The promise of personalized cancer vaccination

Among the different immunotherapies, cancer vaccination has lately regained attention due to promising results obtained in clinical trials with personalized vaccines. Nevertheless, many hurdles still need to be overcome in terms of vaccine design and manufacturing alongside the need for a combined approach to ensure complete tumor eradication.

The Promise of Personalized Cancer Vaccines

The main advantages of cancer vaccination comprise of the **absence of severe side effects** and its **potency to induce a memory response**. The latter can provide the patient with prolonged protection, even after treatment, possibly protecting the patient against relapse and metastasis[1]. This is considered to be a huge advantage as the majority of the cancer death-rate is caused by metastasis and relapse rather than the primary tumor. Relapsed tumors are harder-to-treat due to obtained resistance and increased aggressive growth[2,3].

Nevertheless, the promise of **one-fits-all cancer vaccines** has been negated by the unfortunate discrepancy between highly encouraging preclinical data and **disappointing clinical results**[4]. Multiple clinical trials have failed to prove survival benefit involving the gp100 vaccine[5], the GVAX vaccine[6], and the MAGE-3 vaccine[7], among others. This can be likely attributed to two main issues, i.e. suboptimal vaccine design and the immune-suppressive tumor microenvironment (vide infra). These insights have led to the design of optimized, personalized vaccines, and highly promising clinical results[8,9].

Optimization of vaccine design

Vaccine design is a crucial factor in targeting and activating the immune system efficiently. **The choice of an immunogenic antigen, an effective delivery system alongside a potent TH1-response inducing adjuvant are of the essence** in priming a strong T cell-mediated immune response with optimal specificity and amplitude[10].

Selection of immunogenic antigens

Different types of antigens can be selected for vaccine formulation of which the most prevalent are **tumor-associated antigens (TAAs) and tumor-specific antigens (TSAs)**. TAAs are peptides overexpressed by cancer cells but also present on normal cells, whereas TSAs, i.e. neoantigens, involve tumor-specific mutated antigens hence are uniquely expressed by cancer cells.

The obvious advantage of **TAAs** is the fact that these vaccines can be manufactured beforehand and used instantly whenever needed. The disadvantages, however, have the upper hand in the sense that these antigens are not relevant for every patient, thymic tolerance can occur and for numerous cancer types TAAs are yet to be discovered[11]. The clinical trial failure of the gp100 vaccine among others has clearly uncovered the lack of potency of TAA-based vaccines.

In contrast, **TSAs or neoantigens** do not face these disadvantages as they are unique for each patient. On that account, personalized vaccination has been shown to be highly promising based on multiple clinical results[12,13]. Moreover, high tumor mutational burden (TMB) malignancies (high neoantigen burden) have been associated with good clinical outcome upon checkpoint inhibition (CPI) treatment[14]. It should be noted, however, that neoantigens do not always induce a strong anti-tumor immune response as a high TMB does not always correlate with a clinical response due to neoantigen intra-tumoral heterogeneity[10]. Both clonal and sub clonal neoantigens exist which are distributed throughout the tumor and only expressed in a restricted region respectively[15]. In other words, it is the quality rather than the quantity of neoantigens that is associated with increased prognosis and survival[16].

Selection of the delivery system

Next, the **type of antigen** needs to be chosen which can comprise synthetic long peptides (SLPs), recombinant proteins, and RNA- or DNA-encoding proteins derived from antigens, each with their own pros and cons. Overall, RNA-based vaccines are preferred because RNA allows rapid and small scale-production and does not face issues regarding solubility, HLA-restriction, or genome-integration.

Also, cancer vaccination can be ***ex vivo* or *in vivo* directed**, where the former involves the adoptive transfer of autologous or allogenic dendritic cells (DCs) that are stimulated with a mix of adjuvants and cancer antigens. Cancer vaccination *in vivo*, on the other hand, aims to target dendritic cells through infusion of the patient with micro- or nanoparticles that resemble pathogens and contain the tumor antigens[17,18]. *Ex vivo* cancer vaccination is considered by many to be the better option for taking data into account showing that a large percentage of the DCs of cancer patients is dysfunctional[19]. In contrast, advocates for *in vivo* vaccination are convinced by the fact that physiological stimuli can occur in case DCs are targeted *in vivo* and because this vaccination method is less complex, labour-intensive, and costly[20]. Overall, clinical evidence is needed to determine which approach has the most potential to induce a strong tumor-directed immune response.

