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Trial Watch: Peptide-based anticancer vaccines

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Abbreviations: APC, antigen-presenting cell; CMP, carbohydrate-mimetic peptide; FDA, Food and Drug Administration; EGFR, epidermal growth factor receptor; GM-CSF, granulocyte macrophage colony stimulating factor; HPV, human papillomavirus; IDH1, isocitrate dehydrogenase 1 (NADP+), soluble; IDO1, indoleamine 2, 3-dioxygenase 1; IFNα, interferon α; IL-2, interleukin-2; MUC1, mucin 1; NSCLC, non-small cell lung carcinoma; PADRE, pan-DR binding peptide epitope; PPV, personalized peptide vaccination; SLP, synthetic long peptide; TAA, tumor-associated antigen; TERT, telomerase reverse transcriptase; TLR, Toll-like receptor; TRA, tumor rejection antigen.

Malignant cells express antigens that can be harnessed to elicit anticancer immune responses. One approach to achieve such goal consists in the administration of tumor-associated antigens (TAAs) or peptides thereof as recombinant proteins in the presence of adequate adjuvants. Throughout the past decade, peptide vaccines have been shown to mediate antineoplastic effects in various murine tumor models, especially when administered in the context of potent immunostimulatory regimens. In spite of multiple limitations, first of all the fact that anticancer vaccines are often employed as therapeutic (rather than prophylactic) agents, this immunotherapeutic paradigm has been intensively investigated in clinical scenarios, with promising results. Currently, both experimentalists and clinicians are focusing their efforts on the identification of so-called tumor rejection antigens, i.e., TAAs that can elicit an immune response leading to disease eradication, as well as to combinatorial immunostimulatory interventions with superior adjuvant activity in patients. Here, we summarize the latest advances in the development of peptide vaccines for cancer therapy.

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Introduction

It is now widely accepted that malignant cells do not go completely unnoticed by the immune system. Indeed, in most if not all cases, established neoplasms develop when natural immunosurveillance, i.e., the process whereby the immune system keeps under control potentially malignant cells, fails.[1-7] Such an escape from immunosurveillance originate from several, non-mutually exclusive mechanisms, including changes in the antigenic/immunogenic properties of cancer cells themselves as well as the establishment of robust immunosuppressive networks that operate both locally and systemically.[8-14] Nonetheless, neoplastic cells often express a set of polypeptides that differs from that of their normal counterparts and, at least theoretically, can be harnessed to elicit a relatively specific immune response.[15-21] The peculiar antigenic profile of cancer cells reflects (1) malignant transformation itself, which is normally associated with primary genetic and epigenetic changes that not only can result in the synthesis of mutant/fusion proteins, but also influence gene expression at a global level;[22-25] (2) genetic/genomic instability, i.e., the tendency of neoplastic cells to accumulate additional genetic changes (be them punctual or of higher magnitude), further increasing the amount of potentially immunogenic polypeptides;[26-30] (3) intracellular and microenvironmental factors that promote adaptive responses linked to changes in protein translation and proteasomal degradation, and hence directly affecting the so-called immunopeptidome, i.e., the set of peptides presented on the cell surface in complex with MHC molecules.[31-33] Thus, malignant cells near-to-invariably express so-called "tumor-associated antigens" (TAAs), i.e., antigens that qualitatively or quantitatively differ from those expressed by normal cells of the same type.[18-20] Of note, TAAs can be (1) viral, in the case of virus-

induced tumors (e.g., the E6 and E7 proteins of human papillomavirus type 16, HPV-16, which is associated with cervical and oropharyngeal carcinoma); (2) unique, when they reflect a genetic alteration that is proper of a single cancer cell and its progeny (e.g., the B-cell receptor expressed by some form of lymphoma); (3) tumor-specific, when they are not expressed by normal cells but are found in different neoplasms of the same type (e.g., the BCR-ABL fusion protein, which is expressed by a vast majority of chronic lymphocytic leukemia); (4) shared, when they are expressed by malignant cells as well as by non-transformed cells of some type.[18-20,34] Shared TAAs include oncofetal antigens, which are expressed only during embryonic development, as well as cancer-testis antigens, whose normal expression is restricted to male germ cells in the testis[20,35-38]

