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Trial watch
Peptide vaccines in cancer therapy

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Abbreviations: AML, acute myeloid leukemia; APC, antigen-presenting cell; BCG, bacillus Calmette-Guérin; BCR, B-cell receptor; CDCA1, cell division cycle-associated 1; CEA, carcinoembryonic antigen; CHP, cholesterol-bearing hydrophobized pullulan; CML, chronic myelogenous leukemia; CRC, colorectal carcinoma; CTA, cancer-testis antigen; CTL, cytotoxic T lymphocyte; DC, dendritic cell; DEPDC1, DEP domain containing 1; EBV, Epstein-Barr virus; EGFR, epidermal growth factor receptor; FBP, folate-binding protein; GAA, glioma-associated antigen; GBM, glioblastoma multiforme; GM-CSF, granulocyte macrophage colony-stimulating factor; GnRH, gonadotropin releasing hormone; HBV, hepatitis B virus; HCV, hepatitis C virus; HHV-8, human herpesvirus 8; HPV, human papillomavirus; HSP, heat-shock protein; hTERT, human telomerase reverse transcriptase; HTLV, human T lymphotropic virus; IFN, interferon; Ig, immunoglobulin; IL, interleukin; IMP3, insulin-like growth factor II mRNA-binding protein 3; KIF20A, kinesin family member 20A; KLH, keyhole limpet hemocyanin; LY6K, lymphocyte antigen 6 complex locus K; MAGE, melanoma-associated antigen; MART-1, melanoma antigen recognized by T cells 1; MDA, melanoma differentiation antigen; MDS, myelodysplastic syndrome; MIATA, Minimal Information About T Cell Assays; MM, multiple myeloma; MPHOSPH1, M phase phosphoprotein 1; MPLA, monophosphoryl lipid A; mTOR, mammalian target of rapamycin; MUC1, mucin 1; NSCLC, non-small cell lung carcinoma; PMSA, prostate membrane-specific antigen; polyICLC, polyriboinosinic-polyribocytidylic acid stabilized with poly-*L*-lysine in carboxymethylcellulose; PSA, prostate-specific antigen; RCC, renal cell carcinoma; RHAMM, receptor for hyaluronic acid-mediated motility; SART, squamous cell carcinoma antigen recognized by T cells; SLP, synthetic long peptide; TAA, tumor-associated antigen; TARP, T-cell receptor gamma chain alternate reading frame protein; TCR, T-cell receptor; TLR, Toll-like receptor; TRA, tumor rejection antigen; Treg, FOXP3$^+$ regulatory T cell; URLC10, upregulated in lung cancer 10; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor; WT1, Wilms' tumor 1

Prophylactic vaccination constitutes one of the most prominent medical achievements of history. This concept was first demonstrated by the pioneer work of Edward Jenner, dating back to the late 1790s, after which an array of preparations that confer life-long protective immunity against several infectious agents has been developed. The ensuing implementation of nation-wide vaccination programs has de facto abated the incidence of dreadful diseases including rabies, typhoid, cholera and many others. Among all, the most impressive result of vaccination campaigns is surely represented by the eradication of natural smallpox infection, which was definitively certified by the WHO in 1980. The idea of employing vaccines as anticancer interventions was first theorized in the 1890s by Paul Ehrlich and William Coley. However, it soon became clear that while vaccination could be efficiently employed as a preventive measure against infectious agents, anticancer vaccines would have to (1) operate as therapeutic, rather than preventive, interventions (at least in the vast majority of settings), and (2) circumvent the fact that tumor cells often fail to elicit immune responses. During the past 30 years, along with the recognition that the immune system is not irresponsive to tumors (as it was initially thought) and that malignant cells express tumor-associated antigens whereby they can be discriminated from normal cells, considerable efforts have been dedicated to the development of anticancer vaccines. Some of these approaches, encompassing cell-based, DNA-based and purified component-based preparations, have already been shown to exert conspicuous anticancer effects in cohorts of patients affected by both hematological and solid malignancies. In this Trial Watch, we will summarize the results of recent clinical trials that have evaluated/are evaluating purified peptides or full-length proteins as therapeutic interventions against cancer.

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Introduction

Jenner's pioneering observations. Edward Anthony Jenner (1749–1823) was an English physician nowadays considered by many as the father of modern immunology.[1,2] In the 1790s, Jenner, who beyond medicine cultivated various interests spanning from natural history to air balloons, was practicing as a family doctor and surgeon in Berkeley (Gloucestershire), the small town he was born in some 40 y earlier. In that period, Jenner was particularly intrigued by the observation that milkmaids were generally immune to smallpox, and he postulated that such a protection would be conferred by the pus contained in blisters that milkmaids developed along with cowpox (a disease similar to, yet much less virulent than, smallpox).[1,2] In 1796, to test his hypothesis, Jenner inoculated 8 year old James Phipps with pus that he had scraped from the blisters of a cowpox-affected milkmaid. Sometimes later, Jenner challenged James Phipps with variolous material, i.e., material obtained from a smallpox pustule of a selected mild case (supposedly affected by the relatively less virulent *Variola minor* smallpox virus). The boy developed no signs of disease, nor did he after a further similar inoculation performed a few weeks later. Jenner pursued his investigations on additional 22 cases and then reported his findings to the Royal Society, which accepted to publish them only after consistent revisions.[1,2] The term "vaccination" (from the Latin adjective "vaccinae," which literally means "pertaining to cows, from cow") was coined by Jenner himself for the technique he had devised to prevent smallpox, and only more than 50 years later it was attributed a more general meaning by the French microbiologist Louis Pasteur, another pioneer in the history of vaccination.[3,4]

When Jenner first inoculated James Phipps, variolation, i.e., the inoculation of variolous material into healthy subjects as a prophylactic measure against smallpox, was a well known procedure (it had been imported in 1721 from Turkey by Lady Mary Wortley Montagu), yet was associated with a very high incidence of (often lethal) smallpox cases.[1,2] Thus, Jenner was not the first to realize that a sublethal smallpox or cowpox infection can confer protection to subsequent, potentially lethal, challenges. Similarly, he was not the first who de facto inoculated cowpox-derived material as a prophylaxis against smallpox, since at least six investigators from the UK and Germany, including the farmer Benjamin Jesty, had done so (with variable success) earlier.[5] Still, it is thanks to Jenner's observations that the British government eventually banned variolation and decided to provide cowpox-based vaccination free of charge (but optional) nation-wide (Vaccination Act, 1840). This constituted the first large-scale vaccination campaign of history, paving the way to a series of similar measures taken worldwide and culminating with the eradication of natural smallpox sources, as first certified by a committee of experts in 1979 and confirmed by WHO one year later.[6] Since then, the development of efficient vaccines and their widespread administration has strikingly abated the incidence of life-threatening infectious diseases including (but not limited to) rabies, typhoid, cholera, measles, plague, chickenpox, mumps, poliomyelitis and hepatitis B.[3] Such an extraordinary medical achievement has been possible also thanks to the critical contribution of Pasteur, who in the last decades of the 19th century demonstrated for the first time that the rationale behind smallpox vaccination could be extended to several other infectious diseases.[3,4]

Ehrlich and Coley's hypotheses. The hypothesis that—similar to infectious diseases—cancer could be treated with active immunotherapy first arose nearly one century after Jenner's investigations, along with the work of the German physician Paul Ehrlich and the American surgeon William Bradley Coley.[3] On one hand, driven by the findings made a few years earlier by Pasteur, Ehrlich (who is best known for the vaccination-unrelated concept of a "magic bullet" that would specifically kill cancer cells while sparing their normal counterparts) attempted to generate immunity against cancer by injecting weakened tumor cells, with no success.[3] On the other hand, inspired by multiple sporadic cases of cancer patients who underwent complete (and often long-lasting) regression following acute streptococcal fevers, Coley became convinced that he could efficiently use bacteria to cure tumors. To this aim, Coley developed a mixture of heat-killed *Streptococcus pyogenes* and *Serratia marcescens* bacteria (best known as the Coley toxin), which he begun to test in cancer patients as early as in 1896.[7] This preparation de facto operates as an adjuvant, facilitating the maturation of dendritic cells (DCs) via Toll-like receptor (TLR)-transduced signals,[8] rather than as a bona fide tumor-specific vaccine. However, similar to other relatively unspecific immunotherapeutic approaches such as the administration of high-dose interleukin (IL)-2 to melanoma and renal cell carcinoma (RCC) patients,[9,10] Coley's toxin soon turned out to mediate potent antitumor effects.[11,12] Of note, the use of the Coley toxin has been suspended in the early 1960s, owing to concerns following the thalidomide case (this antiemetic was withdrawn 11 years after its approval by FDA as it was found to be highly teratogenic, leading to more than 10,000 children born with deformities worldwide).[13] Still, both Coley and Ehrlich represent true pioneers of modern oncoimmunology, theorizing concepts that have been disregarded for nearly one century and have received renovated interest only recently.[14]

