Cancer-Testis Antigen Peptide Vaccine for Cancer Immunotherapy: Progress and Prospects

Abstract
Cancer vaccines, including peptide-based vaccines, have been considered a key tool of effective and protective cancer immunotherapy because of their capacity to provide long-term clinical benefit for tumors. Among a large number of explorations of peptide antigen-based vaccines, cancer-testis antigens (CTAs), which are activated in cancers but silenced in normal tissues (except testis tissue), are considered as ideal targets. Currently, personalized treatment for cancer has become a trend due to its superior clinical efficacy. Thus, we envisage rational selection of CTA peptides to design “personalized” CTA peptide vaccines. This review summarizes the advances in CTA peptide vaccine research and discusses the feasibility of establishing “personalized” CTA peptide vaccines.

The field of cancer vaccines, including peptide-based vaccines, has moved forward drastically during the last 2-3 decades after the demonstration that in both animal models and, later, in patients, it is possible to generate antitumor immune responses [1]. Naive T cells can be induced to proliferate and be activated by antigen-presenting cells, particularly dendritic cells (DCs), which present tumor antigens via the major histocompatibility complex (MHC). As T cells recognize and kill tumor cells that express these antigens on their surface, selecting appropriate tumor antigens as targets is crucial for the preparation of peptide vaccines.

Tumor antigens have been grouped into three categories: tumor-associated antigens (TAAs); cancer-specific antigens, which are also called neoantigens; and cancer-testis antigens (CTAs) [2]. The unfavorable tumor specificity of TAAs carries the risk of inducing autoimmunity against corresponding normal tissues. The neoepitopes generated by somatic mutations can be recognized by T cells and therefore are regarded as ideal cancer vaccine targets [3]. Nonetheless, each tumor has a unique combination of mutations, with only a small fraction shared among cases [4], resulting in the difficulty of identifying neoepitopes and preparing mutanome vaccines. In contrast, as CTAs are normally expressed in the testis but are also highly expressed across cancers [5,6] and associated with disease stage, an unfavorable prognosis, and cancer invasion, CTAs may constitute potentially promising targets and allow convenient establishment of vaccines based on “off-the-shelf” CTA peptides. This review summarizes the recent advances in CTA peptide-based cancer vaccines. In particular, we describe the details of our novel immunotherapeutic approach, called the CTA personalized peptide vaccine.

“Conventional” CTA Peptide Vaccines
Accumulating experimental evidence favors CTAs as highly suitable antigens for cancer vaccination. Compared to DC vaccines, peptide vaccines do not require the use of autologous cells, which has resulted in strong interest in CTA peptide vaccines in recent years. However, the complexity and diversity of cancer antigens and tumor cell characteristics seem to limit the clinical application of this knowledge. Below, we discuss the progress thus far in the identification of CTA antigens.
immunogenic peptides and the clinical trials of peptide vaccines, as summarized in Tables 1-2. In addition, advances in developing effective cancer peptide vaccines are reviewed.

### CTA Peptide-Based Clinical Trials

Among a large number of explorations of CTA peptide-based vaccines, the investigations of the widely expressed tumor antigens MAGE-A3 and NY-ESO-1 are noteworthy as paradigms. The melanoma antigen gene (MAGE) protein family is a large, highly conserved group of proteins that share a common MAGE homology domain [7,8]. MAGE-A3, as one of the most immunogenic MAGE proteins, is restricted in expression to reproductive tissues but is aberrantly expressed in a wide variety of cancer types [9]. NY-ESO-1 is a CTA that was first described in a patient with esophageal cancer in 1997 [10] and has subsequently been reported to be expressed in a wide range of tumor types [11-15]. Humoral immune responses and cellular immune responses against NY-ESO-1 and MAGE-A3 have been detected [16], and the restricted epitopes have been identified as the recognition sites for CD8+ cytotoxic T lymphocytes (CTLs) [17,18]. Numerous preclinical and clinical studies have indicated that MAGE-A3 peptide vaccines can trigger immune responses, and promising findings have been achieved in cancer subjects [19-24].

Two phase III clinical trials, known as DERMA and MAGRIT, have been approved for patients with melanoma and non–small cell lung cancer (NSCLC) [25,26]. However, the MAGRIT trial was stopped in 2014 due to a lack of clinical benefit for NSCLC patients. Despite the disappointing result, other ongoing clinical trials remain, and the field anticipates satisfactory outcomes. However, cancer vaccines based on NY-ESO-1–restricted immunogenic peptides combined with various adjuvants exhibit antitumor potential [27-30].

