cross-presentation of tumor antigens released by the lysed tumor cells. In this way, therapeutic vaccines may induce a broader, and potentially more clinically relevant, immune response than the one initially targeted by the vaccine, a phenomenon known as antigen spreading [9].

There are general aspects that have emerged with advancements in prostate cancer immunotherapy, all of which may have an impact on clinical outcomes. These include the time interval required for antitumor immunity to be initiated and translated into clinical responses with subsequent improvement in OS, initial progression of disease, and lack of intermediate biomarkers that could provide definitive information as to whether and to which extent immune-based therapies are working. In this review, we focus on the promising issues in immunotherapy that may be translated into established treatments in prostate cancer.

Kinetics of clinical response to a therapeutic vaccine

Although it took some time, it is now well understood that therapeutic vaccines have different targets and follow different kinetics compared to cytotoxic drugs [10]. The primary target of vaccines is not the tumor, as this is the case with chemotherapeutic drugs, but the immune system which subsequently attacks the tumor. Upon conventional cytoreductive treatments, the tumor load will be affected during or shortly after administration, but tumors will usually rebound after discontinuation of the drug [10]. In contrast, vaccine-induced immune responses will take time to robustly develop enough to escalate into antitumor responses. Additionally, a therapeutic vaccine should be capable of inducing tumor-specific immunological memory, so that the vaccine-induced antitumor immunity can persist long after the end of vaccinations or boosters [11]. In this way, a therapeutic vaccine will induce a cumulative slowing pressure on tumor growth rates, which will continue beyond the end of the vaccinations. Consequently, tumor growth initially may not be affected at all, but eventually it will be stabilized and will slow down before the tumor shrinks, which implies that it will take a considerable period of time before the antitumor responses can be translated into clinical responses [12]. Thus, despite successful activation of a patient's immune system through vaccination, the elicited antitumor responses will most likely not translate into progression-free survival (PFS) improvements, but, rather, it will take several months before these will induce substantial improvements in OS. Indeed, in clinical trials of sipuleucel-T [13] and PROSTVAC-VF with metastatic castrate-resistant prostate cancer (CRPC) patients and of ipilimumab with advanced melanoma patients, immunotherapies appeared to have provided marked benefit which, although not apparent during treatment, was consistent with subsequent development of

a beneficial immune response. In these trials, PFS as an endpoint was not met, although a statistically significant and clinically meaningful improvement in OS was demonstrated. It is, therefore, conceivable and has also been suggested [14] that immunotherapies will induce a novel pattern of response rates which may be misinterpreted by RECIST criteria and as a consequence, novel immune response criteria have been proposed for the evaluation of immunotherapy-induced clinical outcomes.

Cross-presentation and epitope spreading

Cross-presentation takes place when exogenous antigenic peptides are displayed on MHC class I molecules for T cell recognition either after direct binding or after gaining access to the processing and presentation machinery of a DC, which consequently leads to the induction of CD8+ T cell responses [15]. Efficient triggering of tumor-specific CD8+ T cells is a most important therapeutic modality because it generates potent tumor cell killing, but also provides the host with long-lasting memory responses that may prevent cancer recurrences. Cross-priming of tumor-reactive T cells through tumor vaccines constitutes a major goal in cancer immunotherapy. Moreover, natural adaptive antitumor immunity is thought to be generated via cross-priming of tumor-reactive cytotoxic CD8+ T cells [16]. Although there is convincing evidence that cross-presentation of tumor antigens is efficiently taking place in lymphoid organs [17], this may not correlate with tumor regression [17], indicating poor infiltration of the cancer microenvironment by effector T cells or resistance mechanisms by the tumor [1]. This suggests that cross-priming within the cancer microenvironment would be mostly desirable under conditions allowing activation of therapeutic antitumor immunity. Therefore, it is reasonable to ponder the situation within the tumor microenvironment which would tip the balance in favor of an effective immunosurveillance. Infiltration of tumors by vaccine-induced T cells secreting Th1 cytokines could activate local tumor DCs by restoring their antigen-processing machinery, upregulate MHC as well as accessory molecules, and trigger IL-12 production, all of which would enhance cross-priming. Thus, providing optimal conditions for effective cross-presentation may be an essential prerequisite for determining host response to tumor induced by active immunomodulation. The development of epitope spreading could be considered a consequence of cross-priming.

