

Intradermal immunotherapy: A promising solution to cure prostate cancer?

Danielle Pasmans | Koen Beyers | Vanessa Vankerckhoven
Antwerp, Belgium

Introduction

With an estimated almost 1.546 million cases and 420,000 deaths worldwide, prostate cancer was the fourth most frequent cancer and the eighth leading cause of cancer death 2024 [1].



5-year survival rate
“early stages” close to 100%



5-year survival rate
“metastasized PCa” reduced to 30%

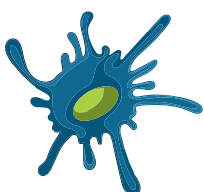
In its early stages, prostate cancer is highly treatable with surgery and radiotherapy, with five-year survival rates close to 100%, but once prostate cancer (PCa) has metastasized, the 5-year survival rate is reduced to less than 30% [2].

For patients with metastatic prostate cancer, androgen deprivation therapy is the standard treatment. However, as the tumors become resistant, most of these patients progress into metastatic castration resistant prostate cancer (mCRPC) and eventually die after progression [3]. As a result, new therapeutic approaches are needed to decrease the mortality rate of metastatic castration resistant prostate cancer.

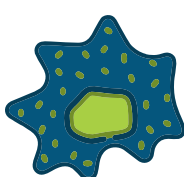
Immunotherapy, a breakthrough treatment for many cancer subtypes

In recent years, cancer immunotherapy, or the use of the body's immune system to attack tumor cells, has received recognition as a viable cancer treatment strategy [4]. There are two principal ways to enhance the immune system's antitumor activity.

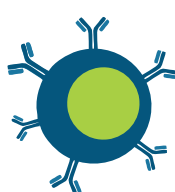
1. Blocking the immune-suppressive signals responsible for the decreased antitumor response. In this case, immune checkpoint inhibitors (ICIs) block checkpoint proteins that stop the immune system from attacking cancer cells.
2. Stimulating the immune activation of antigen-presenting cells against specific tumor-associated antigens (TAAs) [5]. Although a variety of cells can function as antigen-presenting cells, three cell types are classified as “professional” antigen-presenting cells: dendritic cells, macrophages and B cells.



Dendritic cells



Macrophages



B cells

Today, most cancer vaccines are therapeutic vaccines that aim to clear active disease instead of preventing disease. The mechanism relies on the effective activation of dendritic cells (DCs), the most potent antigen-presenting cells (APCs), and the subsequent initiation of native T cell responses and boosting cytotoxic T cell responses [4].

Next to therapeutic vaccines, there are a few vaccines available that aim at preventing cancers: (1) cancers caused by Human Papilloma Virus (HPV), like cervical cancer and head & neck cancer [6]; (2) cancers caused by Hepatitis B virus (HBV), the most common etiologic agent of hepatocellular carcinoma (HCC), which is one of the five leading causes of cancer death in humans [7].

Vaccination as a treatment option for Prostate Cancer

Prostate cancer vaccines can be categorized into several types, including peptide vaccines, viral vaccines, DNA-based vaccines, RNA-based vaccines, cellular vaccines, and dendritic cell-based vaccines [8].



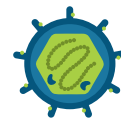
Peptides



DNA



RNA



Viral vectors



Modified tumor cells

Administered intradermally or intramuscularly, these vaccines enable the effective processing of tumor antigens by autologous antigen-presenting cells (APCs).

mRNA vaccines: a more potent and versatile cancer vaccine platform?

More than two decades ago, the first proof-of-concept- and feasibility studies regarding RNA cancer vaccines were published. Since then, numerous preclinical and clinical studies have demonstrated the viability of mRNA vaccines to combat cancer [8]. Compared to other approved cancer vaccines, oncology mRNA vaccines may be more versatile, pragmatic, affordable, and effective [9]. Especially in the field of oncology, advantages such as rapid and versatile development, convenient modular design, and entirely cell-free synthesis, are being progressively recognized. There are different routes for therapeutic mRNA vaccine delivery that may impact the induced immune response [9]. As a variety of antigen-presenting cells reside in the skin, the intradermal route of delivery has been widely used for mRNA cancer vaccines [8]. Compared to other types of vaccination, intradermal injection provokes indeed an improved immune response [10]. This superior immune response may even reduce the need for adjuvants for some vaccines [11].

In contrast, mildly toxic vaccine adjuvants are often added to vaccines to boost the immune response and are considered appropriate for seasonal applications, but when repurposed for continual oncology usage, toxicity may be problematic [9].

