Targeted lymphatic delivery: a key role for intradermal injection devices?

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The lymphatic system: a key-player in health and disease

The lymphatic system consists of a network of lymphatic vessels, tissues, and nodes and plays critical roles in tissue fluid homeostasis and immunity [1].

In contrast to the closed circulatory system characterized by high pressure in the blood vessels, the lymphatic vascular network operates as a low-pressure, one-way flow system [2,3].

The Pathophysiology of Lymphedema

The lymphatic system is critical to maintain the tissue fluid balance. Consequently, failure of lymphatic networks to adequately perform this function manifests in lymphedema. Lymphedema is classified as primary if it results from inherited genetic mutations and secondary if it results from trauma, such as surgery, radiation, or obstruction [2].

An increasing interest is seen in targeted lymphatic delivery of imaging agents and drugs. This is clearly driven by the recognition of the lymphatic system's involvement in the development of many different pathologies, including autoimmune/inflammatory disorders, cancer, infections, and metabolic syndrome [4].

Lymphatic imaging

Clinical imaging can deliver a variety of relevant information about the morphology and function of the lymphatic vessels and lymph nodes. It can be used to identify and stage numerous conditions such as lymphedema, cancer, chronic inflammation, and many others. Additionally, it is often used in surgical procedures in which lymphatics are involved as in the Sentinel Lymph Node (SLN) mapping [5].

More recently, different molecular imaging modalities allowed non-invasive visualization of the biodistribution and trafficking of active cells (cell-tracking) throughout a living organism. Cell-tracking supports the development and evaluation of the efficacy of cell-based treatments (e.g. CAR T-cells, stem cells) and has extensively been used in both preclinical and clinical studies.

Successful imaging remains however challenging. Even during surgery, the lymphatic system is not apparent to the naked eye and the unidirectional flow system makes it difficult to inject imaging agents directly into the lymphatics [4].
Therefore, lymphatic imaging is usually performed after interstitial injection (e.g., intradermal, subcutaneous, or intramuscular) of imaging agents [1].

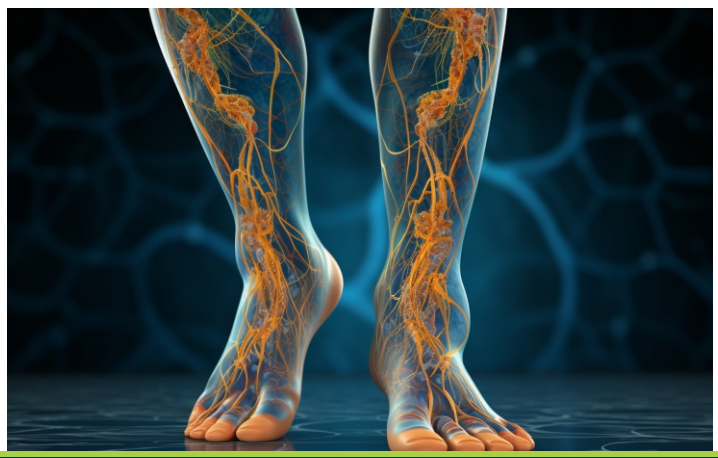
Tracer characteristics such as molecular size impact the lymphatic uptake that may be regulated by interstitial transport and/or endothelial permeability [6]. Particle sizes between 10–100 nm are preferred for lymphatic transfer.

- Small molecules or moderately sized macromolecules (<10 nm or ~16–20 kDa for proteins) are primarily absorbed via the blood capillaries draining the injection site. With increasing molecular size, transport across the vascular endothelium is reduced, whereas entry into the more permeable lymphatic capillaries is retained or becomes the preferred route of uptake.
- Proteins and macromolecules (10–100 nm or 20–30 kDa for proteins) move through the interstitium and enter the lymphatic vessels.
- Particles >100 nm in diameter are poorly transported through the interstitium because the water channels that provide conduits for transfer within the interstitium are typically 100 nm in diameter.

Due to its accessibility, the greater density of initial lymphatics in the dermis and the high interstitial pressure generated by the dense collagen matrix, intradermal injection is usually the preferred interstitial delivery method. These characteristics are driving the rapid uptake of the injected tracer into the initial lymphatics [6,7].