Epitope and/or antigen spreading occurs when a specific epitope elicits an immune response initially, but as the immune reaction progresses, antigens distinct from and not cross-reactive with the priming antigen become new targets [9, 18]. Usually, the “driver” epitope is the one included in the vaccine formulation, while the new antigens, which are targeted later on, do not constitute part of the vaccine. Recent studies have suggested that epitope spreading is associated with improved outcomes after the administration of a cancer vaccine [19]. The generation of epitope spreading during active immunotherapies and its relation to clinical efficacy have been reported in patients with melanoma, renal cell carcinoma, and breast cancer [19]. There are also reports from clinical trials in prostate cancer describing this phenomenon. In a phase II trial, PBMCs from patients with localized prostate cancer vaccinated with PROSTVAC-VF plus GM-CSF as an adjuvant were evaluated for the presence of T cells specifically recognizing HLA-A2 restricted epitopes of prostate cancer-associated antigens including PSMA, PAP, PSCA, and MUC-1 besides PSA [20]. The vast majority of patients developed T cell responses to at least one of the above TAAs post-vaccination. In a similar study using PROSTVAC-VF plus interleukin-2 as an adjuvant [21], patients with localized prostate cancer developed immunoreactivity to XAGE-1 and to PAGE-4, both members of the PAGE/GAGE gene family of antigens that are expressed in prostate carcinoma cells. T cell responses specific to MUC-1 were also detected. Antigen spreading has also been reported in a phase I dose escalation trial with vaccinated metastatic CRPC patients under combined treatment with ipilimumab. Patients undergoing treatment developed T cell responses against TAAs PSA, MUC1, ANO7, and brachyury peptide RP2 [22]. Patients with metastatic CRPC on docetaxel who also received vaccine treatment displayed a progression-free survival that was significantly prolonged versus those who received chemotherapy alone [23]. Although being negative before vaccinations, most of these patients developed T cell responses to at least one of the prostate-associated TAAs, PSMA, PAP, and MUC-1 at various time-points post-vaccination. Thus, it seems that antigen spreading can be used as a biomarker in peripheral blood to measure the magnitude of type I immune responses generated with vaccination. Given its nature as an iterative process, antigen spreading may persist for longer periods following termination of the vaccinations. Therefore, in addition to the T cell immune memory generated by specific recognition of the tumor antigen targeted by a vaccine, antigen spreading may further curtail the growth rate of the tumor for months to years after vaccine administration. This slowed growth rate can eventually lead to improved survival.

Immunogenic modulation through combination therapy

There is accumulating evidence that suggests that conventional therapies in malignant diseases may provide survival benefits not only through direct killing of tumor cells but also via immunogenic modulation, a phenomenon which refers to changes in both the immune phenotype of tumor

cells rendering them more susceptible to lysis by elements of the immune system, as well as the immune system itself [24, 25]. Thus, tumor therapies should have the potential to generate or, when preexisting, to enhance endogenous antitumor immunity via immunogenic modulation. By doing so, conventional therapies in synergy with immunotherapies may optimize clinical responses. Data suggest that taxane-based chemotherapy actually exerts beneficial immunomodulatory effects through a variety of mechanisms, including cytokine production, T cell infiltration of tumors, and maturation of DCs [6, 26, 27]. Consequently, cytotoxic drugs may have effects that go beyond direct inhibition of tumor growth rates. The taxane docetaxel, in combination with active immunotherapies in metastatic CRPC patients, has been demonstrated to increase T cell reactivity to PSA and to improve clinical responses measured as PSA decreases and increases in disease-free survival [23, 28].

