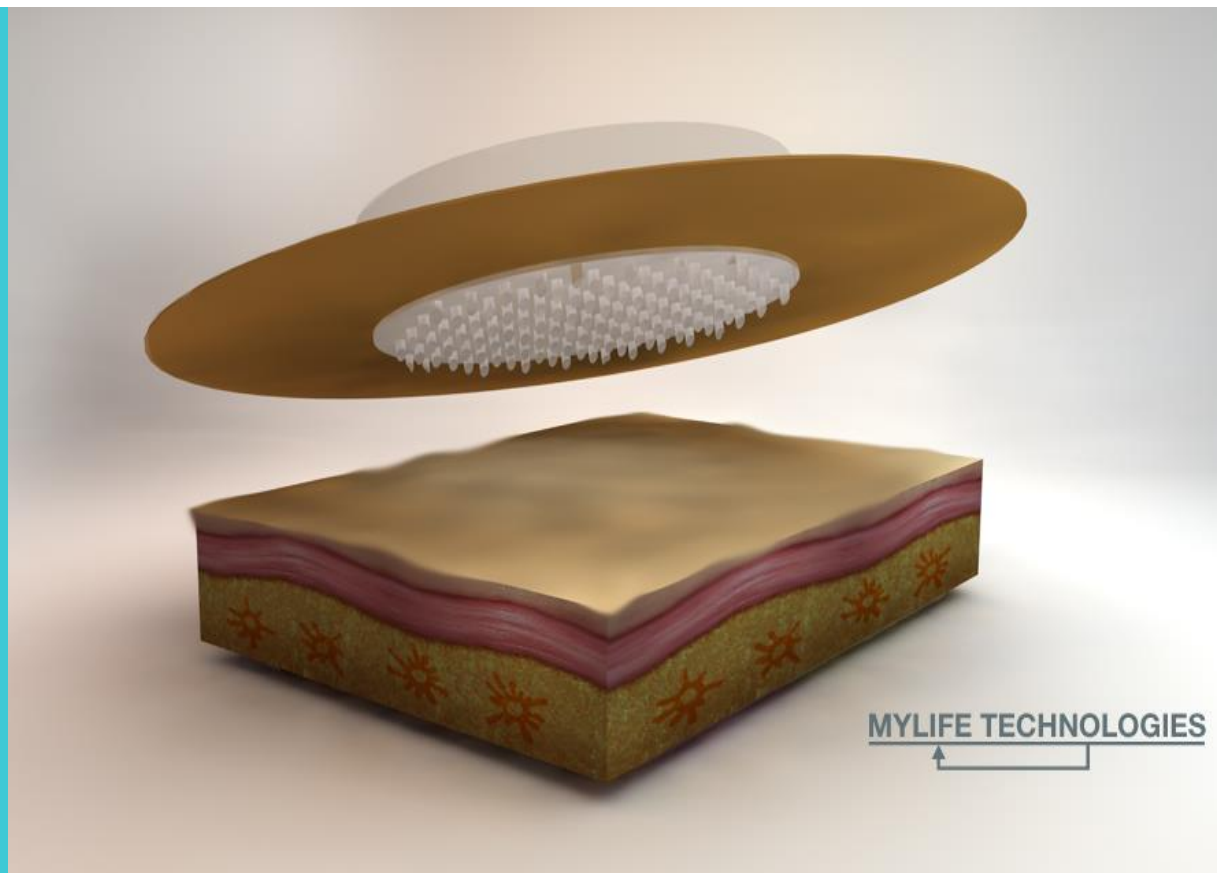




MicroNeedle technology for dermal drug delivery

*Presentation for Clinical Supplies Forum
Pieter Jan Vos, CEO*



COMPANY

- MyLife Technologies (MLT) is a spin-off from University of Twente, MESA+, Institute for Nanotechnology (NL), Feb 2012
- IP related to technology for ceramic nanoporous microneedle arrays (npMNAs)
- Production is outsourced: npMNAs are manufactured in ISO certified factory for high-tech ceramics (NL)
- Analytical lab in incubator of Leiden BioScience Park



Company - Team Members

*PieterJan Vos, MSc,
CEO, co-founder*

- *Former New Business Director Diosynth branch of Organon, NL)*



*Koen van der Maaden, PhD,
Development Officer*

- *PhD with honors on microneedles at Leiden University, C.J. Kok Award 2015 (best PhD thesis)*



*Nico Kuijt, BSc,
Research Analyst*

- *Former To-BBB / Janssen Biologics*



*Nikki van Trigt, MSc
Research Analyst*

- *Biomedical Researcher, Article 9 certificate*



Leonie de Best, MSc

- *Regulatory / Quality consultant*



*Regina Lüttge, PhD,
Co-founder*

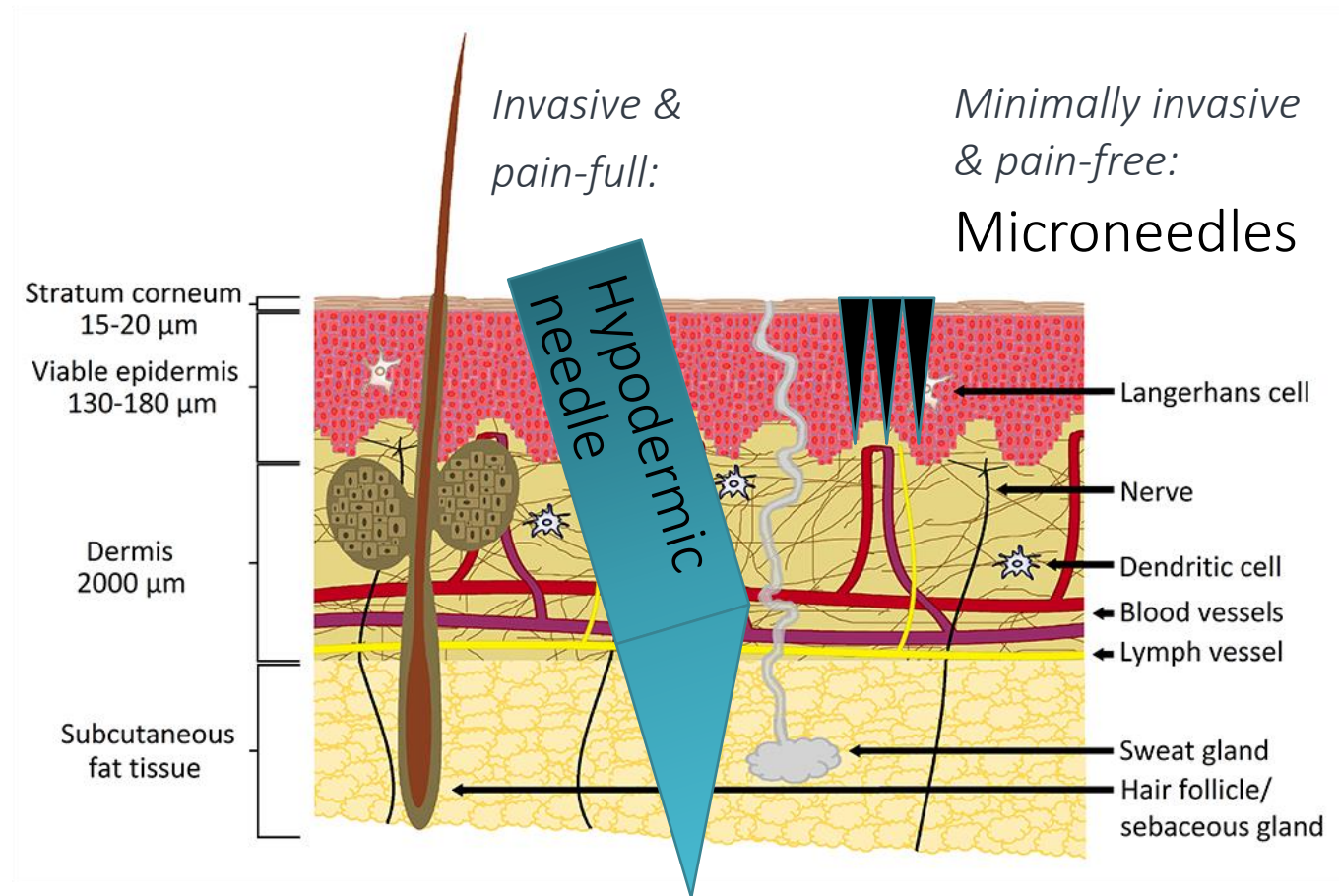
- *Co-inventor npMNA technology, Assoc. Prof. at Eindhoven University of Technology (NL)*



