Enhanced Pathway beyond skin with micro needles for Medical cares

Biomolecular Needling System for Medicals

Painless Transdermal Drug Delivery & Self-testing Diagnostic Bio-sensors

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Director of LIMMS KIKO (Integrated Research Systems)
Director of CREMeB (Center for Research on Engineering in Medicine & Biology)

Taking home Messages

Micro Needle array patch

What is **MAP**?

MAP- Bio Dissolvable Polymer

Where is MAP in Medicals

1. Drug Delivery for Cure & Medical Treatment

What is better for your Drug Delivery system

患者負担大
Large patient burden

Hypodermic Injection

Oral Inoculation

患者負担小
Small patient burden

Drug Patch

ointment

Today, Topic “MAP”

What is Micro needles Array Patch?

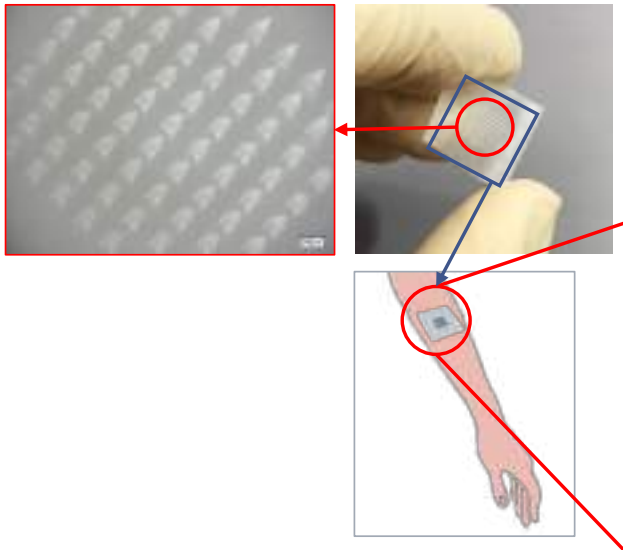
Microneedle Array Patch

Microneedles (MNs), MN array

micrometer sized needles made of various biocompatible materials.

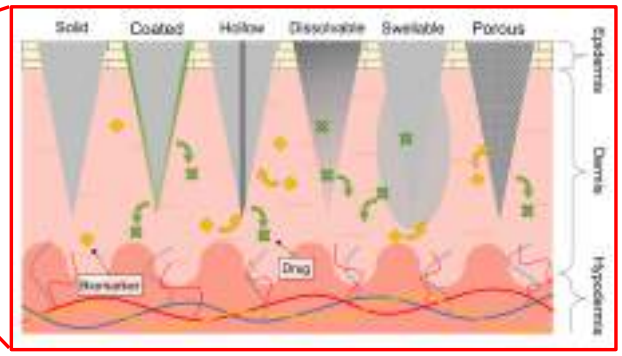
- can create the pathways into epidermis or dermis layers to transport drug molecules.
- minimally invasive, no medical professionals, convenient in storage as well as logistics