Several immunotherapeutic interventions have been developed throughout the past decade to harness TAAs for eliciting tumor-specific adaptive immune responses of therapeutic value.[39-41] One of such approaches relies on the administration of purified or recombinant TAAs (or peptides thereof) in the presence of adequate immunostimulatory molecules (so-called adjuvants).[42-46] Accumulating preclinical and clinical data demonstrate that TAAs or peptides thereof administered as standalone adjuvanted interventions can indeed elicit tumor-targeting immune responses. However, the antineoplastic activity of such responses is often limited.[47-49] On the one hand, this reflects immunoediting, i.e., the fact that neoplasms become established under the selective pressure imposed by a continuous interaction with the immune system of the host.[3,6,50-55] Immunoediting has 2 major consequences: (1) established malignant cells often express very low levels of antigenic peptides and immunostimulatory signals on their surface; and (2) tumors normally generate a complex immunosuppressive network that operate both locally and systemically, involving soluble signals as well as cellular components.[8-12] On the other hand, the limited anticancer activity of TAA-targeting vaccines originates from the fact that, contrary to vaccines against infectious diseases (which are used for prophylaxis), these preparations are generally employed in a therapeutic setting.[47-49] Vaccines against an increasing number or infectious agents are indeed highly effective as they generate humoral immunity against one or a few exogenous antigenic epitopes.[56-59] Although the importance of humoral immunity in anticancer immunosurveillance is being reconsidered,[60-62] tumor-targeting humoral responses developing in a therapeutic setting are generally insufficient to mediate tumor rejection.[63-66] Thus, anticancer vaccines must elicit cellular responses that are (1) specific for an endogenous (and in some cases potentially cross-reactive) antigen; (2) sufficiently intense to mediate robust cytotoxic effects against malignant cells; and (3) sufficiently broad to overcome the intrinsic heterogeneity of neoplastic cells and mediate tumor eradication rather than immunoediting only. Several approaches have been developed to ameliorate the ability of TAAs and peptides thereof to elicit therapeutically relevant anticancer immune responses. Nowadays, great interest is attracted by combinatorial regimens involving other immunostimulatory interventions,[67] including (but not limited to) immunogenic chemotherapeutics,[68-71] radiotherapy,[72,73] and immune checkpoint blockers.[74,75] Importantly, immune responses against antigens that are not directly targeted by the original vaccine formulation can also develop as a consequence of "epitope spreading".[76-80] Epitope spreading may occur as cancer cells succumbing to vaccine-elicited T lymphocytes release potentially antigenic TAAs along with damage-associated molecular patterns, which deliver potent immunostimulatory signals.[81-85] Of note, the repertoire of T cells elicited in this setting is broad and relatively prone to mediate bona fide therapeutic effects.[86]

As it stands, no anticancer vaccine based on recombinant/purified TAAs or peptides thereof is approved by international regulatory agencies for use in subjects affected by malignant conditions. Indeed, Cervarix® and Gardasil®, 2 multivalent recombinant vaccines that have been approved by the US Food and Drug Administration (FDA) for use in humans as soon as in 2009, constitute a prophylactic measure against infection by HPV-16 and -18,[87-89] and hence cannot be considered as bona fide anticancer vaccines. In line with this notion, while Cervarix® and Gardasil® efficiently protect young women against HPV infections and hence the development of HPV-related cervical carcinoma,[56,87-89] they fail to mediate significant antineoplastic effects in HPV^+ cervical carcinoma patients.[47,48]

Along the lines of our Trial Watch series, here we report recent progress in the clinical development of recombinant/purified TAAs or peptides thereof as therapeutic interventions for cancer therapy.