Drug delivery challenges

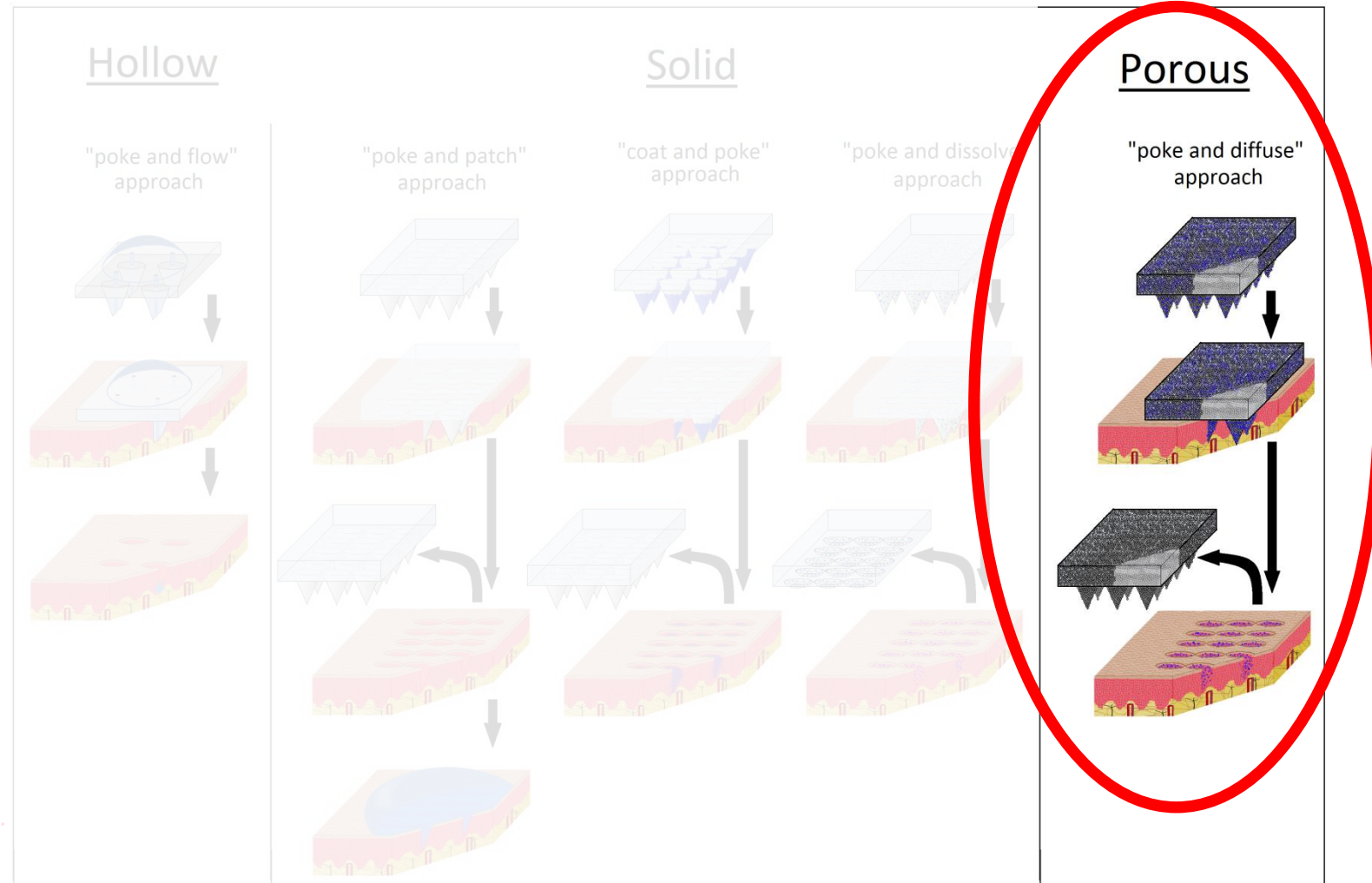
- **Parenteral route:** requires medically trained personnel, pain, needle phobia
- **Oral route:** impossible for specific drug types, side-effects in GI tract, first pass effect
- **Nasal sprays:** often low and variable bio-availability
- **Conventional TD patches:** slow transport through the skin, high residual drug levels in the patch after usage

Needle & syringe injection vs. microneedles



Adapted from: K. van der Maaden et al.,
J. Control. Release, 2012

npMNA technology: nanoporous MicroNeedle Arrays, poke & diffuse



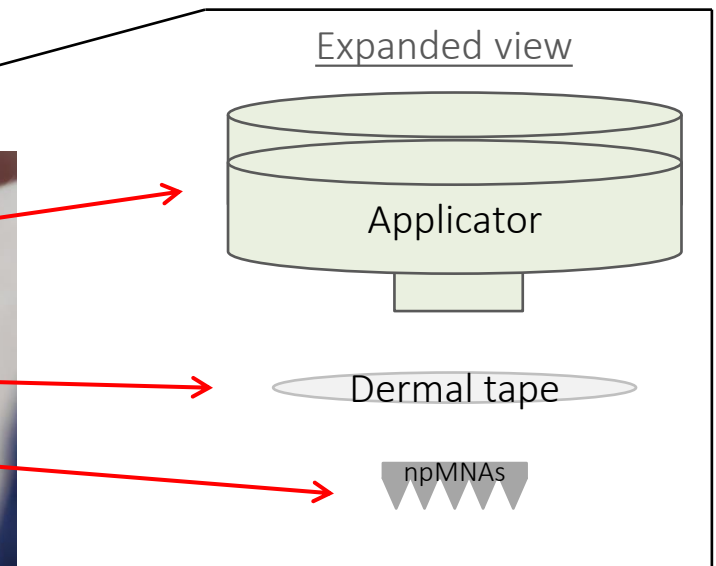
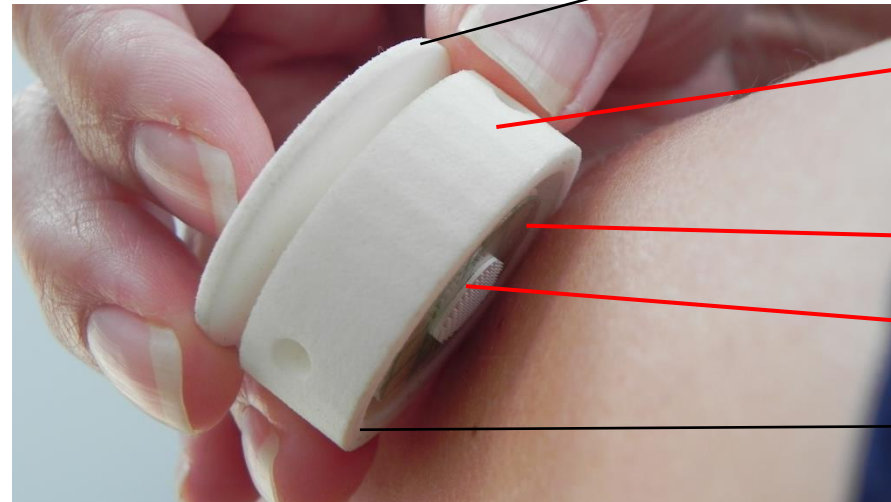
*K. van der Maaden et al., Drug
Deliv. and Transl. Res., 2015*

Drug delivery solution

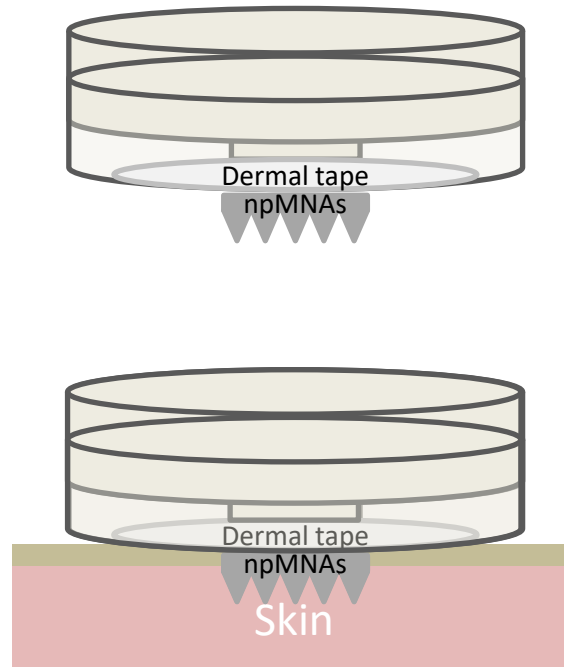
Easy and safe transdermal delivery:

- A drug containing nanoporous microneedle array (npMNA)
- An insertion device (“applicator”) to ensure easy, operator-independent application
- Dermal adhesive tape to keep the npMNA on the skin

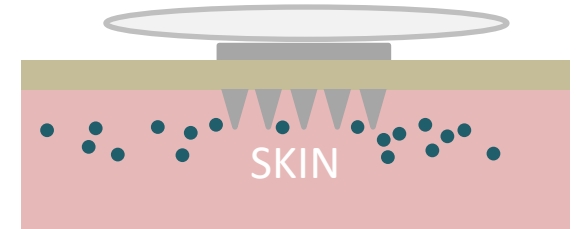
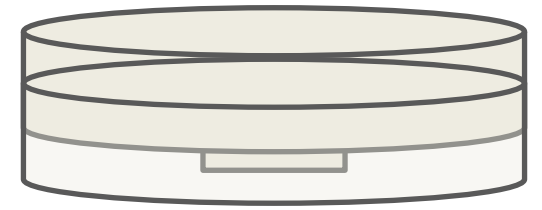
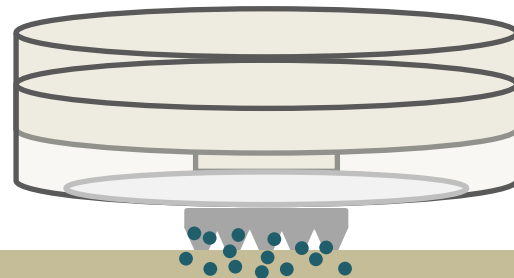
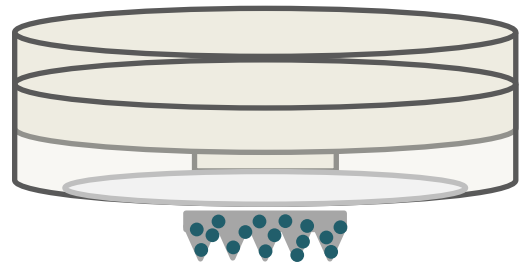
*npMNA-patch with
prototype applicator*



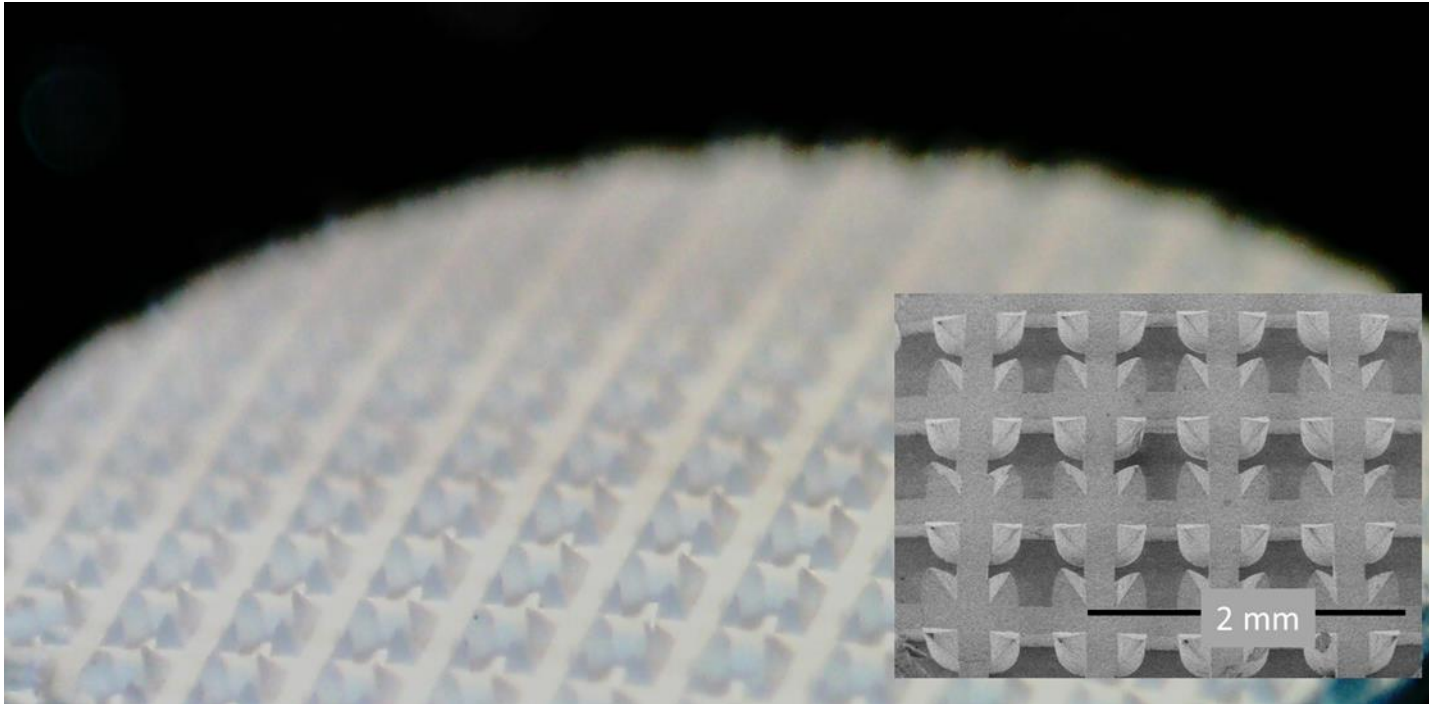
Dermal application of npMNAs



Drug delivery of npMNA



Core of the solution: nanoporous microneedle arrays



We hold a unique position:

- **Nanoporous material:** nanopores allow for storage of pharmaceuticals
- Microneedles are made of a **bio-inert ceramic** (Al_2O_3) and allow to overcome the skin's main barrier, i.e. the stratum corneum
- npMNA **design freedom:** microneedle density, porosity, length / shape, surface
- Technology **patented** in USA, Europe, Japan, and China

COMPANY FOCUS AREAS

- Specific **small molecules**: transdermal delivery
- **Peptides**: transdermal delivery
- **Prophylactic & therapeutic vaccines**: intradermal delivery, targeting dendritic cells

Vaccine Challenges & Motivation

Vaccine challenges:

- Many vaccines lack efficacy
- Vaccines lack efficiency
- Painful injections
- Risks: needle stick injuries & contamination risk
- Administration requires medically trained personnel



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Answers by npMNA technology:

- Targeting dendritic cells in (epi)dermis
- Dose sparing potential of factor 5-100
- Minimally invasive & pain-free
- Safe and easy to administer vaccine microneedle patch product
- Possibility of self-administration by patient

Small molecules: drivers supporting npMNA technology

Oral delivery

- Products with severe adverse effects
- Orals with low and / or variable bioavailability
- Patients with swallowing problems
- Patient populations with poor therapy compliance
- Oral delivery -> liver's first pass effect

Inhalors / nasal sprays

- Often low and variable bioavailability

Conventional transdermal patches

- Slow clinical effect
- Inefficient: big residual drug quantities in patch after usage

npMNA technology

- Certain adverse effects can be avoided
- May improve the bioavailability compared to oral delivery & nasal sprays
- Improvement of therapy compliance
- Liver's first pass effect = avoided
- Much quicker clinical effect compared to conventional patches
- Less residual drug compared to conventional patches

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Peptide drugs: drivers supporting npMNA technology

Peptide drugs: mainly administered by injection

- Often painful
- Needle phobia
- Needle injections require medically trained personnel

Peptide drugs: alternative administration routes

- Inhalation / nasal sprays: low & variable bio-availability
- Oral delivery: very seldom, as peptides desintegrate in the GI tract

npMNA technology

- Easy & painfree self-administration
- npMNA patches particularly suitable for chronic diseases & improve quality of life
- Considerably higher and more constant bio-availability compared to inhalation / nasal sprays / orals