The "self/non-self" dichotomy and the "danger theory". One of the major impediments against the rapid development of tumor immunology as a self-standing discipline directly stemmed from one of the most central concepts in immunology: the "self/non-self" dichotomy, as first theorized by the Australian virologist Sir Frank Macfarlane Burnet in 1949.[15] This model has surely been instrumental for the understanding of phenomena that underpin graft rejection and several other disorders involving an immune component.[16] However, it has also promoted the (incorrect) view that tumors, de facto being self tissues, must be non-immunogenic and (as a corollary) insensitive to immunotherapeutic interventions. The self/non-self model was first questioned in the late 1980s, when the cellular circuitries behind the activation of T cells, and notably the requirement for antigen presentation, began to be elucidated.[17] A few years later, the American scientist Polly Matzinger proposed a revolutionary theory according to which the immune system would not simply react to non-self (while sparing self) constituents, but would rather respond to situations of danger, irrespective of their origin.[18] The first

corollary of such a "danger theory" was that trauma, cancer and other conditions that had long been viewed as immunologically silent de facto are capable of activating the immune system,[18,19] a notion that nowadays is widely accepted.[20,21] Approximately in the same period, van der Bruggen and colleagues from the Ludwig Institute for Cancer Research (Brussels, Belgium) were the first to clone the gene coding for MZ2-E, a protein expressed by multiple distinct melanoma cell lines as well as by tumors of unrelated histological origin, but not by a panel of normal tissues.[22] Moreover, cytotoxic T lymphocytes (CTLs) that specifically reacted against malignant cells in vitro were being found in patients affected by a variety of hematological and solid neoplasms.[22,23] Thus, in line with by Polly Matzinger's model,[18,19] it appeared that the adult T-cell repertoire preserves the ability to react against self antigens, at least in specific circumstances.

Tumor-associated antigens. Nowadays, MZ2-E, best known as melanoma-associated antigen (MAGE)-A1, is considered as the "founder" of the large family of tumor-associated antigens (TAAs), i.e., antigens that, at least in some settings, are capable of eliciting a tumor-specific immune response manifesting with the expansion of TAA-specific CTLs.[24–27] Unfortunately, TAA-directed immune responses are most often incapable of mediating sizeable antineoplastic effects, owing to multiple reasons (see below).[28] Still, the findings by van der Bruggen and colleagues generated an intense wave of investigation worldwide, not only leading to the identification of dozens, if not hundreds, of additional TAAs, but also providing additional insights into the mechanisms whereby TAAs, in selected circumstances, are capable to break self-tolerance and elicit an immune response.[29–31] So far, four distinct classes of TAAs have been described: (1) truly exogenous, non-self TAAs; (2) unique, mutated TAAs; (3) idiotypic TAAs and (4) shared TAAs.

Exogenous TAAs. Bona fide non-self TAAs are specifically expressed by neoplasms that develop as a result of (or concomitant with) viral infections. According to WHO, the viruses that are currently known to be associated with human malignancies are limited to the Epstein-Barr virus (EBV), which is linked to lymphomas and nasopharyngeal cancer, hepatitis B virus (HBV) and hepatitis C virus (HCV), both of which are associated with hepatocellular carcinoma, human papillomaviruses (HPV), in particular HPV-16 and HPV-18, which are associated with head and neck, cervical and anal carcinomas, human T lymphotropic virus Type 1 (HTLV-1) and Type 2 (HTLV-2), which are linked to adult T-cell leukemia and hairy-cell leukemia, respectively, and human herpesvirus 8 (HHV-8), which is associated with Kaposi's sarcoma.[32–34] The possibility to develop recombinant vaccines against these viruses has been extensively investigated in the last decade, and multiple clinical trials have been concluded with encouraging results.[35–39] In this context, a special mention goes to Cervarix® and Gardasil®, two multivalent, recombinant anti-HPV vaccines that have been approved by FDA in 2009 as preventive measures against HPV infection and the consequent development of cervical carcinoma.[40] The success of Cervarix® and Gardasil® as compared with other vaccination strategies against viral cancers that have not yet moved from the bench to the bedside, depends—at least in part—on the fact that both these vaccines were developed as fully preventive measures, aimed at blocking de novo HPV infection, rather than as at therapeutic strategy against established cervical carcinoma. Indeed, both Cervarix® and Gardasil® induce high levels of neutralizing antibodies and result in the generation of HPV-specific long-lasting memory B cells,[41] which efficiently prevent infection, yet are less efficient in promoting T-cell responses that may be beneficial for cervical carcinoma patients. In line with thin notion, official documents report that Cervarix® is not efficient against histopathological endpoints in HPV-infected women (source http://www.fda.gov).

Unique TAAs. Malignant cells near-to-invariably accumulate genetic alterations, which can be as gross as chromosomal rearrangements (e.g., t(9;22)(q34;q11), resulting in the very well known Philadelphia chromosome and leading to chronic myelogenous leukemia, CML) or as specific as point mutations affecting the activity of tumor suppressor genes (e.g., *ATM, TP53*) or oncogenes (e.g., *ALK, EGFR*, *KRAS*).[42] Some of these alterations (such as the Philadelphia chromosome and the resulting fusion kinase BCR-ABL) are so prevalent among specific populations of cancer patients that their detection decisively contributes to diagnosis.[43,44] Others (such as R175H, R248W and R273H *TP53* substitutions) are highly prevalent, too, yet affect a rather heterogeneous and very large population of patients, bearing malignancies that encompass (but are not limited to) breast, lung, gastric and colorectal cancer.[45] Irrespective of whether these changes actually drive oncogenesis and tumor progression (driver mutations) or whether they appear alongside with carcinogenesis and are retained by tumor cells (passenger mutations),[46] non-synonymous mutations that affect exons are expected to generate new, tumor-specific (unique) and potentially immunogenic antigens.[47] In line with this notion, patients affected by neoplasms bearing one of such unique TAAs have been shown to naturally develop anti-TAA antibodies and/or TAA-specific $CD8^+$ cells, although these responses—in the near-to-totality of cases—are unable to exert significant antitumor effects.[48–50] As unique TAAs are only expressed by malignant cells, immune responses arising against their epitopes have a very low probability to result in autoimmune reactions. In addition, the development of efficient immunotherapies against unique TAAs that are expressed by a wide array of tumors would provide clinical benefits to a large population of cancer patients. During the last two decades, the intense wave of research stemming from these considerations has demonstrated that targeting unique TAAs constitutes a meaningful immunotherapeutic approach against cancer.[51–55]

Idiotypic TAAs. One particular class of unique TAAs is constituted by idiotypic TAAs. Hematological malignancies arising from B cells that have functionally rearranged immunoglobulin (Ig)-coding genes are characterized by the cell surface expression of a clonal B-cell receptor (BCR). Such a BCR is de facto a self protein, yet contains a unique variable region that defines its specificity (idiotype), to which the immune system has never been exposed, and hence that is potentially immunogenic.[56] In line with this notion, anti-idiotypic antibodies arise naturally in the course of humoral immune responses (when high levels of clonal Igs are produced by plasma cells), which they contribute to

terminate.[57,58] In 1972, Lynch et al. were the first to demonstrate that peptides corresponding to idiotypic regions of the BCR exposed by myeloma cells are capable of eliciting an efficient immune response,[59] de facto providing the rationale for the development of idiotypic anticancer vaccination. In practical terms, this can be achieved not only by injecting purified peptides that correspond to the idiotype expressed by malignant cells, but also by means of anti-idiotype antibodies.[60] The latter constitute bona fide structural mimics of TAAs (which in this specific case—but not in many other settings—are represented by the idiotype), owing to the fact that antigens and the corresponding antibodies exhibit a consistent degree of complementarity.[60] In general, anti-idiotype antibodies are advantageous as compared with purified peptides as they can be easily and cost-effectively produced in high amounts by immunizing laboratory animals with TAA-targeting antibodies.[60] Irrespective of how they are elicited, anti-idiotype immune responses are patient- and tumor-specific, implying (1) that the development of idiotypic anticancer vaccines requires the precise characterization of neoplastic cells on a per patient basis, and (2) that the efficacy of this approach can be fully compromised by the arisal of a new malignant cell clone as well as by processes of somatic (hyper)mutation, which normally affect the idiotype.[61] Still, following the pioneer work by Lynch and colleagues,[59] the fact that idiotypes constitute a meaningful target for the therapy of B-cell neoplasms has been validated in multiple preclinical and clinical settings.[62–65]

