

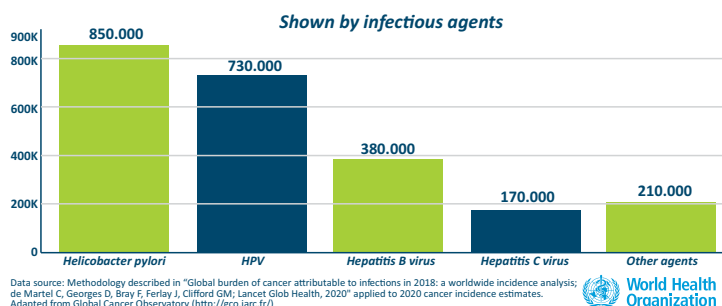
Targeted skin drug delivery: a new era in cancer therapy?

Danielle Pasmans | Merel Bartels | Arya Mehta | Koen C.L. Beyers | Vanessa V.J. Vankerckhoven

Idevax BV, Belgium

Introduction

Worldwide, an estimated 20 million new cancer cases and almost 9.7 million cancer deaths occurred in 2021 and the global burden of cancer continues to grow rapidly and is expected to be 28.4 million cases in 2040 [1]. In 2018, 13% of the new cancer cases were attributable to infections [2].

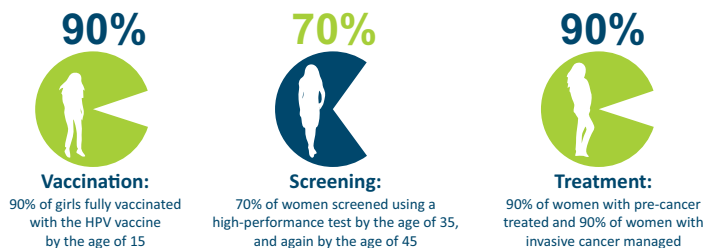


Cancers caused by Human Papilloma Virus (HPV) or Hepatitis B Virus (HBV) infections can be prevented by prophylactic vaccination. Therefore, strong statements and calls for action from the scientific community and public health organizations have been made, including WHO's targets towards hepatitis and cervical cancer elimination [2].

Indeed, WHO's global hepatitis strategy, endorsed by all WHO Member States, aims to reduce new hepatitis infections by 90% and deaths by 65% between 2016 and 2030 [3]. Read more on HBV in the white paper by Rbeihat et al. 2023 [4].

To achieve elimination of cervical cancer each country should meet the 90–70–90 targets by 2030. Achieving that goal rests on three key pillars and their corresponding targets [5]:

WHO Global Strategy for cervical cancer elimination.



Read more on HPV in the white paper by Rbeihat et al. 2023 [6].

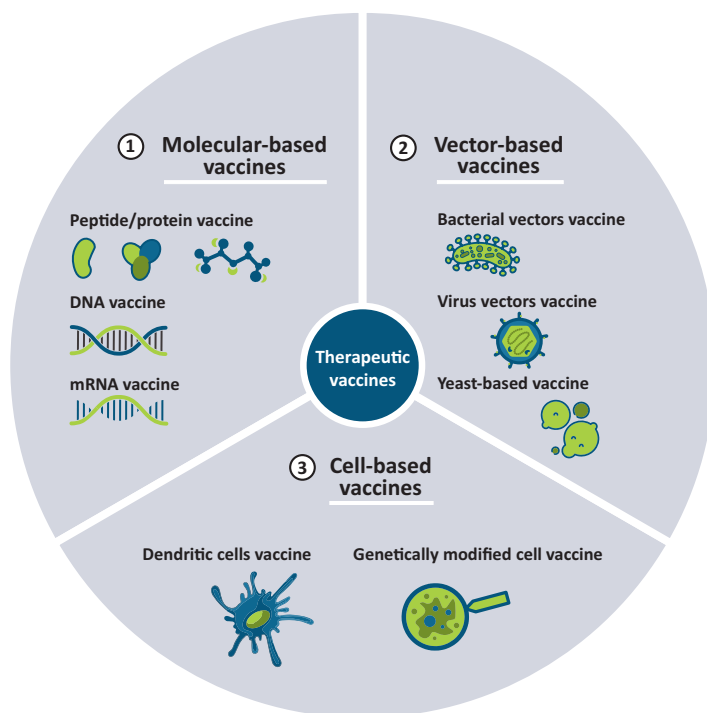
Therapeutic vaccines

In addition to immunity against cancer-inducing pathogens, the immune system plays an important role in cancer immunosurveillance and immunity against cancers [7]. Hence therapeutic vaccination has the potential to boost the body's natural defenses in individuals already diagnosed with.

Today, only two therapeutic vaccines have been approved. These include Bacillus Calmette-Guerin (BCG) vaccine for treatment of early-stage bladder cancer, and Sipuleucel-T (Provenge), a dendritic cell (DC)-based vaccine for treatment of castration-resistant prostate cancer [7].