Lymphatic drug delivery

Immunotherapies, including vaccines, are extremely promising for curing diseases such as cancer, chronic inflammation, and transplantation. The draining lymph nodes thereby play a critical role in the immune response by serving as a site of antigen presentation and immune cell activation.
Delivery of these immunotherapies to the draining lymph nodes, can improve their efficacy and clinical outcome [8,9].
To effectively reach the lymph nodes, lymphatic vessel transport after non-invasive oral or intradermal/subcutaneous delivery can be used [8].

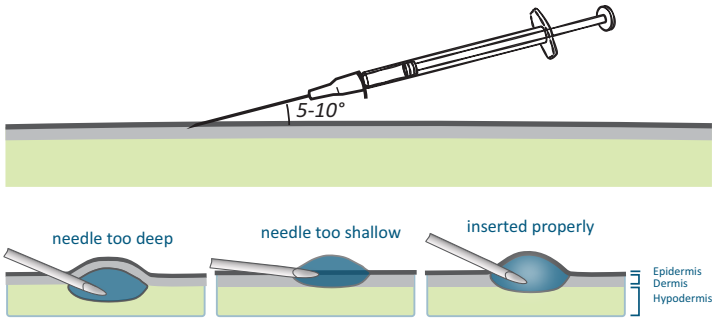


Additionally, compared to other parenteral routes, uptake of material into dendritic cells and draining lymph nodes is enhanced after intradermal vaccination due to the higher number of dendritic cells in the skin [6].

Intradermal Injection: challenging but promising

Delivery through the skin, which is rich in antigen-presenting cells, has distinct benefits, such as minimal-invasiveness, elimination of first-pass effect, reduction of adverse effects, and greater patient compliance [10].

The human dermis is a thin tissue (approximately 1–3 mm depending on the local site of the body) located at a depth of less than 1 mm from the skin surface; only trained and experienced practitioners can perform an accurate and consistent ID injection, i.e., Mantoux technique. This technique is the current standard of care for intradermal injection, but it is notoriously difficult and prone to failure, thus requiring a lot of training for healthcare professionals [11].
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 to shallow [12].



Additionally, intradermal injections with a standard needle and syringe are perceived as painful for the patient.

VAX-ID®: An innovative solution for reliable intradermal drug 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.

Several studies showed that VAX-ID® is easy to use and very well accepted by patients and healthcare workers. The low pain sensation and the deactivation mechanism to avoid needle stick injuries ensure that the device is well accepted and safe for both patients and clinicians [13].

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 and allows for delivery of small volumes (0.05cc – 0.2cc per injection). As accuracy of penetration depth is very important, the penetration depth of the needle was predefined based on skin thickness evaluations executed in adults, adolescents as well as children [14,15].

IDEVAX's mathematical model, developed to define injection vs penetration depth, allows for different VAX-ID® variants targeting a variety of depths that can be used for a broad range of lymphatic applications. Together with VAX-ID®'s compatibility with low-viscosity liquid formulated substances, the mathematical model allows the device to be widely used without extensive formulation development work [16].
Enabling standardized, accurate and reliable intradermal delivery, VAX-ID® offers a potential convenient solution for targeted lymphatic delivery of imaging agents and drugs.

References

1. Polomska et al. 2021. PMID: 32891679
2. Breslin et al. 2018. PMID 30549020
3. Petrova et al. 2020. PMID: 32646971
4. Han et al. 2022. PMID 36120382
5. Rbeihat et al. 2023. Innovative intradermal injection device for lymphoscintigraphy and sentinel lymph node mapping.
6. Travaskis et al. 2021. PMID 26471369
7. Russell et al. 2022. PMID 35935839
8. McCright et al. 2022 PMID: 35721179
9. Li et al. 2023. PMID: 37415161
10. Pawar et al. 2023. PMID: 36721802
11. Tuzoka et al. 2016. PMID: 26674124
12. Micheels, Patrick, and Lisa Goodman. "Injection Depth in Intradermal Therapy: Update and Correction of Published Data." Journal of drugs in dermatology : JDD vol. 17,1 (2018): 88-96.
13. https://idevax.com/dataroom/
14. Van Mulder et al. 2017. PMID: 27496276
15. Van Mulder et al. 2020. PMID: 31767463
16. Beyers et al. 2023. Assessment of injection and penetration depth of a novel intradermal drug delivery device.