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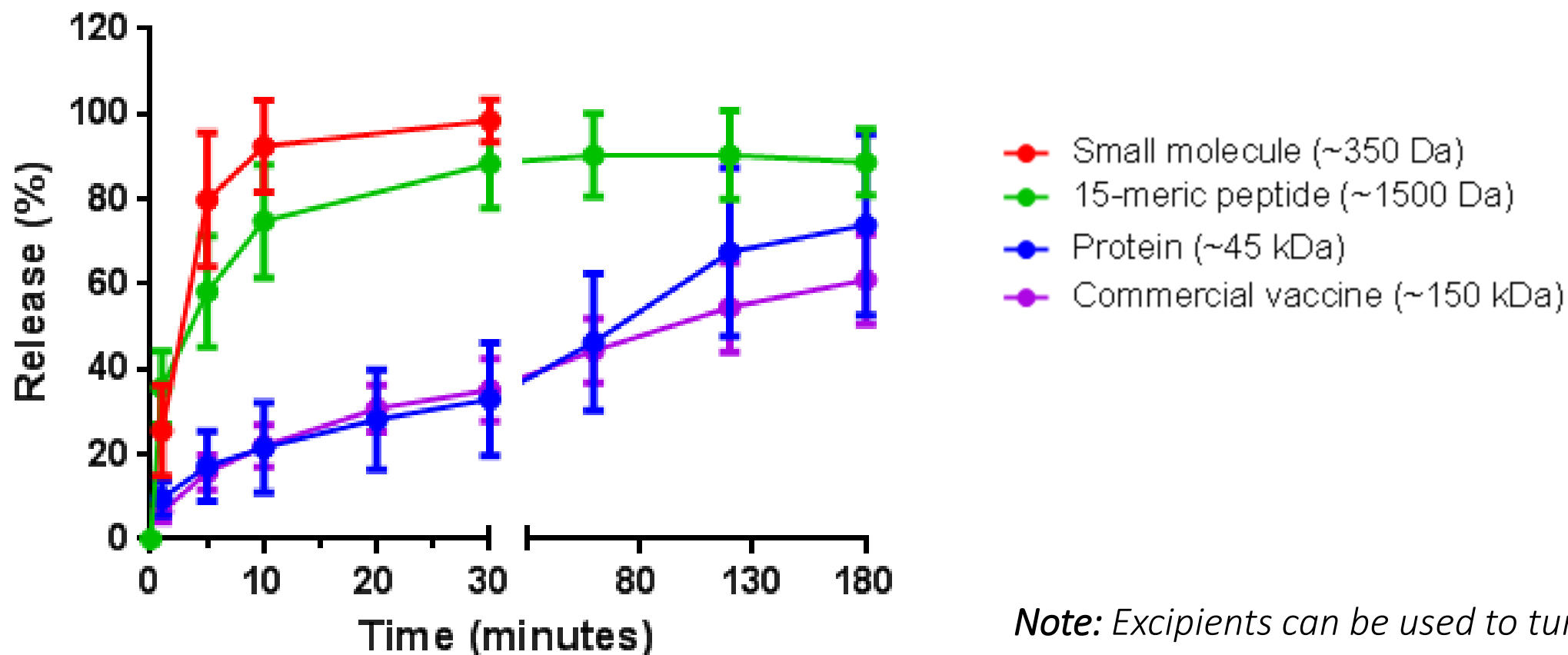
Current status of npMNA technology

- Dermal drug delivery shown in various animal models
- Dermal drug delivery of small molecules demonstrated in *ex vivo* skin experiments
- Tuning of release profiles
- External reservoir connected to npMNA devices available
- Effective induction of antibodies upon immunization with DT / TT vaccines, comparable to SC immunization (accepted for publication)
- Challenge study influenza subunit vaccine successful (data not yet published)
- npMNA devices are manufactured in an ISO 9001 certified plant for high-tech ceramics in the Netherlands
- ***First-in-human study*** under preparation for execution in 2018