As cancer immunotherapy represents a promising strategy for improving cancer treatment outcomes, numerous preclinical and clinical studies using different types of therapeutic vaccines are ongoing [8].

These include: molecular-based vaccines, vector-based vaccines, cell-based vaccines.



Major technological innovation has enabled mRNA, a non-infectious, non-integrating platform, to become a promising therapeutic tool. The recent approval of two COVID-19 mRNA vaccines (mRNA-1273 and BNT162b2) and significant research investments have further accelerated mRNA vaccine technology [9].

To overcome the instability and inefficient *in-vivo* delivery of mRNA, new delivery systems were developed:

lipid-based delivery, polymer-based delivery, peptide-based delivery, virus-like replicon particle delivery, cationic nano-emulsion delivery.

The naked mRNA vaccine can also be directly introduced into cells. As antigen presenting dendritic cells (DCs) not only generate effective adaptive immunity, they can also be used to deliver mRNA-based cancer vaccines. For this purpose, the patient's DCs are loaded with antigen-encoding mRNA and administered back to the patient [10].

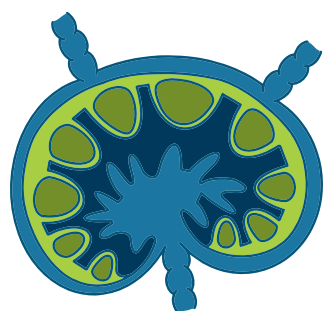
As a result of these breakthrough technologies, multiple mRNA vaccine platforms against infectious diseases and several types of cancer have demonstrated encouraging results in both animal models as well as humans.

Vaccine delivery methods

The efficacy of vaccines not only relies on the selection of appropriate antigens but also on the development of efficient delivery methods [11].

A potential strategy to enhance the immune response against cancer cells is the targeted delivery of antigens to the lymph nodes which play a critical role in the immune response by serving as a site of antigen presentation and immune cell activation [12].

Read more on lymphatic delivery in the white paper by Pasmans et al. 2023 [13].

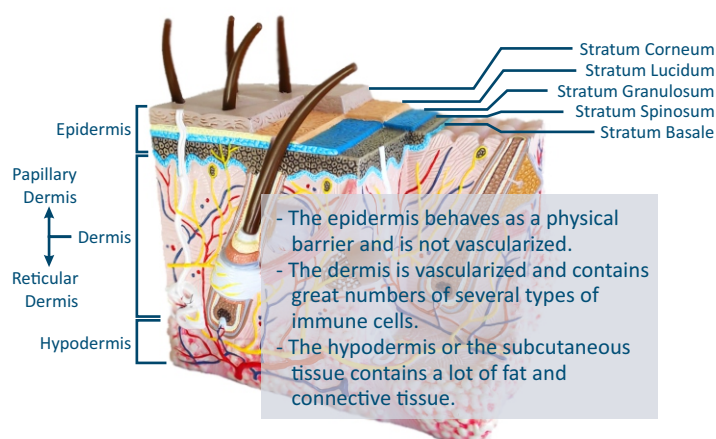


Lymph nodes are part of a network of vessels interrelated with lymphoid tissue and populated by various types of immune cells including T cells, B cells, DCs, macrophages, and neutrophils [14].

Additionally, ID delivery offers a promising alternative to conventional parental routes, as the skin contains high numbers of DCs and lymphatic vessels, facilitating efficient antigen uptake and the generation of robust immune responses. [15].

Why? The skin is an easily accessible, rich in immune cells and therefore an excellent vaccination site.

Vaccination into the different layers of the skin is referred to as epidermal (epidermis), intradermal (dermis), and subcutaneous (hypodermis) and may induce a variety of immune responses [16].

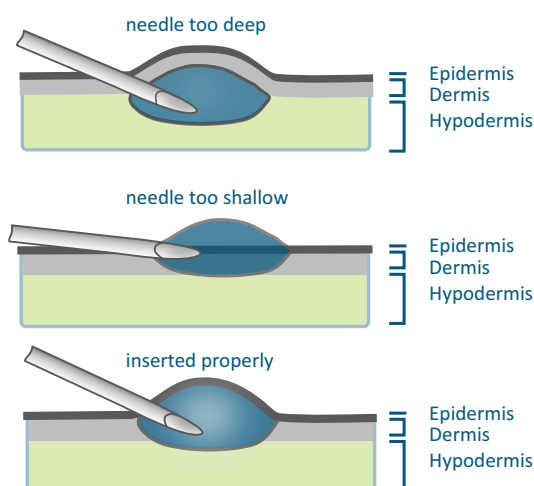


However, the composition and thickness of the skin is impacted by age, gender and BMI, shows great inter- and intrapersonal variability, and is interconnected with the human microbiome [16, 17, 18].