By upregulating MHC class I, adhesion molecules and Fas, and inducing production of cytokines, chemokines, in the tumor immune microenvironment [29], radiotherapy (RT) has a potential impact on tumor growth which may be pertinent to immunological correlates [30]. In a patient with melanoma treated with ipilimumab, tumor shrinkage after radiotherapy was associated with antibody responses to the cancer–testis antigen NY-ESO-1, increases in peripheral blood IFNγ-producing CD4+ T cells, and humoral epitope spreading [31]. A combination regimen including a pox viral PSA-targeting vaccine with standard radiotherapy in patients with localized prostate cancer has been successful in potentiating T cell immunity to PSA as well as to other prostate cancer-associated antigens not included in the vaccine [20]. Samarium (Sm)-153 is a radiopharmaceutical which targets osteoblastic bone lesions. In experimental tumor models, Sm-153 could change tumor phenotype by upregulation of Fas, MHC class I, and tumor-associated antigens, thereby rendering tumor cells more susceptible to immune-mediated killing [32]. In a phase II multicenter trial of Sm-153 with or without the PROSTVAC-VF vaccine in metastatic CRPC patients after docetaxel, the combined treatment with vaccine plus radiation induced increased responses to PSA and clinical responses measured as PFS [33]. There is also a biologic rationale for combining hormonal treatment with immunotherapy. Androgen deprivation therapy (ADT) has been shown to quantitatively affect T cells in peripheral lymphoid tissues and to enhance their antigen-specific activation as well as their proliferation upon T cell receptor and CD28-mediated co-stimulation [34, 35]. Moreover, androgen ablation induced prominent T cell infiltration of the human prostate normal epithelial and tumor sites. T cell infiltration consisted predominantly of CD4+ T cells and comparatively fewer numbers of CD8+ T cells [36]. Androgen ablation was also shown to mitigate prostate-specific tolerance, allowing prostate-specific T cells to expand and develop effector function after vaccination [37]. Enzalutamide, a novel androgen receptor antagonist, has been shown to enhance thymic function in experimental animals and, in this way, to increase the frequency of T cells responding to an antitumor therapeutic vaccine [38]. Enzalutamide has also been shown to mediate immunogenic modulation in prostate tumor cells rendering them more susceptible to immune attack. Studies in TRAMP mice demonstrated significant prolongation in survival when an otherwise inert vaccine was combined with enzalutamide [38]. In a case report, a patient with CRPC with PSA progression after an initial response to enzalutamide experienced a complete PSA response to the immunotherapeutic agent sipuleucel-T while continuing with enzalutamide [39]. The results from this report suggest that the combination of sipuleucel-T plus enzalutamide warrants further investigation in a larger cohort of prostate cancer patients with advanced disease. Clinical trials evaluating the efficacy of the combination of PROSTVAC-VF and enzalutamide in patients with CRPC (NCT01867333), as well as those with non-metastatic castration-sensitive prostate cancer (NCT01875250), are currently underway (www.clinicaltrials.gov).

Contribution of preexisting antitumor immune responses to the therapeutic management of prostate cancer

One of the most compelling fields for investigation in cancer immunotherapy is the potentiation of endogenous anticancer adaptive immunity to ameliorate conventional therapies. The era of exploitation of endogenous antitumor immunity for improving clinical outcome began more than a decade ago via the immunoediting theory, which supports the notion that the immune system generates and maintains an inflammatory status resulting in the activation of innate and adaptive immune responses which prevent the expansion of tumor cells during the elimination phase. These responses may also operate during equilibrium for preventing the outgrowth of residual tumor cells. However, such extrinsic tumor-suppressor mechanisms of immunity will be circumvented by progressively growing tumors in the escape phase through a variety of mechanisms mostly based on the generation of a hostile suppressive milieu within the tumor environment. As a continuum of the immunoediting theory, a plethora of convincing evidence provided strong support for the idea that the history of immune surveillance in established tumors is associated with a more favorable prognosis and/or response to treatment. Thus, in order to be effective, immunotherapies need to mitigate cancer-induced immunosuppression by reinstating preexistent immunosurveillance. Theoretically, immunomodulatory strategies should be able to activate patients' T cell repertoires against the entire antigenic repertoire of their tumor cells rather than to a single tumor antigen. Therefore,