Examples: in vitro release of drugs from npMNAs

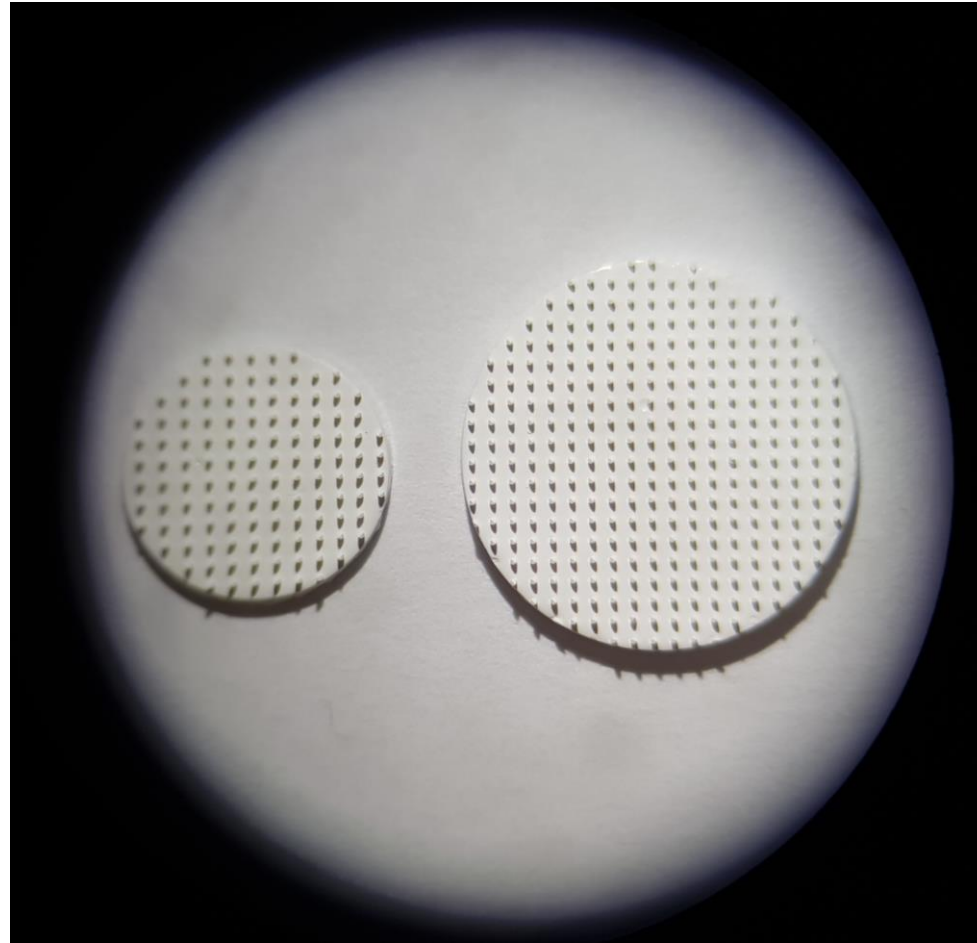
Typical release profiles



Note: Excipients can be used to tune release rates

In vitro release studies for different npMNA diameters small molecule

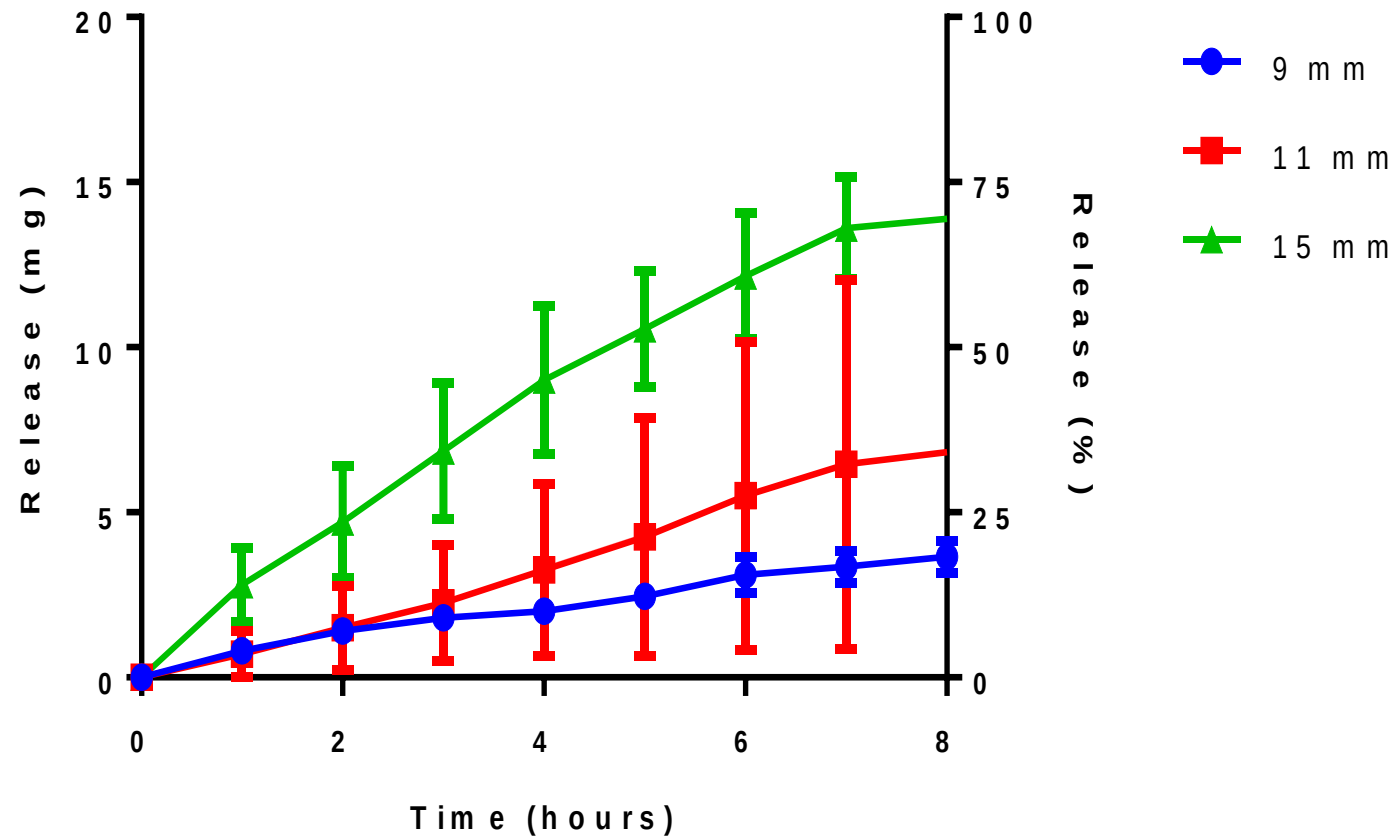
*npMNA with $\varnothing = 9\text{ mm}$
105 needles per device*



*npMNA with $\varnothing = 15\text{ mm}$
290 needles per device*

In vitro release studies for different npMNA diameters small molecule

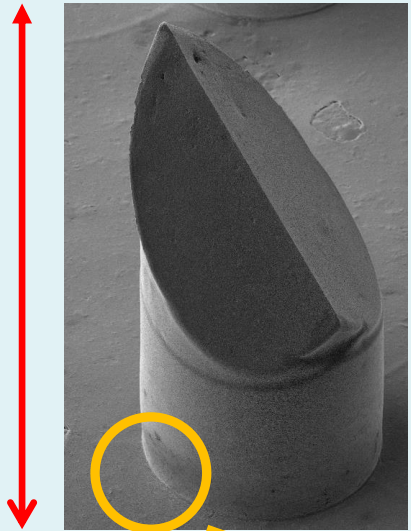
Release via microneedle tips



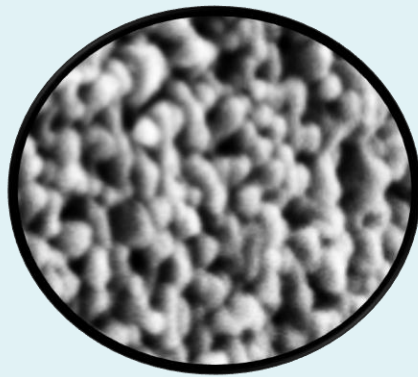
npMNAs for vaccination

Properties of npMNAs for vaccination

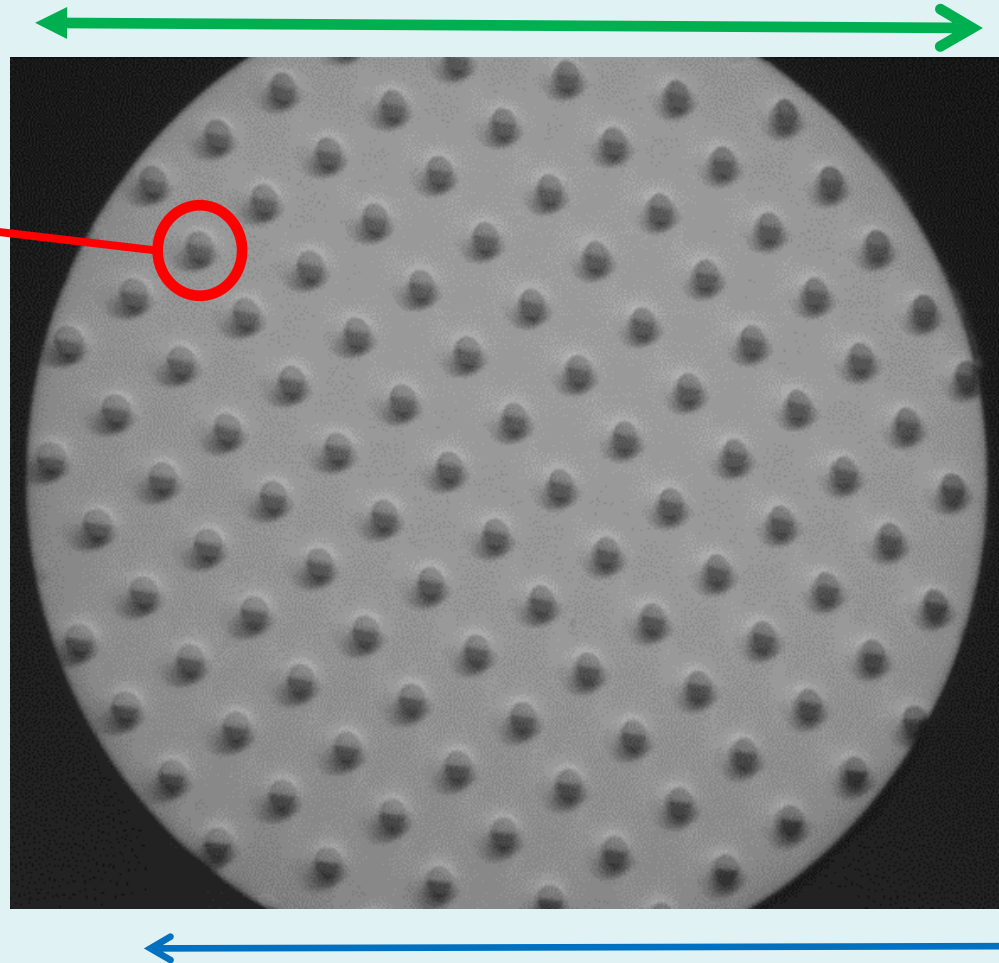
Microneedle length:
 $\pm 475 \mu\text{m}$



