Debiotech’s NanoJect™ device was conceived in order to overcome the problems encountered with classical intradermal delivery techniques. Convenient, precise, well controlled and reproducible intradermal injection of drugs – from small molecules to large peptides – have become possible thanks to an original design of microneedles combined with a specifically developed insertion/infusion system (see Figure 1).

For the patient, this is now a pain-free procedure. It also satisfies clinicians, since they can very easily inject up to 500 μL in three seconds, while precisely controlling the injection depth of the drug.

The NanoJect™ device is easy to use and requires only a short training. It could therefore be widely used for diverse applications across the world (see Figure 2).

THE CHALLENGE OF INTRADERMAL INJECTIONS

Interest in intradermal immunisations began in the early 20th Century with the work of Charles Mantoux. This French physician developed an approach for the intradermal injection of tuberculin as a diagnostic skin test for tuberculosis disease. Two decades later, a study conducted by Louis Tuft showed that a smaller dose of typhoid vaccine injected intradermally had an equivalent immune response and an improved adverse event profile compared to the full dose injected subcutaneously. Subsequently, several studies aiming at evaluating the efficiency and utility of intradermal delivery route such as vaccine dose reduction were conducted using different commercially available vaccines including, amongst others, influenza, measles, cholera, rabies, hepatitis B and polio.

Today it is well documented that the immune response after intradermal administration of one-tenth of an intramuscular dose for rabies is equivalent to the full dose given intramuscularly. For influenza, a recent study demonstrated a much better immunisation of the older population – which is most at risk – with an intradermal injection than if done by a subcutaneous injection when using the same dose of vaccine.

The routine use of intradermal injection has however been limited by the complexity of applying Charles Mantoux’s method – where a standard needle (Figure 3) is inserted at a grazing angle into the skin. In particular, success is known to be highly dependent upon the experience and technique of the healthcare worker. Control of injection depth is very poor and reproducibility is low.

“TREATMENTS THAT WERE TURNED DOWN BEFOREHAND BECAUSE OF THE COMPLEXITY OF THEIR IMPLEMENTATION WILL BECOME STANDARD APPROACHES”
The introduction of a device that deeply simplifies this type of injection will undoubtedly open several new avenues in intradermal drug therapy. Treatments that were turned down beforehand because of the complexity of their implementation will become standard approaches.

**NANOJECT™: THE SOLUTION FOR SUCCESSFUL INTRADERMAL DELIVERY**

The NanoJect™ device consists of short (less than 1mm), sharp and hollow microneedles produced using Micro-Electro Mechanical System (MEMS) techniques (see boxed text, p 20).

Manufactured as single needles or as arrays of three needles in a row, their channel opens on the side (Figure 4) at a depth in the skin between 300 μm and 600 μm, allowing the delivery of small boluses up to 500 μl in only three seconds.

The opening can be orientated at will to control the orientation of the liquid distribution into the skin. The device also comprises an inserter which plays an important role in facilitating the use of the device, while guaranteeing the success of the injection. The whole system is disposable, that is, for single use only, thus avoiding any cross-contamination issues.

The extremely sharp tip and the limited length of the microneedles (see Figure 5) ensure very gentle penetration while avoiding most pain receptors in the skin. The presence of the hole on the side of the needle limits the risk of coring and consequent clogging of the fluidic channel. It also potentially permits faster healing of the skin thanks to the absence of tissue removal. Because of the extremely well controlled dimensions of the microneedles guaranteed by the MEMS technology, the depth of injection is also very precise and reproducible.

Compression of tissue as well as high hydrostatic pressure within the tissue is known to be a limiting factor for the diffusion of fluids. The side positioning of the opening therefore permits the delivery of the fluid in a region that is not compressed during the insertion of the needle (as is the case at the tip of the needle).

**“DURING THE DEVELOPMENT OF THE DEVICE, OVER 500 INJECTIONS IN HEALTHY VOLUNTEERS HAVE BEEN CONDUCTED”**

Figure 1: The Nanoject™ assembled with an example syringe.

The force required to push the liquid is therefore minimised, limiting the risk of needle dislodgment and consequent leaks.

The microneedles are mounted on a single-use inserter on which any type of luer lock syringe can be attached. The role of this inserter is to guarantee the perfect and easy placement of

Figure 2: The Nanoject™ device is easy to use.

Figure 3: The microneedle’s length in comparison with a 25G needle.

Figure 4: Schematic cross-section of the needle, showing fluidic channel and side-opening.

Figure 5: SEM images of (left) the microneedle and (right) the needle tip.
the microneedles within the upper layer of the skin and to maintain the ideal conditions for a reproducible and successful injection, avoiding any possible leak during injection. The entire system (microneedles plus inserter) is covered by six families of patents that ensure exclusivity for Debiotech until 2032.

The manufacture and assembly process of the NanoJect™ devices take place in a clean and controlled environment – ISO class 5 down to ISO class 3 clean rooms (see Figure 6). The production is now an established and GMP-compliant industrial process delivering substantial amounts of devices for various trials and CE marking is in progress.

**CLINICAL INVESTIGATIONS UNDERWAY**

During the development of the device, over 500 injections in healthy volunteers have been performed in addition to in vitro and in vivo experiments conducted in animal models. An in-depth analysis of the interactions between the skin, the needles and the injected fluid has been conducted using computed tomography, optical coherence microscopy as well as histological cross-sections. Mouse, rat, pig and human skin models have been used to understand the key mechanisms of intradermal injection with microneedles – the importance of the skin elasticity, the role of the pressure applied onto the skin before, during and after injection, the behaviour of the fluid once injected or the influence of the device design on the final success of the injection – and to optimise the penetration-injection process.

