3D-printed Lattice Micro-Array Patches (L-MAPs) for Tunable and Versatile Intradermal Delivery

Netra Unni Rajesh

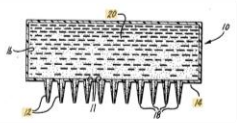
PhD Candidate, DeSimone Lab
Stanford University

CONTROLLED RELEASE SOCIETY
CRS 2024 Annual Meeting AND Exposition
JULY 8-12, 2024 • BOLOGNA, ITALY

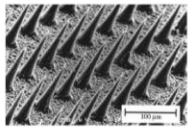
INTEGRATING
Delivery Science
ACROSS DISCIPLINES

Microarray Patches (MAPs)

1970s



Gerstel, Place, US Patent, *Drug Delivery Device*, 1976]

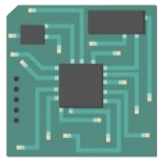


Henry et al. (1998) 'Microfabcricated Microneedles.. ", *Journal of Pharm. Sci.*

GEN 1.0

microfab of uniform geometries

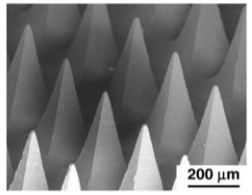
Rajesh et al. (2022) *JACS Au*



Microfabrication

Silicon etching

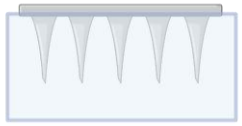
1990s



Yang et al. (2020) "Smartphone-powered iontophoresis-microneedle array...", *Microsystems & Nanoengineering*

GEN 2.0

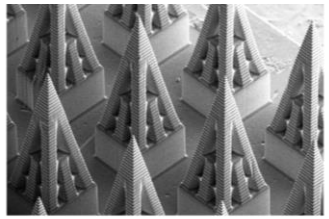
molding with limited materials



Molding

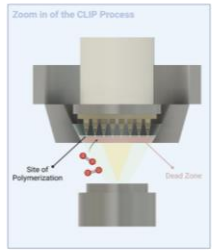
Lithography

2020s



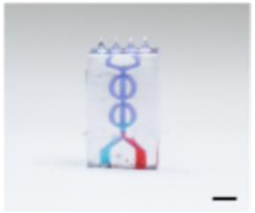
GEN 3.0

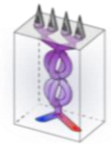
complex geometries with direct fab



CLIP/ hi-res CLIP

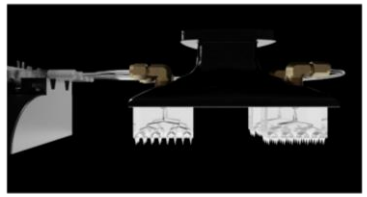
Additive Manufacturing





GEN 4.0

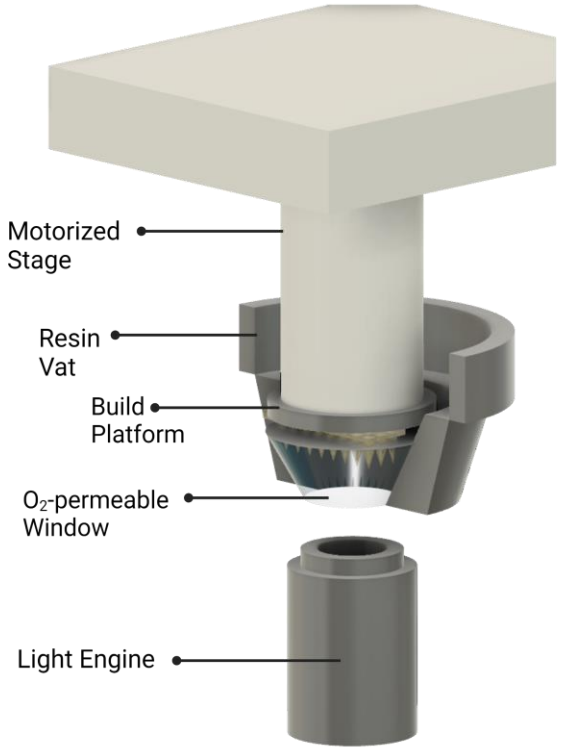
MAPs with backing for added functionality

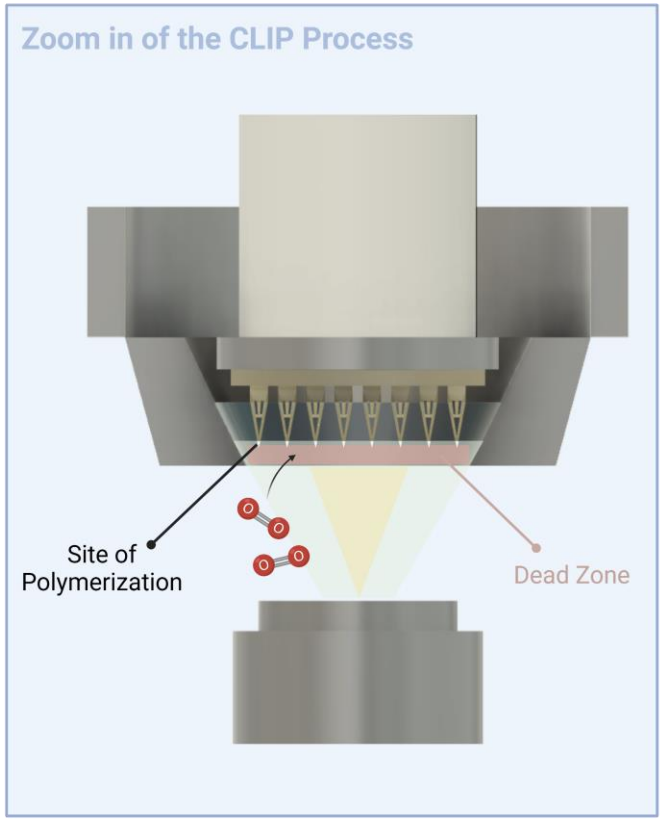


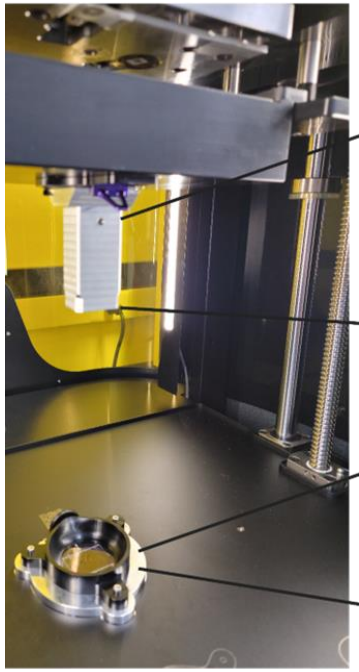
injection CLIP

AM of negative spaces and features

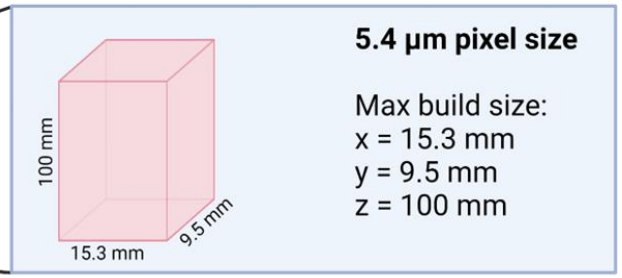
Continuous Liquid Interface Production





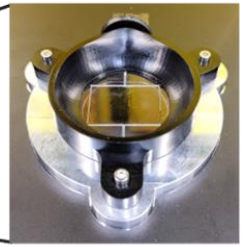


Scalable printing at a high resolution



5.4 µm pixel size

Max build size:
x = 15.3 mm
y = 9.5 mm
z = 100 mm



Custom vat design

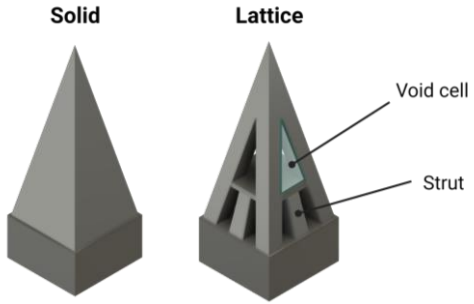
Channels to improve oxygen delivery

- reduce suction forces
- improve overall quality of the print

Rajesh et al. (2024) *In Review*

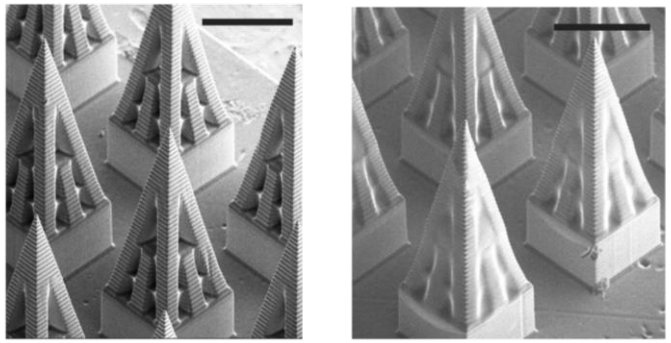
Lattice Microarray Patches (L-MAPs)