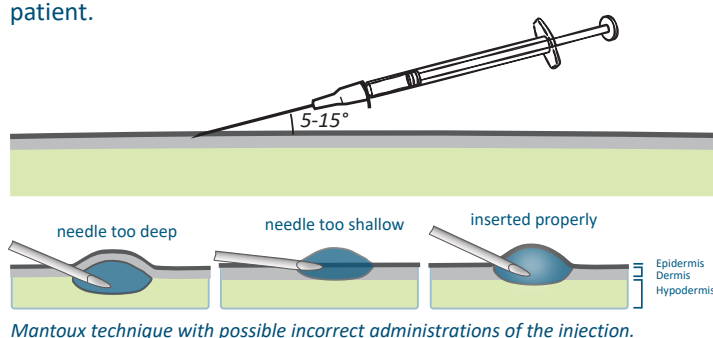
Dendritic cell vaccination: a personalized immunotherapy to fight prostate cancer

Sipuleucel-T was the first DC therapy approved by the FDA in 2010 for the treatment of metastatic castrate resistant prostate cancer (mCRPCa). Since then, emerging technologies have been driving further research into improved dendritic cell therapies [12]. Regardless significant differences in vaccine development and treatment protocols, a recent review showed that dendritic cell-based vaccines induce satisfactory immune responses [13]. Most of these vaccines are produced using patient-derived DC's or their mononuclear precursor cells, which are loaded with tumor antigens in-vitro before being administered back to the patients [14].

The route of administration, however, directs the distribution of a DC vaccine upon injection and consequently may lead to differences in immunologic responses. In several DC vaccination trials (melanoma, prostate- and metastatic renal cell carcinoma) patients were more likely to achieve immunologic and clinical responses after intradermal (ID) administration than after intranodal (IN) injection. These results, in addition to the more invasive nature and technical difficulties associated with IN injection, strongly argue in favor of the ID route of administration [15]. However, one of the main challenges during the administration of ex vivo-generated DCs is exposure to shear stress, which can reduce cell viability and induce phenotypic changes that may impair their therapeutic function [16, 17, 18].

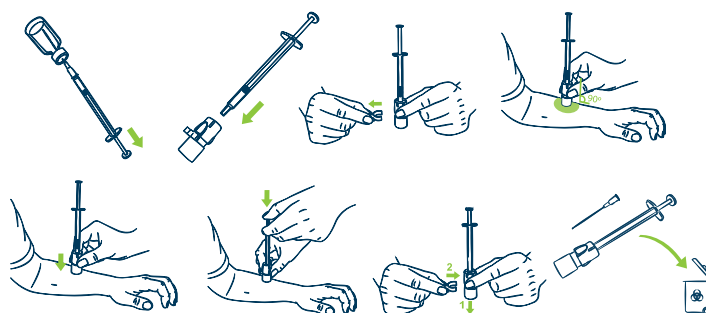
Current challenges with intradermal injection as route of administration for immunotherapies

Intradermal injections are usually performed using the Mantoux technique, in which the needle is inserted at a shallow angle [19]. This technique is the current standard of care for ID injection, but is difficult to perform and prone to failure. It has been shown that about 70% of ID injections using the Mantoux technique are incorrectly administered by injecting either too deep (into the hypodermis) or too shallow [20]. Additionally, ID injections with a standard needle and syringe are perceived as painful by the patient.



VAX-ID®: a potential game-changing solution for intradermal delivery of vaccines and cells

To overcome the challenges with the traditional Mantoux technique, IDEVAX developed VAX-ID® an easy-to-use intradermal injection device enabling standardized, accurate and reliable delivery in the dermal layer of the skin, addressing the interpersonal variability of the skin. VAX-ID® can be preconfigured with a 32G, 30G, or 27G needle with a penetration depth of 0.5, 0.6 and 0.8mm, respectively



Importantly, during a small feasibility study, it was shown that VAX-ID® configured with needles ranging from 27G up to 32G showed no increase in shear stress upon ejection of tolerogenic dendritic cells (tolDCs). The four phenotypic markers (CD86, CD80, HLADR, CD40) as well as the cell viability did not show significant differences before and after ejection [21].

1. <https://gco.iarc.who.int/today/en/fact-sheets-cancers/27/prostate>
2. <https://www.cancerresearch.org/cancer-types/prostate-cancer>
3. Šamija et al. 2019. doi:10.20471/acc.2019.58.s2.13 PMID: 34975203
4. Nguyen TT, et al. 2020. doi:10.1016/j.biopha.2020.110753 PMID 33152919
5. Maiorano, et al. 2021. doi:10.3390/vaccines9060623 PMID: 34207536
6. Paston, et al. 2021. doi:10.3389/fimmu.2021.627932 PMID: 33859638
7. Chang MH. 2021 PMID: 33200362
8. Zhou et al, 2024, PMID: 39772046
9. Bansal, et al. 2021. doi:10.3390/cancers13020334 PMID: 33477569
10. Tsao. 2022. doi:10.5306/wjco.v13.i8.663 PMID: 36160466
11. Zehrung, et al. 2013. doi:10.1016/j.vaccine.2012.11.021 PMID: 23176978
12. Sutherland et al, 2021, PMID: 33854509
13. Pacheco et al, 2025, PMID: 40430079
14. He et al, 2024, PMID: 39463159
15. Lesterhuis et al, 2011, PMID: 21771874
16. Aguado et al, 2012, PMID: 22011213
17. Amer et al, 2015, PMID: 25623928
18. Wahlberg et al, 2018, PMID: 29907825
19. Van Mulder et al, 2020, PMID 31767463
20. Micheels et al, 2018, PMID: 29320593
21. Rheibat et al, Poster P-081, EACR – AACR – SIC Conf. Florence, Italy, March 2023