Representative MN array patch



Different types of MN array

Solid	**Coated**	Hollow
Dissolvable	Swellable	**Porous**



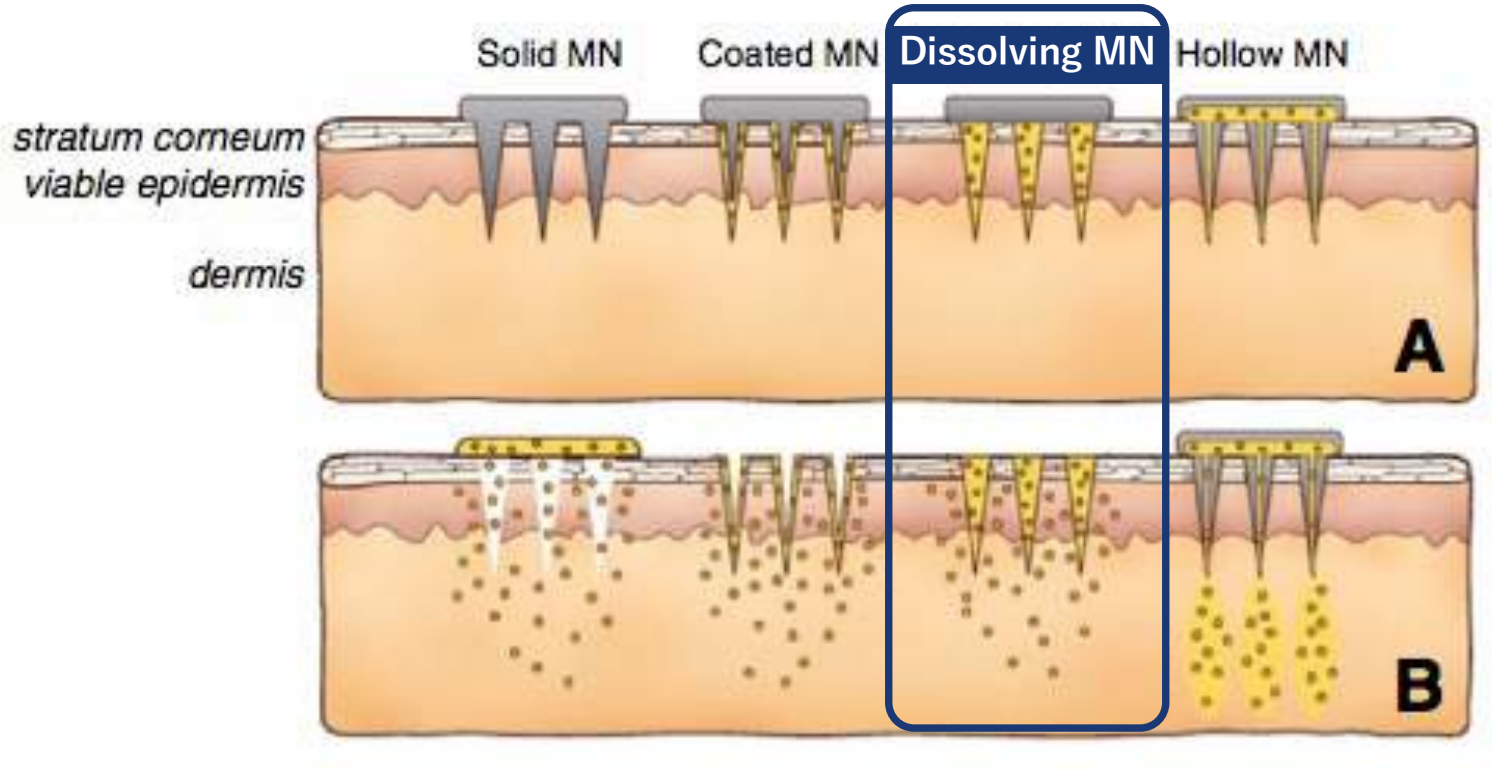
No Pain, Patient-friendly Non-invasive

Less space for storage

No biohazardous waste

No medical staff required

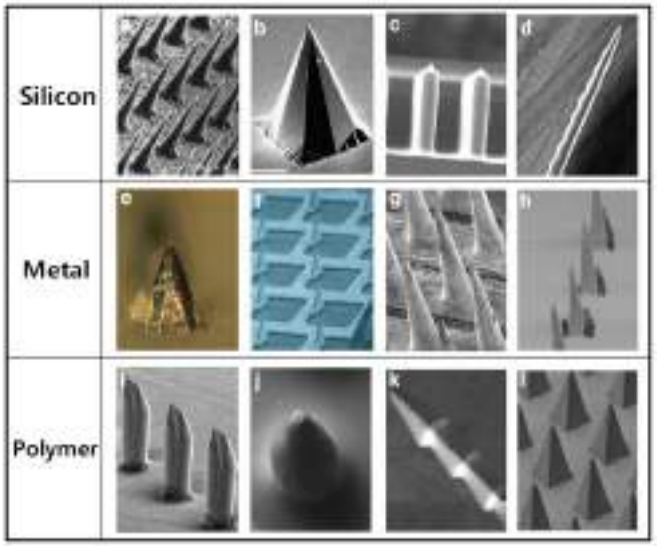
Conventional Micro Needles for Drug Delivery System