Pore size: $\pm 80 \text{ nm}$

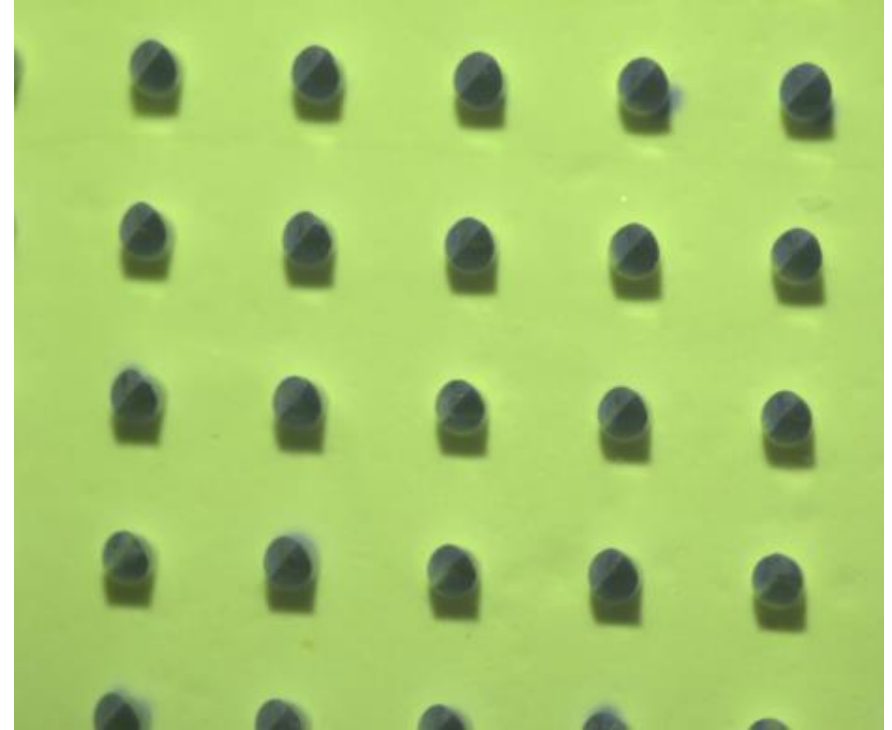
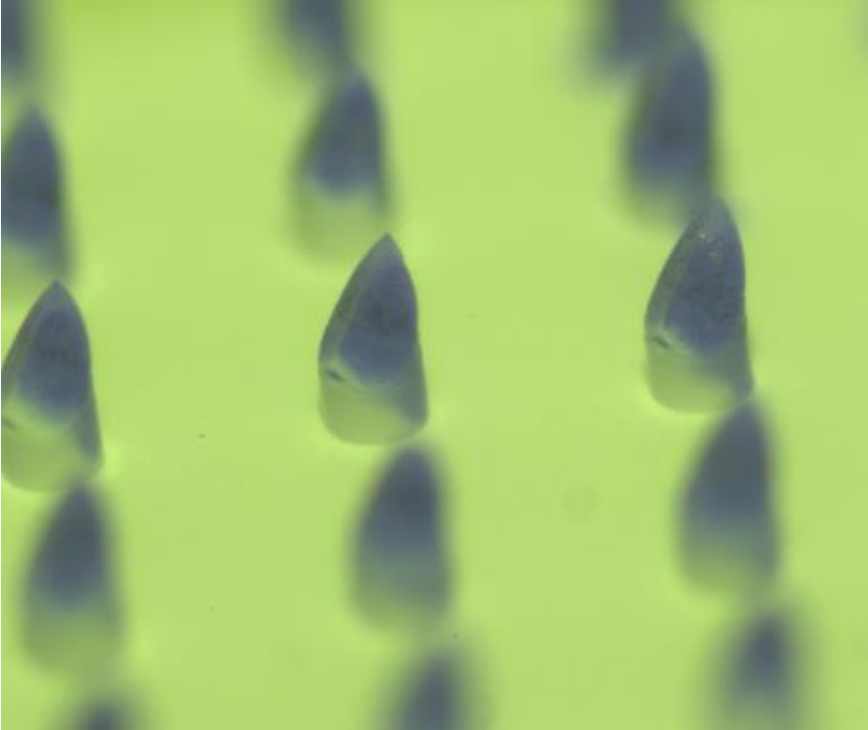


npMNA diameter: 9 mm



Microneedles/
array: 105

Vaccine loading into npMNAs



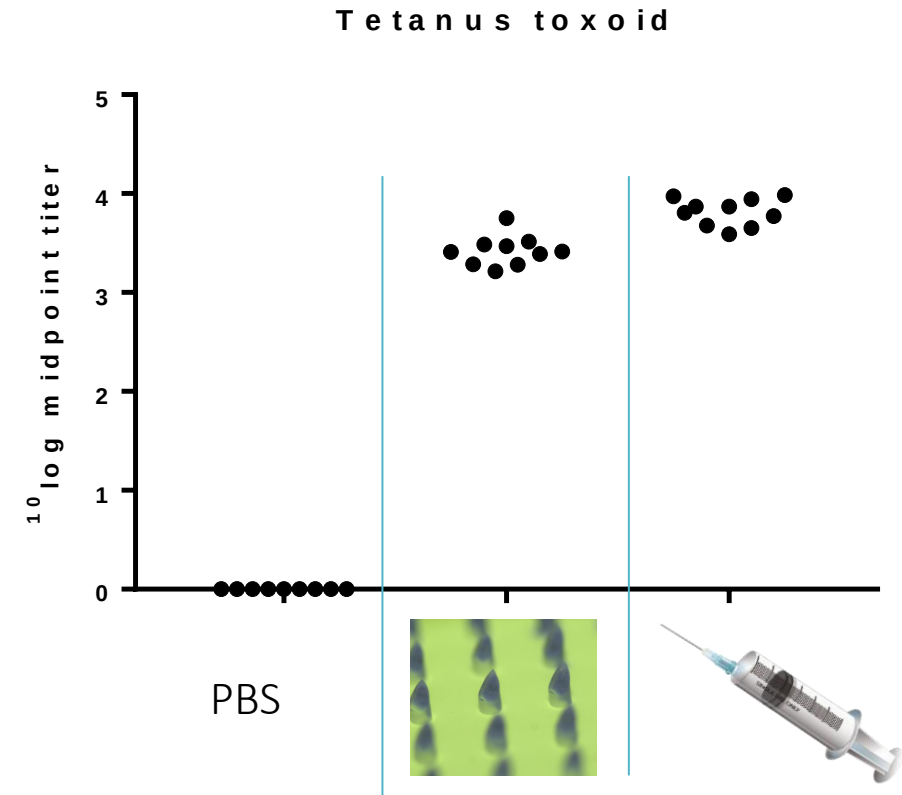
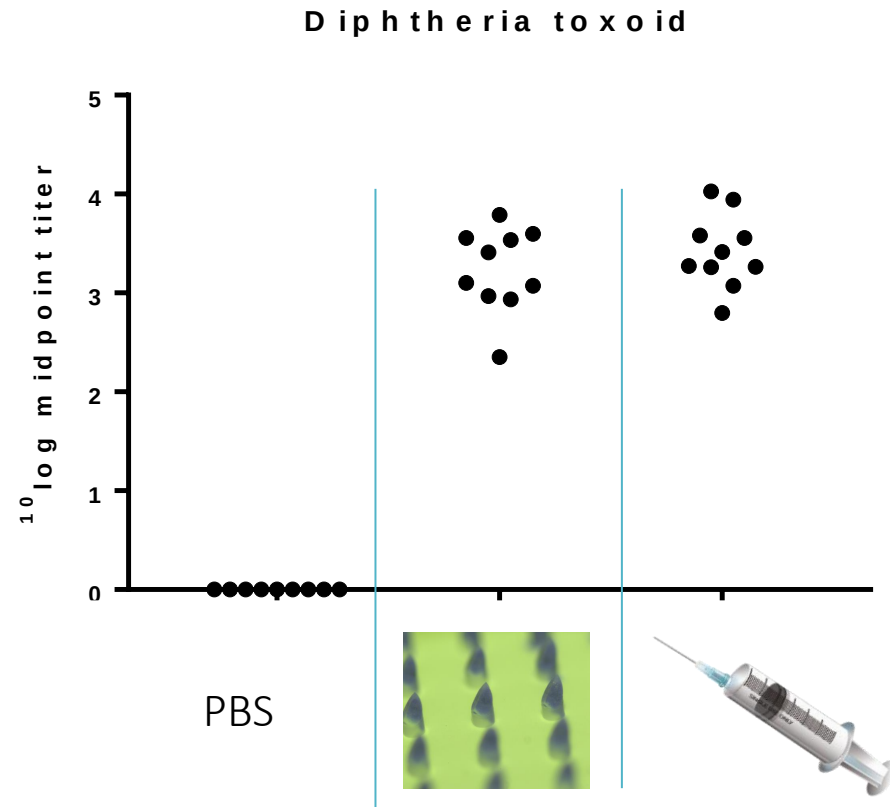
Conclusion: Successful method to only load
microneedle tips

Diphtheria- & tetanus toxoid vaccination

- **Antigen loaded microneedle tips:**
 - Diphtheria toxoid, 25% of human dose
 - Tetanus toxoid, 30% of human dose
- **Vaccinations:**
 - 10 mice per group (Balb/c), *3 immunizations*
 - npMNAs vs classical injection needle (S.C.)