Shared TAAs. Obviously, cancer cells express (and sometimes overexpress) a majority of self antigens, which they share with the normal tissue they originated from.[66] According to the "self/non-self" theory, these antigens should not elicit an immune response, due to central and/or peripheral tolerance mechanisms that are in place to prevent autoimmune reactions.[17] This prediction is actually inaccurate, as (1) both antibodies and $CD8^+$ T cells recognizing shared TAAs (e.g., wild type epidermal growth factor receptor, EGFR and p53) appear to be enriched in the circulation of cancer patients as compared with healthy subjects;[67,68] and (2) a consistent fraction of paraneoplastic syndromes derives from tumor-elicited autoimmune reactions targeting normal tissues.[69] Thus, as postulated by the "danger theory," self-shared TAAs are capable of eliciting an immune response, most likely because they are presented to the immune system in the context of appropriate activation signals.[18,19] Such an immune response is frequently held in check by local immunosuppressive mechanisms (see below),[70,71] and hence does not exert antitumor effects, yet it may be functional at distant sites, thus underlying life-threatening paraneoplastic syndromes.[69] During the last two decades, great efforts have been dedicated at understanding whether and based on which strategies shared TAAs would constitute meaningful targets for the elicitation of antitumor immune responses. Promising results have been obtained in both preclinical and clinical models.[52,72,73] Of note, although so-called "cancer-testis" antigens (CTAs) are expressed not only by a variety of malignant cells but also by germline cells,[74] they are most often considered as unique, rather than shared, TAAs, mostly due to the fact that testes represent an immune privileged site and are de facto spared by most, if not all, autoimmune reactions.[75]

Considerations on the development of anticancer vaccines. Along with the recognition that the immune system is not completely irresponsive to tumors (as it was initially thought to be) and that malignant cells express antigens that are capable of eliciting a tumor-specific immune response, great efforts have been dedicated to the development of anticancer vaccines.[29] Thus, several approaches have been evaluated for their potential to elicit efficient, tumor-specific immune responses, including (but not limited to): recombinant TAAs, in the form of short synthetic epitopes (expected to directly bind, and hence be presented to T cells on, MHC molecules); recombinant full-length proteins (whose presentation requires the uptake and processing by antigen-presenting cells, APCs) or tumor cell-purified preparations (containing TAAs alone or in complex with chaperon proteins), administered as such or via multiple delivery systems (e.g., nanoparticles, DC-derived exosomes, DC-targeting vectors); TAA-encoding vectors; and DC preparations. The results of such an intense wave of investigation/vaccine development have been encouraging. Still, exception made for Cervarix® and Gardasil® (which are approved for prophylactic use, see above), only one product is currently commercialized as a therapeutic anticancer vaccine, namely, sipuleucel-T (also known as Provenge®), a cellular preparation for the treatment of asymptomatic or minimally symptomatic metastatic hormone-refractory prostate cancer.[76] This is in strike contrast with the large array of vaccines that have been developed against infectious agents during the last century. Indeed, there are at least three major obstacles that complicate the development of anticancer vaccines as compared with prophylactic vaccines against infectious diseases. First: the antigenic properties of cancer cells. Although a number of specific and potentially immunogenic TAAs have been identified (see above), only a few of them operate as bona fide tumor rejection antigens (TRAs) as they elicit an immune response that leads to tumor eradication.[26,77] Of note, it has recently been shown that TRAs not necessarily correspond to TAAs that arise as a result of driver mutations, indicating (1) that there is no direct correlation between the oncogenic potential of mutations and their immunogenicity, and (2) that passenger mutations might generate therapeutically useful targets for immunotherapy.[78] Second: the fact that anticancer vaccines must operate, in the vast majority of cases, as therapeutic interventions. Conventional prophylactic vaccines against infectious agents elicit strong humoral responses and promote the establishment of long-term B-cell memory.[79] While this results in an efficient protection against invading pathogens (including HPV strains associated with cervical carcinoma, see above), it has limited (if any) efficacy against established tumors. Indeed, the rejection of established neoplastic lesions requires the activation of robust cell-mediated immune responses, which can be achieved only by specific vaccination strategies.[3,80] In particular, the elicitation of cell-mediated immunity requires TAAs to be conveniently processed by APCs, mainly DCs, and presented to T cells in vivo in the context of appropriate stimulatory signals.[30] This is a critical point and explains why vaccines are invariably administered in the presence of adjuvants (encompassing classical agents such as alum, montanide and incomplete Freund's adjuvant as well as recently developed TLR agonists like monophosphoryl

lipid A, MPLA and imiquimod).[11,12] Indeed, in the absence of activation signals, immature DCs present TAAs to T cells in the context of inhibitory interactions, hence promoting the establishment of tolerance via multiple mechanisms.[81–84] Third, the existence of distinct immunosuppressive pathways that are elicited by tumor cells, both locally and systemically. Cancer cells not only co-opt the stromal components of the neoplastic lesion to serve their metabolic and structural needs,[85,86] but also secrete a wide array of mediators that (1) stimulate the bone marrow to release specific subsets of (relatively immature) myeloid cells into the bloodstream; (2) attract such cells and others to the tumor microenvironment and promote their expansion; (3) condition the differentiation program and/or functional behavior of tumor-infiltrating leukocytes.[87–91] Overall, this results not only in the establishment of a potently immunosuppressive tumor microenvironment but also in some extent of systemic immunosuppression, and explains, at least in part, why natural TAA-directed immune responses are near-to-always unable to exert antitumor effects.

Along the lines of our Trial Watch series,[11,12,92–97] here we will discuss recently published and ongoing clinical trials that have investigated/are investigating the safety and efficacy of purified peptides or full-length proteins as therapeutic interventions against cancer.

Hematological Malignancies

During the past 15 years, the safety and efficacy of recombinant peptides/proteins employed as therapeutic vaccines against hematological neoplasms have been evaluated in a few clinical trials. Peptides derived from Wilms' tumor 1 (WT1), a transcription factor that is overexpressed by several neoplasms,[98] have been tested (most often combined with the carrier keyhole limpet hemocyanin, KLH) in CML patients (n = 1)[99] acute myeloid leukemia (AML) patients (n = 10 and n = 10),[100,101] as well as in a mixed cohort of AML and myelodysplastic syndrome (MDS) patients (n = 19).[102] A peptide derived from receptor for hyaluronic acid-mediated motility (RHAMM, a hyaluronate-binding protein that influences cell motility) has been evaluated in AML, MDS and multiple myeloma (MM) patients (n = 10 and n = 9).[103,104] Idiotype vaccines have been investigated in cohorts of myeloma (n = 5 and n = 6)[105,106] and lymphoma (n = 20, n = 16 and n = 177) patients.[63,107,108] Finally, two clinical trials have investigated the therapeutic potential of autologous, tumor-derived heat-shock protein (HSP)-complexed antigens in CML (n = 20) and non-Hodgkin's lymphoma (n = 20) patients.[109,110] Altogether, these studies demonstrated that recombinant TAA-derived peptides are well tolerated by patients bearing hematological malignancies. These vaccines elicited TAA-specific immune responses in a variable fraction of patients, some of whom also exhibited partial or complete clinical responses.

Nowadays (September 2012), official sources list 11 recent (started after January, 1st 2008), ongoing (not withdrawn, terminated or completed at the day of submission) Phase I-II clinical studies assessing the safety and efficacy of recombinant peptides as therapeutic interventions against hematological neoplasms (**Table 1**). Six of these studies are investigating WT1-derived peptides, either as a standalone intervention or combined with granulocyte macrophage colony-stimulating factor (GM-CSF) or regimens for the depletion of immunosuppressive FOXP3$^+$ regulatory T cells (Tregs), in cohorts of AML and MDS patients. The remaining five studies involve MM patients or subjects affected by various hematological malignancies, who are receiving, either as single agents or in combination with various immunostimulatory strategies, peptides derived from the MAGE-A1-related protein MAGE-A3,[111] from mucin 1 (MUC1, an extensively glycosylated transmembrane protein that is overexpressed by a wide variety of cancers),[112] from the catalytic subunit of human telomerase reverse transcriptase (hTERT)[113] or from the anti-apoptotic protein survivin[114] (source www.clinicaltrials.gov).

