Cancer Peptide Vaccine

- Targeted suppression of glioma by ultralow-dose x-ray-induced photodynamic therapy and gold-based nanoclusters in preclinical models
- Survivin Interference and SurVaxM as an Adjunct Therapy for Glioblastoma Multiforme
- The immunopeptidomic landscape of ependymomas provides actionable antigens for T-cell-based immunotherapy
- Strategies for neoantigen screening and immunogenicity validation in cancer immunotherapy (Review)
- Integrative multi-omic profiling of the neoantigen landscape of glioblastoma for the development of therapeutic vaccines reveals vast heterogeneity in immunogenic signatures
- Autologous tumor lysate-loaded dendritic cell vaccination in glioblastoma patients: a systematic review of literature
- Biomimetic Dendritic Cell-Based Nanovaccines for Reprogramming the Immune Microenvironment to Boost Tumor Immunotherapy
- Roles of DEPDC1 in various types of cancer (Review)

A cancer peptide vaccine is a type of therapeutic vaccine designed to stimulate the immune system's response against cancer cells. These vaccines are tailored to target specific antigens found on the surface of cancer cells, including tumor-specific antigens (TSAs) or tumor-associated antigens (TAAs). The goal of cancer peptide vaccines is to activate the immune system, particularly T cells, to recognize and attack cancer cells while sparing healthy tissues.

Key features and components of cancer peptide vaccines include:

Antigen Selection: Cancer peptide vaccines contain peptides derived from antigens that are typically unique to cancer cells. These antigens may be mutated proteins, overexpressed proteins, or other cancer-specific markers.

Immune Activation: When administered, cancer peptide vaccines prime the immune system to recognize and mount an immune response against the targeted cancer-specific antigens. This immune response may involve the activation of cytotoxic T cells, which can directly destroy cancer cells.

Specificity: Cancer peptide vaccines are highly specific, as they focus on antigens associated with the cancer being treated. This specificity minimizes the risk of off-target effects or autoimmune reactions.

Personalization: Some cancer peptide vaccines can be personalized for individual patients. This is particularly relevant in the field of cancer immunotherapy, where neoantigen-based vaccines are tailored to a patient's unique cancer mutations.

Combination Therapy: Cancer peptide vaccines can be used in combination with other cancer treatments, such as immune checkpoint inhibitors, chemotherapy, radiation therapy, or targeted therapies, to enhance their effectiveness.

Clinical Trials: Cancer peptide vaccines are often evaluated in clinical trials to assess their safety and efficacy in patients with various cancer types. These trials help determine the feasibility of using the vaccines in a clinical setting.

Cancer peptide vaccines represent a promising approach in the field of cancer immunotherapy, offering the potential for targeted and personalized treatments. They are part of the broader effort to

leverage the immune system's capabilities to recognize and eliminate cancer cells, providing a novel strategy in the fight against cancer.

Classification

Cancer peptide vaccines can be classified based on various criteria, including their source, purpose, and specific targets. Here's a classification of cancer peptide vaccines:

1. Source of Peptides:

Tumor-Specific Antigen (TSA) Peptide Vaccines: These vaccines target antigens that are unique to cancer cells and not found in normal cells. TSAs can be highly specific for cancer cells and are ideal targets for cancer immunotherapy.

Tumor-Associated Antigen (TAA) Peptide Vaccines: TAAs are antigens found in both cancer and normal cells but are overexpressed or abnormally expressed in cancer. Peptide vaccines containing TAAs aim to stimulate an immune response against these cancer-associated proteins.

Neoantigen Peptide Vaccines: Neoantigen peptide vaccines are personalized for each patient and target neoantigens, which are unique antigens created by somatic mutations in cancer cells. These antigens are not present in normal cells.

2. Purpose of Vaccination:

Preventive (Prophylactic) Peptide Vaccines: These vaccines aim to prevent the development of cancer, particularly in high-risk populations. They may target viruses associated with cancer, such as HPV, to prevent cancer development.

Therapeutic Peptide Vaccines: Therapeutic vaccines are used to treat existing cancer. They aim to activate the immune system to target and destroy cancer cells, potentially slowing down disease progression.