Literature Update

During the last 13 months, the results of no less than 60 clinical trials investigating the safety and efficacy of recombinant/purified TAAs or peptides thereof as therapeutic interventions in cancer patients have been published in the peer-reviewed scientific literature (sources http://www.ncbi.nlm.nih.gov/pubmed and http://meetinglibrary.asco.org/abstracts). Most of these studies relied on the administration of one or more short (i.e., 8–12 residues), MHC-restricted, TAA-derived peptides as standalone adjuvanted interventions or in combination with one or more (immuno)therapeutic or immunostimulatory agents.[90-142] These epitopes are expected to bind MHC molecules on the surface of antigen-presenting cells (APCs) and hence be directly presented to T cells.[143-145] In addition, a few clinical teams tested the therapeutic profile of full-length TAAs,[146] "synthetic long peptides" (SLPs), i.e., TAA-derived peptides of 25–35 amino acids;[147-150] or "carbohydrate-mimetic peptides" (CMPs), i.e., synthetic polypeptides that mimic the structure of carbohydrate TAAs.[151] The use of SLPs as therapeutic anticancer vaccines presents several advantages as compared to that of short TAA-derived peptides. Notably, it does not require patient selection based on MHC profile.[152] Still, SLPs must be taken up, processed and presented by dendritic cells or other APCs for eliciting an immune response.[152] CMPs represent a novel approach to harness non-protein TAAs for the activation of tumor-specific immunity.[153-155] Patients affected by virtually all types of neoplasms have been enrolled in these clinical trials, including (but not limited to) various hematological malignancies,[90,111,122,126]

melanoma,[99,100,113,141] as well as breast,[94,96,134,138,151] head and neck,[102,103] gastroesophageal,[108,121,130] pulmonary,[95,105,114,142] pancreatic,[109,115,117,124,125,132,135,137,148] prostate,[97,98,104,107,112,119,139] ovarian,[116,131] and colorectal[91,120,129,136,140] carcinomas. In a majority of cases, peptide-based vaccines were tested as standalone adjuvanted interventions injected intradermally or intratumorally,[94,102,104,105,108-110,112,115,116,119,121,123,124,128,129,131,138,140-142,146,147,149,156] the most common adjuvant being Montanide ISA-51 (an FDA approved water-in-oil emulsion).[157,158] Alternatively, recombinant TAAs or peptides thereof were administered in combination with Toll-like receptor (TLR) agonists like Picibanil® and Hiltonol®;[114,126,133,150] cytokines including interferon α (IFNα), interleukin-2 (IL-2) and granulocyte macrophage colony stimulating factor (GM-CSF);[90,98,99,103,107,118,126,127,132,134,135,137] immunostimulatory antibodies such as nivolumab, which targets programmed cell death 1 (PDCD1, best known as PD-1);[100,113,159] so-called "pan-DR binding peptide epitopes" (PADREs), synthetic peptides that deliver robust help signals in vivo;[122,151,160-162] adoptive cell transfer;[111,126] hormone therapy;[96,107] as well as conventional[91,92,95,120,130,136] or immunogenic[93,101,117,125,135,137] chemotherapeutics.

The TAAs specifically harnessed in these studies to elicit an anticancer immune response include (but are not limited to) *v-erb-b2* avian erythroblastic leukemia viral oncogene homolog 2 (ERBB2, best known as HER2),[94,112,139] which is expressed to high levels by 20-30% breast carcinomas;[163-169] telomerase reverse transcriptase (TERT),[135,137,142] which is often reactivated/overexpressed in several types of cancer;[170-172] baculoviral IAP repeat containing 5 (BIRC5, best known as survivin),[101,118] which is highly expressed by a wide panel of malignancies;[173-175] Wilms' tumor 1 (WT1),[90,111,122,125] which is expressed to elevated levels by (at least some variants of) colorectal carcinoma, melanoma, acute myeloid leukemia.[176-179] In addition, several of these trials tested the safety and therapeutic activity of mixtures comprising up to 12-15 distinct TAA-derived peptides,[91,100,102,103,105,106,113,120,121,123,124,128-130,133,136,140,141,147,150] or "personalized peptide vaccination" (PPV), i.e., the administration of one or more peptides derived from TAAs against which the patient have previously (naturally or in response to other therapies) developed an immune response.[92,93,95-97,104,109,119,131,138,148,156,180]