Neurological and Pulmonary Cancers

To the best of our knowledge, the first clinical trials investigating the safety and therapeutic potential of TAA-derived peptides in brain and lung cancer patients have been completed in the mid 2000s,[115–118] followed by a few additional studies addressing the same question.[119–123] In particular, a personalized multi-peptide preparation combined with a mineral oil-based adjuvant (Montanide ISA51) has been tested in glioma patients (n = 25),[118] tumor-derived peptides complexed with HSPs have been evaluated in astroglyoma, oligodendrocytoma and meningioma patients (n = 5),[120] and a WT1-derived 9mer has been tested in individuals affected by glioblastoma multiforme (GBM) (n = 21).[122] In addition, cohorts of non-small cell lung carcinoma (NSCLC) patients have been treated with peptides derived from ERBB2/HER2 (a member of the epidermal growth factor receptor family frequently overexpressed in lung and breast cancer patients),[124] in combination with GM-CSF (n = 2 and n = 1),[115,117] with hTERT-derived peptides, combined with either GM-CSF or radiotherapy (n = 26 and n = 23),[119,123] and with peptides corresponding to mutated regions of RAS (n = 18).[121] Taken together, these studies demonstrated that the administration of TAA-derived peptides to patients affected by neurological or pulmonary malignancies is safe and has the potential of inducing—in a fraction of cases—immunological and clinical responses.

Today (September 2012), official sources list 13 recent, ongoing, Phase I-III clinical trials investigating the safety profile and efficacy of TAA-derived vaccines as therapeutic interventions against neurological neoplasms (**Table 2**). Six of these studies involve GBM patients, 4 glioma patients, 1 astrocytoma patients, 1 neuroblastoma patients and 1 individuals bearing not-better specified brain tumors. In four trials, a peptide corresponding to the EGFR in-frame deletion mutant EGFRvIII (rindopepimut, also known as CDX-110)[125,126] is employed, either as a single agent or in combination with GM-CSF, temozolomide or radiotherapy. Alternatively, patients are administered with glioma-associated antigens (GAAs), frequently associated to the TLR3 activator polyriboinosinic-polyribocytidylic acid stabilized with poly-*L*-lysine in carboxymethylcellulose (polyICLC), with survivin-derived peptides, with HSP-TAA complexes or with a multi-peptide vaccine containing 11 distinct TAAs (IMA950)[127] (source www.clinicaltrials.

Table 1. Clinical trials testing TAA-derived peptides as therapeutic interventions in patients affected by hematological neoplasms*

Tumor type	Trials	Phase	Status	Type	TAAs	Co-therapy	Ref.
ALL AML MDS	5	I	Not yet recruiting	Peptide	WT1	As single AA	NCT00725283
							NCT01051063
		I-II	Recruiting			Combined with Treg depletion	NCT01513109
		II				As single AA	NCT01266083
		n.a.				Combined with GM-CSF	NCT00665002
Hematological malignancies	1	I	Recruiting	Peptide	WT1	Combined with GM-CSF	NCT00672152
Multiple myeloma	5	n.a.	Enrolling by invitation	Peptide	MUC1	As single AA	NCT01423760
		I	Recruiting		MAGE-A3	As single AA	NCT01380145
		I-II	Active, not recruiting		CMV hTERT Survivin	Combined with GM-CSF and PCV	NCT00834665
					MUC1	Combined with GM-CSF	NCT01232712
		II	Recruiting		MAGE-A3	Combined with ASCT, lenalidomide, and immunostimulants	NCT01245673

AA, adjuvanted agent; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia, ASCT, autologous stem cell transplantation; CMV, cytomegalovirus N495 peptide; GM-CSF, granulocyte macrophage colony-stimulating factor; hTERT, human telomerase reverse transcriptase; MAGE-A3, melanoma-associated antigen A3; MDS, myelodysplastic syndrome; MUC1, mucin 1; n.a., not available; PCV, pneumococcal conjugate vaccine; poly ICLC, polyriboinosinic-polyribocytidylic acid stabilized with poly-*L*-lysine in carboxymethylcellulose; TAA, tumor associated antigen; Treg, FOXP3$^+$ regulatory T cells; WT1, Wilms' tumor 1. *started after January, 1st 2008 and not withdrawn, terminated or completed at the day of submission.

gov). In addition, official sources list 17 recent, ongoing, Phase I-III clinical trials investigating the potential of TAA-derived peptides for the treatment of lung cancer, mainly NSCLC, patients (**Table 2**). These studies involve a variety of recombinant vaccines, including (but not limited to) peptides derived from MUC1, MAGE-A3, hTERT, kinesin family member 20A (KIF20A), cell division cycle-associated 1 (CDCA1), vascular endothelial growth factor receptor 1 and 2 (VEGFR1 and VEGFR2) and CTAs (such as NY-ESO-1 and upregulated in lung cancer 10, URLC10).[74] In the majority of cases, peptides or full-length proteins are administered as standalone adjuvanted agents, with the exceptions of trial NCT01579188, in which hTERT-derived peptides are combined with GM-CSF, trials NCT00409188 and NCT01015443, in which MUC1-derived peptides are administered after a single dose of cyclophosphamide, and trial NCT00455572, in which recombinant full-length MAGE-A3 is combined with radiotherapy, cisplatin (a DNA-damaging agent) or vinorelbine (a semi-synthetic vinca alkaloid). Importantly, trial NCT00480025, in which advanced NSCLC patients are treated with adjuvanted full-length MAGE-A3 upon tumor resection, constitutes the (or at least one of the) largest clinical study(ies) ever commenced to evaluate the efficacy of an immunotherapeutic intervention against lung cancer.[128] Another particularly intriguing approach in this context is represented by trial NCT00655161, in which NSCLC patients receive an inactivated strain of *Saccharomyces cerevisiae* that has been engineered for the expression of mutant RAS (GI-4000) (source www.clinicaltrials.gov).

Breast, Ovarian and Prostate Carcinoma

During the last two decades, the potential of recombinant vaccines employed as therapeutic interventions against breast, ovarian and prostate carcinoma patients has been extensively investigated. Thus, cohorts of breast carcinoma patients have been administered with HER2-derived peptides in combination with GM-CSF (n = 31, n = 9, n = 9 and n = 195),[115–117,129] with peptides derived from a specific splicing variant of survivin (n = 14),[130] with a broad panel of peptides naturally presented by ovarian cancer cells in combination with GM-CSF (n = 7),[131] with full-length CA15–3, CA125 and carcinoembryonic antigen (CEA), three circulating markers of breast cancer recurrence,[132]

Table 2. Clinical trials testing TAA-derived peptides and/or full length proteins as therapeutic interventions in patients affected by neurological and pulmonary malignancies

Tumor type	Trials	Phase	Status	Type	TAAs	Co-therapy	Ref.
Astrocytoma	1	0	Active, not recruiting	Peptide	GAA	Combined with poly ICLC	NCT00795457
Brain cancer	1	I	Active, not recruiting	Peptide	TAAs	As single AA	NCT00935545
Glioblastoma multiforme	6	I	Recruiting	Peptide	IMA950	Combined with various immunostimulants	NCT01403285
						Combined with GM-CSF and radiotherapy	NCT01222221
		I-II			EGFRvIII	Combined with chemotherapeutics	NCT00626015
		II	Active, not recruiting			Combined with GM-CSF	NCT00643097
				HSP complex	HSPPC96	Combined with temozolomide	NCT00905060
		III	Recruiting	Peptide	EGFRvIII	Combined with GM-CSF and temozolomide	NCT01480479
Glioma	4	n.a.	Recruiting	Peptide	GAA	Combined with poly ICLC	NCT01130077
		0	Active, not recruiting				NCT00874861
		I	Recruiting		EGFRvIII	As single AA	NCT01058850
					Survivin	Combined with GM-CSF	NCT01250470
Lung cancer	1	I-II	Recruiting	Peptide	NY-ESO-1	As single AA	NCT01584115

AA, adjuvanted agent; EGFR, epidermal growth factor receptor; GAA, glioma-associated antigen; GM-CSF, granulocyte macrophage colony-stimulating factor; HSP, heat-shock protein; HSPPC96, HSP-peptide vaccine 96; n.a., not available; poly ICLC, polyriboinosinic-polyribocytidylic acid stabilized with poly-*L*-lysine in carboxymethylcellulose; TAA, tumor associated antigen; *started after January, 1st 2008 and not withdrawn, terminated or completed at the day of submission.