one should expect that by applying therapies targeting negative regulators of natural immunity, a massive antitumor response would be generated enabling multiple T cell clones, specifically recognizing an abundance of tumor antigens to become activated and thus function in the immunosuppressive tumor microenvironment. Indeed, checkpoint inhibitors such as ipilimumab (anti-CTLA-4) and nivolumab (anti-PD-1), applied alone or in combination, have shown remarkable antitumor effects against a range of different cancers including melanoma, non-small cell lung cancer, and renal carcinoma. Moreover, immunomodulatory immunotherapies have been combined with vaccines in an effort to improve the immune response against the targeted tumor antigens. Combination of immune checkpoint protein blockade with immune-enhancing therapeutic modalities might subvert effector T cell immunosuppression while increasing the clinical efficacy of T cell-mediated immunotherapies. This will ultimately amplify immune responses that are focussed on relevant tumor antigens resulting in long-lasting antitumor immunity. In a phase I dose escalation trial in patients with CRPC, GVAX and ipilimumab had an acceptable safety profile with almost 30 % of the patients experiencing manageable grade 3 immune-related adverse effects. From an immunologic point of view, tumor-reactive antibodies induced by treatment were identified, including antibodies to filamin B, PSMA, and NY-ESO-1. Biopsies of injection sites showed T cell infiltration and granzyme B expression. Clinically, 25 % of the patients responded with PSA declines of >50 %. Median OS for all patients was 34.4 months, with a 2-year overall survival of 73 %. Importantly, flow cytometric analyses showed CTLA-4+ by CD4+ T cells to be a dominant predictor for OS after GVAX/ipilimumab [40, 41]. PROSTVAC-VF has also been combined with ipilimumab. A phase I trial in chemotherapy-naïve metastatic CRPC patients, demonstrated an OS of 31.8 months with a 74 % survival probability at 24 months. The median Halabi-predicted OS for all patients was 18.5 months [40]. An updated follow-up of this study showed strong associations of prolonged OS with certain T and natural killer (NK) cell subsets [8]. Additional, randomized studies are required to further explore immune checkpoint blockade in combination with therapeutic vaccines in metastatic CRPC.

Preexisting immunity in prostate cancer patients correlates with immunological and clinical responses to immunotherapy: the AE37 vaccine paradigm

As outlined above, immune manipulations via conventional treatments or immunomodulatory antibodies aiming at boosting naturally occurring immunosurveillance, in combination with vaccines, may tip the balance between tumor progression and elimination. Although clinical responses have been induced in a significant number of patients, identifying the appropriate immune biomarkers would optimize patient selection for such interventions. The immune score which reflects the number, type, and location of T lymphocytes infiltrating human solid tumors has been considered to be critically important for tumor progression and shown to affect the prognosis of patients [42]. In addition to scoring T lymphocytes at tumor sites, the frequency and functions of T cells circulating in the peripheral blood of cancer patients have also been examined as potential biomarkers [43]. Recently, it was shown that the presence of naturally occurring circulating T cells responding to tumor antigens had strongly independent prognostic relevance on survival in advanced melanoma [44]. Therefore, biomarkers reliably reflecting preexisting antitumor immune responses are indispensable for enhancing the success of conventional and immune-based cancer therapies.

By retrospectively analyzing the data from our clinical trial with prostate cancer patients vaccinated and boosted with a HER-2/neu vaccine, we found that patients who had increased preexisting interferon gamma (IFNγ) immunity to the vaccine developed immunological responses during and post-vaccinations, which were correlated with clinical benefits. In contrast, we found that patients with high transforming growth factor beta (TGFβ) levels at baseline had low preexisting immunity, which was associated with decreased vaccine-induced immunological responses and shorter OS [45]. Based on the inverse relation between preexisting TGFβ and INFγ immunity, we may propose that low levels of TGFβ at baseline may reflect a less hostile immunosuppressive milieu, inefficient in robustly suppressing patients' immune systems, thus allowing the generation of potent immunological responses upon vaccination (Fig. 1). Given the synergism between immunotherapy with standard chemotherapies and hormonal treatments [5], patients with low preexisting TGFβ levels, having a more or less intact immune system, would benefit from standard therapies. In such a case, standard therapies could act synergistically with endogenous antitumor immunity producing measurable clinical benefits in addition to extending survival. Thus, TGFβ as well as IFNγ immunity to the HER-2/neu vaccine at baseline may function as factors for both OS prognosis and prediction of immunological responses to AE37 vaccination. Our retrospective analyses also indicated significant benefit of AE37 vaccination among patients expressing HLA-A24 and/or HLA-DR11 [Anastasopoulou et al. submitted for publication]. The vast majority of these patients had low preexisting TGFβ and developed strong immunological responses, which were correlated with prolonged survival, demonstrating that these two HLA alleles have good prognostic impact. In contrast, we found that AE37-vaccinated patients of ours who carried the HLA-A2 allele had increased suppressor elements and a worse prognosis [Perez et al. unpublished observations]. This finding is in line with reports from Masucci's group who have described HLA-A2 as an independent poor prognostic factor in ovarian