- **Biocompatible resin:**
  - KeySplint hard (used in FDA-approved dental products)



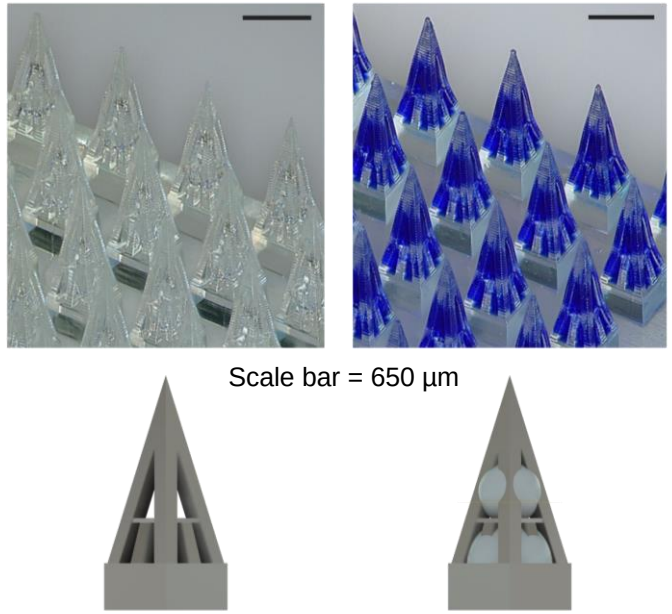
- **A platform capable of versatile cargo delivery:**