Taken together, the results of these studies corroborate the notion that TAA-derived peptides as well as full length TAAs and SLPs are well tolerated by cancer patients, the most common side effects associated with this immunotherapeutic paradigm being skin reactions at the injection site, fatigue and nausea. In a limited percentage of patients, Grade III-IV reactions develop, but these are generally temporary and resolve spontaneously or upon treatment interruption coupled to the administration of corticosteroids in a few weeks.[90-119,123-142,146-151,156] These studies also demonstrate that recombinant TAAs or peptides thereof can elicit tumor-targeting immune responses.[90-119,123-142,146-151,156] Of note, with a few notable exceptions including a randomized Phase III study testing a TERT-targeting peptide plus gemcitabine and capecitabine (2 FDA-approved nucleoside analogs with immunostimulatory activity)[181,182] in 1062 individuals with pancreatic carcinoma,[122,135,137,147] such immune responses mediate bona therapeutic effects, at least in specific patient subsets.

Among recent preclinical studies dealing with peptide-based anticancer vaccines, we found of particular interest the works of: (1) Schumacher and colleagues (from the University Hospital Heidelber; Heidelberg, Germany), who demonstrated that peptides derived from a mutant variant of isocitrate dehydrogenase 1 (NADP+), soluble (IDH1),[183] can be used to elicit therapeutically relevant immune responses in glioma-bearing mice;[63] (2) Liu and collaborators (from the Massachusetts Institute of Technology; Cambridge, MA, US), who engineered peptides and adjuvants to bind endogenous albumin, resulting in superior accumulation within sentinel lymph nodes, improved T-cell priming, robust antineoplastic immune responses and limited systemic toxicity;[184] (3) Berezhnoy and co-workers (from the University of Miami; Miami, FL, US), demonstrating that aptamers targeted to tumor necrosis factor receptor superfamily, member 9 (TNFRSF9, best known as CD123 or 4-1BB) can be employed to specifically inhibit mechanistic target of rapamycin (MTOR) complex 1 in activated T cells, driving robust memory responses upon peptide vaccination but not impairing effector cytotoxic functions;[185] and (4) Hopewell et al. (from the University of South Florida; Tampa, FL, US), who proved that the activation of NF-κB in malignant cells is required for the full blown antineoplastic activity of TAA-derived peptides,[186] presumably as it underlies the local production of several immunostimulatory cytokines, including chemokine (C-C motif) ligand 2 (CCL2).[187-189]

Ongoing Trials

When this Trial Watch was being redacted (September 2014), official sources listed no less than 19 clinical trials initiated after September 1st, 2013 to evaluate the safety and efficacy of recombinant/purified TAAs or peptides thereof as anticancer vaccines in patients (source http://www.clinicaltrials.gov). Of these studies, 13 rely on one or more TAA-derived short peptides injected as such (NCT01949688; NCT01949701; NCT01950156; NCT01961115; NCT01970358; NCT01989559; NCT01989572; NCT02019524; NCT02077114; NCT02126579; NCT02134925; NCT02149225; NCT02193347), 2 on TAA-derived short peptides encapsulated within liposomes (NCT01978964; NCT02065973), 1 on an SLP (NCT02128126), 1 on a CMP (NCT02229084), 1 on a full length, recombinant TAA (NCT02015416), and one on purified TAAs complexed with heat shock protein 90kDa β (Grp94), member 1 (HSP90B1, best known as gp96)[190-194] (NCT02122822) (**Table 1**).

In particular, (1) mucin 1 (MUC1)-derived peptides are being tested as standalone, Hiltonol®-adjuvanted or PET-Lipid A-adjuvanted and liposome-encapsulated interventions in patients with colorectal adenomas or other MUC1-expressing solid tumors (NCT02134925; NCT01978964); (2) HPV-16 E6- and E7-derived epitopes are being investigated as liposome-

Table 1. Clinical trials recently initiated to test the therapeutic profile of peptide vaccines in cancer patients