Diphtheria- & tetanus toxoid vaccination



Diphtheria- & tetanus toxoid vaccination

Conclusions

- Antibody induction via npMNAs comparable to injection via classical needle

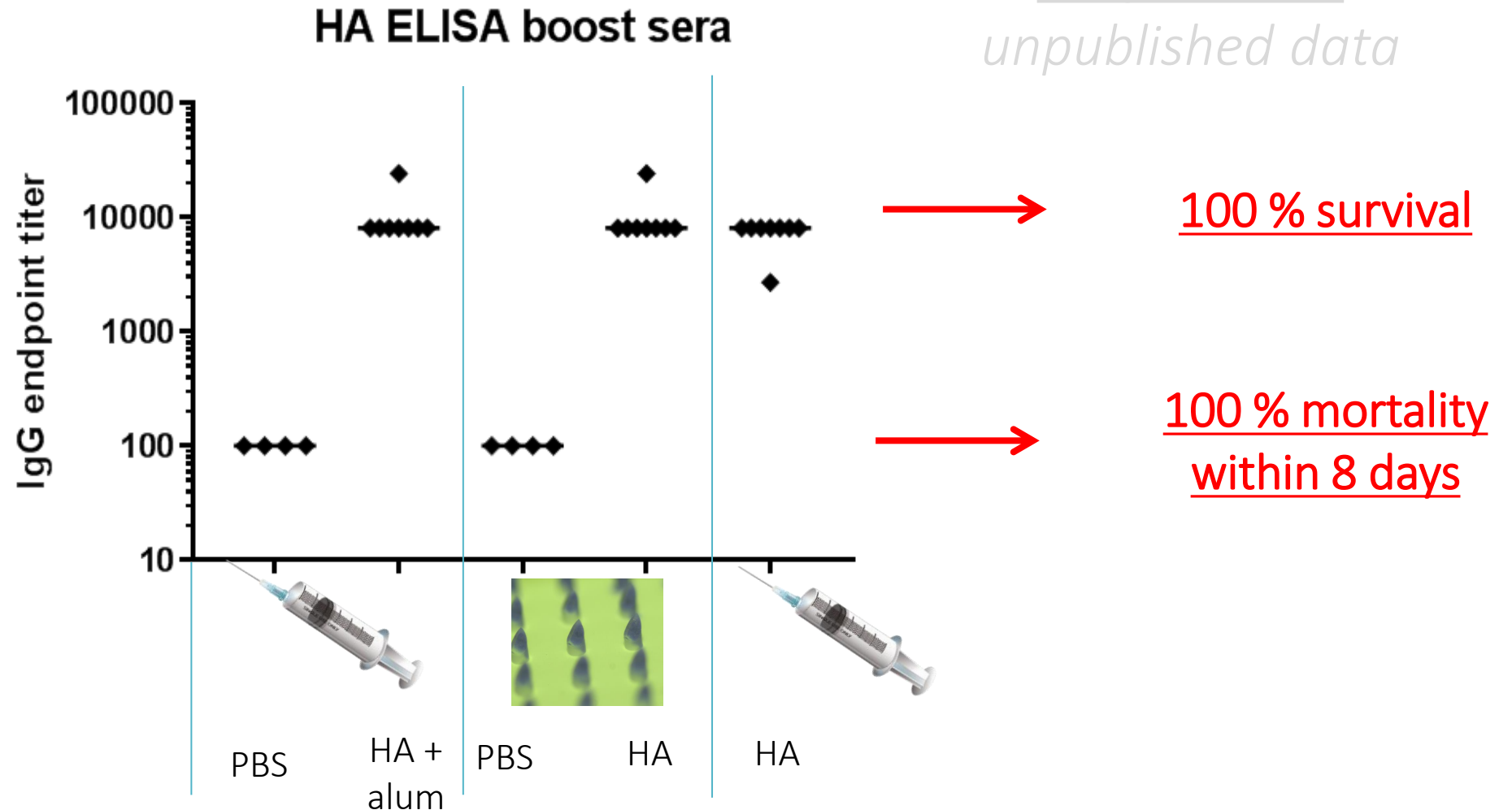
Influenza challenge study

- **Antigen loaded microneedle tips:**
 - Hemagglutinin (HA), 20% of human dose
- **Vaccinations:**
 - 8 mice per group (Balb/c), *2 immunizations*
 - npMNAs vs classical injection needle (I.M.)
 - Lethal dose influenza virus (20 LD₅₀)



Influenza challenge study

*Confidential:
unpublished data*



Influenza challenge study

Conclusions

- Antibody induction via npMNAs comparable to injection via classical needle
- 100% protection against lethal virus challenge using npMNAs



Intellectual Property

Invention “WO 2009113856 (A1) - INTEGRATED MICRONEEDLE ARRAY AND A METHOD FOR MANUFACTURING THEREOF”.

Following patents have been granted:

- United States: 8603384
- Japan: 5517956 & 5948308
- China: 200980117052.4 & 201310656222.4
- Europe: 2262722

One more patent application is pending at present.



Electronic applicator & npMNA-reservoir combination

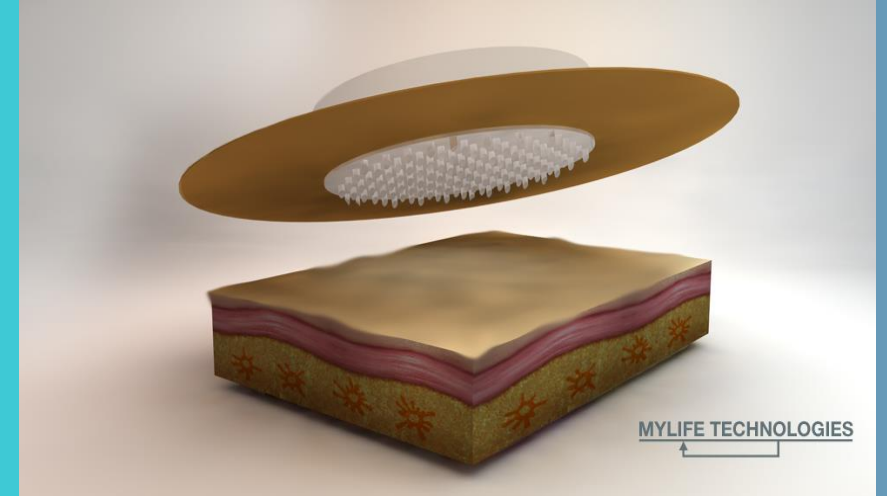
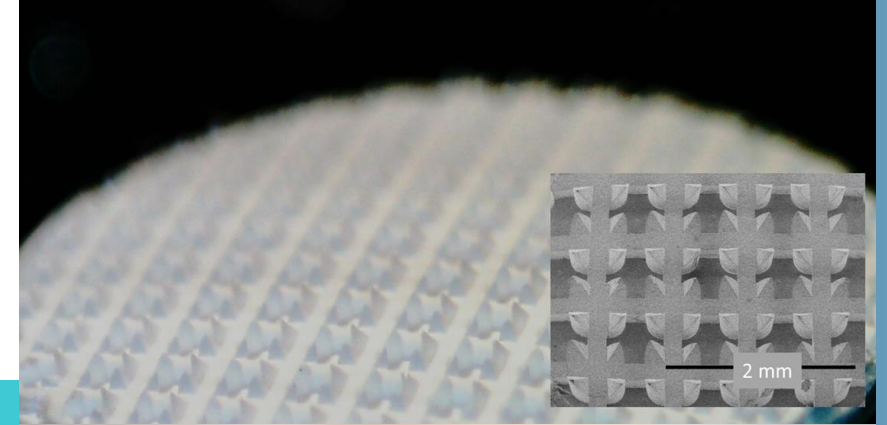


Contact us for more details!

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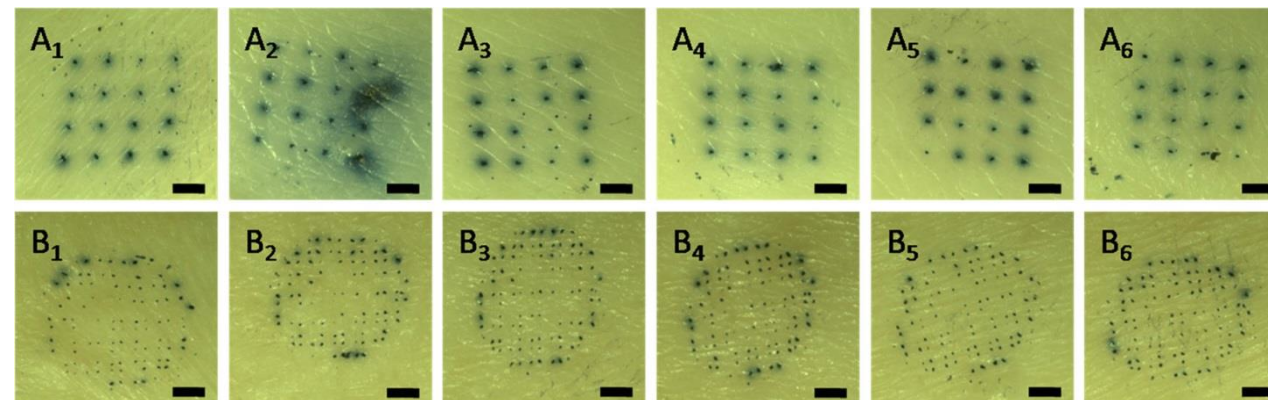
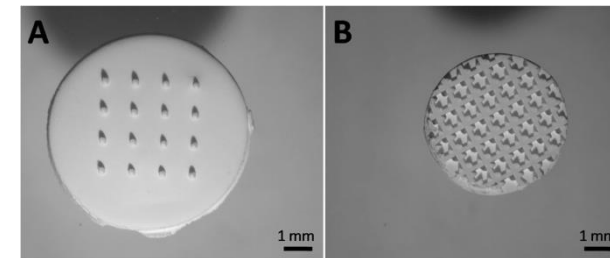
Scientific output (1)