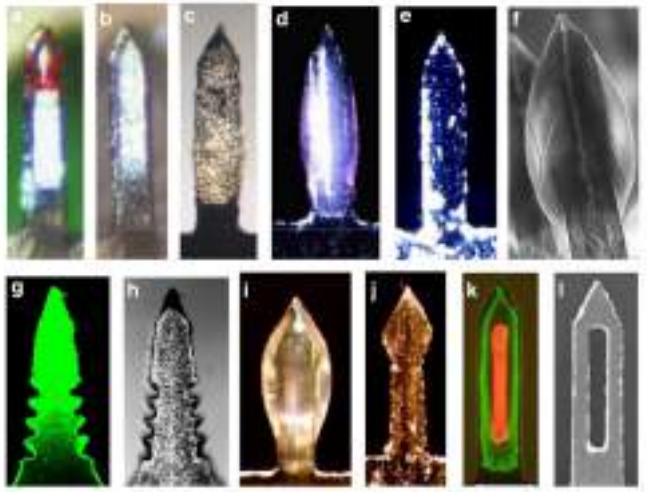
Refs: Y.C. Kim, J.H. Park, MR Prausnitz, Advanced Drug Delivery Reviews 64 (2012) 1547–1568

Various Types of Micro Needles for DDS

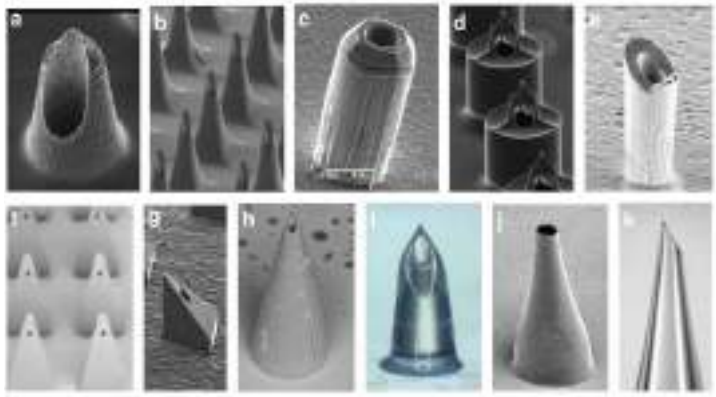
Solid Micro needle



Coated Microneedle (solid)