Type	Indications	Phase	Status	TAAs	Notes	Ref.
CMPs	Breast carcinoma	I/II	Not yet recruiting	GD2 LeY	Adjuvanted with PADRE- and Montanide ISA-51, combined with standard chemotherapy	NCT02229084
Encapsulated TAA-derived peptides	CIN	I	Enrolling by invitation	E6 E7	As standalone adjuvanted intervention	NCT02065973
	Solid tumors	I	Enrolling by invitation	MUC1	As PET-Lipid A-adjuvanted intervention	NCT01978964
Full-length TAAs	Solid tumors	I	Recruiting	NY-ESO-1	As GLA-SE-adjuvanted intervention	NCT02015416
Purified TAAs	Glioma	I	Recruiting	PPV	Combined with standard chemotherapy	NCT02122822
Short TAA-derived peptides	Breast carcinoma Ovarian carcinoma	I/II	Recruiting	FOLR1	As GM-CSF-adjuvanted intervention	NCT02019524
	Colorectal adenoma	II	Recruiting	MUC1	As Hiltonol®-adjuvanted intervention	NCT02134925
	Glioblastoma	I	Not yet recruiting	PPV	As Hiltonol®-adjuvanted intervention	NCT02149225
	Glioma	I	Not yet recruiting	IDH1	As GM-CSF-adjuvanted intervention	NCT02193347
	Melanoma	I	Recruiting	IDO1	Combined with ipilimumab or vemurafenib	NCT02077114
		I	Recruiting	PPV	As Hiltonol®-adjuvanted intervention	NCT01970358
		I/II	Recruiting	n.a.	Adjuvanted with Montanide ISA-51, Hiltonol®, tetanus toxoid and resiquimod	NCT02126579
		II	Recruiting	Multiple	Combined with an IDO1 inhibitor	NCT01961115
		III	Completed	Multiple	As Montanide ISA-51- and GM-CSF-adjuvanted intervention	NCT01989572
		n.a.	Completed	E7 PMEL	Adjuvanted with Montanide ISA-51	NCT01989559
	NSCLC	I/II	Recruiting	LY6K	Adjuvanted with Montanide ISA-51	NCT01949701
		I/II	Recruiting	Multiple	Adjuvanted with Montanide ISA-51	NCT01950156
	Solid tumors	I/II	Recruiting	FLT1 KDR	Adjuvanted with Montanide ISA-51	NCT01949688
SLPs	Cervical carcinoma	I/II	Recruiting	E6 E7	As IFNα-adjuvanted intervention, combined with carboplatin and paclitaxel	NCT02128126

Abbreviations: CIN, cervical intraepithelial neoplasia; CMP, carbohydrate-mimetic peptide; FLT1, fms-related tyrosine kinase 1; FOLR1, folate receptor 1; GM-CSF, granulocyte macrophage colony-stimulating factor; IDH1, isocitrate dehydrogenase 1 (NADP+), soluble; IDO1, indoleamine 2,3-dioxygenase 1; IFNα, interferon α; KDR, kinase insert domain receptor; LeY, Lewis Y; LY6K, lymphocyte antigen 6 complex, locus K; MUC1, mucin 1; n.a., not available; NSCLC, non-small cell lung carcinoma; PADRE, pan-DR binding peptide epitope; PMEL, premelanosome protein; PPV, personalized peptide vaccination; SLP, synthetic long peptide; TAA, tumor-associated antigen. *Based on clinical trials initiated after September 2014, 1st (source www.clinicaltrials.gov).

encapsulated adjuvanted interventions or combined with pegylated IFNα, carboplatin (an FDA-approved platinum derivative commonly used for the treatment of ovarian carcinoma)[195-197] and paclitaxel (an FDA-approved microtubular poison employed against various neoplasms),[198,199] in women with histologically confirmed cervical intraepithelial neoplasia or cervical carcinoma (NCT02065973; NCT02128126); (3) peptides derived from folate receptor 1 (FOLR1, also known as FBP)[200,201] are being tested as GM-CSF-adjuvanted standalone interventions in breast and ovarian carcinoma patients (NCT02019524); (4) peptides derived from HPV-16 E7 and premelanosome protein (PMEL, best known as gp100) are being assessed as Montanide ISA-51-adjuvanted standalone interventions in melanoma patients (NCT01989559); (5) IDH1-derived epitopes are being tested as