Selection of a potent adjuvant

Finally, an essential compound for vaccines, in general, is a potent adjuvant as these molecules are required to induce maturation of DCs which in turn leads to optimal activation of cytotoxic T-cells and subsequent tumor cell elimination. For cancer vaccine purposes, **a strong TH1-type immune response is desired**, and thus only adjuvants that can induce such a response should be considered.

In this respect, only two of the currently licensed adjuvants for human use in vaccines are possible, i.e. virosomes and MPLA (monophosphoryl lipid A), both derived from pathogens and are very potent. Because these compounds are natural, variability in composition, and risk of infection can cause issues. An interesting alternative on that account could be synthetic toll-like-receptor (TLR) ligands, i.e. ligands that resemble pathogenic sequences known to strongly trigger DC maturation, however, they have yet to be approved for human use.

Personalized Vaccination – Where are we now?

Many are now convinced that personalized vaccination is very promising and will have a significant impact on the treatment regimen of many malignancies. It has been shown in several clinical trials that neoantigens can be recognised by CD4 and CD8 T-cells and can trigger an *in vivo* anti-tumor response[21,22]. At this moment (May 2020), ClinicalTrials.gov lists almost sixty ongoing clinical trials for neoantigen vaccination showing the increased interest in neoantigen-based vaccination[23].

In the last five years, six clinical trials have been completed involving one *ex vivo* DC vaccine, four *in vivo* vaccines (SLP or RNA-based), and one T-cell vaccine[8,9,12,13,24,25]. An overview of the trials is given in Table 1.

Table 1. Overview of completed neoantigen-vaccine clinical trials and their clinical benefit

Year	Therapy Type	# neoantigens	Cancer type	# patients	Clinical response	Sponsor
2015	DC vaccine	7	Melanoma	3	Induction of neoantigen-specific T-cells	University of Pennsylvania
2017	SLP vaccine	20	Melanoma	6	4 patients CR 2 patients recurrence but both CR after anti-PD1	Neon Therapeutics
2017	RNA vaccine (IVAC mutanome)	10	Melanoma	13	8 patients CR 5 patients recurrence (1 patient CR after anti-PD1)	BioNTech
2018	TIL-ACT	4	Breast	1	CR > 22 months (in combi with IL-2 and anti-PD1)	National Cancer Institute
2019	SLP vaccine	20	Glioblastoma	8	Increased neoantigen T-cell response	Neon Therapeutics
2019	SLP vaccine (GAPVAC)	20	Glioblastoma	15	Increased neoantigen T-cell response	Immatics Biotech (Collaborator: BioNTech)

Although the clinical results are very promising, personalized vaccination faces a major challenge as it requires personalized analysis of the patient's tumor which negatively impacts the cost and time of the vaccine production. Personalized precision medicine is negatively impacted by **complex logistics and labour-intensive methodologies propelling the costs sky-high**, in particular for cell therapeutics. For instance, the total price of Kymriah® ranges from USD 373 to 475k per treatment regimen.

One way to circumvent this could be by setting up well-oriented, centralized companies that offer an **accelerator platform for GMP-synthesis of cell therapeutics** throughout countries. This could reduce production costs and increase speed and quality which would, in turn, result in lower therapy costs. Another way to lower the production costs and time is the optimization of the manufacturing processes. Cells are still manually cultured in open systems and cannot be personalized, including the supporting quality system. The existing methods are not easy to scale-up or scale-out, have large variability in quality, and pose logistic challenges considering the short shelf life. In Belgium, there are ongoing initiatives aiming to make personalized cell therapies available to a larger public by developing newly closed, scalable, and economic manufacturing methods including personalized quality systems[26].

Taken together, this whitepaper highlights the clear promise of personalized vaccination while also describing its challenges. Great effort should be put in the optimization of vaccine design and manufacturing to make personalized vaccines available to the larger public. Hereby it will be of the essence to also consider the immune type of the malignancy[27], in order to select the correct combinational treatment.

About myNEO Therapeutics

myNEO Therapeutics (Ghent, Belgium) is a distinguished biopharmaceutical powerhouse, dedicated to pioneer breakthrough immunotherapies to fight cancer. myNEO Therapeutics is leveraging its ImmunoEngine discovery platform to tap into novel promising tumor targets found in the dark genome – named camyotopes™ – which have the potential to unlock immunotherapy for large patient populations who currently do not respond.

Contact us

Interested in more information about myNEO Therapeutics?

Lien Lybaert, PhD
Chief Development Officer
lien.lybaert@myneotx.com

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