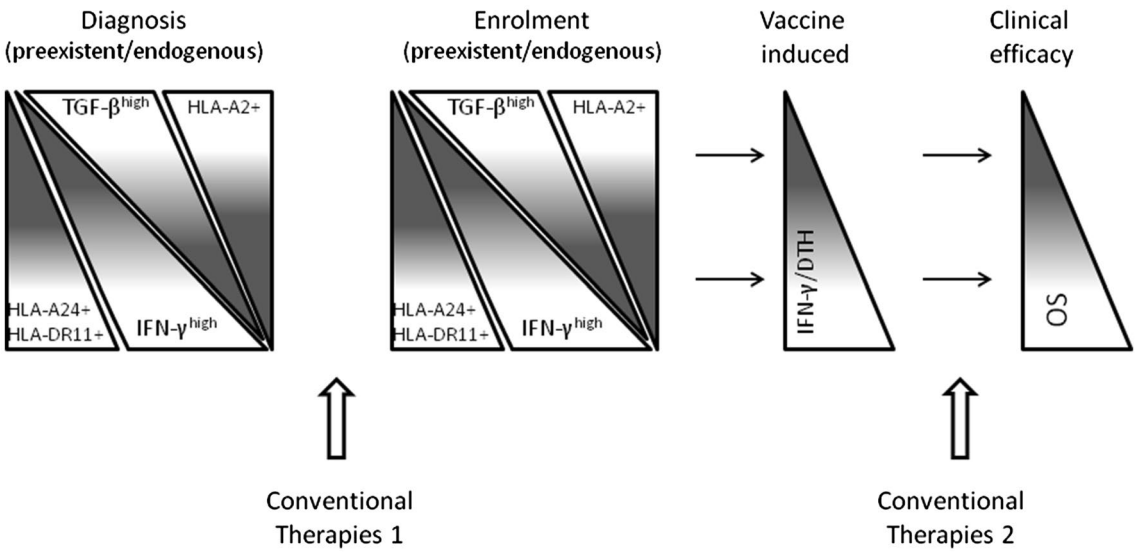

Fig. 1 Roadmap and biomarkers indicative of OS in patients vaccinated with AE37. Preexistent immunity to AE36 dictates both immunological and clinical responses to AE37 vaccination in prostate cancer patients. The majority of non-vaccinated patients having increased frequencies of circulating T cells producing IFNγ in response to stimulation with AE36 will benefit from vaccination with the hybrid AE37 vaccine developing immunological (IFNγ and DTH) as well as clinical (OS) responses. The majority of patients expressing HLA-A24 and/or HLA-DR11 have lower circulating TGFβ levels and higher preexistent immunity as opposed to their HLA-A2-expressing counterparts. *Triangles* in their *bright parts* indicate increased frequencies for patients (1) expressing the depicted HLA alleles, (2) having higher IFNγ or TGFβ levels or (3) displaying higher vaccine-induced immunity and increased OS. The *dark parts* of these *triangles* represent the transition from high to low/no expression of the respective biomarkers. *Note 1* We only hypothesize for the preexistent levels of IFNγ and TGFβ at diagnosis (since such measurements were not undertaken). *Note 2* Conventional therapies applied before enrollment and after vaccinations may have synergized with the vaccine for the outcome of immunological and clinical responses