Hollow Microneedle

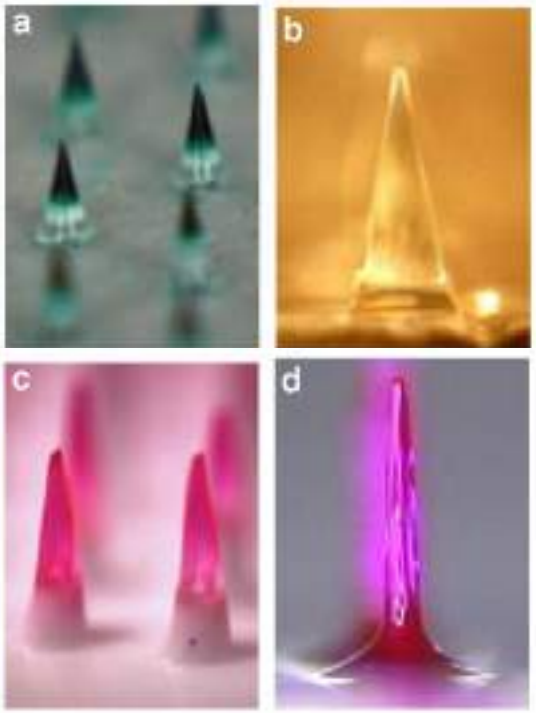


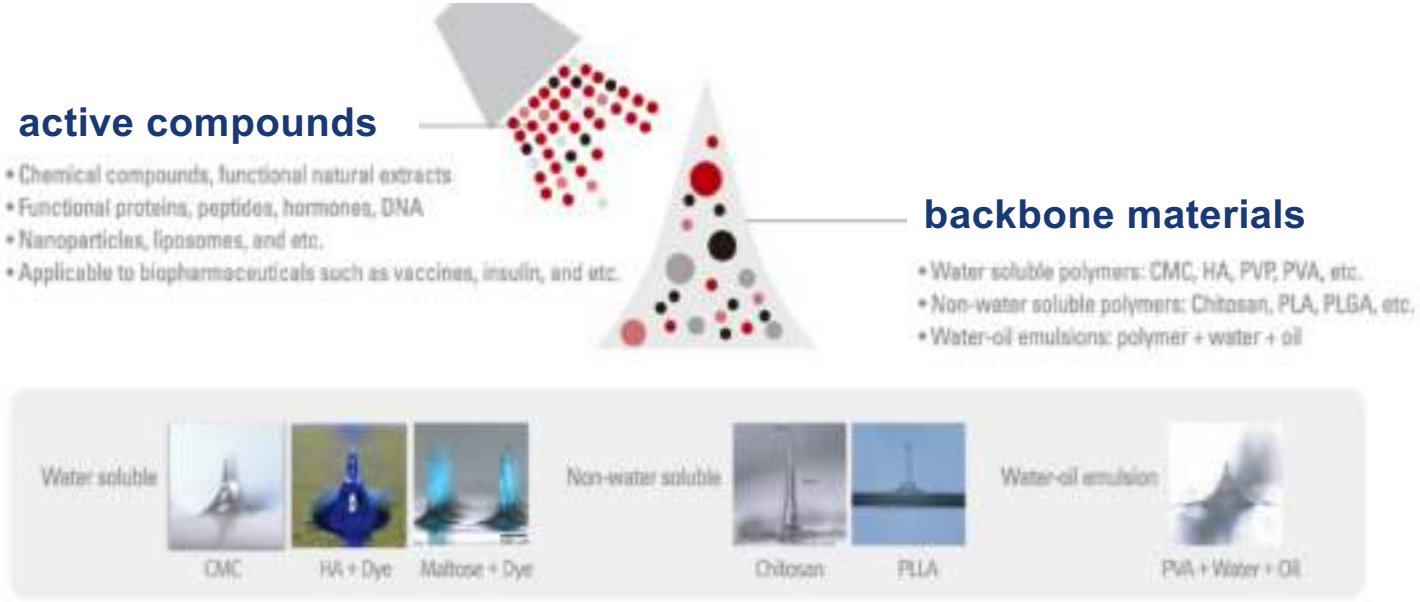
Existing conventional Dissoluble Micro Needle Patch for DDS

生体分解性マイクロニードルを用いたドラッグデリバリーシステムの革命と予防医学の実現

100 % transdermal local delivery of high molecule API (Active Pharmaceutical Ingredient)

Micro Needles : Dissolving Micro needle (Biodegradable)





100 % transdermal local delivery of high molecule API (Active Pharmaceutical Ingredient)

Commercialization Dissolving Micro needle

EGF

(Epidermal Growth Factor,上皮成長因子)

and

Hyaluronic Acid

+

Argireline

(Acetylhexapeptide-3)

