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Trial Watch

Peptide vaccines in cancer therapy

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Abbreviations: AML, acute myeloid leukemia; APC, antigen-presenting cell; CTL, cytotoxic T lymphocyte; DC, dendritic cell; DTH, delayed type hypersensitivity; ERBB2, *v-erb-b2* avian erythroblastic leukemia viral oncogene homolog 2; GM-CSF, granulocyte macrophage colony-stimulating factor; HPV, human papillomavirus; IFA, incomplete Freund's adjuvant; IFN, interferon; MAGEA3, melanoma antigen, family A, 3; MDS, myelodysplastic syndrome; MLANA, melan-A; NSCLC, non-small cell lung carcinoma; TAA, tumor-associated antigen; TERT, telomerase reverse transcriptase; TLR, Toll-like receptor; VEGFR, vascular endothelial growth factor receptor; WT1, Wilms tumor 1

Throughout the past 3 decades, along with the recognition that the immune system not only influences oncogenesis and tumor progression, but also determines how established neoplastic lesions respond therapy, renovated enthusiasm has gathered around the possibility of using vaccines as anticancer agents. Such an enthusiasm quickly tempered when it became clear that anticancer vaccines would have to be devised as therapeutic, rather than prophylactic, measures, and that malignant cells often fail to elicit (or actively suppress) innate and adaptive immune responses. Nonetheless, accumulating evidence indicates that a variety of anticancer vaccines, including cell-based, DNA-based, and purified component-based preparations, are capable of circumventing the poorly immunogenic and highly immunosuppressive nature of most tumors and elicit (at least under some circumstances) therapeutically relevant immune responses. Great efforts are currently being devoted to the identification of strategies that may provide anticancer vaccines with the capacity of breaking immunological tolerance and eliciting tumor-associated antigen-specific immunity in a majority of patients. In this sense, promising results have been obtained by combining anticancer vaccines with a relatively varied panels of adjuvants, including multiple immunostimulatory cytokines, Toll-like receptor agonists as well as inhibitors of immune checkpoints. One year ago, in the December issue of *OncoImmunology*, we discussed the biological mechanisms that underlie the antineoplastic effects of peptide-based vaccines and presented an abundant literature demonstrating the prominent clinical potential of such an approach. Here, we review the latest developments in this exciting area of research, focusing on high-profile studies that have been published during the last 13 mo and clinical trials launched in the same period to evaluate purified peptides or full-length proteins as therapeutic anticancer agents.

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Introduction

Prophylactic vaccination constitutes one of the major achievements in the history of medicine, Indeed, thanks to the pioneer work of the English physician Edward Anthony Jenner (1749–1823)[1-3] and other prominent scientists including the French microbiologist Louis Pasteur (1822–1895),[1,4] the administration of attenuated infectious agents (or purified components thereof) in the presence of adequate immunostimulatory agents (commonly referred to as adjuvants) is nowadays employed as part of routine, nationwide programs of disease prevention.[1] The most significant objective attained by the implementation of these global vaccination campaigns (starting in UK in 1840, with the promulgation of the Vaccination Act) is undoubtedly constituted by the eradication of natural smallpox sources, which was first

certified by a committee of experts in 1979 and confirmed by the WHO 1 y later.[5] In addition, nationwide vaccination programs have dramatically abated the incidence of several other life-threatening infectious diseases including rabies, typhoid, cholera, measles, plague, chickenpox, mumps, poliomyelitis, and hepatitis B.[1]

The possibility that patients affected by neoplastic diseases might also benefit from active immunotherapy, i.e., the elicitation of an endogenous adaptive immune response, first surged at the end of the 19th century (that is, nearly 1 century after Jenner's experiments), along with the work of Paul Ehrlich, an German physician, and William Bradley Coley, an American surgeon.[1,6] Erlich, who is best known for the concept of a "magic bullet" that would specifically eliminate malignant cells while sparing their non-transformed counterparts, attempted intensively to generate an anticancer vaccine by using attenuated cancer cells, with no success.[1,6] Conversely, Coley developed a preparation of heat-killed *Streptococcus pyogenes* and *Serratia marcescens* bacteria (best known as the Coley toxin) that soon turned out to mediate potent antineoplastic effects.[7-9] Nonetheless, the Coley toxin does not constitute an anticancer vaccine *sensu stricto*, but rather acts as an adjuvant, hence stimulating the maturation of dendritic cells (DCs) via Toll-like receptor (TLR)-dependent signal transduction cascades.[10]