Solid-State Film Coating



Scale bar = 500 µm

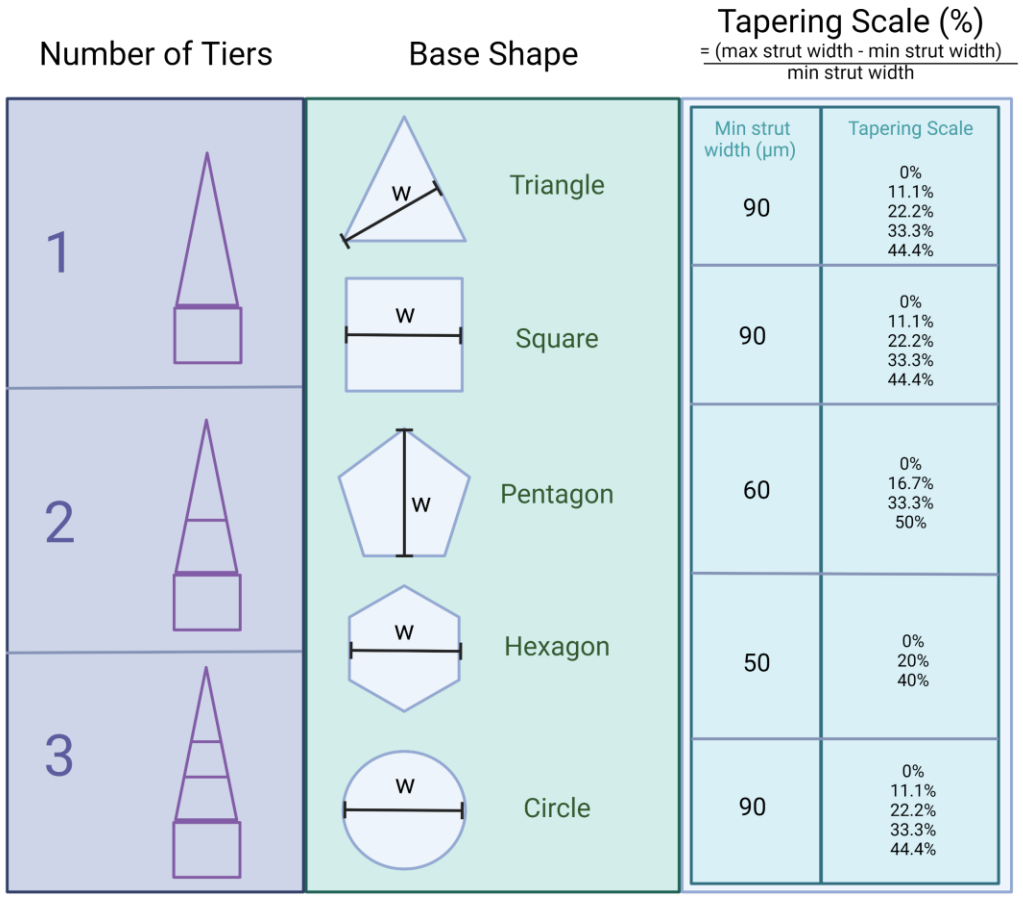
Liquid Droplet Coating

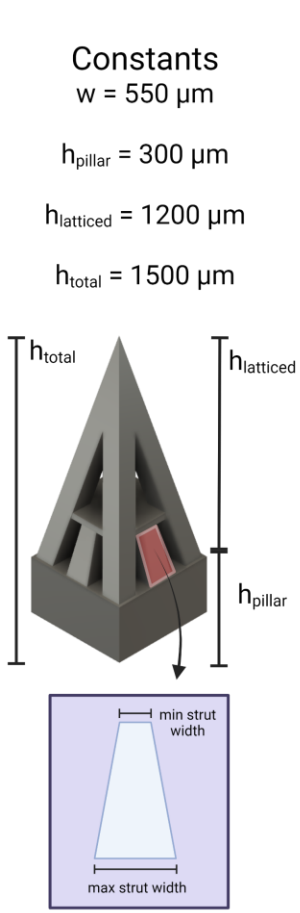


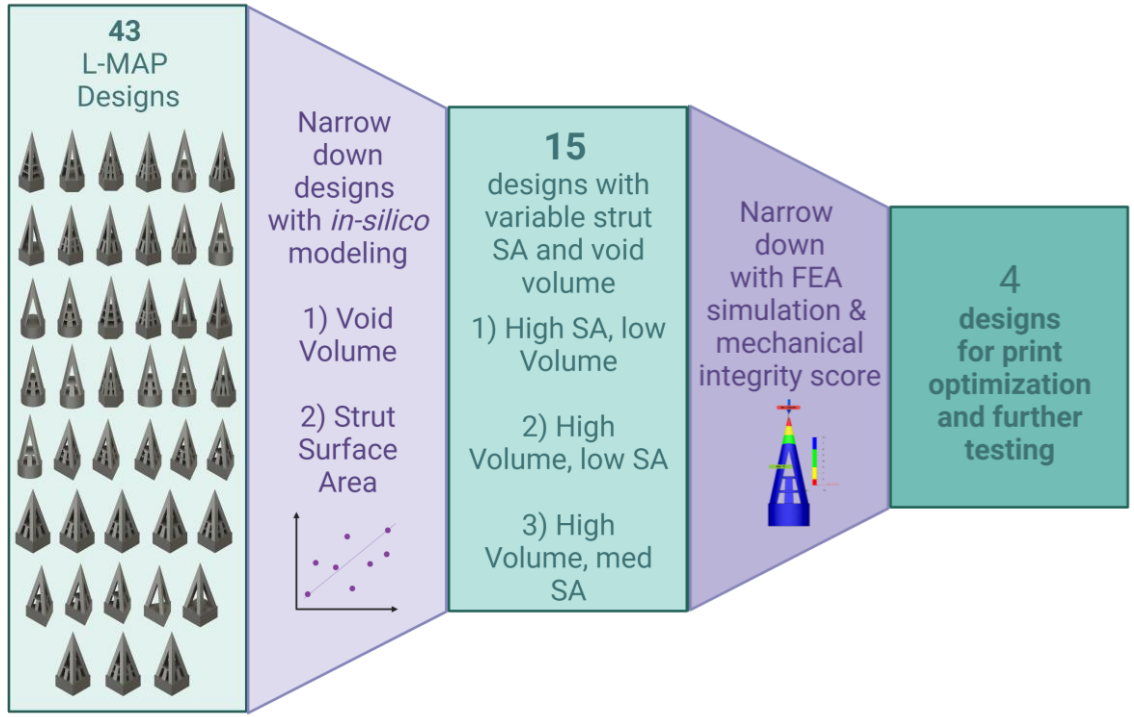
Scale bar = 650 µm

Rajesh et al. (2024) *In Review*

Designing an L-MAP Library

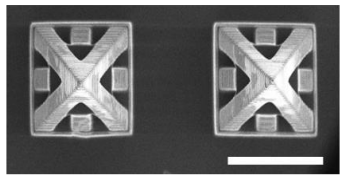
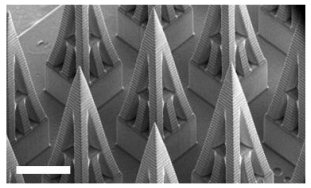
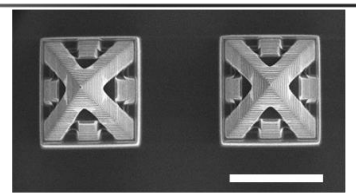
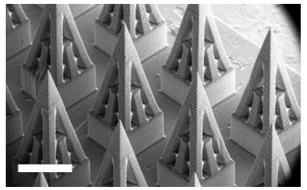
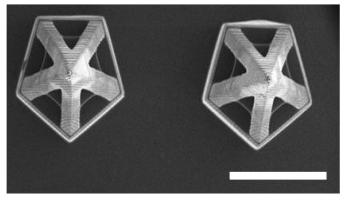
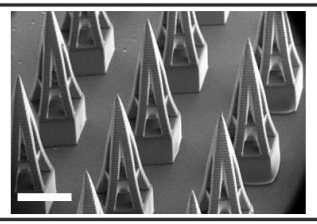
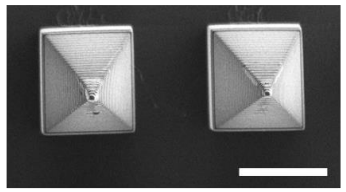
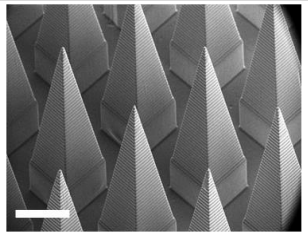