GM-CSF-adjuvanted standalone interventions in subjects bearing IDH1^{+} recurrent Grade II gliomas (NCT02193347); (6) the safety and efficacy of peptides derived from indoleamine 2,3-dioxygenase 1 (IDO1)[202-206] combined with the FDA-approved immune checkpoint blocker ipilimumab (also known as Yervoy^{TM})[207-212] and vemurafenib (an FDA-approved inhibitor of mutant BRAF)[213-217] are being evaluated in melanoma patients (NCT02077114); (7) the therapeutic profile of a CMP targeting ganglioside GD2 and the so-called Lewis Y antigen (2 non-peptide TAAs),[218-220] employed as a PADRE- and Montanide ISA-51-adjuvanted intervention in combination with standard chemotherapy, is being assessed in breast carcinoma patients (NCT02229084); (8) full-length, recombinant cancer/testis antigen 1B (CTAG1B, best known as NY-ESO-1)[107,221-224] is being tested as a standalone intervention adjuvanted with GLA-SE, a synthetic TLR4 agonist,[225-228] in subjects with solid tumors (NCT02015416); (9) the safety and efficacy of peptides derived from lymphocyte antigen 6 complex, locus K (LY6K, also known as URLC10)[105,108,229-231] administered as a standalone Montanide ISA-51-adjuvanted intervention are being evaluated in non-small cell lung carcinoma (NSCLC) patients (NCT01949701); (10) epitopes derived from fms-related tyrosine kinase 1 (FLT1, best known as VEGFR1) and kinase insert domain receptor (KDR, best known as VEGFR2) are being tested as standalone Montanide ISA-51-adjuvanted intervention in subjects affected by various solid tumors (NCT01949688); (11) the clinical profile of a not-better defined peptide-based vaccine (LPV7) adjuvanted with Montanide ISA-51, Hiltonol®, the tetanus toxoid (an FDA-approved adjuvant),[232] and resiquimod (a hitherto experimental TLR7 agonist)[233-237] is being assessed in melanoma patients (NCT02126579); (12) PPV approaches are being tested as Hiltonol®-adjuvanted standalone interventions in combination with standard chemotherapy in patients with melanoma, glioblastoma or glioma (NCT01970358; NCT02122822; NCT02149225); and (13) the clinical profile of multipeptide-based vaccines employed as standalone Montanide ISA-51-adjuvanted intervention, as standalone Montanide ISA-51- and GM-CSF-adjuvanted intervention, or combined with the IDO1 inhibitor INCB024360,[202,238,239] is being tested in melanoma or NSCLC patients (NCT01950156; NCT01961115; NCT 01989572). Of note, both NCT01989572 and NCT01989559 are listed as "Completed" on http://www.clinicaltrials.gov. However, to the best of our knowledge, the results of neither of these studies have already been disseminated.

As for the clinical trials listed in our 2 previous Trial Watches dealing with this topic,[47,48] the following studies have changed status since the publication of the latter: NCT01854099, now listed as "Withdrawn;" NCT00624182 and NCT01264731, now listed as "Suspended;" NCT00455572, NCT00977145 and NCT01058850, now listed as "Terminated;" NCT00480025, NCT00643097, NCT00694551, NCT00819806, NCT00821652, NCT01149343, NCT01222221, NCT01250470, NCT01355393, NCT01425749, NCT01437605, NCT01462838, NCT01507103, NCT01580696, NCT01592617, NCT01606241 and NCT01632332, and now listed as "Active, not recruiting;" NCT00911560, NCT00960752, NCT01220128, NCT01307618, NCT01479244, NCT01526473, NCT01532960, NCT01570036 and NCT01922921, now listed as "Recruiting;" NCT00626015, NCT00655161, NCT00773097, NCT00841399, NCT00854789, NCT01639885 and NCT01673217, now listed as "Completed" (source http://www.clinicaltrials.gov). NCT01854099 has been withdrawn prior to enrollment following the decision of the investigator, while NCT01264731 has been suspended because the study staff is out on medical leave. NCT00455572, NCT00977145 and NCT01058850 were all terminated owing to issues with patient accrual (source http://www.clinicaltrials.gov).