In (large) part owing to the broad acceptance of the "self/non-self" model, as posited by Sir Frank Macfarlane Burnet (an Australian virologist) in 1949,[11] the possibility that attenuated neoplastic cells or components thereof might induce clinically relevant anticancer responses was disregarded until the mid-1990s, when the American scientist Polly Matzinger first proposed the so-called "danger theory."[12] According to this model, the immune system does not react against non-self entities while sparing self ones, but rather responds to states of danger, irrespective of whether they are elicited by non-self or self constituents.[12,13] Together with the identification of the first antigen specifically expressed by transformed (as opposed to normal) cells[14] and the characterization of tumor-specific cytotoxic T lymphocytes (CTLs) in the circulation of cancer patients,[14,15] the danger theory de facto laid the foundations of modern tumor immunology, alongside resurrecting the interest of researchers and clinicians in the use of vaccines as antineoplastic interventions.

Throughout the last 2 decades, a wide panel of preparations has been tested for their ability to elicit tumor-associated antigen (TAA)-specific immune responses and mediate robust antineoplastic effects in vivo, encompassing (but not limited to): (1) recombinant TAAs, in the form of either short synthetic peptides, which are expected to bind MHC molecules on the surface of antigen-presenting cells (APCs) and hence be directly presented to T cells, or full-length proteins, the presentation of which relies on the uptake and processing by APCs; (2) cancer cell lysates, containing TAAs alone or complexed with chaperones; (3) TAA-encoding vectors, in the form of naked DNA or RNA molecules as well as of viral delivery systems; (4) DC-based vaccines, including DCs loaded with TAAs ex vivo as well as fusion proteins that allow for the selective delivery of TAAs to DCs in vivo.[6,16-21] Such an intense wave of investigation has generated profound insights into the molecular and cellular mechanisms that control the elicitation of anticancer immune responses. In addition, it has prompted the development of several vaccines that are currently being investigated in the clinic, in patients affected by a large panel of neoplasms.[6,16-18] Nonetheless, with the notable exceptions of Cervarix® and Gardasil®, 2 multivalent vaccines that have been approved by the US FDA in 2009 as prophylactic measures against infection by human papillomavirus (HPV) type 16 and 18 and the consequent development of cervical carcinoma,[22-24] no vaccines based on recombinant TAAs are currently licensed for use in subjects affected by malignant conditions. Along similar lines, no DNA-based preparation is nowadays approved by international regulatory agencies for use as prophylactic or immunotherapeutic intervention against cancer in humans, and only one cell-based product is, i.e., sipuleucel-T (also known as Provenge®), which has been licensed for the treatment of patients with asymptomatic or minimally symptomatic metastatic hormone-refractory prostate cancer in 2010.[25,26] Conversely, Oncept®, a DNA-based vaccine coding for human tyrosinase (a differentiation-associated TAA),[27-29] is currently approved by the US Department of Agriculture for the treatment of canine melanoma.[30]

The paucity of clinically effective anticancer vaccines of all types, in particular recombinant ones, is in stark contrast with the hundreds of preparations that have been developed and commercialized throughout the last century for the prevention of infectious diseases. In fact, the development of effective anticancer vaccines may be problematic due to (1) issues related to the intrinsically low antigenicity of transformed cells; (2) the fact that anticancer vaccines are expected to operate most often as therapeutic—as opposed to prophylactic—agents; and (3) the capacity of neoplastic cells to establish robust immunosuppressive networks, at both local and systemic levels. We dissected these points in detail one year ago, in the December issue of *OncoImmunology*, when we first discussed clinical efforts aimed at testing TAA-derived peptides and full-length TAAs as therapeutic anticancer agents.[6] Multiple factors have been shown to influence the therapeutic potential of this approach, including not only the TAA of choice, but also the vaccine administration schedule and route as well as the presence and type of adjuvants. A detailed discussion of these parameters can be found in Refs. 6,18,31-33.