Intradermal vaccine delivery

Intradermal delivery is capable of improving immune responses but delivering antigen into skin is difficult. Intradermal injections are usually performed using the Mantoux technique, in which the needle is inserted at a shallow angle and requires special training to reliably target the skin [19].

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



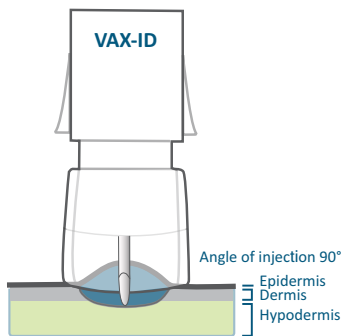
Due to the lack of depth-controlled drug delivery systems enabling safe, reproducible, and patient-friendly immunization, intradermal delivery is not yet a common clinical practice.

VAX-ID® a solution for reliable intradermal vaccine delivery

To overcome the challenges with the traditional Mantoux technique, IDEVAX developed VAX-ID® an easy-to-use drug delivery device enabling standardized, accurate and reliable delivery in the dermal layer of the skin, addressing the interpersonal variability of the skin.

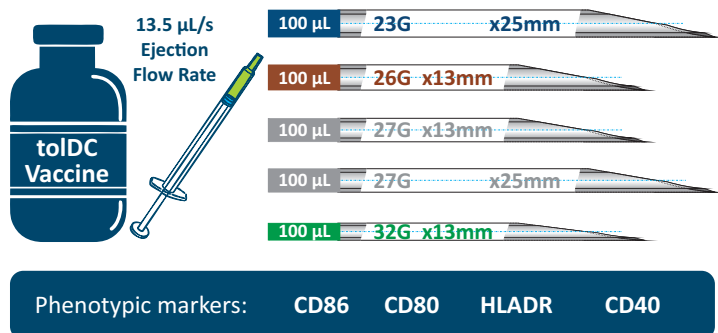
VAX-ID® can be preconfigured with a 32G, 30G, or 27G needle with a penetration depth of 0.85, 1.15 and 1.55mm, respectively.

As accuracy of penetration depth is very important, the penetration depth of the needle was predefined based on skin thickness evaluations by high frequency ultrasound executed in adults, adolescents as well as children [17,18]. These measurements were key in defining the optimal needle length for targeting drug delivery in the dermal layer of the skin with VAX-ID®.



Injection of *ex-vivo* generated dendritic cells can only be effective if a large number of viable, functional cells reach the site of action. The main cause of potential cell damage during intradermal injection is shear stress [21, 22, 23]. This will damage the cells, causing a decrease in cell viability and a potential change in cell phenotype.

To avoid shear stress damage and ensure optimal patient comfort, the optimal needle diameter for intradermal injection of tolerogenic dendritic cells (tolDCs) was determined.



During a small feasibility study, it was shown that VAX-ID® configured with needles ranging from 23G up to 30G showed no increase in shear stress upon ejection of tolerogenic dendritic cells. The four phenotypic markers (CD86, CD80, HLA DR, CD40) as well as the cell viability did not show significant differences before and after ejection.

Enabling standardized, accurate and reliable intradermal delivery, VAX-ID® offers a potential game-changing solution for intradermal delivery of vaccines and cells.



REFERENCES

1. Bray et al. 2024 (PMID: 38572751)
2. De Martel et al, 2020 (PMID: 31862245)
3. https://www.who.int/health-topics/hepatitis#tab=tab_1
4. https://idevax.com/wp-content/uploads/2023/07/White_Paper_HepB_20230728.pdf
5. <https://www.who.int/initiatives/cervical-cancer-elimination-initiative>
6. https://idevax.com/wp-content/uploads/2023/01/White_Paper_Idevax_HPV_20230120_final.pdf
7. Grimmett et al, 2022 (PMID: 35576080)
8. Tian et al, 2022 (PMID 36477638)
9. Chakraborty et al, 2021 (PMID 34305909)
10. Wang et al, 2021 (PMID 33593376)
11. Kaczmarek et al, 2023 (PMID: 37681891)
12. Li et al, 2023 (PMID:37415161)
13. https://idevax.com/wp-content/uploads/2023/11/Targeted-lymphatic-delivery_20230907.pdf
14. Wang et al, 2023 (PMID: 37719676)
15. Trevaskis et al, 2015 (PMID 26471369)
16. Hettinga et al, 2020 (PMID: 32947966)
17. Van Mulder et al, 2017 (PMID 27496276)
18. Van Mulder et al, 2020 (PMID 31767463)
19. Joyner et al, 2019 (PMID: 31071375)
20. Micheels et al, 2018 (PMID: 29320593)
21. Aguado et al. (2012): 22011213
22. Amer et al. (2015): 25623928
23. Wahlberg et al. (2018): 29907825