Drug Deliv. and Transl. Res.
DOI 10.1007/s13346-015-0238-y

RESEARCH ARTICLE

Microneedle-based drug and vaccine delivery via nanoporous microneedle arrays

Koen van der Maaden¹ • Regina Luttge¹ •
Pieter Jan Vos¹ • Joke Bouwstra² • Gideon Kersten³ •
Ivo Ploemen³



Six subsequent penetrations of ex vivo human skin by a ceramic nanoporous microneedle array (1–6 respectively), that contained 16 microneedles with a length of 370 μm (a) or 126 microneedles with a length of 200 μm (b). The size bar represents 1 mm

Scientific output (2)



Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm



Pharmaceutical nanotechnology

Controlled release of a model vaccine by nanoporous ceramic microneedle arrays

Martine A. Boks^{a,d,1}, Wendy W.J. Unger^{a,1}, Steef Engels^a, Martino Ambrosini^{a,d}, Yvette van Kooyk^a, Regina Luttge^{b,c,d,*}

^aDepartment of Molecular Cell Biology and Immunology, VU University Medical Center, Amsterdam, The Netherlands

^bDepartment of Mechanical Engineering, Microsystems group and ICMS Institute for Complex Molecular Systems, Eindhoven University of Technology, The Netherlands

^cMESA+ Institute for Nanotechnology, University of Twente, The Netherlands

^dMyLife Technologies B.V., The Netherlands

Delivery method by nanoporous microneedles (npMNA)

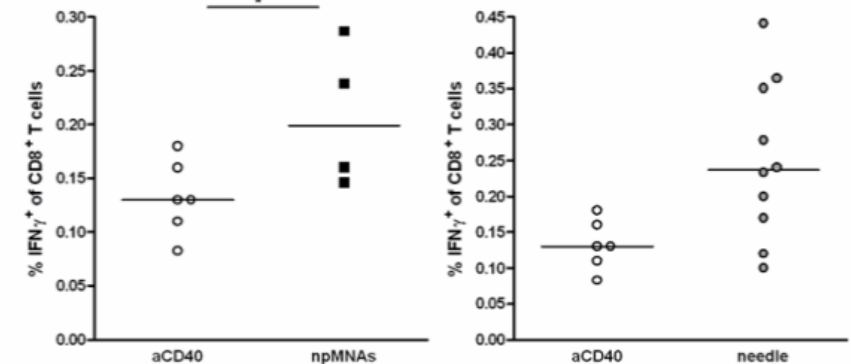
Delivery method by needle & syringe

Intradermal (i.d.)
DC targeting
region

DC

Skin

Cytokine-secreting CD8⁺ T cells



Scientific output (3)

Pharmaceutics **2015**, *7*, 503–522; doi:10.3390/pharmaceutics7040503

OPEN ACCESS

pharmaceutics

ISSN 1999-4923

www.mdpi.com/journal/pharmaceutics

Article

Insertion Process of Ceramic Nanoporous Microneedles by Means of a Novel Mechanical Applicator Design

Xavier H. M. Hartmann ^{1,†}, Peter van der Linde ^{2,3,†}, Erik F. G. A. Homburg ¹,
Lambert C. A. van Breemen ⁴, Arthur M. de Jong ⁵ and Regina Luttgé ^{1,2,3,*}

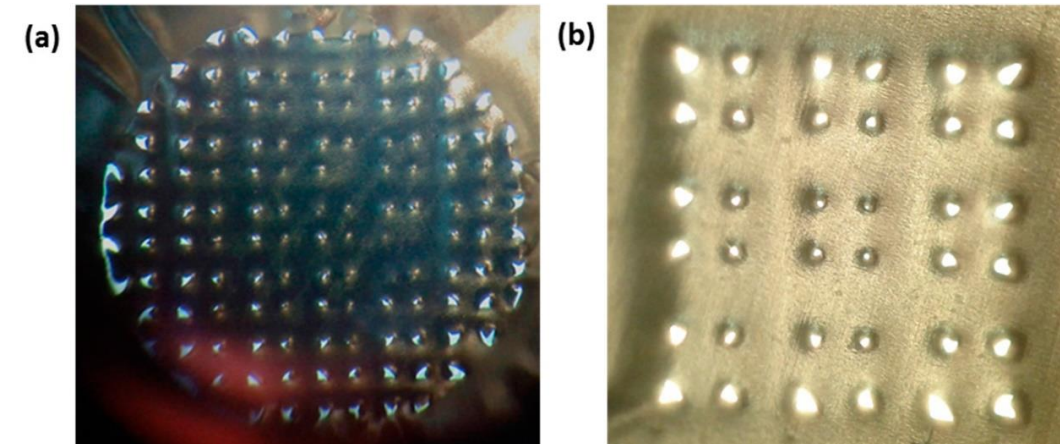
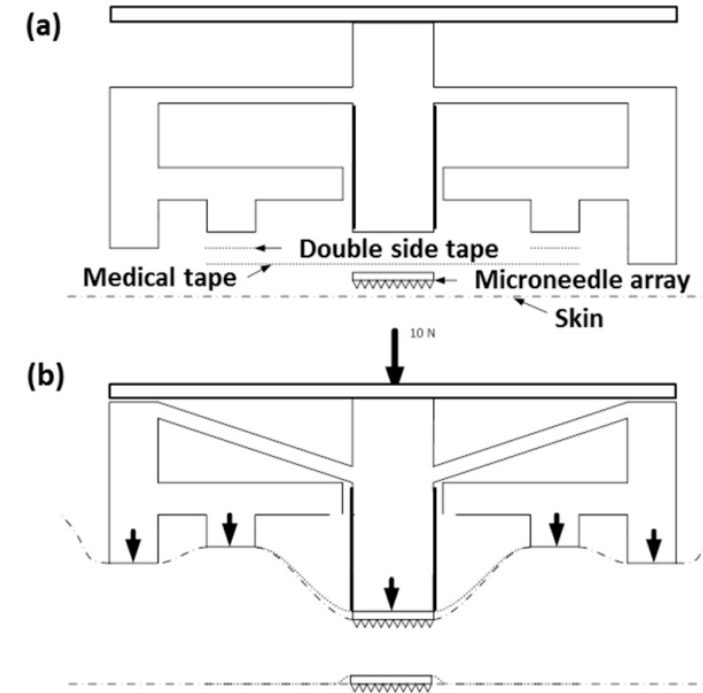
1 Microsystems Group, Materials Technology Institute (MaTe) and ICMS Institute for Complex Molecular Systems Eindhoven University of Technology, the Netherlands

2 MESA+ Institute for Nanotechnology, University of Twente, the Netherlands

3 MyLife Technologies B.V., 7522 NH Enschede, The Netherlands

4 Polymer Technology Group, Materials Technology Institute (MaTe), Eindhoven University of Technology, the Netherlands

5 Molecular Biosensing for Medical Diagnostics and ICMS Institute for Complex Molecular Systems, Eindhoven University of Technology, the Netherlands



Scientific output (4)

Front. Immunol. | doi: 10.3389/fimmu.2017.01789

Nanoporous Microneedle Arrays Effectively Induce Antibody Responses against Diphtheria and Tetanus Toxoid

Anne Marit de Groot¹, Anouk C. Platteel¹, Nico Kuijt², Peter J. van Kooten¹, Pieter Jan Vos², Alice J. Sijs¹ and Koen Van Der Maaden^{2*}

¹Utrecht University, Netherlands

²MyLife Technologies, Netherlands