Here, along the lines of our monthly Trial Watch series,[34-39] we summarize the latest advances in the development of peptide-based vaccines, focusing on preclinical studies that have been published during the last 13 mo and clinical trials initiated in the same period to evaluate this approach as a therapeutic intervention against cancer.

Literature Update

During the last 13 mo, the results of no less than 22 clinical studies investigating the therapeutic potential of full length TAAs or peptides thereof in cancer patients have been published in peer-reviewed scientific journals (source http://www.ncbi.nlm.nih.gov/pubmed). With a single exception, a clinical trial testing the safety and antineoplastic activity of autologous heat-shock protein-TAAs

complexes in 12 patients affected by high-grade glioma,[40] all these studies involved recombinant TAA-derived peptides.[41-63] In a majority of settings, peptides were given as standalone therapeutic interventions, most frequently in incomplete Freund's adjuvant (IFA, a water in oil emulsion).[64,65] Alternatively, peptide-based vaccination was combined with additional adjuvant-like interventions, including CpG oligodeoxynucleotides, which act as TLR9 agonists;[48,66,67] polyinosinic:polycytidylic acid, poly-L-lysine, and carboxymethylcellulose (polyICLC), which triggers TLR3 signaling;[58,68,69] imiquimod, a TLR7 agonist;[49] interferon (IFN)α, a potent immunostimulatory cytokine,[42,47,62,70-73] and low-dose interleukin (IL)-2 combined with metronomic cyclophosphamide, a regimen that exerts robust immunogenic effects.[50,74-77]

These studies were performed on patients affected by a large panel of solid (but not hematological) neoplasms, including glioma,[40] lung carcinoma,[48,52] sarcoma,[59,62] melanoma,[41,50,61] esophageal squamous cell carcinoma,[51] gastric cancer,[55] hepatocellular carcinoma,[43,56,60] pancreatic cancer,[47] colorectal carcinoma,[42,45,53] metastatic renal cell carcinoma,[49,54] castration-resistant prostate cancer,[26,46,49] ovarian carcinoma,[58] gynecologic malignancies,[63] and various other tumors.[44,57] The TAAs specifically targeted in these clinical trials (most of which were Phase I studies) encompassed cancer-testis antigens such as NY-ESO-1,[46,48,50,58,78] TTK protein kinase (also known as MOS),[51,52,79] lymphocyte antigen 6 complex, locus K (LY6K, best known as URLC10),[51,52,55,80,81] insulin-like growth factor 2 mRNA binding protein 3 (IGF2BP3, best known as IMP3),[51,82,83] ring finger protein 43 (RNF43),[45,53,84-86] and translocase of outer mitochondrial membrane 34 (TOMM34);[45,53,87,88] carcinoembryonic antigens like glypican-3;[43,56,60,89,90] differentiation antigens such as melan-A (MLANA) and premelanosome protein (PMEL, best known as gp100);[50,91-93] tumor-restricted TAAs, such as the SYT-SSX fusion (which is selectively expressed by synovial sarcomas as a result of a t(X;18)(p11;q11) chromosomal translocation);[62,94,95] as well as so-called "shared TAAs" (antigens that are overexpressed by malignant cells but also produced in normal amounts by one or several healthy tissues), including vascular endothelial growth factor receptor 1 (VEGFR1) and VEGFR2,[44,52-54,57,96,97] survivin,[47,50,61,98,99] Wilms tumor 1 (WT1),[63,100,101] telomerase reverse transcriptase (TERT),[49,102] and p53.[42,103,104] Thus, a relatively heterogeneous panel of approaches and indications has been explored during the last 13 mo to get further insights into the safety and clinical potential of peptide-based anticancer vaccines.