Rajesh et al. (2024) *In Review*

Optimal L-MAP Geometries

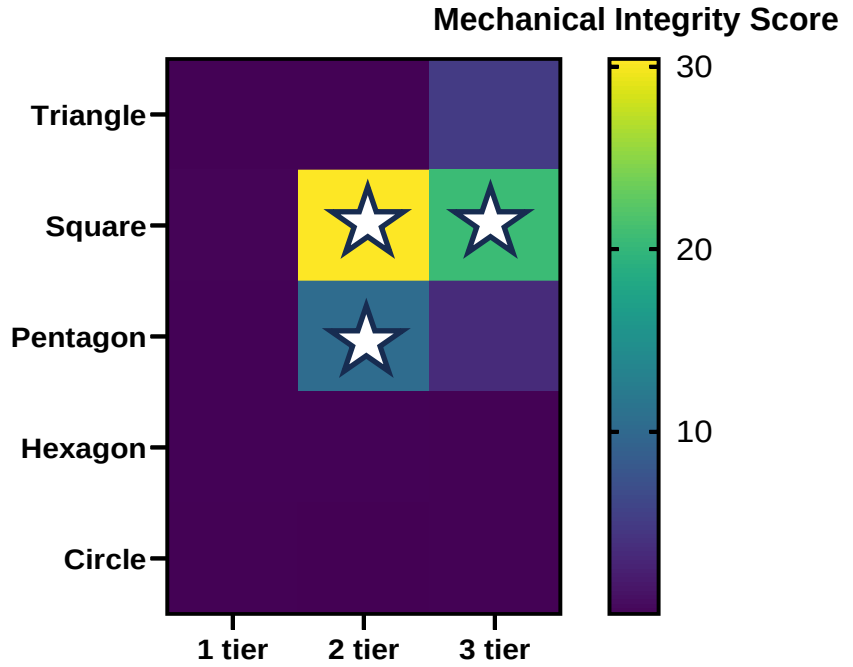
Needle Design	Top View	Side View
Square 2 Tier		
Square 3 Tier		
Pentagon 2 Tier		
Solid		

** Scale Bars = 500 µm

Rajesh et al. (2024) *In Review*

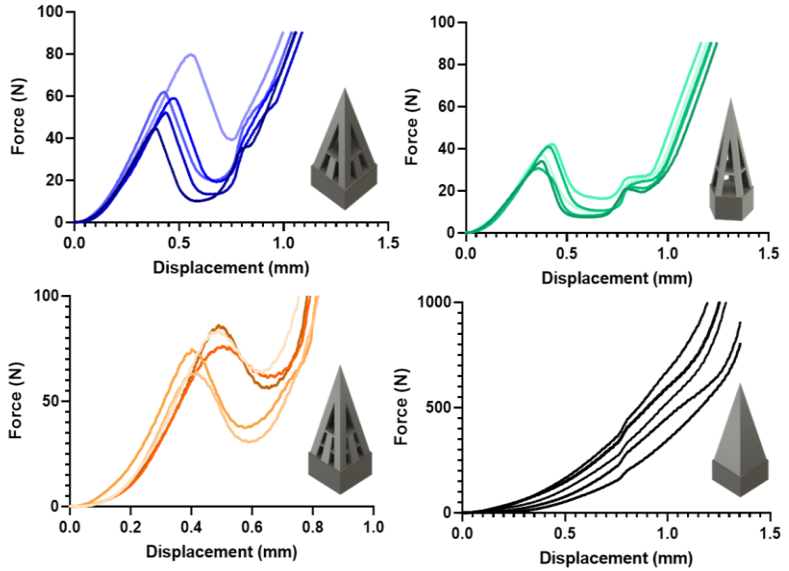
These geometries have:

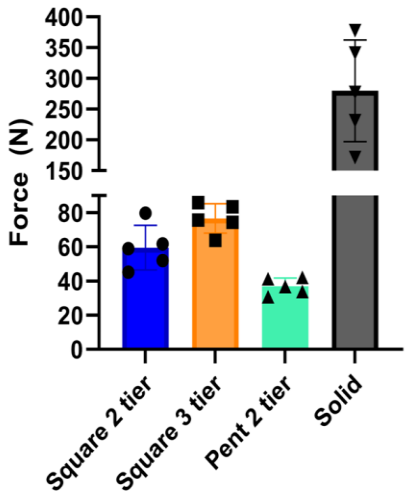
- The highest mechanical integrity (*in silico* modeling)
- Diverse SA : Volume for differing release kinetics

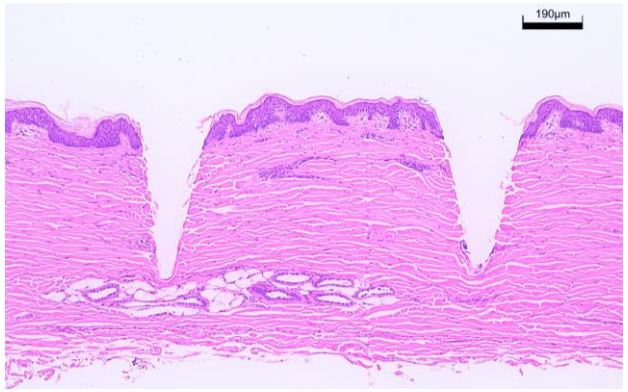


Mechanical Properties of L-MAPs

L-MAPs are strong enough to pierce skin:

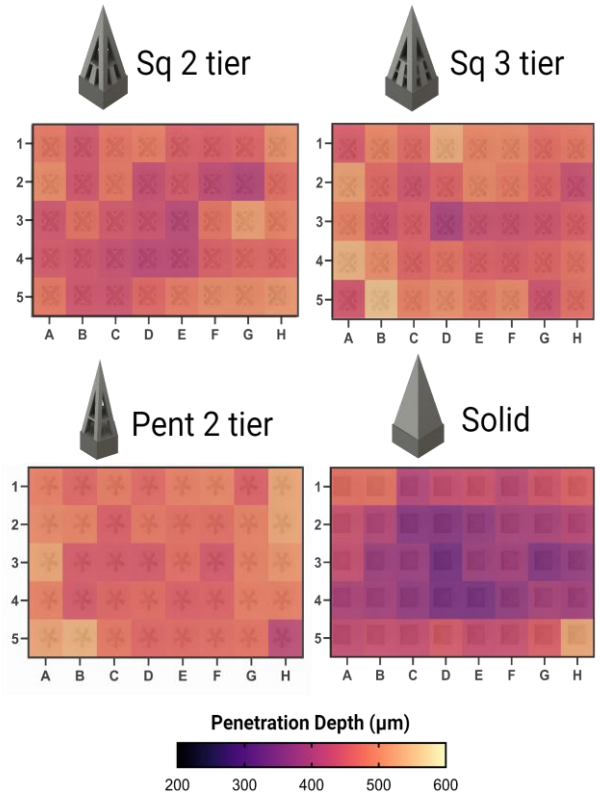


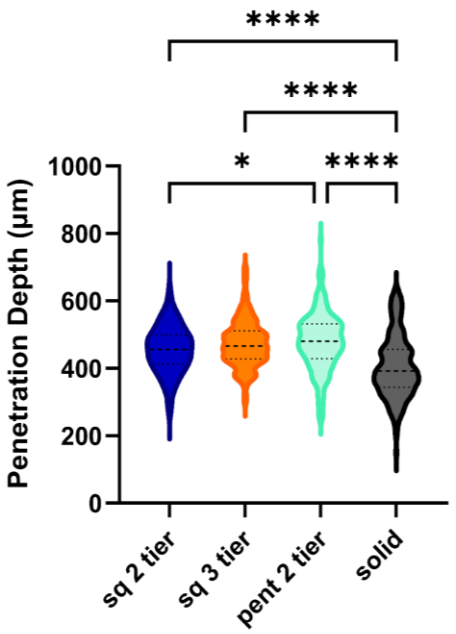




Sq 2 Tier L-MAP

L-MAPs have more uniform penetration compared to solid MAPs

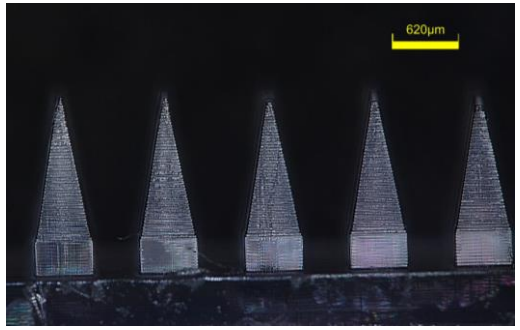




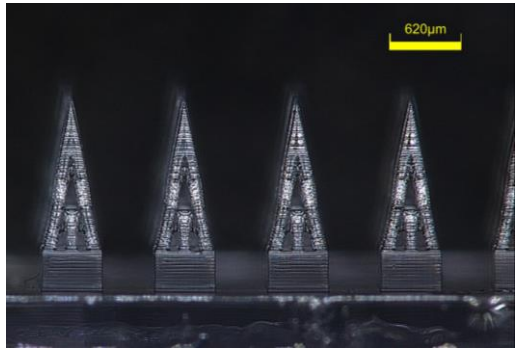
N = 5 patches

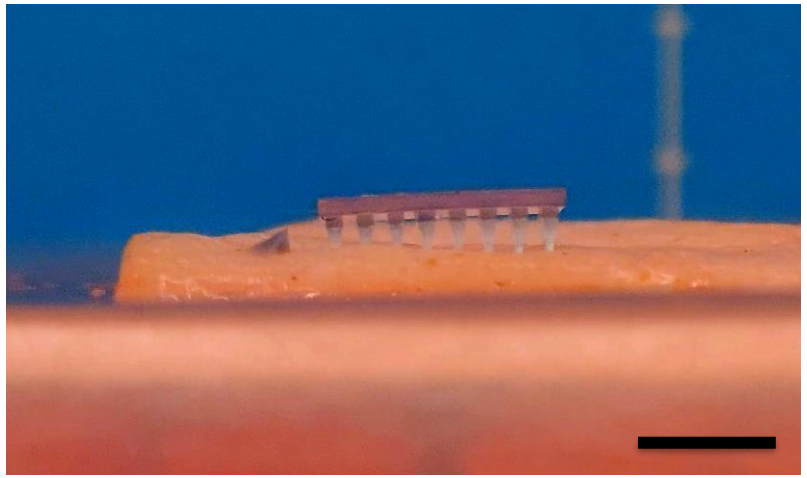
L-MAP penetration and adhesion in skin

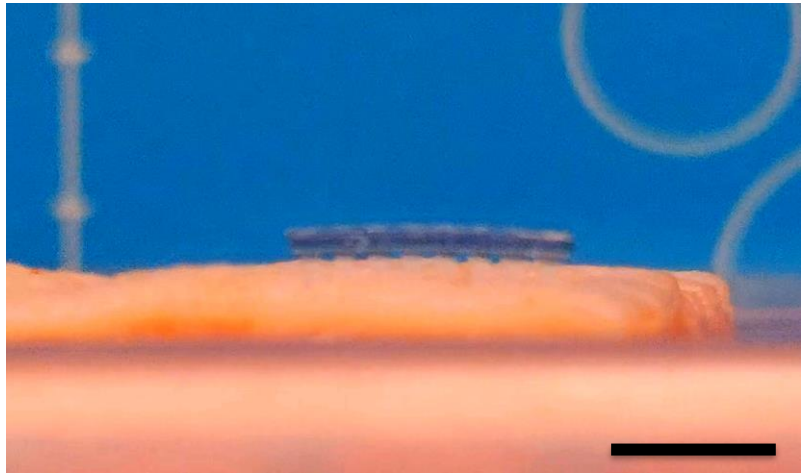
Solid MAP



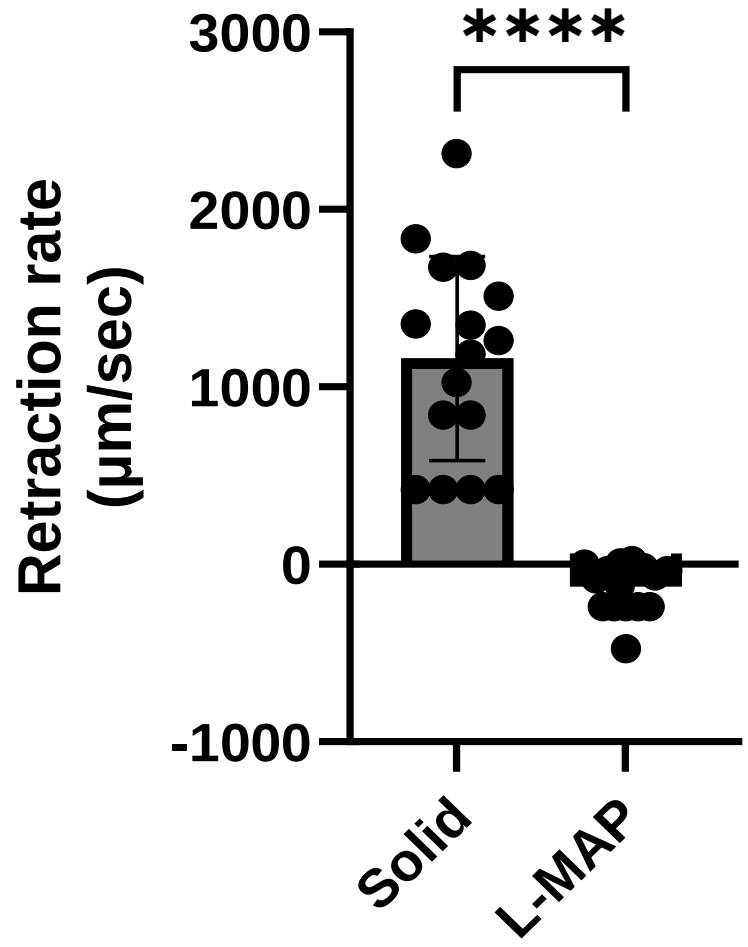
L-MAP







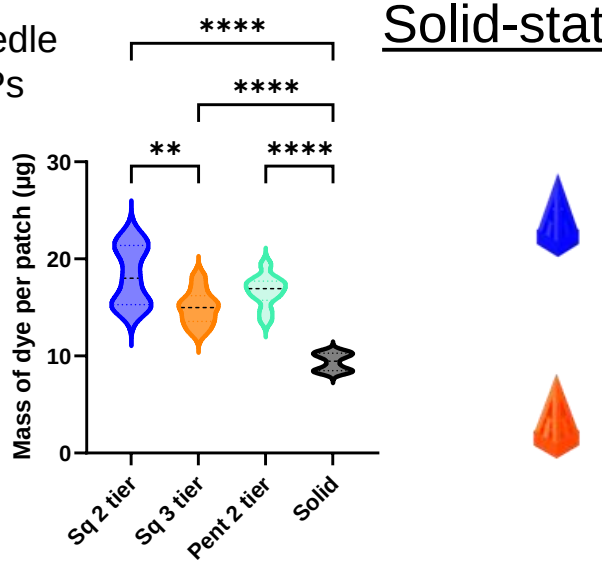
Scale bars = 5 mm

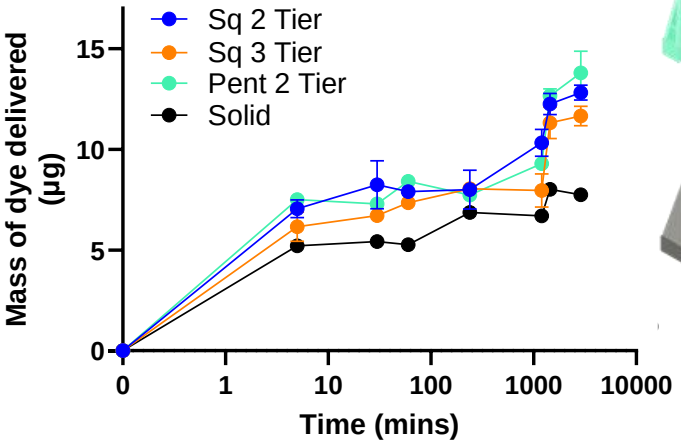


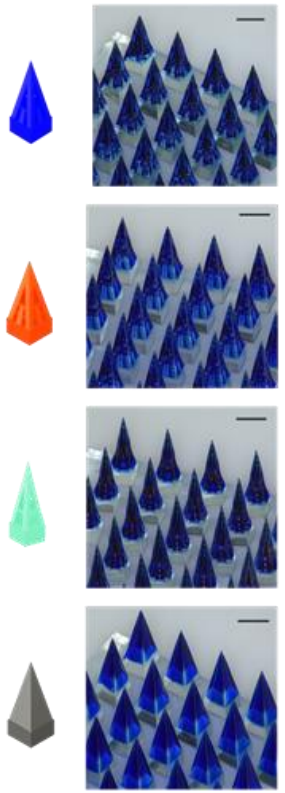
Solid and Liquid State Small Molecule Delivery