combined with autologous breast cancer cells, allogeneic breast cancer MCF-7 cells, GM-CSF and recombinant IL-2 (n = 42),[133] and with Sialyl-Tn (a MUC1-associated carbohydrate) chemically coupled to KLH (n = 33).[134] Some of these approaches have alongside been tested in ovarian cancer patients,[115,116,131,134] owing to the fact that breast and ovarian carcinomas share a relatively consistent number of TAAs.[135] Moreover, ovarian carcinoma patients have been treated with a synthetic form of an immunodominant disaccharide of the Thomsen-Friedenreich antigen conjugated to KLH (n = 10),[136] with not better specified pre-designated or evidence-based peptides (n = 5),[137] with a p53-derived synthetic long peptide (SLP) coupled to immunostimulatory doses of cyclophosphamide (n = 10),[138] and with multiple courses of recombinant poxviruses encoding full-length NY-ESO-1 (n = 22).[139] Finally, prostate carcinoma patients have received HER2-derived peptides, as such or in the form of hybrids with a moiety of the MHC Class II-associated invariant chain, plus GM-CSF (n = 40 and n = 32),[140,141] prostate-specific antigen (PSA)-derived peptides, as a single adjuvanted agent (n = 5) or combined with GM-CSF (n = 28),[142,143] full-length NY-ESO-1 complexed with cholesterol-bearing hydrophobized pullulan (CHP) (n = 4, n = 4 and n = 2),[144–146] an adjuvanted globo H hexasaccharide-KLH fusion (n = 20),[147] and a number of multi-peptide preparations often, but not always, including PSA- and squamous cell carcinoma antigen recognized by T cells (SART)-derived peptides and combined with GM-CSF or estramustine phosphate, an alkylating estradiol derivative (n = 13, n = 10, n = 16, n = 19 and n = 23).[148–153] Altogether, these studies demonstrated that the administration of recombinant peptides or full length proteins to breast, ovarian and prostate carcinoma patients is generally safe and can induce, in a fraction of cases, immunological and clinical responses.

Nowadays (September 2012), official sources list 16 recent, ongoing Phase I-III clinical trials assessing the safety and efficacy of recombinant peptides in breast carcinoma patients (**Table 3**). A majority of these studies involve the administration of HER2-derived peptides, either as adjuvanted standalone interventions or combined with additional immunostimulatory agents, including low doses of cyclophosphamide, GM-CSF and polyICLC. Alternatively, vaccination regimens based on CDCA1-, CEA-, hTERT-, KIF20A-, MUC1-, survivin-, URLC10- and WT1-derived peptides are being evaluated (source www.clinicaltrials.

Table 2 (Continued). Clinical trials testing TAA-derived peptides and/or full length proteins as therapeutic interventions in patients affected by neurological and pulmonary malignancies

Tumor type	Trials	Phase	Status	Type	TAAs	Co-therapy	Ref.
Neuroblastoma	1	I	Active, not recruiting	Peptide	GD2L GD3L	Combined with KLH and oral β-glucan	NCT00911560
NSCLC	15	n.a.	Enrolling by invitation		MUC1		NCT01423760
		I	Recruiting	Peptide	CDCA1 KIF20A URLC10	As single AA	NCT01069575
					IDO		NCT01219348
					URLC10		NCT01069640
				FL protein	MAGE-A3	Combined with CDDP, radiotherapy or vinorelbine	NCT00455572
					CDCA1 URLC10 VEGFR1/2		NCT00874588
		I-II	Unknown	Peptide	TTK URLC10 VEGFR1/2	As single AA	NCT00633724
					KOC1 TTK URLC10		NCT00674258
					URLC10 VEGFR1/2		NCT00673777
		II	Recruiting	Vector	RAS		NCT00655161
					CTAs		NCT01592617
				Peptide	hTERT	Combined with GM-CSF	NCT01579188
		III	Not yet recruiting		MUC1	Combined with cyclophosphamide	NCT00409188
				FL protein	MAGE-A3	As single AA	NCT00480025
			Recruiting	Peptide	MUC1	Combined with cyclophosphamide	NCT01015443
SCLC	1	I	Recruiting	Peptide	CDCA1 KIF20A	As single AA	NCT01069653

AA, adjuvanted agent; CDCA1, cell division cycle-associated 1; CDDP, cisplatin; CTA, cancer-testis antigen; FL, full-length; GM-CSF, granulocyte macrophage colony-stimulating factor; hTERT, human telomerase reverse transcriptase; IDO, indoleamine 2, 3-dioxygenase; KIF20A, kinesin family member 20A; KLH, keyhole limpet hemocyanin; KOC1, K homology domain containing protein overexpressed in cancer; MAGE-A3, melanoma-associated antigen A3; MUC1, mucin 1; n.a., not available; NSCLC, non-small cell lung carcinoma; SCLC, small cell lung cancer; TAA, tumor associated antigen; URLC10, upregulated gene in lung cancer 10; VEGFR, vascular endothelial growth factor receptor. *started after January, 1st 2008 and not withdrawn, terminated or completed at the day of submission.

gov). In addition, official sources list 8 recent, ongoing, Phase I-II clinical trials investigating TAA-derived peptides for the therapeutic vaccination of ovarian (3 studies) and prostate (5 studies) carcinoma patients (**Table 3**). The trials enrolling ovarian carcinoma patients involve the administration a p53-derived SLP combined with pegylated interferon (IFN), full-length NY-ESO-1 adjuvanted with MPLA or a peptide derived from folate-binding protein (FBP, which is often overexpressed by ovarian neoplasms)[154] in association with GM-CSF. The studies recruiting prostate carcinoma patients are based on peptides derived from T-cell receptor gamma chain alternate reading frame protein (TARP, a nuclear protein overexpressed in a large proportion of prostate carcinomas),[155,156] administered either as a single agent or combined with ex vivo TARP peptide-pulsed DCs, peptides derived from prostate membrane-specific antigen (PMSA, a glycoprotein specifically expressed by normal and malignant prostate cells), CDCA1-derived epitopes, a synthetic peptide derived corresponding to amino acids 22–31 of mouse gonadotropin releasing hormone

(GnRH), or full-length NY-ESO-1, all given as standalone adjuvanted interventions (source www.clinicaltrials.gov).

Melanoma

Together with RCC, melanoma constitutes by far the clinical setting in which immunotherapeutic interventions have been most extensively investigated, at least in part due to the fact that both these neoplasms naturally generate immune responses and appear to be very sensitive to immunostimulatory interventions, even as unspecific as the systemic administration of high-dose IL-2.[9,10] This intense research effort has lead not only to an improved understanding of the biology of melanoma cells, but also to the detailed characterization of a wide panel of melanocyte differentiation antigens (MDAs), underpinning the development of potential anticancer vaccines.[157] The safety and therapeutic profiles of many of such vaccination strategies have been tested in clinical trials starting from the late 1990s. These studies involved peptides derived from MDAs including, but not limited to: the Type I transmembrane glycoprotein gp100 (n = 22, n = 15, n = 26, n = 12, n = 60, n = 25, n = 24, n = 8, n = 11, n = 51, n = 12, n = 121, n = 197 and n = 185),[158–171] the 18 KDa transmembrane protein melan A (also known as melanoma antigen recognized by T cells 1, MART-1) (n = 1, n = 3, n = 15, n = 28, n = 12, n = 60, n = 25, n = 6, n = 24, n = 8, n = 11, n = 12, n = 17, n = 18 and n = 15),[159,161,163–166,168,172–178] several members of the MAGE-A protein family such as MAGE-A1, MAGE-A3 and MAGE-A10 (n = 24, n = 51, n = 121 and n = 197),[164,167,169,170] and tyrosinase, an enzyme required for melanin synthesis (n = 18, n = 43, n = 15, n = 26, n = 60, n = 25, n = 24, n = 11, n = 51, n = 121, n = 197 and n = 18).[159,160,162–164,166,167,169,170,177,179,180] In addition, clinical trials enrolling melanoma patients have been performed to assess the safety profile and therapeutic potential of NY-ESO-1-derived peptides (n = 37, n = 8, n = 13 and n = 121),[169,181–183] hTERT-derived peptides (n = 25),[184] full-length recombinant NY-ESO-1 (n = not available, n = 51, n = 1, n = 1 and n = 18),[144,145,185–187] HSP-complexed antigens (n = not available),[188] and subsequent courses of recombinant poxviruses encoding full-length NY-ESO-1 (n = 25).[139] Most often, MDA- and/or TAA-derived peptides were administered as part of multi-peptide preparations and combined with immunostimulatory interventions including conventional adjuvants, GM-CSF, IL-2 and cyclophosphamide. In line with the high sensitivity of melanoma cells to immunostimulatory approaches, the vast majority of these clinical trials reported no significant side effects and satisfactory rates of durable clinical responses.