Taken together, the results of these clinical trials demonstrate that the local administration of recombinant TAAs or peptides thereof is generally well tolerated by cancer patients, the most common adverse effects being grade 1–3 erythema or induration at the injection site,[44,51,53,54,61,63] grade 1–2 proteinuria,[44,57] and hypertension.[44,57] Moreover, the authors of most of these studies could document the ability of TAA-derived peptides to elicit an immune response, most often as (1) an increase in circulating TAA-specific CTLs,[42,43,45-54,56-58,61,94] (2) a surge in serum TAA-targeting antibodies,[42,58] (3) a delayed type hypersensitivity (DTH) reaction developing at the injection site;[55,62,63,94] (4) the infiltration of neoplastic lesions by $CD4^+$ or $CD8^+$ T lymphocytes,[40,60] or (5) the activation of transcriptional programs associated with CTL effector functions in peripheral blood mononuclear cells.[44] Often, but not always,[50] such an immune response to vaccination was associated with (at least some degree of) clinical benefit.[40,47,51-54,56,61] This correlation was particularly robust in the Phase II study published by Becker and collaborators, pointing to survivin-specific T-cell reactivity as an independent predictor of survival in a cohort of metastatic melanoma patients receiving survivin-derived peptides.[61] Along similar lines, Miyatake and colleagues reported a statistically significant correlation between the development of a WT1-specific DTH reaction upon the administration of WT1-derived peptides and the overall survival of patients with gynecologic malignancies.[63] These findings add to the large amount of clinical data suggesting that the implementation of appropriate immunomonitoring procedures is of the utmost importance not only to correctly interpret the results of clinical trials testing immunotherapeutic anticancer regimens, but also to prospectively identify the subsets of patients who are likely to obtain (at least some degree of) clinical benefit from treatment.[105,106] This said, the possibility that immunological responders might exhibit a survival advantage over non-responders irrespective of vaccination has not yet been ruled out.

We have also found of particular interest a few recent studies that investigated fundamental aspects of the molecular and cellular circuitries underlying the therapeutic efficacy of TAA-derived anticancer vaccines. Salerno et al. revealed that activated ($CD69^+$) effector memory $CD8^+$ T cells expressing chemokine (C-X-C motif) receptor 3 (CXCR3) as well as retention molecules such as integrins αEβ7 and α1β1 tend to accumulate at recall vaccination sites irrespective of the presence of TAA-derived peptides, presumably owing to the immunostimulatory effect of IFA.[41] As these cells appear to be strikingly dysfunctional, producing minimal amounts of IFNγ in response to stimulation, the transient immune reactions and relatively low rates of clinical responses associated with (at least some) IFA-adjuvanted peptide vaccines may reflect the capacity of IFA to recruit and retain effector T cells, eventually resulting in their functional impairment.[41] In line with this notion, Hailemichael and collaborators demonstrated that TAA-specific $CD8^+$ T lymphocytes accumulate at vaccination sites to become functionally impaired and undergo antigen-driven, IFNγ- and FAS ligand (FASL)-dependent apoptosis.[107] In this setting, the provision of CD40 agonist antibodies, a TLR7 agonist or IL-2 limited the demise of T cells but not their accumulation at vaccination sites. Conversely, the capacity of TAA-derived peptides to elicit robust anticancer immune responses was significantly ameliorated when short-lived vaccines were employed, a notion that may have important therapeutic implications.[107] Ma and colleagues developed a molecular platform for the selective delivery of anticancer peptide vaccines to B lymphocytes.[108] To this aim, they fused the extracellular domain of *v-erb-b2* avian erythroblastic leukemia viral oncogene homolog 2 (ERBB2, also known as HER2/neu) to a single chain variable fragment specific for CD19. Such a chimeric peptide activated B cells to produce high titers of ERBB2-specific antibodies and elicit robust $CD4^+$ helper T-cell responses, hence supporting the activation and differentiation of $CD8^+$ T cells and

