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

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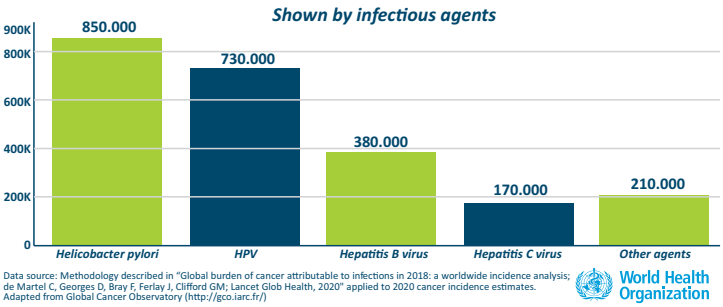
Introduction

Worldwide, an estimated 19.3 million new cancer cases and almost 10.0 million cancer deaths occurred in 2020 and the burden of incidence and mortality continues to grow rapidly. [1]
In 2018, 13% of the new cancer cases were attributable to infections. [2]



Data source: Methodology described in "Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis; de Martel C, Georges D, Bray F, Ferlay J, Clifford GM; Lancet Glob Health, 2020" applied to 2020 cancer incidence estimates. Adapted from Global Cancer Observatory (http://gco.iarc.fr/)

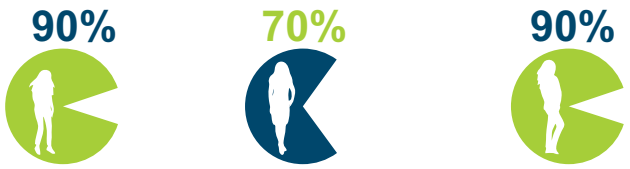
World Health Organization

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 Gobal Strategy for cervical cancer elimination.



Vaccination: 90% of girls fully vaccinated with the HPV vaccine by the age of 15

Screening: 70% of women screened using a high-performance test by the age of 35, and again by the age of 45

Treatment: 90% of women with pre-cancer treated and 90% of women with invasive cancer managed

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

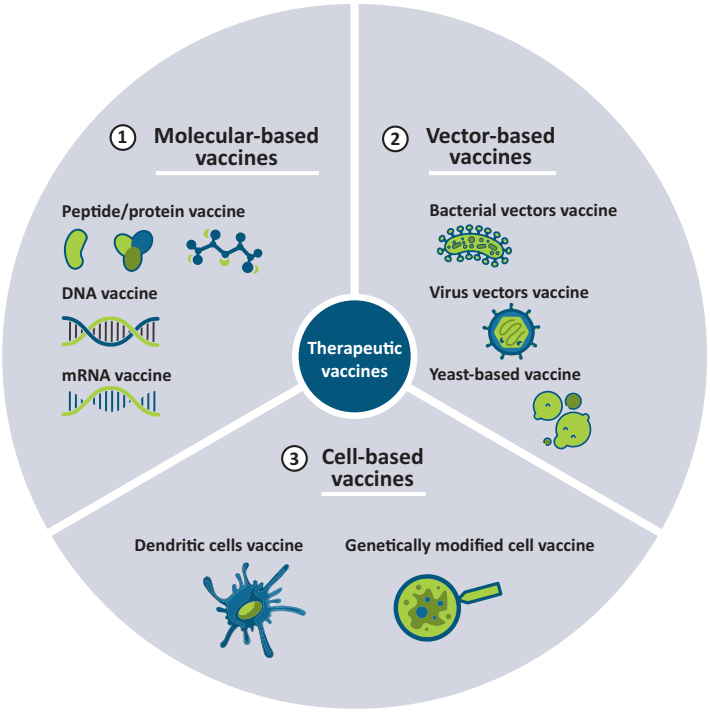
Therapeutic vaccines

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 defense of people already diagnosed with potentially any type of cancer.

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.