3. Specific Target:

Cancer Peptide Vaccines: These vaccines are designed to target cancer cells, often by containing peptides associated with tumor-specific antigens, tumor-associated antigens, or neoantigens. They are widely used in cancer immunotherapy. 4. Personalization:

Personalized Peptide Vaccines: Some cancer peptide vaccines are personalized for individual patients. This is particularly relevant in the case of neoantigen-based vaccines, which are tailored to a patient's unique cancer mutations. 5. Combination Therapy:

Combination Peptide Vaccines: These vaccines can be used in combination with other therapies, such as immune checkpoint inhibitors, chemotherapy, radiation therapy, or targeted therapies, to enhance their effectiveness in treating cancer. 6. Clinical Development Stage:

Experimental Peptide Vaccines: These are vaccine candidates in preclinical development or in early-phase clinical trials to assess their safety and efficacy.

Approved Peptide Vaccines: A few cancer peptide vaccines have received regulatory approval for specific cancer indications and are available for clinical use.

Cancer peptide vaccines represent a diverse and evolving field in cancer immunotherapy, with the potential for personalized, targeted treatments. The classification of these vaccines depends on the specific characteristics of the vaccine and its intended application in the prevention or treatment of cancer.

Trials

INTERCEPT H3 is a non-controlled open-label, single-arm, multicenter national phase 1 trial to assess safety, tolerability and immunogenicity of H3K27M-vac in combination with standard radiotherapy and the immune checkpoint inhibitor atezolizumab (ATE). 15 adult patients with newly diagnosed K27M-mutant histone-3.1 (H3.1K27M) or histone-3.3 (H3.3K27M) DMG will be enrolled in this trial. The 27mer peptide vaccine H3K27M-vac will be administered concomitantly to standard radiotherapy (RT) followed by combinatorial treatment with the programmed death-ligand 1 (PD-L1) targeting antibody ATE. The first three vaccines will be administered bi-weekly (q2w) followed by a dose at the beginning of recovery after RT and six-weekly administrations of doses 5 to 11 thereafter. In a safety lead-in, the first three patients (pts. 1-3) will be enrolled sequentially.

Perspective: H3K27M-vac is a neoepitope targeting long peptide vaccine derived from the clonal driver mutation H3K27M in DMG. The INTERCEPT H3 trial aims at demonstrating (1) safety and (2) immunogenicity of repeated fixed dose vaccinations of H3K27M-vac administered with RT and ATE in adult patients with newly diagnosed H3K27M-mutant DMG.

Trial registration: NCT04808245 [1)].

The INTERCEPT H3 trial represents a significant step in the ongoing exploration of immunotherapy for DMG patients. The strategy of targeting the H3K27M mutation using H3K27M-vac and ATE is innovative and promises new insights into the management of this devastating disease. While the trial's design and small sample size pose limitations, its emphasis on safety and immunogenicity is crucial for a novel approach to treating H3K27M-mutant DMG. Future results from this trial may inform further research and potentially pave the way for a more effective and personalized treatment strategy for DMG patients. This trial underscores the importance of innovative approaches in the fight against rare and aggressive brain tumors.

Peptide vaccines targeting mutated EGFR have been tested in multiple clinical trials, demonstrating an excellent safety profile and encouraging clinical efficacy. For example, the CDX-110 (rindopepimut) NeoAg peptide vaccine derived from the EGFRvIII deletion mutant in combination with temozolomide and radiotherapy has shown efficacy in treating EGFRvIII-harboring glioblastoma multiforme (GBM) patients undergone surgery in multiple Phase I and II clinical trials. Furthermore, pilot clinical trials that have administered personalized NeoAg peptides for treating advanced-stage NSCLC patients have shown this approach to be a feasible and safe method to increase antitumor immune responses. Amongst the vaccine peptides administered, EGFR mutation-targeting NeoAgs induced the strongest T cell-mediated immune responses in patients and were also associated with objective clinical responses, implying a promising future for NeoAg peptide vaccines for treating NSCLC patients with selected EGFR mutations. The efficacy of NeoAg-targeting peptide vaccines may be further improved by combining with other modalities such as tyrosine kinase or immune checkpoint inhibitor (ICI)

therapy, which are currently being tested in animal models and clinical trials. Herein, we review the most current basic and clinical research progress on EGFR-targeted peptide vaccination for the treatment of NSCLC and other solid tumor types [2].