mediating antineoplastic effects in vivo.[108] These findings suggest that the therapeutic efficacy of anticancer peptide vaccines may be enhanced by strategies that allow for the simultaneous activation of B and T lymphocytes. The importance of humoral immunity in cancer immunosurveillance is further underlined by recent results from Zhang and collaborators, demonstrating that a multipeptide vaccine based on B-cell epitopes from heparanase (a metastasis-associated antigen)[109] exerts prominent antimetastatic effects in vivo.[110] Finally, Dosset et al. obtained further data in support of the notion that TERT elicits CTL responses in patients affected by a wide panel of solid and malignancies.[111,112] In particular, these authors demonstrated that a mixture of TERT-derived peptides can induce high-avidity $CD4^+$ T-cell responses in vivo, resulting in the breakdown of tolerance and the activation of therapeutic CTL antitumor reactivity.[111,112]

TERT-targeting anticancer vaccines have spurred great interest among clinicians throughout the past decade, as demonstrated by the consistent number of Phase I-II clinical trials completed in this period.[49,102,112-134] In spite of encouraging safety data and clinical findings, however, only a few Phase III trials have been launched to test the antineoplastic potential of TAA-derived peptides in cancer patients, including TELOVAC (NCT00425360), a randomized study testing a promiscuous class II epitope of TERT ($TERT_{611–626}$, best known as GV1001) in patients with locally advanced or metastatic pancreatic cancer previously treated with gemcitabine and capecitabine,[135,136] and DERMA (NCT00796445), a randomized, double-blind, placebo-controlled study investigating the efficacy of recombinant melanoma antigen, family A, 3 (MAGEA3) administered in AS15 (a liposomal formulation of QS-21 Stimulon®, monophosphoryl lipid A and CpG-7909, a TLR9 agonist) as adjuvant therapy to patients with Stage IIIB/C resected $MAGEA3^+$ melanoma.[137,138] As recently disclosed at the Annual Meeting of the American Society of Clinical Oncology (ASCO) held in Chicago last June, the administration of GV1001 fails to ameliorate the overall survival of pancreatic cancer patients previously treated with conventional chemotherapy.[135] However, the CEO of GemVax and KAEL Co., the company that is currently developing GV1001, declared that 2 candidate biomarkers were identified that may predict immunological responses to the vaccine as well as increased survival in a subset of patients (source http://online.wsj.com/article/PR-CO-20130603-906288.html). On 2013, September 5th, GlaxoSmithKline plc announced that the DERMA study also failed to meet its first co-primary endpoint as recombinant MAGEA3 administered in AS15 did not extend the disease-free survival of patients with Stage IIIB/C resected $MAGEA3^+$ melanoma as compared with placebo (source http://www.gsk.com/media/press-releases/2013/the-investigational-mage-a3-antigen-specific-cancer-immunotherap.html). Nonetheless, following the Independent Data Monitoring Committee's (IDMC) unanimous recommendation, the DERMA study will be protracted until the assessment of the second co-primary endpoint, i.e., disease-free survival in a patient subset characterized by a 84-component gene signature that may predict the clinical efficacy of recombinant MAGEA3.[138] The preliminary results of these randomized studies lend further support to the notion that clinical immunomonitoring may constitute a critical step for the development of novel anticancer immunotherapeutics (see above).