NCT00626015 (a Phase I trial) tested the safety and efficacy of a peptide vaccine targeting the mutant epidermal growth factor receptor (EGFR) in combination with daclizumab (a monoclonal antibody specific for the IL-2 receptor α chain, CD25),[240,241] temozolomide (an immunogenic alkylating agent)[70,71,242] and radiation therapy[72,243,244] in glioblastoma patients.[245] In this patient cohort, daclizumab provoked a decline in the circulating levels of CD4^{+}CD25^{+}FOXP3^{+} regulatory T cells[246] that correlated with the elicitation of humoral EGFR-specific immune responses.[245] NCT00773097 (a Phase II trial) tested the safety and immunological activity of a MUC1-derived peptide administered in combination with a TLR3 ligand in 46 advanced colorectal carcinoma patients. In this setting, all patients that completed the study (39 individuals) developed anti-MUC1 antibodies. No severe (Grade III-IV) side effects were recorded, but all patients experienced mild (Grade I-II) toxicities, notably skin reactions at the injection site (source http://www.clinicaltrials.gov). NCT00841399 (a Phase I-II study) investigated the clinical profile of an HER2-derived peptide combined with GM-CSF in node-positive breast carcinoma patients. Of 195 enrolled patients, 187 were assessable at the end of the study, 108 of which were vaccinated as per compatible MHC profile. Vaccination was well tolerated and associated with a disease-free survival rate of 89.7%, even though many individual received suboptimal vaccine doses (80.2% among non-vaccinated patients, 94.6% among optimally dosed patients).[134] A randomized, Phase III clinical trial has been initiated to confirm these results in a large patient cohort (NCT01479244, see above). To the best of our knowledge, the results of NCT00655161, NCT00854789, NCT01639885 and NCT01673217 have not been released yet (source http://www.clinicaltrials.gov).

Concluding Remarks

Accumulating data indicate that recombinant/purified TAAs and peptides thereof administered as standalone adjuvanted interventions are capable of triggering a TAA-specific immune response in a sizeable fraction of subjects with cancer. Such immune responses, however, are rarely sufficient to provide cancer patients with objective clinical benefits. On the one hand, this reflects the emergence of cancer cells that do not express anymore the antigenic epitopes targeted by vaccination (so called antigen-loss variants).[11,55,247-250] This is obviously not possible

when tumor-specific immune responses are raised against a TAA that is strictly required for the survival of malignant cells. Such "tumor rejection antigens" (TRAs) are relatively rare, as the majority of molecular functions required for the survival and proliferation of neoplastic cells is shared with their non-transformed counterparts.[20,251-253] At least in part, the emergence of antigen-loss variants can be circumvent with vaccination strategies that simultaneously target several TAAs. As it stands, however, the identification of bona fide TRAs appears as a crucial goal for the development of next-generation peptide-based anticancer vaccines.

On the other hand, the limited clinical efficacy of tumor-targeting immune responses elicited by recombinant/purified TAAs and peptide thereof reflects the ability of the tumor microenvironment to keep potentially oncolytic immune responses under strict control.[8-14,254] During the past decade, reversing the profound immunosuppressive nature of the tumor microenvironment has generated an intense wave of investigation, culminating in the development of several immunostimulatory agents that are currently being tested in clinical trials or already approved for use in cancer patients.[237,255-258] Perhaps the most successful (immuno)therapeutic paradigm of this type is represented by so-called immune checkpoint blockers, i.e., molecules that inhibit the delivery of immunosuppressive signals to activated T lymphocytes and other immune effector cells.[74,75,259-262] Besides exerting clinical activity as standalone interventions against various neoplasms, these agents, including the FDA-approved monoclonal antibodies ipilimumab, which targets cytotoxic T lymphocyte-associated protein 4 (CTLA4),[207-212] and pembrolizumab (also known as Keytruda™), which targets PD-1,[263-265] significantly improve the antineoplastic profile of many immunotherapeutics,[266-268] including peptide-based anticancer vaccines.[100,113] Large, randomized clinical studies are urgently awaited to identify the combinatorial immunotherapeutic regimens that are best suited to boost the antineoplastic activity of recombinant/purified TAAs and peptides thereof. In addition, as for many other (immuno)therapeutic interventions, it will be crucial to identify biomarkers that reliably predict the propensity of individual patients to respond to peptide-based anticancer vaccines.[269-273] Time will tell whether these avenues are those that lead to the approval of peptide vaccination by international regulatory agencies for use in cancer patients.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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