40-needle L-MAPs

Solid-state







Mass delivered at t = 5 mins

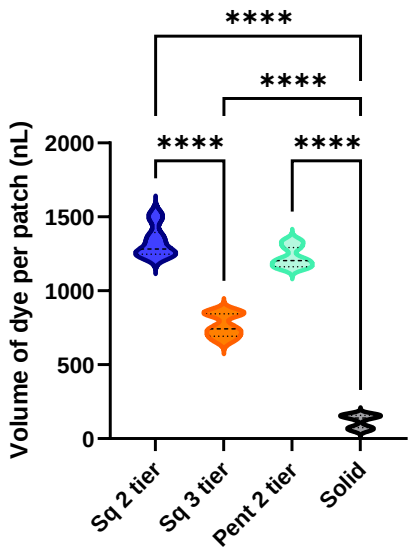
7.1 µg

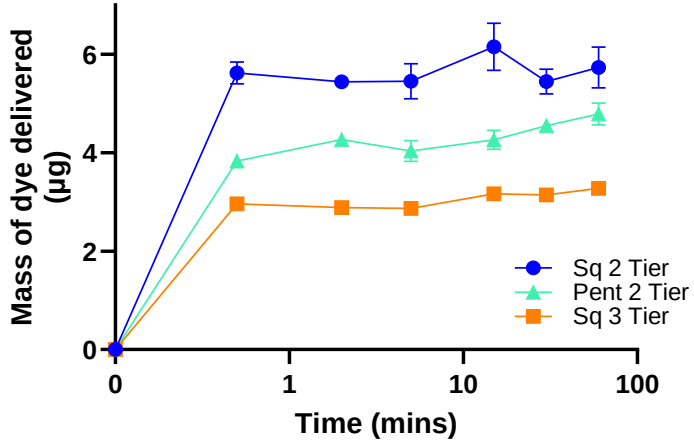
6.2 µg

7.5 µg

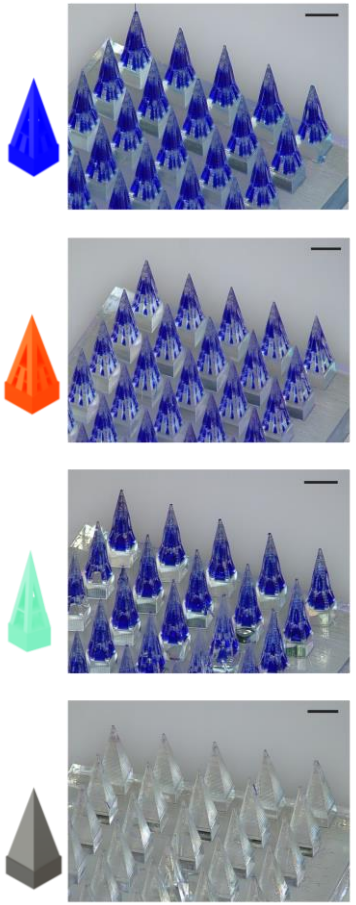
5.2 µg

Liquid-state





Mass delivered at t = 5 mins



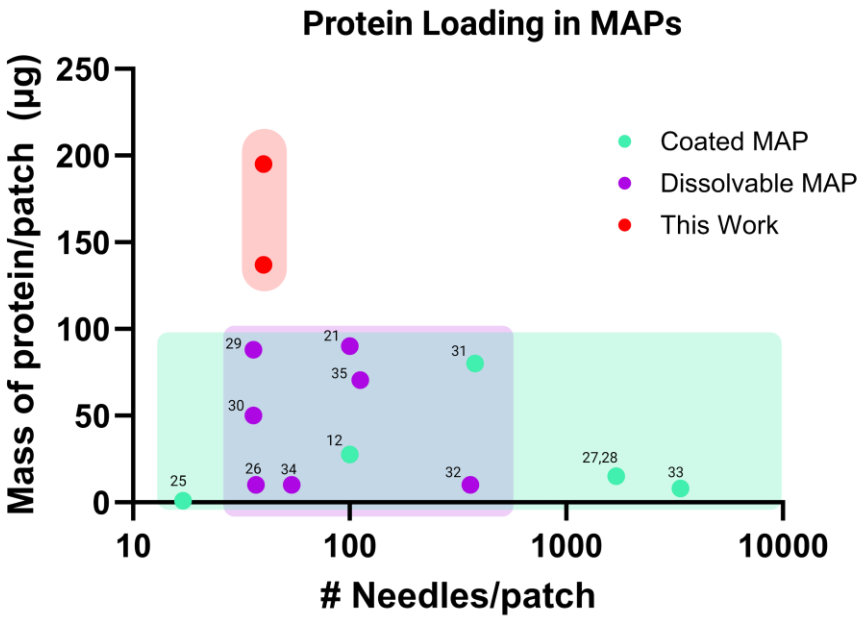
5.6 µg

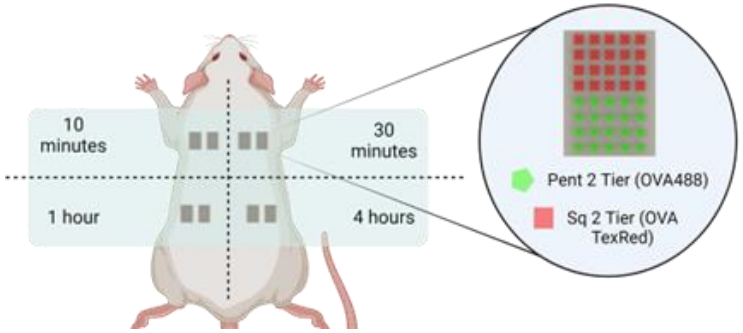
3.8 µg

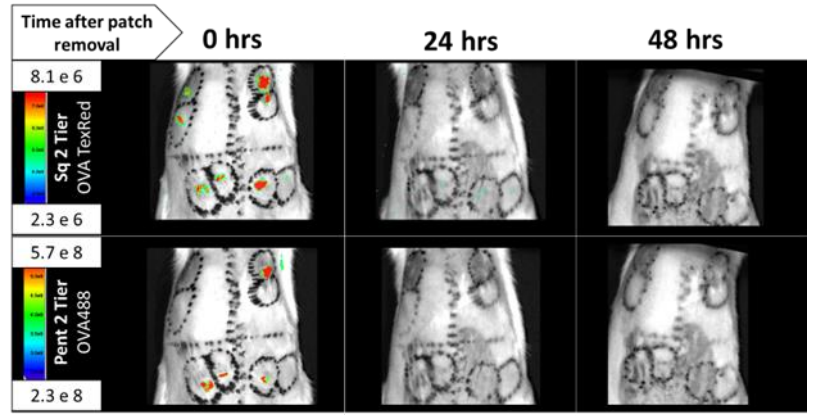
3.0 µg

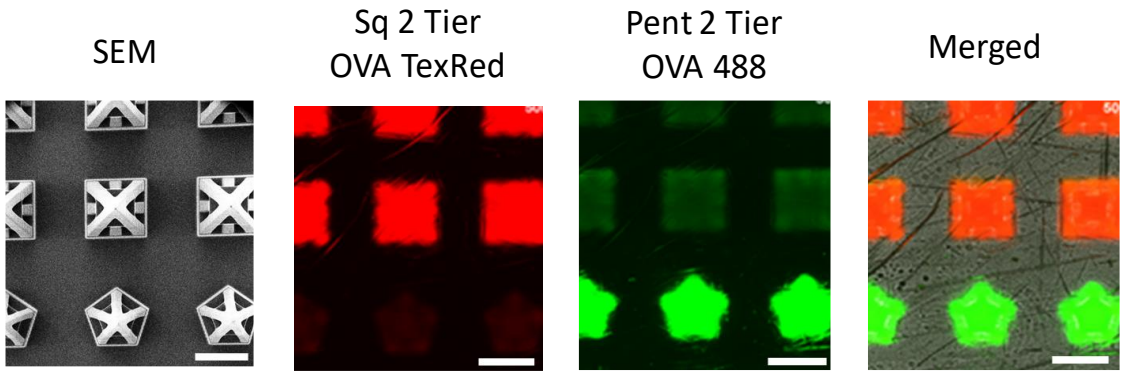
** Scale bars = 620 µm

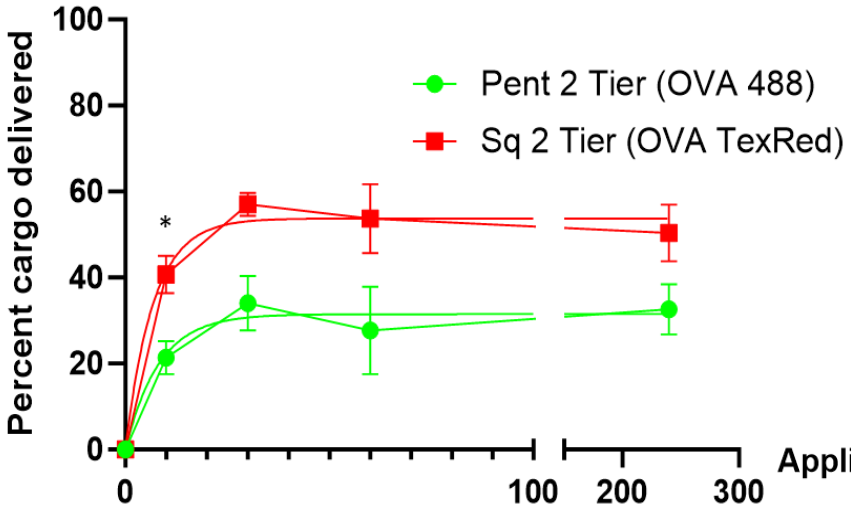
Hybrid L-MAP for Solid-state OVA Protein Delivery









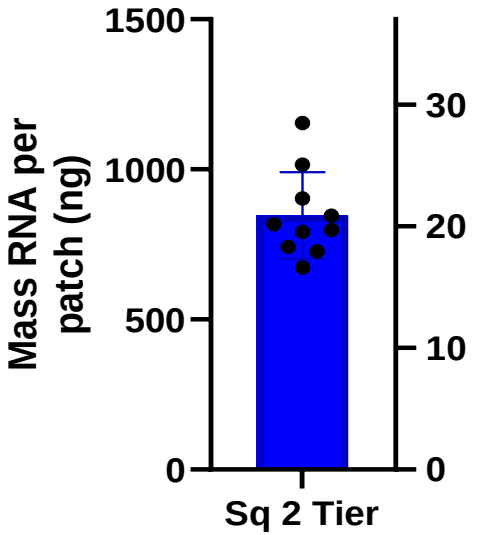


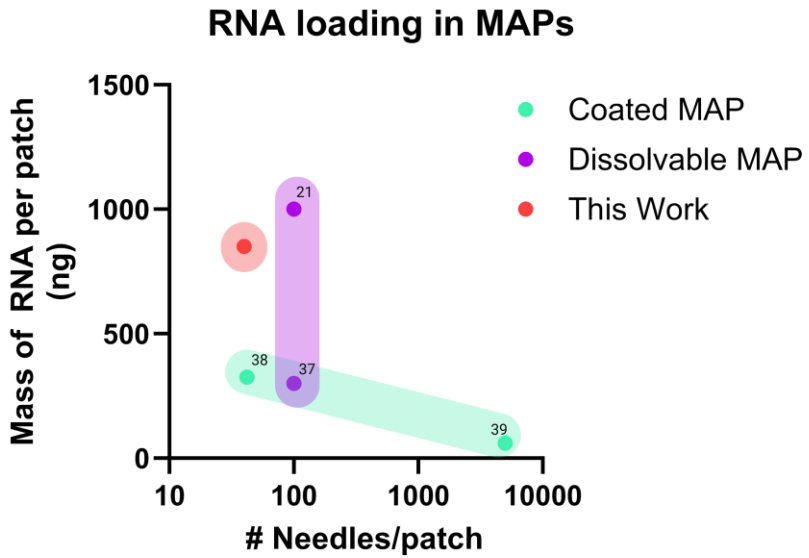
Multiple release profiles can be achieved on a single patch

3 wt% methylcellulose + 30 wt% sucrose + 0.4 w/v% OVA

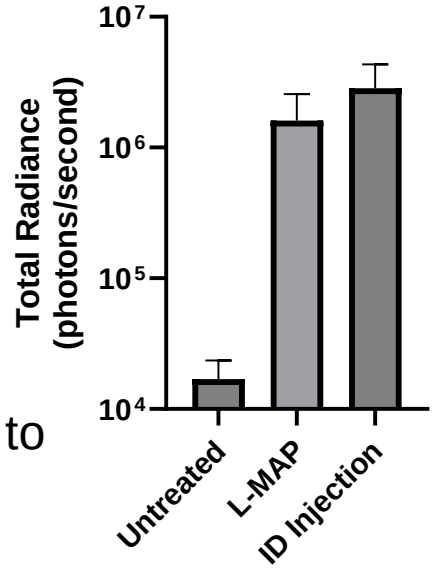
N=3 rats, N = 2 patches per condition | * = p < 0.1 ANOVA