In addition to the CTAs described above, other CTAs could be ideal targets, such as DEPDC1 [31-33], CDCA1 [34], LY6K [35,36], IMP3 [37-39], and TTK [40,41]. These antigens are all members of a class of CTAs with specific expression characteristics. With the identification of immunogenic epitopes, particularly HLA-A*24–restricted peptides, studies of these CTA multipeptide–based vaccines continue and are achieving promising results. For example, Wataru Obara et al. [42] reported the DEPDC1 immunogenic peptide 294EYYELFVNI302 and successfully constructed the peptide vaccine S-288310. In the ensuing phase I/II clinical trial, S-288310 was found to be well tolerated and to effectively increase survival time for patients with advanced urothelial carcinoma of the bladder. Additionally, 177RYCNLEGPP186, 567SYRNEIAYL575, 508KTVNELQNL516, and 56VYGIRLEHF64 (derived from LY6K, TTK, IMP3, and CDCA1, respectively) have been reported to be promising HLA-A*24–restricted epitope peptides [43,44]. A clinical cancer vaccination study, based on the peptides above, demonstrated satisfactory safety and good disease control in patients with solid tumors [45-49]. Remarkably, due to a lack of effective and standard treatment, pancreatic carcinoma is associated with a high mortality rate, but a phase I clinical cancer vaccination trial with a combination of peptides derived from CDCA1, KIF20A, VEGFR2, and VEGFR1 showed a detectable clinical benefit in four patients, suggesting this vaccine as a novel treatment for pancreatic cancer [50]. In general, CTA peptide-based vaccines can elicit a potent immune response against cancers, particularly solid tumors. Because additional studies have explored and established other HLA-restricted immunogenic epitopes [51-54], a CTA peptide-based vaccine is expected to have wide applications for patients.

### Modified Vaccine Strategies

Since CTA peptide vaccines seem to be an effective treatment to combat cancers, strategies to modify vaccines to improve their clinical efficacy have attracted great interest for superior clinical benefits. A pressing concern for CTA peptide vaccines is the considerable heterogeneity of CTA tumor expression. Thus, further studies are required to explore new CTAs as candidates. For instance, Kita-Kyushu lung cancer antigen-1 (KK-LC-1) [55-57] and sperm protein 17 (SP17) [58] are reportedly expressed frequently in tumors and carry epitope peptides recognized by CTLs [61-63], making them new candidate tumor biomarkers and immunotherapy targets. Additionally, many other CTAs are expected to be ideal targets for peptide vaccines, and further exploration is needed. Moreover, various adjuvants have been tested for their ability to enhance cytotoxic CD8+ T lymphocyte activity. These adjuvants include GM-CSF, Flt3-ligand, incomplete Freund’s adjuvant, and saponin-based adjuvant (ISCOMATRIX) [64,65]. Stronger adjuvants have been shown to improve the frequency of eliciting T cells [66].

Another strategy to enhance vaccination efficacy is to induce CD4+ immune responses to support the priming and maintenance of CD8+ CTLs [67]. Interestingly, an NY-ESO-1 peptide containing the HLA-DP4–restricted epitope can also generate HLA-A2–restricted