and prostate cancer [46] and in patients with HPV-positive tonsillar and base of tongue cancer [47]. Taken altogether, our studies underscore the importance of ascertaining a positive HLA-A24 and HLA-DR11 status or a negative HLA-A2, as putative prognosticators for immunological and clinical responses to AE37 vaccination (Fig. 1). Given that the relation between preexisting increased IFNγ-HER-2/neu immunity and low TGFβ levels was decisive for enhanced immunological and improved clinical responses to AE37 vaccination, we may suggest that less suppressed endogenous immunity can be positively modulated by vaccinations, resulting in clinical benefit (Fig. 1). Additionally, less suppressed endogenous immunity could successfully synergize with standard therapies, with or without concomitant immunotherapy, for producing measurable clinical benefits in addition to extending survival.

Conclusion

Recent advancements in cancer therapies have highlighted the essential role of endogenous antitumor immunity in the generation of long-lasting clinical responses. An endogenous immune response against an immunogenic tumor would consist of a multitude of T cell clones, specifically targeting different immunogenic tumor-protein epitopes and mounting a robust and durable immune response. Even so, the evolutionary process of complimentary interactions between the immune system and the tumor will likely culminate in tumor escape [1]. Accumulating knowledge derived from clinical studies strongly supports the cooperation between preexisting tumor-directed immunological responses with conventional chemotherapy, targeted therapies, and immunotherapies [6, 29, 30, 34]. In essence, all these combination modalities act as immunomodulators by restoring and/or enhancing endogenous T cell responses after counteracting tumor-induced immunosuppressive mechanisms. It is, therefore, important to know which immunologic mechanisms are active in cancer patients in order to apply the appropriate therapy(ies). To this end, predictive biomarkers will be useful for selecting patients most likely to benefit from tumor-targeted and/or immune-based therapies. Emerging therapies in prostate cancer include therapeutic vaccination and immune checkpoint blockade [22, 39, 40, 48]. Clinical results from phase III trials [BNIT-PRV-301/NCT01322490, NCT01057810] are expected to reveal which immunologic circuits are active or suppressed so that these can be appropriately co-targeted by combination treatments in order to optimally harness patients' immune systems to fight the autologous tumor. Tumor-specific memory will be a desirable result from these combined approaches to inducing permanent tumor

immunosurveillance and preventing or delaying tumor escape, thus extending overall survival in prostate cancer patients.

Epilog

It has been a long time now (almost 15 years) since therapeutic vaccines entered preclinical and clinical studies as treatment options for prostate cancer [49]. As a result, sipuleucel-T was the first cellular vaccine product to be approved by the FDA in 2010, as active immunotherapy for mCRPC patients [8]. However, criticism raised against sipuleucel-T-induced survival benefit from the IMPACT phase III trial has more or less mitigated our initial enthusiasm for the promotion of immunotherapy as a standard modality in prostate cancer. On the other hand, after 2010, a plethora of new treatment modalities (ADT and radiotherapy and chemotherapies) for mCRPC have emerged with measurable clinical efficacy [48], challenging the role of immunotherapies in prostate cancer. At present, the most efficacious, possibly beneficial way to utilize the unique properties of vaccination, such as specificity and memory, and to enhance its therapeutic potential, will be to combine this active form of immunotherapy with standard tumor-directed chemotherapy, radiotherapy, and hormonal therapy or with targeted therapies such as immunomodulatory antibodies and small molecule inhibitors which are on the rise in prostate cancer therapy [5, 50]. Indeed, a recent report suggested that the addition of immune checkpoint inhibition may augment the clinical benefit of vaccines in mCRPC [22]. Thus, although therapeutic vaccines for prostate cancer treatment are no longer in their "infancy" and the results so far from their application as single agents are not quite as promising for inducing permanent clinical responses as anticipated (maybe "Too Old to Rock 'n' Roll"), still there is plenty of room for improving their efficacy. Moving along this direction, we look forward to integrating vaccination with other treatment modalities for prostate cancer to harness both vaccine-induced tumor-specific immunity and the endogenous, prevailing one, thus establishing a renaissance ("Too Young to Die") in the progress toward realization of therapeutic cancer vaccines.

Conflict of interest The authors declare no conflict of interest.

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