Update on Clinical Trials

When our latest Trial Watch dealing with the use of recombinant TAAs or peptides thereof as anticancer vaccines was submitted for publication to *OncoImmunology* (September, 2012), official sources listed 118 recent (started after 2008, January 1st) clinical trials (not withdrawn, terminated or completed at the day of submission) that would assess the safety and efficacy of this immunotherapeutic strategy in cancer patients.[6] Of these studies, 11 involved patients affected by hematological neoplasms, 30 subjects bearing neurological or pulmonary malignancies, 24 individuals with breast, ovarian or prostate carcinomas, 25 melanoma patients, 15 subjects affected by esophageal, gastric, pancreatic or colorectal tumors, 10 patients bearing bladder carcinoma or neoplasms of the reproductive tract, and 12 individuals with other tumors or mixed patients cohorts. The status of most of these trials has remained unchanged since, exception made for NCT01232712, NCT00633724, NCT00655785, NCT00711334, NCT00773097, NCT00874588, NCT00887796, NCT00892567, NCT00952692, NCT01003808, NCT01219348, and NCT01673217 (all of which have been completed), as well as of NCT00706992 (which has been terminated) (source http://www.clinicaltrials.gov). Of note, the preliminary results of this latter Phase II study, demonstrating the ability of T cells genetically engineered to express a MLANA-targeting T-cell receptor (TCR) coupled to a MLANA-derived peptide to induce objective clinical responses in 4 out of 31 high-risk melanoma patients, had first been reported as early as in 2006.[139,140] Along similar lines, the findings of NCT00633724 and NCT00874588 (testing 4 HLA-A*2402-restricted TAA-derived peptides in non-small cell lung carcinoma, NSCLC, patients), NCT00952692 (investigating the clinical profile of a truncated variant of ERBB2 in women with metastatic breast carcinoma) as well as NCT01219348 (assessing the safety and efficacy of an indoleamine 2,3-dioxygenase-derived peptide in NSCLC patients) have already been published, either in the form of a scientific report,[52,141] or within a review article.[142] Conversely, the results of the other (recently completed) clinical trials mentioned above have not yet been disseminated.

When this Trial Watch was being redacted (September 2013), official sources listed 20 clinical trials launched after 2012, September 1st to investigate the safety and therapeutic potential of purified/recombinant TAAs or peptide thereof in cancer patients (**Table 1**) (source http://www.clinicaltrials.gov). The vast majority of these studies (18 trials) involves recombinant preparations, be them TAA-derived peptides (14 trials), full-length TAAs (1 trial) or TAA-containing fusion proteins (3 trials), most often administered as standalone adjuvanted interventions. In addition, 2 trials intend to investigate the therapeutic profile of recombinant TAAs or tumor cell lysates in complex with chaperones of the heat-shock protein family. Thus, (1) ERBB2-derived peptides are being evaluated, as single immunotherapeutic agents or combined with the ERBB2-targeting antibody trastuzumab,[143,144] in

Table 1. Recent clinical trials testing purified TAAs or peptides thereof as therapeutic interventions in cancer patients.*

Indications	Phase	Status	Type	TAAs	Notes	Ref.
AML CML CMML MDS	I	Recruiting	Fusion proteins	NY-ESO-1	As Hiltonol®-adjuvanted intervention, combined with decitabine	NCT01834248
	I/II	Recruiting	Fusion proteins	MAGEA10 WT1	As AS01B-adjuvanted intervention, following HSCT	NCT01819558
Breast carcinoma	I/II	Not yet recruiting	Peptides	ERBB2	Combined with trastuzumab ± PSK	NCT01922921
	II	Recruiting	Peptides	ERBB2	As standalone adjuvanted intervention	NCT01729884
CIN	I	Active, not recruiting	Fusion proteins	E7	As GPI-0100-adjuvanted intervention	NCT01880411
GBM	I	Not yet recruiting	Peptides	CMV-derived antigens	Combined with temozolomide	NCT01854099
	I/II	Recruiting	Peptides	Multiple	As Hiltonol®-adjuvanted intervention, combined with temozolomide	NCT01920191
	II	Recruiting	HSP-TAA complexes	Multiple	Combined with bevacizumab	NCT01814813
Melanoma	I	Recruiting	Full length TAAs Peptides	NY-ESO-1	As Hiltonol®- and Montanide ISA51-adjuvanted intervention, combined with ipilimumab	NCT01810016
	I	Recruiting	HSP-TAA complexes	gp100	As standalone adjuvanted intervention	NCT01744171
	I	Recruiting	Phosphopeptides	BCAR3 IRS2	As Hiltonol®-, Montanide ISA51- and tetanus peptide-adjuvanted intervention	NCT01846143
	I/II	Recruiting	Peptides	MAGEA3.A1 NA17.A2	Combined with GM-CT-01	NCT01723813
	n.a.	Recruiting	Peptides	MART-1	As resiquimod-and Montanide ISA51-adjuvanted intervention, alone or combined with $Gag_{267–274}$	NCT01748747
MPM	II	Recruiting	Peptides	WT1	As GM-CSF- and Montanide ISA51-adjuvanted intervention	NCT01890980
Multiple myeloma	I	Recruiting	Peptides	Multiple	As standalone adjuvanted intervention	NCT01718899
	n.a.	Recruiting	Peptides	WT1	As GM-CSF-adjuvanted intervention	NCT01827137
NSCLC	I	Withdrawn	Peptide-containing liposomes	MUC1	Combined with cyclophosphamide	NCT01731587
	I/II	Recruiting	Peptides	MUC1	As Hiltonol®-adjuvanted intervention	NCT01720836
	I/II	Recruiting	Peptides	TERT	As GM-CSF-adjuvanted intervention	NCT01789099
Prostate cancer	I/II	Recruiting	Peptides	TERT	As GM-CSF-adjuvanted intervention	NCT01784913