### Table 1. Peptide-Based Vaccination Trials

| Phase | Indication | CTAs | Year of Publication |
|-------|------------|------|---------------------|
| I     | Prostate cancer | NY-ESO-1 | 2014 |
| I     | Advanced malignancies | NY-ESO-1 | 2007 |
| I     | Neuroblastoma and sarcoma | MAGE-A1, MAGE-A3, NY-ESO-1 | 2015 |
| II    | Metastatic melanoma | MAGE-A3, GP100, Tyrosinase, MAGE-A2, MAGEA1 | 2012 |
| III   | NSCLC | MAGE-A3 | 2009 |
| III   | Melanoma skin cancer | MAGE-A3 | 2010 |
| II    | Gastric cancer | DEPDC1, URC130, FoxM1, Ki670A, VEGFR1 | 2017 |
| I/II  | Urothelial carcinoma of the bladder | DEPDC1, MPHOSPH1 | 2016 |
| I/II  | Esophageal squamous cell carcinoma | TTK, LY6K, IMP3 | 2009/2012 |
| I     | Gastric cancer | LY6K | 2014 |
| I     | Gastric cancer | URC10, VEGFR1 | 2014 |
| I     | NSCLC | CDCA1, LY6K, VEGFR1, VEGFR2 | 2013 |
| I     | Pancreatic cancer | CDCA1, Ki670A, VEGFR1, VEGFR2 | 2013 |
| II    | HNSCC | CDCA1, LY6K, IMP3 | 2015 |
| I     | ESSC | TTK, URC10, KCC1, VEGFR1, VEGFR2 | 2014 |
| I     | Advanced solid cancer | KCC1, TTK, URC10, DEPDC1, MPHOSPH1 | 2016 |
suggesting that this peptide may be used as a cancer vaccine to induce both CD4+ and CD8+ T cell responses, which is a promising direction for the development of peptide vaccines and constitutes a beneficial situation for future immunotherapies [69]. DNA vaccination has become a favored strategy for inducing immunity [70]. It offers the opportunity to engineer peptide antigen expression with more detailed design and delivery parameters [71]. Recombinant vectors encoding CTAs and even short hairpin RNA have been used in preclinical models to enhance immune system activation [72]. Other modifications to the vaccine approach currently in clinical trials include the use of combinatorial treatment. The microenvironment is an important factor due to the impact on the outcome of immune-modulating treatments. Therefore, multiple combined therapeutic strategies [73] have the potential for efficient control of tumor burden and improvement of the tumor microenvironment, and the details will be discussed below.

**Selection of Target Peptides for Vaccine Design**

Despite issues with immunogenicity and specificity, CTAs are receiving attention as potential antineoplastic targets. Unfortunately, the immunogenicity of most CTAs is too low to induce antitumor responses, and the poor specificity can result in off-target toxicity. To address these limitations, additional studies are needed to explore new

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**Table 2. Previously Identified CTA Peptides**

| CTAs | Amino Acid Sequence (mer) | Start Position | HLA Type |
|------|---------------------------|----------------|----------|
| NY-ESO-1 | SLLMWITQC | 157 | HLA-A*0201 |
| | YLAMPFATPMQ | 91 | HLA-A*2402 |
| | LLMWITQCF | 158 | HLA-A*2402 |
| MAGE-A3 | FLWGPRALV | 271 | HLA-A*0201 |
| | RVAELVHFL | 112 | HLA-A*0201 |
| | TFPDESEF | 97 | HLA-A*2402 |
| | VAELVHFLL | 113 | HLA-A*2402 |
| DEPDC1 | FLDLP-EPLL | 282 | HLA-A*0201 |
| | EYELFVNI | 294 | HLA-A*2402 |
| LY6K | RYENLEGPI | 177 | HLA-A*2402 |
| CDCA1 | YMPFVSEY | 65 | HLA-A*0201 |
| | KLATAQFKI | 351 | HLA-A*2402 |
| IMP3 | NLSSAEVVV | 515 | HLA-A*0201 |
| | RLYPTQFV | 199 | HLA-A*2402 |
| KTNEQQLN | 508 | HLA-A*2402 |
| TT-K | SRNLIAYL | 567 | HLA-A*2402 |
| KK-LC-1 | RQKRLVNL | 78 | HLA-B*1501 |

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**Fig. 1.** Workflow for targeted peptide selection and vaccine manufacture. Certain CTAs have been discovered in tumor tissues through immunohistochemical and HLA typing and determined by serotyping techniques. Thus, personal CTA HLA-binding peptides can be selected as target peptides for vaccine design. Candidate peptides are selected for incorporation into the personalized peptide vaccine, which is administered to patients in combination with an immune adjuvant to trigger an immune response to attack tumor cells.

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**“Personalized” CTA Peptide Vaccines**