L-MAPs for Liquid-state RNA Delivery

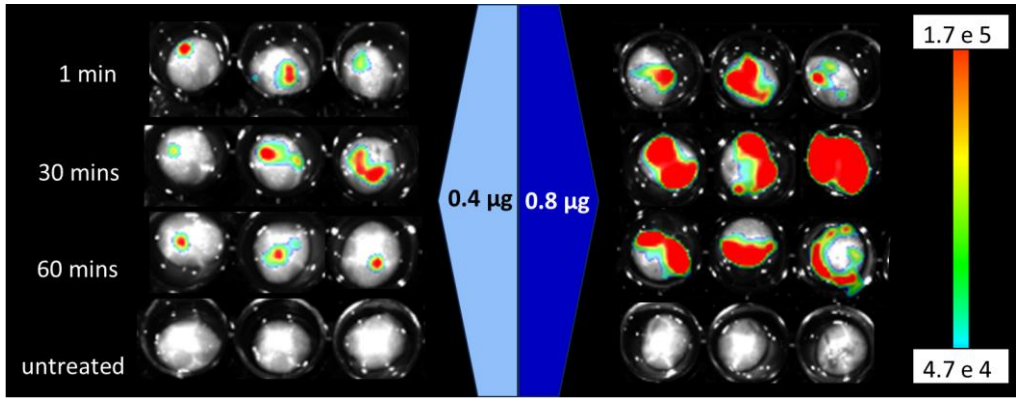


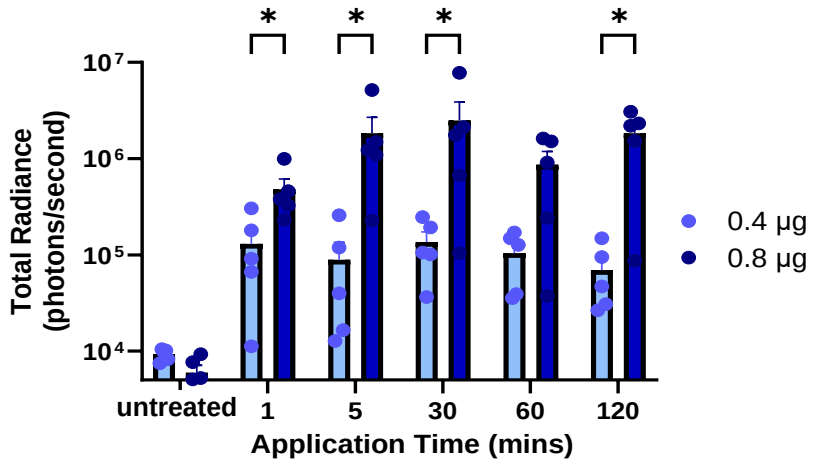


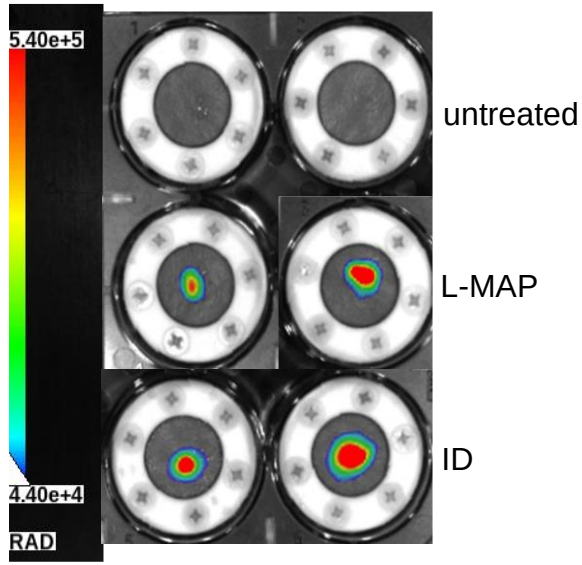
L-MAPs can transfect tensioned human skin to a similar level of magnitude as an ID injection



L-MAPs can deliver FLuc mRNA LNPs in 1 min (live porcine skin)



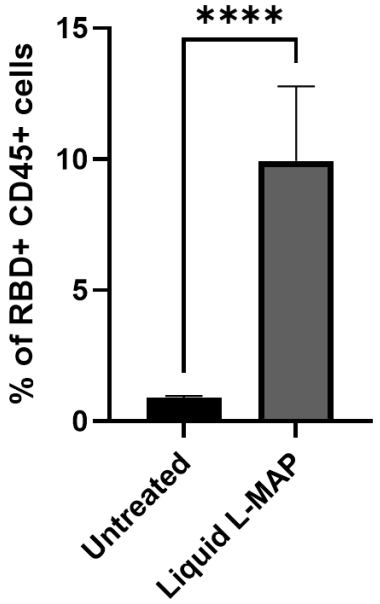




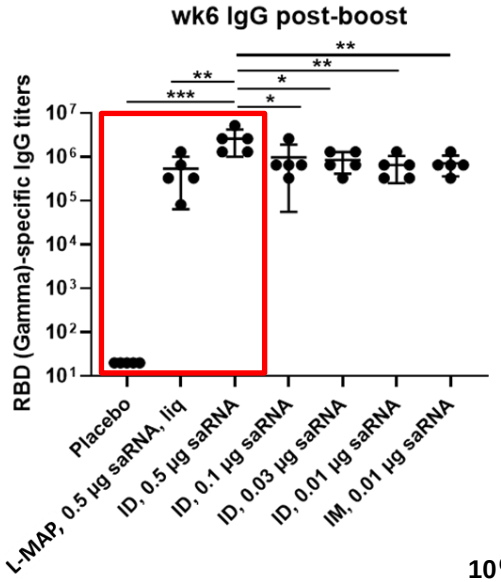
Golombek et al. (2018) *Mol. Ther. Nuc. Acids*

L-MAPs – A Platform for Transdermal Vaccination

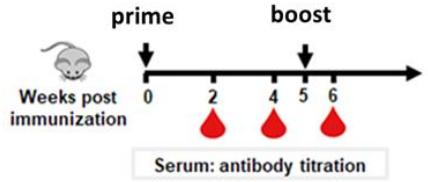
SARS-CoV-2 RBD mRNA/saRNA LNPs



RBD mRNA in Genvoy LNPs delivered via L-MAP transfects CD45+ cells in live porcine skin

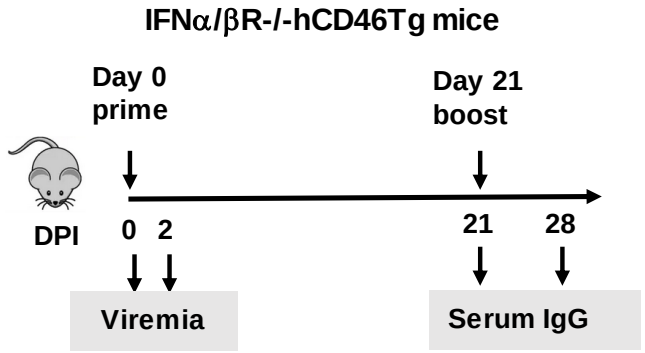


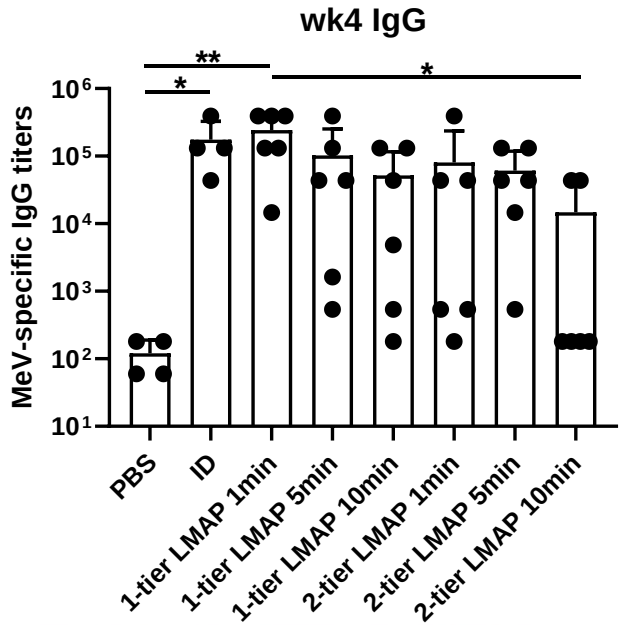
L-MAPs generate robust RBD-specific IgG titers with RBD saRNA delivery in BALB/C mice



Measles Live Attenuated Virus

L-MAPs can elicit Measles-specific antibody titers with a 1-minute application; however, virus stability in the MAP needs to be improved



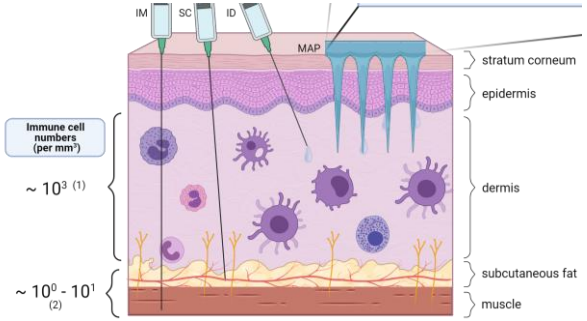


CONFIDENTIAL DATA

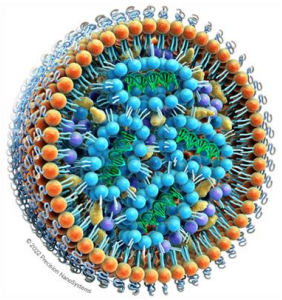
Summary & Future Directions

- **3D-printing** enables generation of unique MAP geometries such as the L-MAP
- **L-MAPs** are capable of **increased cargo loading** and **improved skin penetration**
- L-MAPs are a platform for **solid-state AND liquid-state** cargo delivery of:
    1. Small molecules
    2. Proteins
    3. Nucleic acids
- Cargo **release kinetics** can be **tuned by** altering **L-MAP geometry** and **excipient formulation**
- **Modular L-MAPs** can be made for multi-cargo delivery, with different release profiles on a single patch

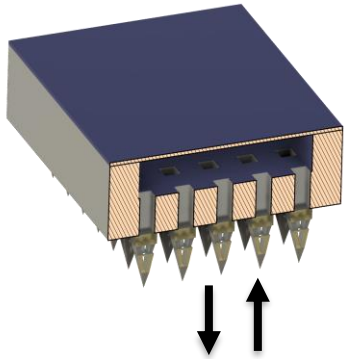
Development of this technology sets the stage for:



Transdermal vaccination strategies



Development of novel carriers for intradermal delivery



A platform for integrating delivery and sampling

Acknowledgements

Joseph DeSimone
Gunilla Jacobson
Shaomin Tian
Jillian Perry
Andy Hung
Roger Wise
Maria T. Dulay
Luna Hwang
Max Saccone
Rosa A. Silva
Ian Coates
Madison Driskill
Dan Ilyin
Yue Xu

All members of the DeSimone Lab!