Today (September 2012), official sources list 25 recent, ongoing Phase I-III clinical trials assessing the safety and efficacy of recombinant peptides/proteins in melanoma patients (**Table 4**). Most of these studies are based on various MDA- or TAA-derived peptides, given either as single adjuvanted agents or combined with additional immunostimulatory interventions including, but not limited to, IL-2, IL-12, pegylated IFNα, IFNγ, GM-CSF, TLR agonists (e.g., polyICLC, imiquimod, resiquimod, lipopolysaccharide) and monoclonal antibodies targeting CD40 or PD1. In this setting, particularly interesting strategies are being undertaken by trial NCT01331915, investigating the safety and anticancer profile of a recombinant, detoxified toxin from *Bordetella pertussis* coupled to a tyrosinase epitope,[189] and by trial NCT00706992, testing the clinical potential of a replication-defective recombinant canarypox virus encoding a melan A-derived epitope coupled to T cells genetically engineered to express a melan A-targeting T-cell receptor (TCR)[190] (source www.clinicaltrials.gov).

Gastrointestinal, Pancreatic and Colorectal Tumors

The results of the first clinical trials investigating the safety and efficacy of TAA-derived peptides or proteins as therapeutic interventions in cohort of patients affected by gastrointestinal, pancreatic and colorectal neoplasms have been published no earlier than in 2004.[191,192] Since then, the following therapeutic and clinical settings have been investigated: survivin-derived peptides, given to colorectal carcinoma (CRC) (n = 15) or pancreatic cancer (n = 1) patients as a single adjuvanted agent,[192,193] a multi-peptide vaccine including epitopes from distinct SART proteins administered to CRC patients as a standalone adjuvanted intervention (n = 10),[191] a personalized, peptide-based vaccine, given to CRC patients in combination with uracil, tegafur and calcium folinate (n = 8),[194] a personalized combination of maximum 4 peptides derived from 16 distinct TAAs including (but not limited to) HER2, CEA, PAP, PSA, SART2 and SART3, given to advanced gastric carcinoma or CRC patients in combination with a 5-fluorouracil derivative (n = 11),[195] full-length NY-ESO-1, administered as a CHP complex to esophageal cancer patients (n = 4, n = 8, n = 4 and n = 8),[144–146,196] an artificially synthesized helper/killer-hybrid epitope long peptide derived from MAGE-A4, given as a dually adjuvanted standalone intervention to a patient with CRC pulmonary metastasis,[197] and three peptides derived from the protein kinase TTK, lymphocyte antigen 6 complex locus K (LY6K), and insulin-like growth factor II mRNA-binding protein 3 (IMP3), administered in incomplete Freund's adjuvant to esophageal cancer patients (n = 10 and n = 60).[198,199] In all these settings, vaccination with TAA-peptides was well tolerated and, in multiple instances, it also elicited immunological and clinical responses.

Nowadays (September 2012), official sources list 9 recent, ongoing Phase I-II clinical trials investigating the safety and efficacy of recombinant peptides/proteins in esophageal cancer (5 trials), gastric cancer (1 trial), pancreatic carcinoma (5 trials) and CRC (4 trials) patients (**Table 5**). CHP-complexed full-length NY-ESO-1 as a single agent as well as peptides derived from common TAAs such as CDCA1, TTK, URLC10, VEGFR1 and VEGFR2, either as standalone interventions or combined with TLR9 agonists, are being tested in esophageal cancer patients. The safety and therapeutic profile of VEGFR1-derived peptides, as single agents, is being investigated in gastric carcinoma patients. CRC patients are being enrolled in trials involving MUC1-derived peptides combined with either chemoradiation therapy plus cyclophosphamide or polyICLC, peptides derived from the CTA RNF43, given as standalone agents, as well as GI-4000 (an inactivated strain of *S. cerevisiae* engineered for the expression of mutant RAS, see above), in combination with conventional

Table 3. Clinical trials testing TAA-derived peptides and/or full length proteins as therapeutic interventions in patients affected by breast, ovarian and prostate carcinoma

Tumor type	Trials	Phase	Status	Type	TAAs	Co-therapy	Ref.
Breast cancer	16		Active, not recruiting	Peptide	HER2 MUC1	Combined with CpG ODNs and/or GM-CSF	NCT00640861
		n.a.			CEA CTAs HER2	As single AA	NCT00892567
						Combined with poly ICLC and tetanus toxoid peptide	NCT01532960
					CMV hTERT Survivin	Combined with basiliximab, GM-CSF and prevnar	NCT01660529
		0	Recruiting		MUC1	Combined with poly ICLC	NCT00986609
		I			CDCA1 DEPDC1 KIF20A MPHOSPH1 URLC10	As single AA	NCT01259505
					FRα	Combined with cyclophosphamide	NCT01606241
					HER2	As single AA	NCT01632332
		I-II	Active, not recruiting		HER2	Combined with lapatinib	NCT00952692
						Combined with GM-CSF	NCT00841399
							NCT00854789
			Recruiting		HER2	Combined with GM-CSF and cyclophosphamide	NCT00791037
						Combined with rintatolimod and/or GM-CSF	NCT01355393
		II	Not yet recruiting			Combined with anti-HER2 mAb and GM-CSF	NCT01570036
		III	Recruiting		WT1	As single agent	NCT01220128
					HER2	Combined with GM-CSF	NCT01479244
Ovarian cancer	3	I-II	Recruiting	Peptide	FBP	Combined with GM-CSF	NCT01580696
				FL protein	NY-ESO-1	As single AA	NCT01584115
				Peptide	p53	Combined with gemcitabine and pegylated IFNα-2b	NCT01639885
Prostate cancer	5	n.a.	Active, not recruiting	Peptide	PSMA TARP	Combined with poly ICLC	NCT00694551
		I			TARP	Combined with ex vivo TARP peptide-pulsed DCs	NCT00972309
			Recruiting		LAGE1 NY-ESO-1	As single AA	NCT00711334
		I-II	Unknown		CDCA1		NCT01225471
					GnRH		NCT00895466

AA, adjuvanted agent; CDCA1, cell division cycle-associated 1; CEA, carcinoembryonic antigen; CMV, cytomegalovirus pp65 peptide; CTA, cancer-testis antigen; DC, dendritic cell; DEPDC1, DEP domain containing 1; FBP, folate binding protein; FL, full length; FR, folate receptor; GM-CSF, granulocyte macrophage colony-stimulating factor; GnRH, gonadotropin releasing hormone; hTERT, human telomerase reverse transcriptase; IFN, interferon; KIF20A, kinesin family member 20A; mAb, monoclonal antibody; MPHOSPH1, M-phase phosphoprotein 1; MUC1, mucin 1; n.a., not available; poly ICLC, polyriboinosinic-polyribocytidylic acid stabilized with poly-*L*-lysine in carboxymethylcellulose; PMSA, prostate membrane-specific antigen; ODN, oligodeoxynucleotide; TAA, tumor associated antigen; TARP, T-cell receptor gamma chain alternate reading frame protein; URLC10, upregulated in lung cancer 10; WT1, Wilms' tumor 1. *started after January, 1st 2008 and not withdrawn, terminated or completed at the day of submission.