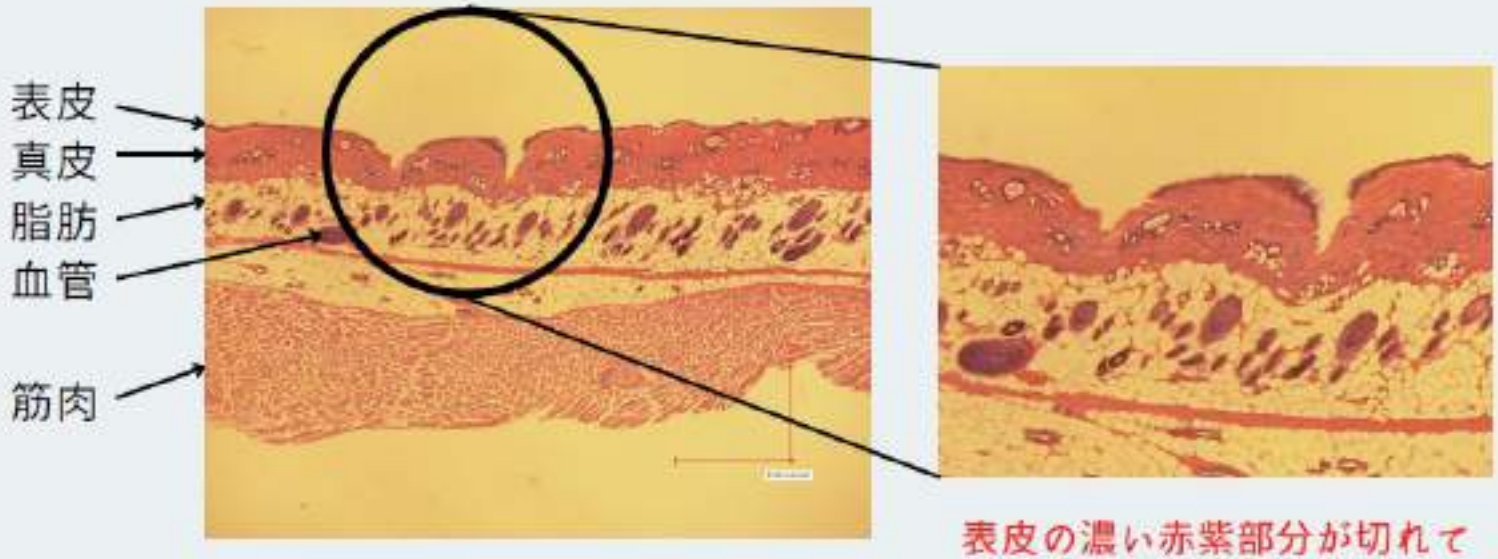
Cosmetic

Prof. Stanley Cohen Nobel prize in Physiology & Medicine to discover EGF (1986)

Percutaneous Image of Dissolvable Microneedle

デジタル顕微鏡で観察した標本

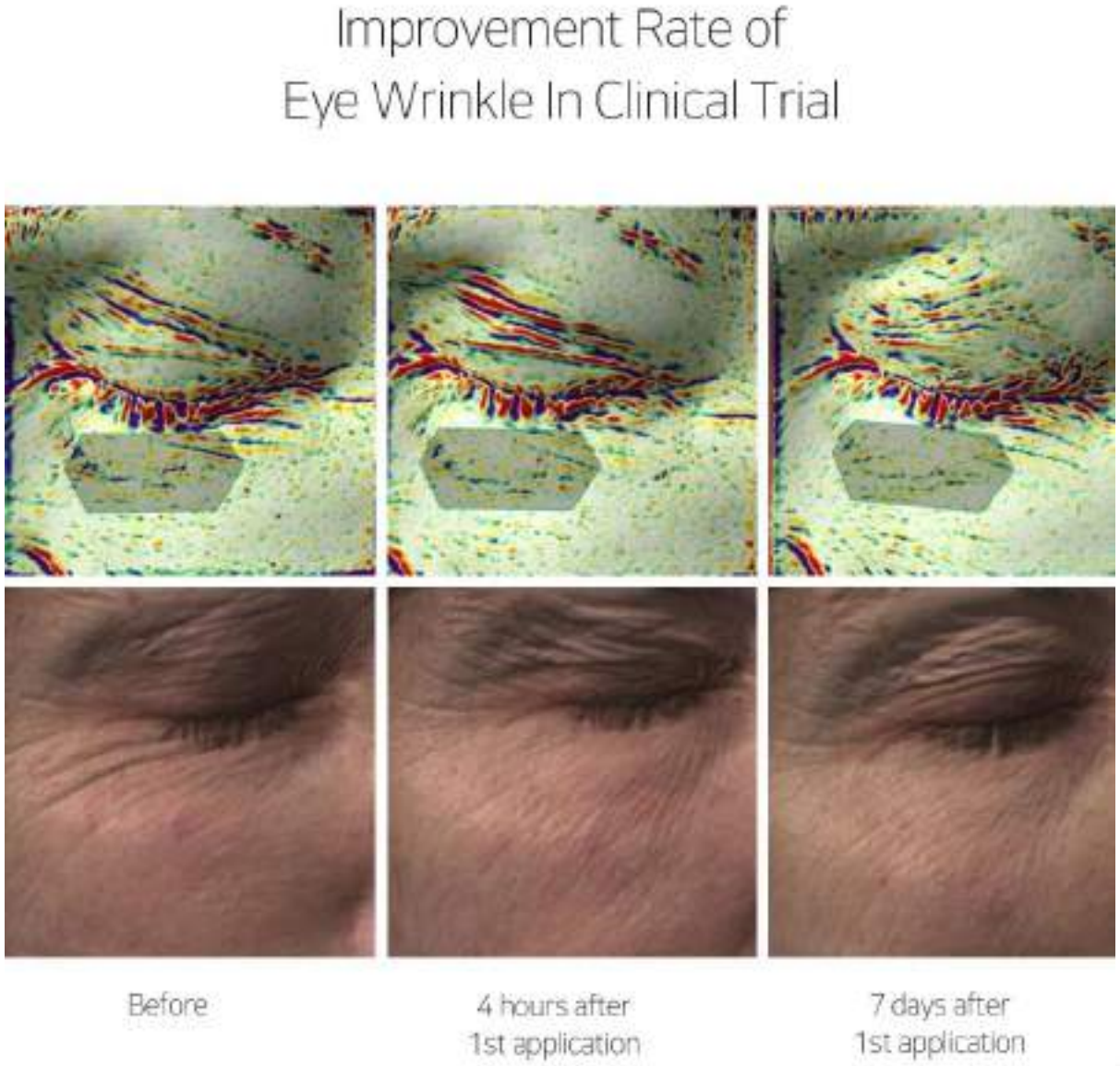
Histological view of Rat skin after MN penetration