Abbreviations: AML, acute myeloid leukemia; CIN, cervical intraepithelial neoplasia; CML, chronic myeloid leukemia; CMML, chronic myelomonocytic leukemia; CMV, cytomegalovirus; GBM, glioblastoma multiforme; GM-CSF, granulocyte-macrophage colony-stimulating factor; HSCT, hematopoietic stem cell transplantation; HSP, heat-shock protein; MDS, myelodysplastic syndrome; MPM, malignant pleural mesothelioma; MTC; medullary thyroid carcinoma; n.a., not available; NSCLC, non-small cell lung carcinoma; PSK, polysaccharide K; TAA, tumor-associated antigen. *started after September, 1st 2012 (source http://www.clinicaltrials.gov).

subjects with breast carcinoma (NCT01729884; NCT01922921); (2) the safety of and antineoplastic profile of WT1-derived peptides delivered in combination with granulocyte macrophage colony-stimulating factor (GM-CSF) are being assessed in cohorts of multiple myeloma and malignant pleural mesothelioma patients (NCT01827137; NCT01890980); (3) peptides derived from mucin 1 (MUC1), which is overexpressed as an aberrantly glycosylated glycoprotein by multiple tumors of epithelial derivation,[145,146] are being tested as standalone adjuvanted interventions or as a liposomal formulation combined with cyclophosphamide[147] in NSCLC patients (NCT01720836; NCT01731587); (4) the safety and efficacy of TERT-derived peptides combined with local GM-CSF are being tested in cohorts of NSCLC and prostate carcinoma patients (NCT01789099; NCT01784913); (5) the clinical profile or recombinant NY-ESO-1 or overlapping peptides thereof in combination with cytotoxic T lymphocyte-associated protein 4 (CTLA4)-targeting antibodies is being evaluated in individuals with unresectable or metastatic melanoma (NCT01810016); (6) peptides derived from MAGEA3[148] and NA17-A2[149] are being tested, alone or combined with each other and/or with a galectin-3 inhibitor, in metastatic melanoma patients (NCT01748747); (7) MLANA epitopes are being tested in combination with a peptide corresponding to residues 267–274 of HIV-1 Gag[150] and the TLR7 agonist resiquimod[151,152] in subjects with stage II-IV melanoma who underwent surgical tumor resection (NCT01723813); and (8) the safety and immunogenicity of phosphorylated peptides derived from breast cancer anti-estrogen resistance 3 (BCAR3) or insulin receptor substrate 2 (IRS2), 2 proteins that are frequently upregulated by malignant cells,[153,154] are being assessed in a cohort of melanoma patients (NCT01846143).