Table 4. Clinical trials testing TAA-derived peptides and/or full-length proteins as therapeutic interventions in melanoma patients

Tumor type	Trials	Phase	Status	Type	TAAs	Co-therapy	Ref.
Melanoma	25	n.a.	Recruiting	Peptide	Class I-restricted peptides	Combined with IFNγ	NCT00977145
						Combined with imiquimod	NCT01264731
		0	Recruiting	Peptide	MAGE-A3	As single AA	NCT01425749
		I	Active, not recruiting	Peptide	gp100 MART-1 NY-ESO-1	Combined with poly ICLC ± anti-CD40-mAb	NCT01008527
					gp100	Combined with pegylated IFNα-2b	NCT00861406
					MAGE-A3	Combined with dacarbazine	NCT00849875
			Not yet recruiting		Class I-restricted peptides	Combined with LPS or poly ICLC	NCT01585350
			Recruiting		gp100 MART-1 NY-ESO-1	Combined with anti-PD1 mAb	NCT01176461
							NCT01176474
					PRAME	As single AA	NCT01149343
		I-II	Recruiting	FL protein	NY-ESO-1	As single AA	NCT01584115
						Combined with poly ICLC	NCT01079741
				Peptide	LAG3 MAGE-3.A2 NA-17 NY-ESO-1	As single AA	NCT01308294
				Vector	Tyrosinase		NCT01331915
			Unknown	Peptide	MAGE-3.A1 NA17.A2	Combined with GM-CSF, IFN-α, IL-2 and imiquimod	NCT01191034
		II	Active, not recruiting	Peptide	MAGE-A3	As single AA	NCT00896480
							NCT00942162
					MART-1	Combined with anti-MART-1TCR-expressing PBLs ± IL-2	NCT00706992
					Not better specified	Combined with GM-CSF and a tetanus helper peptide	NCT00938223
			Recruiting		gp100 MAGE-3	As single AA ± resiquimod	NCT00960752
					gp100 MAGE-3.1 MART-1 NA17-A2	Combined with daclizumab ± IL-12	NCT01307618
					IDO survivin	Combined with GM-CSF, imiquimod and temozolomide	NCT01543464
					MAGE-A3	As single AA ± poly ICLC	NCT01437605
						As single AA ± IL-2	NCT0126660
		III	Active, not recruiting	Peptide	MAGE-A3	As single AA	NCT00796445

AA, adjuvanted agent; FL, full-length; GM-CSF, granulocyte macrophage colony-stimulating factor; gp100, glycoprotein 100; IDO, indoleamine 2, 3-dioxygenase; IFN, interferon; IL, interleukin; LAG3, lymphocyte-activation gene 3; LPS, lipopolysaccharide; mAb, monoclonal antibody; MAGE, melanoma-associated antigen; MART-1, melanoma antigen recognized by T-cells 1; n.a., not available; PBL, peripheral blood lymphocyte; poly ICLC, polyriboinosinic-polyribocytidylic acid stabilized with poly-L-lysine in carboxymethylcellulose; PRAME, preferentially expressed antigen in melanoma; TAA, tumor associated antigen; TCR, T-cell receptor. *started after January, 1st 2008 and not withdrawn, terminated or completed at the day of submission.

Table 5. Clinical trials testing TAA-derived peptides and/or full-length proteins as therapeutic interventions in patients affected by esophageal, gastric, pancreatic and colorectal carcinoma

Tumor type	Trials	Phase	Status	Type	TAAs	Co-therapy	Ref.
Colorectal carcinoma	4	I	Unknown	Peptide	RNF43	As single AA	NCT00641615
		II	Recruiting		GI-4000	Combined with bevacizumab and/or FOLOFOX or FOLFIRI	NCT01322815
					MUC1	Combined with chemoradio-therapy and cyclophosphamide	NCT01507103
						Combined with poly ICLC	NCT00773097
Esophageal carcinoma	5		Active, not recruiting	FL protein	NY-ESO-1	As single AA complexed with CHP	NCT01003808
		I	Unknown	Peptide	IMP3 LY6K TTK	As single AA	NCT00682227
					KOC1 TTK URLC10 VEGFR1/2	Combined with cisplatin and 5-FU	NCT00632333
		I-II	Recruiting		TTK URLC10	Combined with CpG ODNs	NCT00669292
		II			CDCA1 KOC1 URLC10	As single AA	NCT01267578
Gastric cancer	1	I-II	Recruiting	Peptide	VEGFR1	As single AA	NCT01227772
Pancreatic carcinoma	5	I	Active, not recruiting	Peptide	hTERT	Combined with gemcitabine, GM-CSF and tadalafil	NCT01342224
					VEGFR1/2	Combined with gemcitabine	NCT01266720
							NCT00639925
		I-II	Unknown		VEGFR1	As single AA	NCT00683358
					VEGFR1/2	Combined with gemcitabine	NCT00655785

5-FU, 5-fluorouracil; AA, adjuvanted agent; CDCA1, cell division cycle-associated 1; CHP, cholesterol-bearing hydrophobized pullulan; FL, full-length; FOLFIRI, folinic acid, 5-FU, irinotecan; FOLFOX, folinic acid, 5-FU, oxaliplatin; GM-CSF, granulocyte macrophage colony-stimulating factor; hTERT, human telomerase reverse transcriptase; IMP3, insulin-like growth factor II mRNA-binding protein 3; KOC1, K homology domain containing protein overexpressed in cancer; LY6K, lymphocyte antigen 6 complex locus K; MUC1, mucin 1; ODN, oligodeoxynucleotide; poly ICLC, polyriboinosinic-polyribocytidylic acid stabilized with poly-*L*-lysine in carboxymethylcellulose; TAA, tumor associated antigen; URLC10, upregulated in lung cancer 10; VEGFR, vascular endothelial growth factor receptor. *started after January, 1st 2008 and not withdrawn, terminated or completed at the day of submission.

chemotherapy or bevacizumab (a VEGF-targeting monoclonal antibody). Finally, peptides derived from hTERT and VEGFR1/2 are being tested in pancreatic carcinoma patients, in combination with GM-CSF plus tadalafil (a phosphodiesterase Type 5 inhibitor currently approved for the therapy of erectile dysfunction and commercialized under the label of Cialis®) and/or gemcitabine (a nucleoside analog) (source www.clinicaltrials.gov).

Renal, Bladder and Reproductive Tract Tumors

So far, a few clinical studies have investigated the profile of TAA-derived peptides or proteins employed as therapeutic interventions in cohort of patients affected by RCC and distinct malignancies of the reproductive tract, including cervical carcinoma, endometrial cancer, uterine sarcoma and vulvar intraepithelial neoplasia.[137,200–204] In particular, multi-peptide vaccination strategies involving up to six peptides derived from a broad panel of RCC-associated antigens have been tested, invariably in combination with immunostimulatory interventions (including IL-2, IFNα, GM-CSF and low-dose cyclophosphamide), in RCC patients (n = 10 and n = 96).[203,204] In addition, the efficacy of peptides corresponding to distinct regions of the HPV-16 protein E7 has been evaluated in patients affected by cervical carcinoma or vulvar intraepithelial neoplasia, most often as standalone adjuvanted agents or combined with pan-HLA-DR-binding T helper epitopes (n = 19, n = 18 and n = 15).[200–202] Finally, not better specified pre-designated or evidence-based peptides have been tested in a cohort of patients affected by cervical carcinoma or various other neoplasms of the reproductive tract (n = 9).[137] The administration of recombinant peptides combined to immunostimulatory

Table 6. Clinical trials testing TAA-derived peptides and/or full-length proteins as therapeutic interventions in patients affected by bladder carcinoma and tumors of the reproductive tract

Tumor type	Trials	Phase	Status	Type	TAAs	Co-therapy	Ref.
Bladder cancer	3	II	Enrolling by invitation	Peptide	MAGE-A3	As single AA ± BCG	NCT01498172
			Recruiting	FL protein	MAGE-A3	As single AA	NCT01435356
			Unknown	Peptide	DEPDC1 MPHOSPH1		NCT00633204
Endometrial cancer	1	I-II	Recruiting	Peptide	FBP	Combined with GM-CSF	NCT01580696
Reproductive tract cancer	6	I	Active, not recruiting	FL protein	NY-ESO-1	Combined with GM-CSF, decitabine and doxorubicin	NCT00887796 NCT01673217
				Peptide	Seven TAAs	As single AA	NCT01095848
					FRα	Combined with cyclophosphamide	NCT01606241
			Recruiting	Virus	NY-ESO-1	Combined with GM-CSF and rapamycin	NCT01536054
		I-II		Peptide	Survivin	Combined with cyclophosphamide	NCT01416038

AA, adjuvanted agent; BCG, bacillus Calmette-Guérin; DEPDC1, DEP domain containing 1; FBP, folate-binding protein; FL, full-length; FR, folate receptor; GM-CSF, granulocyte macrophage colony-stimulating factor; MAGE-A3, melanoma-associated antigen A3; MPHOSPH1, M-phase phosphoprotein 1; TAA, tumor associated antigen. *started after January, 1st 2008 and not withdrawn, terminated or completed at the day of submission.

interventions was well tolerated by RCC patients and yielded immunological responses that, at least in some cases, were associated with improved patient survival.[203,204] Conversely, E7-derived peptides induced potent immune responses that, in one trial, led to viral clearance from cervical scrapings by the fourth vaccine course,[200] yet were unable to promote efficient antitumor immunity.[137,200–202] These results are in line with the fact that—according to official sources—preventive anti-HPV vaccines (i.e., Cervarix® and Gardasil®) are not efficient against histopathological endpoints when used as therapeutic agents in HPV-infected women (source http://www.fda.gov).