Adapted from Tian et al, 2022 (PMID 36477638)

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.*

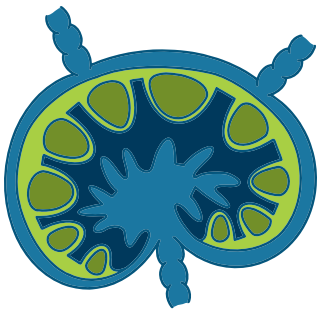
The naked mRNA vaccine can also be directly injected into cells.
As antigen presenting dendritic cells (DCs) not only generate effective adaptive immunity, they can also be used to deliver mRNA-based cancer vaccines. For this purpose, the patient's DCs are loaded with antigen-encoding mRNA and administered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

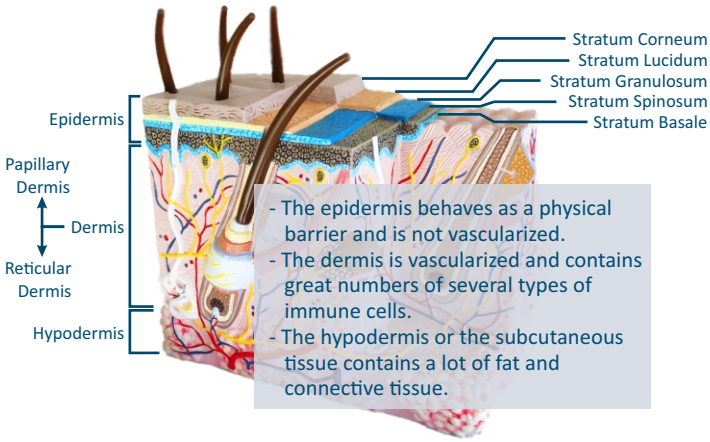
A potential strategy for addressing the limitations of therapeutic vaccines is the targeted delivery of antigens to the lymph nodes which play a critical role in the immune response by serving as a site of antigen presentation and immune cell activation. [12]
Read more on lymphatic delivery in the white 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]

Compared to other parenteral routes, and due to the high number of dendritic cells in the skin, uptake of antigens into dendritic cells and draining lymph nodes is enhanced after skin vaccination. [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]



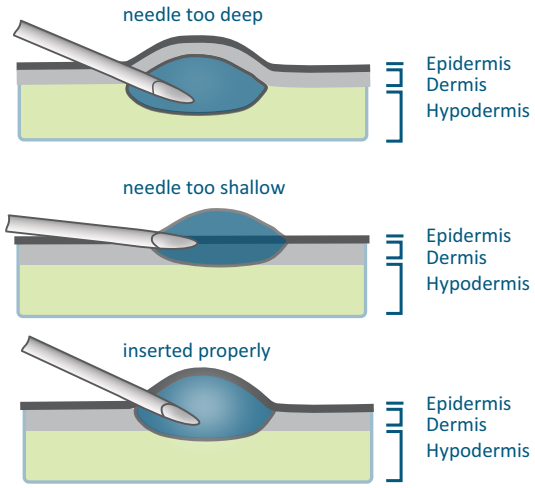
- The epidermis behaves as a physical barrier and is not vascularized.
- The dermis is vascularized and contains great numbers of several types of immune cells.
- The hypodermis or the subcutaneous tissue contains a lot of fat and connective tissue.

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.



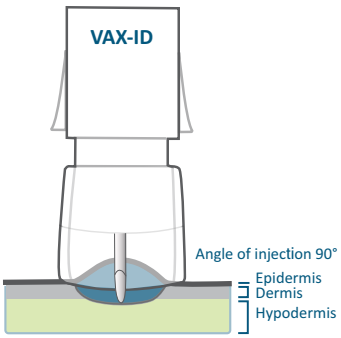
Due to the lack of depth-controlled drug delivery systems enabling safe, reproducible, and patient-friendly immunization, intradermal delivery is not yet a common clinical practice.

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.

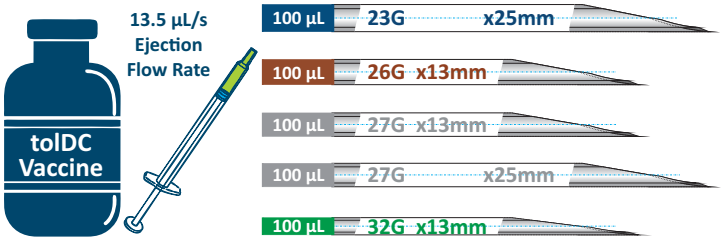
VAX-ID® can be preconfigured with a 32G, 30G, or 27G needle with a penetration depth of 0.85, 1.15 and 1.55mm, respectively.

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. This will damage the cells, causing a decrease in cell viability and a 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.



Phenotypic markers:	CD86	CD80	HLADR	CD40

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, HLADR, 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.

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