In the clinical trials and advances of CTA peptide vaccines described above, multipeptide vaccines exhibited potent antitumor ability, though the immune response induced by the vaccination suggested that the potential could be improved. Currently, personalized treatment for cancer has become a trend after the demonstration of its feasibility, safety, and immunotherapeutic activity against individual tumors. However, the published experiments were conducted using a combination of multiple peptide vaccines rather than individualized administration of peptide vaccines. Therefore, for maximal efficacy, we envisage the establishment of a “personalized” CTA peptide vaccine for eligible patients.
CTAs with high immunogenicity and specificity that can serve as ideal targets for cancer immunotherapy, and CTA peptide vaccines may thus be universal in clinical application. Accordingly, a critical challenge for personalized CTA peptide vaccines is accurate and comprehensive construction of a CTA peptide library to select the most suitable target peptides for optimal immune responses. The processing and presentation of antigens are complex processes. Protease cleavage products of thousands of proteins compete for binding in the pockets of MHC molecules [74], though only a portion of MHC-presented peptides can induce an effective T cell response. MHC-peptide stability can be predicted through epitope prediction algorithms including BIMAS, NetMHC, and NetCTL. These algorithms employ different prediction models but have all been trained using characterized epitope/MHC combinations, resulting in the prediction of the likelihood of short peptide sequences binding to a given HLA-allele. However, compared to MHC class I molecules, accurate prediction of ligands able to bind to MHC class II molecules is more difficult due to the variable lengths of binding peptides and the high abundance of MHC class II binding epitopes [75]. Moreover, considering that CD8+ CTLs have been demonstrated to recognize peptide epitopes derived from CTAs that are presented on MHC class I molecules and to kill tumor cells, the establishment of CTA MHC class I-restricted peptides is worthy of exploration.

Manufacturing of “Personalized” CTA Peptide Vaccines
A comprehensive CTA peptide library can be conveniently employed to design individual CTA peptide vaccines. Tissue samples are diagnosed as positive for certain CTAs via immunohistochemical analysis, and simultaneously, peripheral blood mononuclear cells from patients are evaluated using a serotyping technique to determine their HLA type. Certain CTA HLA-binding peptides have thus been selected as target peptides for design of a vaccine that is administered to patients combined with an immune adjuvant (Fig. 1). Nanovacines represent an emerging area, and advances have been made to improve the delivery system of NY-ESO-1 and provide strong protection against cancer through nanotechnology [76]. In addition, the PC7A nanovaccine is an attractive candidate with potential for T cell activation and synergy with checkpoint inhibition [77]. This nanovaccine platform is expected to be adopted to incorporate peptides and constitute personalized peptide nanovaccines via the CTA peptide library. Compared to the conventional CTA peptide vaccines described above, administration of a personalized CTA peptide vaccine may trigger a stronger immune response for attacking tumor cells and lead to a better prognosis.

Developing Combination Therapy
It is also critical to define the most suitable clinical setting for CTA peptide vaccination. A therapeutic vaccine will most likely be highly functional in an adjuvant or minimal residual disease setting. Efficient control of a larger tumor load may require multiple combined therapeutic strategies to eliminate the tumor burden and improve the overall tumor microenvironment. A promising area of study is the combination of peptide vaccines with chemoradiation therapy, including biotherapeutics such as immunomodulating or antivascular antibodies [78]. For instance, in a phase I vaccination trial with combined chemotherapy, the number of regulatory T cells decreased from the baseline value after administration of cyclophosphamide [79], reflecting the safety, flexibility, and superiority of CTA peptide vaccines combined with chemotherapy. Chemoradiation therapy combined with immunotherapy has demonstrated promising outcomes in clinical trials [80] due to its synergistic effect of enhancing antitumor immunity by inducing antigen expression on tumor cells and activating lymphocytes [81,82]. Immunosuppression in the tumor microenvironment attenuates vaccine-induced immune effectors, and PD-1 is an important inhibitory component in the tumor microenvironment. Thus, combination therapy consisting of immune checkpoint inhibitors and cancer vaccine-enriched populations of CTA-reactive T cells may function synergistically to induce more effective antitumor immune responses. For example, Karyampudi et al. reported that in patients with breast cancer, PD-1 blockade enhances vaccine efficacy by altering both CD8+ T cell and DC components of the tumor microenvironment [83]. Furthermore, cancer vaccines stimulate and enhance active immunity; thus, coadministration of an agent that activates DCs can lead to increased immunogenicity of protein antigens and induction of immune responses [84]. These findings support the use of multiple combined therapeutic approaches that may amplify T cell expansion and increase the durable effect of vaccination, which is necessary to achieve promising results.

Conclusions
The capacity of the immune system to specifically attack cancer cells renders it the most powerful weapon for controlling cancer in the long term. CTAs are promising targets for cancer immunotherapy due to their expression in cancers and their rarity in normal tissues. With the identification of CTA peptides and clinical trials of CTA multipeptide vaccines, establishing personalized CTA peptide vaccines has become possible. Challenges remaining include the search for promising targets, identification of additional immunogenic CTA peptides, choice of suitable clinical settings, and development of feasible combination therapy. It is believed that when these limitations are overcome, personalized CTA peptide vaccines may provide a powerful tool to induce an immune response against cancer and become a universal treatment in cancer immunotherapy.

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