Today (September 2012), official sources list 10 recent, ongoing Phase I-II clinical trials investigating the safety and efficacy of recombinant peptides/proteins in bladder carcinoma (3 trials) and reproductive tract cancer (7 trials) patients (**Table 6**). In the former clinical setting, MAGE-A3-derived peptides, recombinant full-length MAGE-A3 or epitopes derived from DEP domain containing 1 (DEPDC1) and M phase phosphoprotein 1 (MPHOSPH1) are being tested, either as standalone adjuvanted agents or in combination with the bacillus Calmette-Guérin (BCG), an attenuated strain of *Mycobacterium bovis* that is currently employed against superficial bladder carcinoma.[205] In the latter clinical setting, 2 studies involve full-length NY-ESO-1 combined with GM-CSF, the demethylating agents decitabine and doxorubicine (an anthracycline that has recently been shown to promote the immunogenic death of tumor cells),[20,206,207] two studies involve a lyophilized liposomal preparation containing either seven different TAA-derived peptides (DPX-0907, given as a standalone adjuvanted agent) or survivin-derived epitopes (administered in combination with cyclophosphamide), one study involves the administration of folate receptor α-derived peptides plus cyclophosphamide, one study involves FBP-derived epitopes given together with GM-CSF and one study is based on a replication-defective NY-ESO-1-coding canarypox virus combined with GM-CSF and the mammalian target or rapamycin (mTOR) inhibitor sirolimus (source www.clinicaltrials.gov).

Additional Neoplasms and Mixed Clinical Cohorts

Recombinant TAA-derived peptides and full-length proteins have been tested in a few additional clinical settings, encompassing oral and urothelial cancer patients[208,209] as well as rather heterogeneous cohorts including subjects affected by wide arrays of solid neoplasms.[101,210–219] Thus, oral and urothelial cancer patients (n = 11 and n = 9, respectively) have been treated with a survivin-derived 9-mer, either as a subcutaneous or as a intratumoral adjuvanted injection.[208,209] In addition, WT1-derived 9-mers, HER2-derived short epitopes or long peptides complexed with CHP, and not better indicated peptides recognized by circulating T cells in the periphery have been tested, as adjuvanted standalone interventions, in cohort of patients affected by not better specified solid tumors (n = 5, n = 10, n = 9, n = 24 and n = 14),[101,210–212,219] NY-ESO-1-derived peptides have been evaluated in patients bearing metastatic NY-ESO-1-expressing cancers (n = 12),[213] and epitopes corresponding to mutated regions of RAS, CEA-derived peptides, complex multi-peptide preparations as well as HSP-complexed antigens have been used to vaccinate patients affected by distinct types of carcinoma or advanced neoplasms (n = 8, n = 10, n = not available, n = 113 and n = 16).[214–218] In general, the administration of purified peptides/proteins to

Table 7. Clinical trials testing TAA-derived peptides and/or full length proteins as therapeutic interventions in patients affected by additional tumor type and in mixed patient cohorts

Tumor type	Trials	Phase	Status	Type	TAAs	Co-therapy	Ref.
Bile duct cancer	1	I	Recruiting	Peptide	URLC10	Combined with gemcitabine	NCT00624182
Head and neck carcinoma	1	I	Unknown	Peptide	HPV-16 antigens MAGE-A3	As single AA	NCT00704041
Hepatocellular carcinoma	1	I	Recruiting	Peptide	VEGFR1/2	As single AA	NCT01266707
HER2^{+} cancers	1	I	Not yet recruiting	Virus	HER2	As single AA	NCT01526473
HPV-induced cancers	1	I-II	Recruiting	Peptide	p16^{INK4a}	As single AA	NCT01462838
Mesothelioma	2	II	Recruiting	Peptide	WT1	Combined with GM-CSF	NCT01265433
			Not yet recruiting	Virus	5T4	As single AA	NCT01569919
Metastatic solid tumors	1	I	Recruiting	Peptide	HER2	As single AA	NCT01376505
NY-ESO-1^{+} tumors	1	I	Recruiting	FL protein	NY-ESO-1	Combined with CpG ODNs ± cyclophosphamide	NCT00819806
Solid tumors	2	I	Recruiting	Peptide	MUC-1	As single AA	NCT01556789
					WT1		NCT01621542
Various tumors	1	I	Unknown	FL protein	NY-ESO-1	Combined with resiquimod	NCT00821652

AA, adjuvanted agent; FL, full-length; GM-CSF, granulocyte macrophage colony-stimulating factor; HPV, human papillomavirus; MAGE-A3, melanoma-associated antigen A3; MUC-1, mucin 1; ODN, oligodeoxynucleotide; TAA, tumor associated antigen; URLC10, upregulated in lung cancer 10; VEGFR, vascular endothelial growth factor receptor; WT1, Wilms' tumor 1.*. *started after January, 1st 2008 and not withdrawn, terminated or completed at the day of submission.

these patients was well tolerated and promoted—in a few cases—immunological and clinical responses.

Today (September 2012), official sources list 12 recent, ongoing Phase I-II clinical trials investigating the safety and efficacy of recombinant peptides/proteins in patients affected by various tumor types encompassing head and neck carcinoma (1 trial), hepatocellular carcinoma (1 trial), mesothelioma (2 trials), bile duct cancer (1 trial), as well as in relatively heterogeneous patient cohorts (7 trials) (**Table 7**). The vast majority of these studies involves the administration of TAA-derived peptides, either as standalone adjuvanted agents or combined with immunostimulatory compounds such as GM-CSF, TLR agonists or low doses of cyclophosphamide. Two notable exceptions are constituted by NCT01569919, testing a recombinant modified vaccinia Ankara viral vector encoding the 5T4 fetal oncoprotein in mesothelioma patients and NCT01526473, evaluating a non-infective variant of the Venezuelan equine encephalitis virus encoding the extracellular domain and transmembrane region of HER2 in patients affected by not better specific HER2^{+} neoplasms (www.clinicaltrials.gov).

Concluding Remarks

During the last two decades, the molecular and cellular circuitries whereby malignant cells and the immune system mutually interact have been the subject of in-depth investigation. Such a renovated interest, stemming within the conceptual framework provided by Polly Matzinger's danger theory, has been paralleled by the development of multiple strategies for anticancer vaccination. These approaches, involving the use of recombinant proteins, TAA-encoding vectors or DC preparations, have generated encouraging results in both preclinical and clinical settings. However, only a few trials assessing the efficacy of TAA-derived peptides and/or full length proteins have reported consistent rates of objective, long-term clinical responses.[108,129,171,204,220] In line with this notion, no more than three anticancer vaccines are currently approved by FDA for use in humans: Provenge®, employed as a therapeutic intervention in a limited subset of prostate carcinoma patients; Cervarix® and Gardasil®, both given as prophylactic agents against HPV infection (and hence against HPV-associated cervical carcinoma). At least in part, this is due to the fact that the eradication of established malignant lesions requires a robust tumor-specific, cell-mediated immune response that is relatively difficult to obtain, owing to multiple reasons (see above). Moreover, it appears that several TAA-derived peptides and/or full-length protein exhibit (at least some degree of) clinical activity when administered as adjuvant therapy or to patients with minimal residual disease, yet fail to provide any clinical benefit to individuals bearing advanced and/or metastatic lesions.[80,108,220–222] We believe that (1) the discovery of novel bona fide TRAs, (2) the optimization of adjuvant strategies that potently activate DCs in vivo, (3) the rational combination of anticancer vaccines with immunomodulatory agents (such as

anti-CTLA4 and anti-PD1 antibodies), (4) the precise identification of the subsets of patients that are most likely to respond to vaccination with robust immune responses and (5) the establishment of standardized protocols to evaluate the nature, breadth and quality of antigen-specific T-cell responses, an objective recently proposed by the MIATA (Minimal Information About T Cell Assays) project,[223–225] are the keys toward the development of new, efficient and (perhaps) clinically useful anticancer vaccines.

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