The use of NeoAg peptide vaccines targeting mutated EGFR represents a significant advancement in cancer immunotherapy. The review highlights the promising results in GBM and NSCLC, underlining the potential for broader applications in the treatment of solid tumor types. The combination with other treatment modalities, such as ICIs, holds great promise and is a key area of exploration for future research. This critical review emphasizes the potential of NeoAg peptide vaccines as a valuable addition to the armamentarium of cancer treatment strategies.

Case series

Grassl et al. describe a first-in-human treatment with H3K27M-vac of eight adult patients with progressive H3K27M+ diffuse midline glioma on a compassionate use basis. Five patients received H3K27M-vac combined with anti-PD-1 treatment based on physician's discretion. Repeat vaccinations with H3K27M-vac were safe and induced CD4+ T cell-dominated, mutation-specific immune responses in five of eight patients across multiple human leukocyte antigen types. Median progression-free survival after vaccination was 6.2 months and median overall survival was 12.8 months. One patient with a strong mutation-specific T cell response after H3K27M-vac showed pseudoprogression followed by sustained complete remission for >31 months. Our data demonstrate safety and immunogenicity of H3K27M-vac in patients with progressive H3K27M+ diffuse midline glioma [3].

Peptide vaccines offer the opportunity to elicit glioma-specific T cells with tumor killing ability. Using antigens eluted from the surface of glioblastoma samples, we designed a phase I/II study to test safety and immunogenicity of the IMA950 multipeptide vaccine adjuvanted with poly-ICLC in HLA-A2 + glioma patients.

Adult patients with newly diagnosed glioblastoma (n=16) and grade III astrocytoma (n=3) were treated with radiochemotherapy followed by IMA950/poly-ICLC vaccination. The first 6 patients received IMA950 (9 MHC class I and 2 MHC class II peptides) i.d. and poly-ICLC i.m. After protocol amendment, IMA950 and poly-ICLC were mixed and injected s.c. (n=7) or i.m. (n=6). Primary endpoints were safety and immunogenicity. Secondary endpoints were overall survival, progression-free survival at 6 and 9 months, and vaccine-specific peripheral CD4 and CD8 T cell responses.

The IMA950/poly-ICLC vaccine was safe and well tolerated. Four patients presented cerebral edema with rapid recovery. For the first 6 patients, vaccine-induced CD8 T cell responses were restricted to a single peptide and CD4 responses were absent. After optimization of vaccine formulation, we observed multipeptide CD8 and sustained Th1 CD4 T cell responses. For the entire cohort, CD8 T cell responses to a single or multiple peptides were observed in 63.2% and 36.8% of patients, respectively. Median overall survival was 19 months for glioblastoma patients.

They provide, in a clinical trial, using cell surface-presented antigens, insights into optimization of vaccines generating effector T cells for glioma patients [4].

Research

Neuroligin 4 X-linked (NLGN4X) harbors a human leukocyte antigen (HLA)-A2-restricted tumor-associated antigen, overexpressed in human gliomas, that was found to induce specific cytotoxic T cell responses following multi-peptide vaccination in patients with newly- diagnosed glioblastoma.

Methods: T cell receptor (TCR) discovery was performed using droplet-based single-cell TCR sequencing of NLGN4X-tetramer-sorted T cells post-vaccination. The identified TCR was delivered to Jurkat T cells and primary human T cells (NLGN4X-TCR-T). Functional profiling of NLGN4X-TCR-T was performed by flow cytometry and cytotoxicity assays. Therapeutic efficacy of intracerebroventricular NLGN4X-TCR-T was assessed in NOD scid gamma (NSG) major histocompatibility complex (MHC) I/II knockout (KO) (NSG MHC I/II KO) mice bearing NLGN4X-expressing experimental gliomas.

Results: An HLA-A *02-restricted vaccine-induced T cell receptor specifically binding NLGN4X131-139 was applied for therapeutic use. Reactivity, cytotoxicity, and polyfunctionality of this NLGN4X-specific TCR are demonstrated in various cellular models. Intracerebroventricular administration of NLGN4X-TCR-T prolongs survival and leads to an objective response rate (ORR) of 44.4 % in experimental gliomas-bearing NSG MHC I/II KO mice compared to 0.0 % in control groups, respectively.

Conclusion: NLGN4X-TCR-T demonstrates efficacy in a preclinical glioblastoma model. On a global scale, we provide the first evidence for the therapeutic retrieval of vaccine-induced human TCRs for the off-the-shelf treatment of glioblastoma patients [5)]

1)
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