表皮の濃い赤紫部分が切れて
真皮にニードルが到達
血管部には届いていないことを確認

@from Raphas Co. Ltd.

@from Endoderma Co. Ltd.

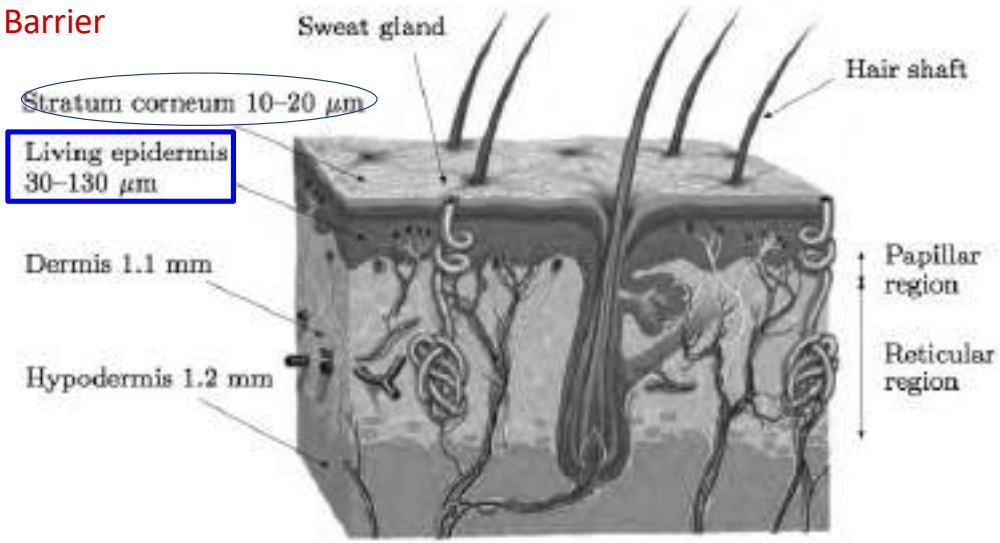


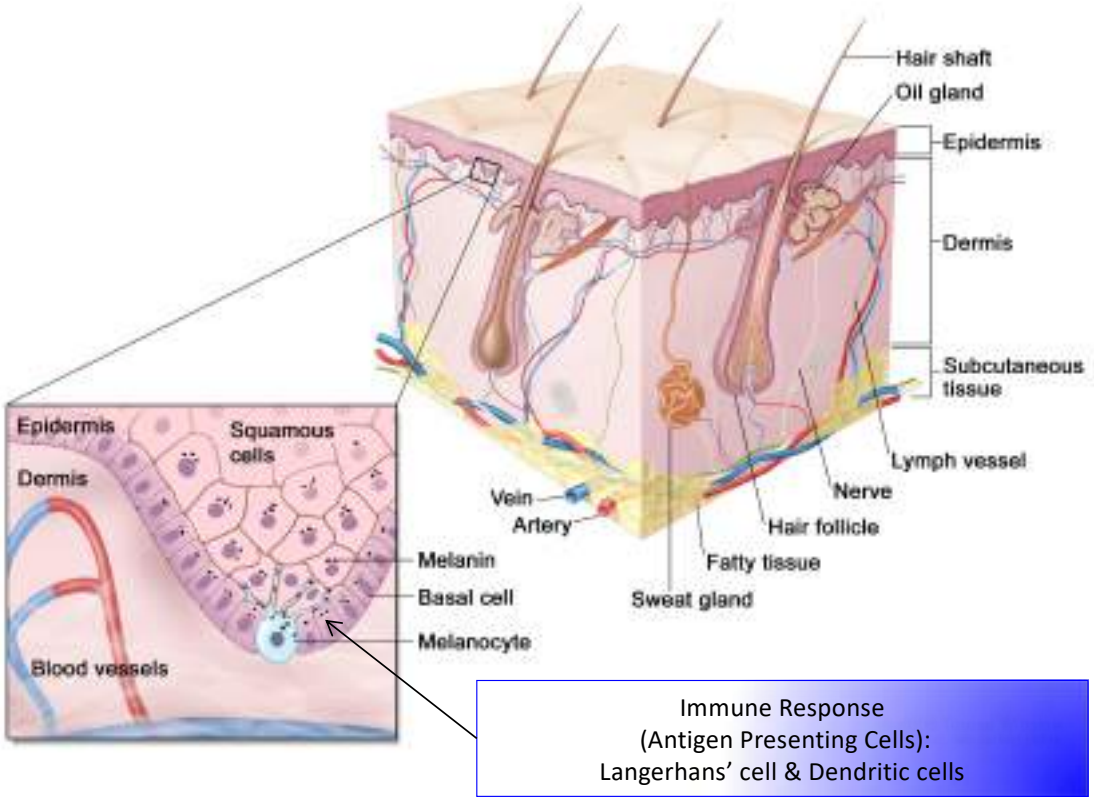
NMN(Nicotinamide Mono Nucleotide：Anti-Aging, 若返り) 搭載＋Sodium Hyaluronate (Hyaluronic Acid ヒアルロン酸：保湿成分）Microneedles array patch

Experts highlight advances with the potential to revolutionize industry healthcare and society

More important: Microneedle for vaccination

Barrier





Immune Response
(Antigen Presenting Cells):
Langerhans' cell & Dendritic cells

Currently, Dissolving Microneedles

Problems

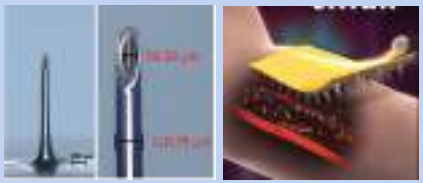
Commercialized only in Cosmetic, skin trouble care products Still very few in DDS
(acne care, influ vaccination, research levels for medical applications)