SCI3 Core
SNF and SNSF
Flow Cytometry Core
Additive Manufacturing Facility (AMPF)

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

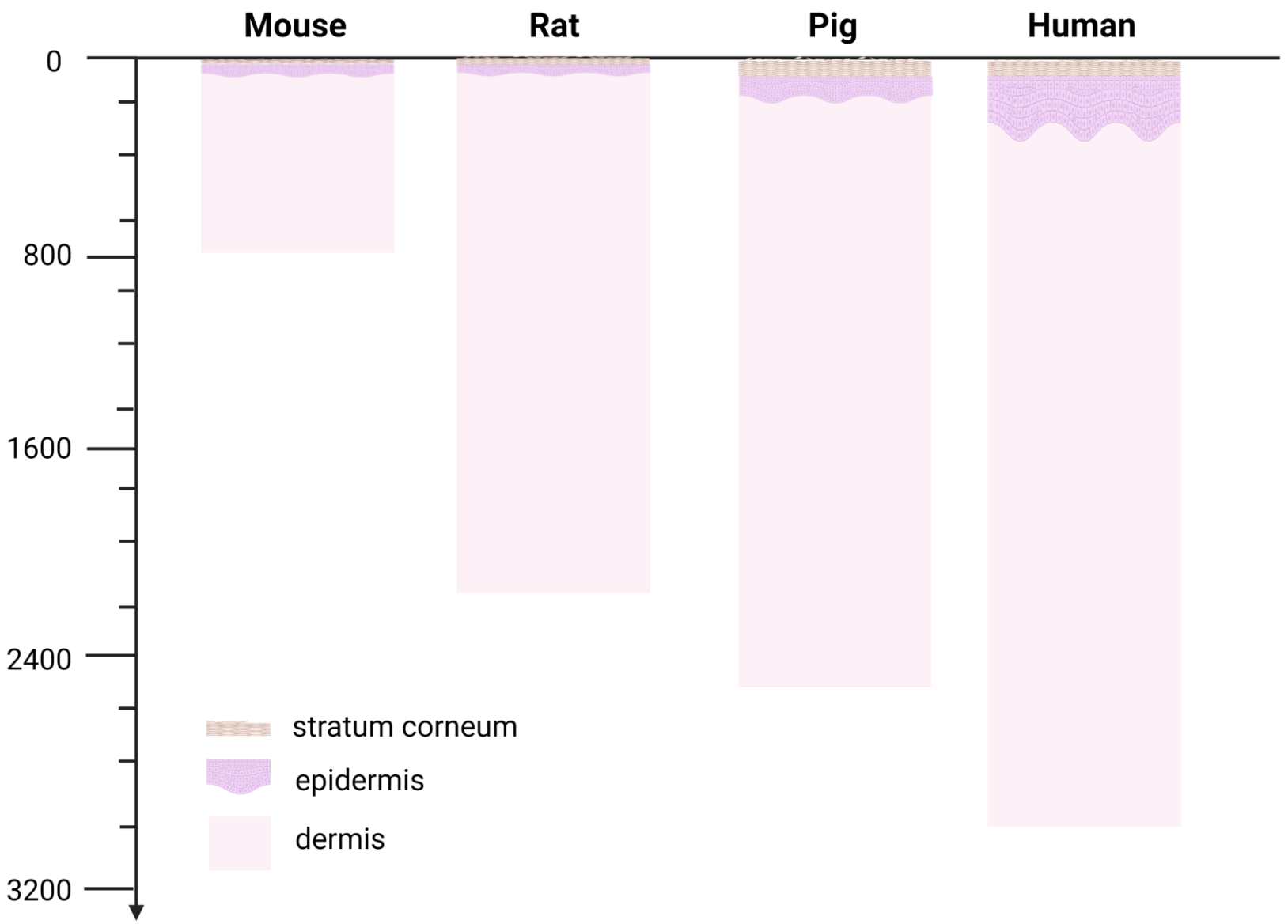
Knight-Hennessy Scholars
Stanford University

wellcome leap

BILL & MELINDA GATES foundation

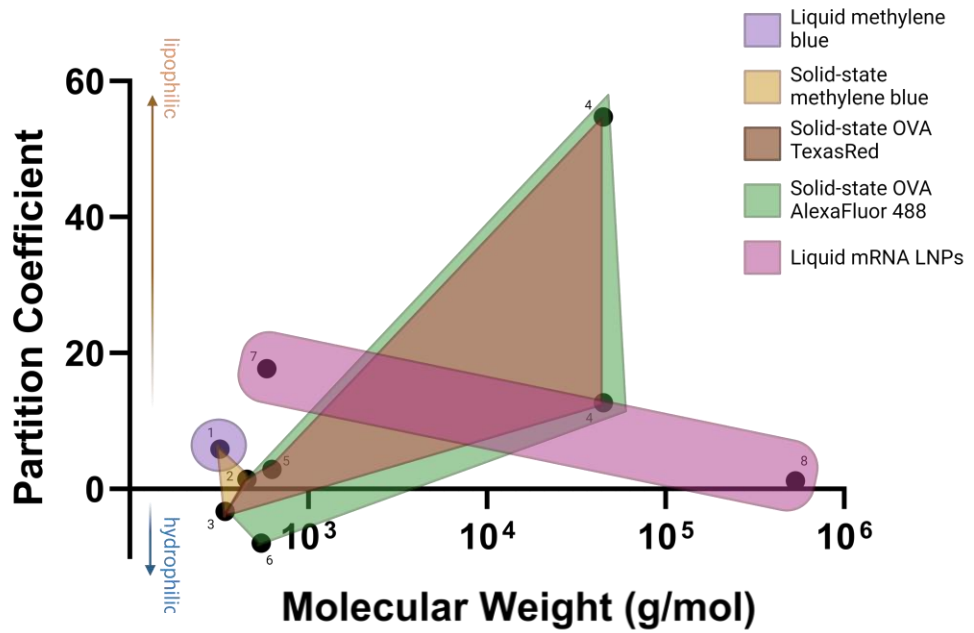
Stanford | Bioengineering
Schools of Engineering & Medicine

Appendix 1

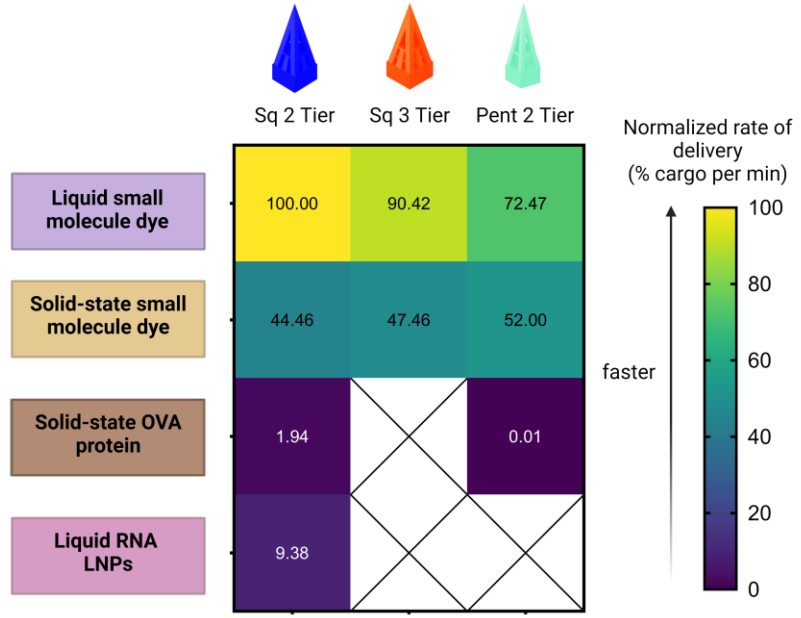

Mouse
Rat
Pig
Human
0
800
1600
2400
3200
stratum corneum
epidermis
dermis

Appendix 2

a



b



	Cargo Component	Molecular Weight	Partition coefficient
1	Methylene Blue Dye	319.85 g/mol [1]	5.85 (hydrophobic) [2]
2	Methylcellulose	454.5 g/mol [3]	1.4 (hydrophobic) [4]
3	Sucrose	342.30 g/mol [5]	-3.3 (hydrophilic) [6]
4	OVA	45000 g/mol [7]	OVA: 12.67 – 54.74 [8]
5	Texas Red Dye	625.2 g/mol [9]	2.87 [10]
6	AlexaFluor 488 Dye	546.4 g/mol [11]	-8 [10]
7	D-Lin MC3 Lipid Mix	586.84 g/mol [12]	17.687 [13]
8	RNA	533,000 g/mol [14]	1.2 [15]

c