In addition, (1) multipeptide preparations encompassing a panel of recombinant TAA-derived or cytomegalovirus-derived epitopes are being tested in glioblastoma and multiple myeloma patients, either in combination with the DNA-damaging agent temozolomide or as a standalone therapeutic intervention, respectively (NCT01854099; NCT01920191; NCT01718899); (2) the safety and therapeutic profile of a gp100-derived peptide in complex with heat shock 105kDa/110kDa protein 1 (HSPH1), administered as a standalone adjuvanted intervention, are being assessed in patients with advanced Stage III-IV melanoma (NCT01744171); and (3) TAA-derived peptides complexed with HSP96 are being tested, in combination with the vascular endothelial growth factor (VEGF)-targeting antibody bevacizumab,[155,156] in individuals bearing resectable recurrent glioblastoma (NCT01814813). Finally, (1) the safety, tolerability, and immunogenicity of a fusion protein comprising HPV E7, administered as a standalone adjuvanted intervention, are being investigated in patients with cervical intraepithelial neoplasia (NCT01880411); (2) the clinical profile of a fusion protein comprising WT1 and MAGE-A10, a nuclear protein frequently expressed by lung, skin and urothelial neoplasms,[157-159] is being assessed in patients with acute myeloid leukemia (AML), chronic myeloid leukemia (CML) and myelodysplastic syndrome (MDS) subjected to hematopoietic stem cell transplantation (NCT01819558); and (3) full-length NY-ESO-1 fused to a monoclonal antibody specific for lymphocyte antigen 75 (LY75, a DC receptor best known as DEC-205),[160,161] given in combination with the demethylating agent decitabine,[162,163] is being tested in AML and MDS patients (NCT01834248).

Taken together, these observations suggest that the interest of clinicians in the possibility of employing purified/recombinant TAAs or peptides thereof as therapeutic anticancer interventions remains high.

Concluding Remarks

During the past decade, the possibility of employing purified/recombinant TAAs or peptides thereof as a means to elicit therapeutically relevant tumor-specific immune responses has been intensively investigated, in both preclinical and clinical settings.[6] Nonetheless, no peptide-based preparation is currently approved by the US FDA or other international regulatory agencies for use as a therapeutic interventions in cancer patients. Indeed, Cervarix® and Gardasil®, both of which have been licensed by the US FDA as soon as in 2009, are to be employed as preventive, as opposed to therapeutic, measures, de facto constituting conventional antiviral vaccines.[22-24]

As mentioned above, multiple biological factors contribute to the limited efficacy of anticancer, as opposed to antiviral, vaccines, including the generally low antigenicity of malignant cells and the robust immunosuppressive mechanisms that are established in the course of oncogenesis and tumor progression. In addition, the scarce success of the clinical trials that so far have tested the therapeutic profile of recombinant TAAs or TAA-derived peptides at least in part reflects: (1) the limited availability of novel, clinical grade adjuvants that operate via specific TLRs;[7,8,164] (2) the lack of immunological biomarkers that would reliably predict the propensity of specific patients to mount an objective response upon vaccination;[105,106] and (3) the fact that often, if not always, the clinical evaluation of innovative (immunotherapeutic) regimens is initially performed on subjects bearing very advanced malignancies. As a matter of fact, several TAA-derived peptides and/or full-length TAAs have been shown to exhibit (at least some degree of) clinical activity when administered to patients with minimal residual disease, yet fail to provide any benefit to individuals affected by advanced and/or metastatic tumors.[31,165-168]

Peptide-based anticancer vaccines hold great promise, but their potential has not been fully developed yet. The characterization of novel tumor-rejection antigens, *i.e.*, TAAs that can elicit an immune response leading to tumor eradication,[169,170] an improved understanding of the molecular and cellular circuitries that regulate the mutual interaction between neoplastic cells and the immune system, the development of potent clinical grade adjuvants, the design of combinatorial immunotherapeutic regimens involving peptide-based anticancer vaccines and strategies that limit tumor-associated immunosuppression[171,172] or stimulate the immunogenic demise of cancer cells,[76,77] as well as the initiation of clinical trials that comprise meticulous immunomonitoring programs, stand out as the main avenues through which a promising therapeutic paradigm may soon be converted into a robust clinical reality.

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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