Minimally invasive manner – still inevitable pain

Limitation of Low-cost, Mass fabrication of microneedle with arbitrary shapes, various dimensions

J.D. Kim et al., J. Controlled Release (2013)

Recently, only few works about ISF extraction sensor applications


C. G. Li et al., Lab on a Chip (2017)
J. Zhu et al., Small (2020)

Conventional MN fabrication technology

1. 95% competitors

Micromolding

Difficulties

- Filling in mold- vacuum, centrifuge
- Drying in mold- long time, Heating or UV
- Detach from mold- surface treatment, cleaning

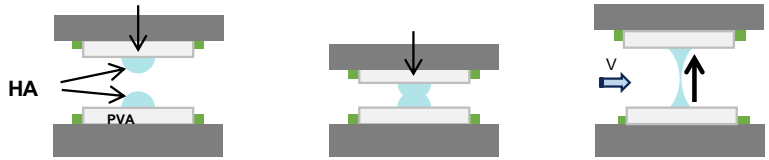
3M Corium TheraJect FUJIFILM

Korean Companies: SNvia Co., Ltd., Dermajet, Small Lab., Endoderma, Karatica Co., Ltd , QuadMedicine..

2. Others

DAB(Droplet- born Air Blowing)

Inkjet (Mushashi Eng.)