A successful injection is characterised by a bleb formation at the skin surface, with the absence of any leak. The bleb disappears within a few minutes, as the injected fluid is drained within the tissues (see Figure 7).

The pain was assessed (and its absence during insertion confirmed) by comparing, on the same patient, different types of injections: various volumes (from 100-500 μl) and various sites (forearm, deltoid and abdomen), taking the established Mantoux method as a reference. Repeatability and ease of use were tested with assistance of different external clinicians. After a short training session, they were able to perform several intradermal administrations appropriately. All these experiments confirmed the ease of use of the device as well as the speed and the efficiency of the injection.

Based on these successful results, the Nanoject™ device has entered into a clinical trial in collaboration with the Vaccine and Immunotherapy Centre of CHUV (Centre Hospitalier Universitaire Vaudois; Lausanne, Switzerland). The study is a single-centre, randomised, double-blind, placebo-controlled, comparative Phase I first-in-man to assess the safety and tolerability of rabies vaccine “Vaccin rabique Pasteur” injected using NanoJect™, and the non-inferior immune response, compared with classical intradermal or intramuscular injection using a syringe. This study is the first in a series of clinical trials.

**TOWARDS NEW APPLICATIONS**

A great variety of applications can be envisaged for intradermal delivery using microneedles. The goal sought is, in some cases, to avoid
the pain induced by needles during their insertion into the skin. Microneedles are also seen as an excellent solution against needle phobia and therefore should encourage a better compliance with treatments that require regular injections. But the most interesting and promising applications of microneedles are probably those where the intradermal route presents a different pharmacological response that could be beneficial for the treatment.

The potential of dose reduction (or increased efficacy) with some vaccine formulations has been identified quite early. More recently, a change in the pharmacokinetics of several drugs, such as insulin, for example, has been reported following intradermal injection.

On one hand, reduced doses of vaccines are of particular interest for regions where vaccination campaigns are difficult to conduct, for diseases presenting a fast evolution and that require regular new formulations or for pandemics that require extremely fast response. On the other, faster peak values of insulin may fundamentally change the treatment of diabetes, greatly facilitating the realisation of an artificial pancreas.

While, in industrialised countries, human rabies is close to being eradicated, it is still responsible for about 55,000 deaths every year in territories where access to the vaccine is difficult. For several years, the WHO has been conducting extensive studies aimed at reducing the dose needed for efficient protection and that require regular new formulations or for pandemics that require extremely fast response. On the other, faster peak values of insulin may fundamentally change the treatment of diabetes, greatly facilitating the realisation of an artificial pancreas.

Influenza presents a different challenge: the virus is mutating extremely rapidly and a complete new immunisation of the population is needed every year. The time between the moment the WHO provides its guidance about the strains to introduce in the new vaccine and the beginning of the vaccination campaign is relatively short, putting a lot of pressure on the manufacturers. In particular, there is a risk of shortage in supply if for any reason the supply chain of one of these manufacturers is disrupted. In fact this very situation arose within the last few years, and prompted a demand from the authorities to identify new ways to reduce the required dose. In addition, following the recent events around avian flu (2004) and swine flu (2009), growing concern is expressed about the threat of pandemic resulting from a virulent strain. Under these circumstances, the need for rapid vaccination of a large population in an efficient manner is critical. Here again the need for methods requiring smaller doses has been expressed.

CONCLUSION

Intradermal injection is a delivery route that has for a long time been neglected due to the lack of user-friendly, reliable and efficient devices. Nonetheless, several studies had emphasised its advantages for certain types of treatments compared with the conventional subcutaneous and intramuscular routes.

Until now, all of the intradermal solutions proposed lacked the ease of use, the reproducibility, the reliability, or the absence of leakage, or were strongly limited in the type of molecules that could be delivered. Microneedles have, since their appearance, been seen as an excellent way to solve all these issues. However, the interaction of these short and fine structures with an elastic structure such as skin has been underestimated. Driving the needle into the skin and keeping it at a given depth, and applying and maintaining the right pressure before, during and after the drug administration, will also determine the final success of the procedure.

The NanoJect™ device, as shown by all the data collected on its efficacy, repeatability and usability, is offering a real solution to tackle this very promising area of drug delivery.

ABOUT DEBIOTECH

Debiotech SA is a Swiss Company with more than 20 years’ experience in developing highly innovative medical devices, based on micro- and nanotechnology, micro-electronics, and innovative materials.

The company concentrates on implantable and non-implantable systems, in particular for drug delivery and diagnostics, with a demonstrated competence lying in the identification of breakthrough technologies and their integration into novel medical devices.

Devices developed by Debiotech are eventually licensed to major international pharmaceutical and medical device companies, with a track record of over 40 license agreements worldwide. Examples of products include the I-Vantage™ IV pump for hospital and home-care, the CT Expres™ Contrast Media injector for CT-Diagnostic Imaging (recently acquired by Bracco Imaging), the JewelPump™ patch insulin pump for diabetes care, the DialEase™ home-care miniaturised dialysis equipment, and others under development.
NanoJect™
Microneedle Intra-Dermal Injection

Simple and Reliable ID System
- easy to use and reproducible
- painless injection
- automatic insertion
- precise depth control
- up to 500 µl in 3 seconds

www.nanoject.net

DEBIOTECHE S.A. Switzerland
Innovative Medical Systems