Raphas Ltd. Co. @Korea

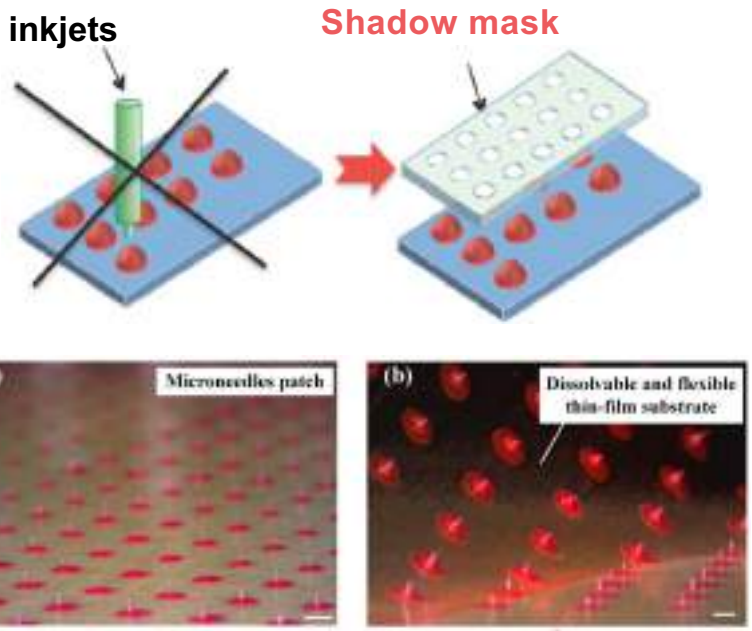
Difficulties

- Limitation of API components
- Difficult to fabricate various shapes/lengths of needles

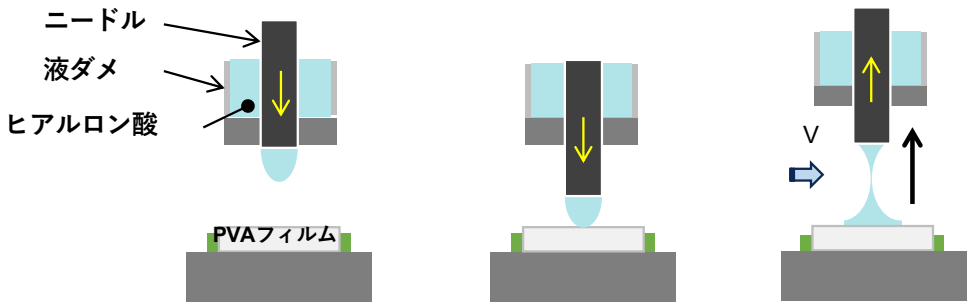
(Prof. H. Jung, Journal of Controlled Release., 170, 2013)

We Can improve

Larger area of uniform microneedles with faster process time



Direct Micro needle type
Dispensor usage or micro stamping



Patents by Raphas. Co., Ltd. (collaboration with UTokyo, BJ Kim one of inventors)

- WO2017/200213 “METHOD FOR MANUFACTURING MICRONEEDLE” (PCT/KR2017/004058)
- (韓国)特許10-2016-0061903号 出願日2016年5月20日, 2017年12月29日登録) 発明名称：マイクロニードル製造方法
- (韓国)特許10-2016-0061909号 出願日2016年5月20日, 2017年9月14日登録) 発明名称：マイクロニードル製造用粘性物質供給装置

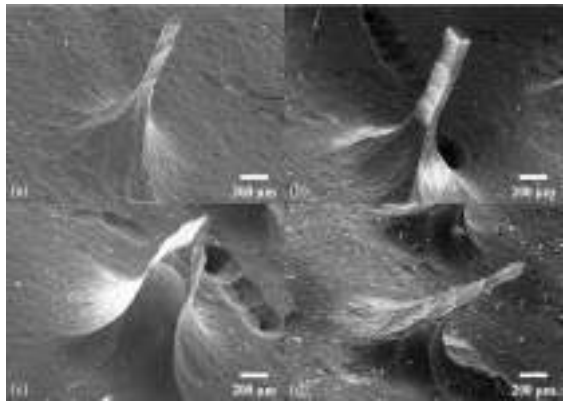
New fabrication methods by Kim Lab.

特許
PCT/JP2018/035899

- Use the 3D printing to easily get the batch fabrication of MN array
- Make the dimension of the 3D printed needle shrink to micro-scale
- Active Pharmaceutical Ingredient (API) with MN for drug delivery

Stronger Biodegradable Microneedles with Coated various drugs

- **Design of arbitrary shapes of needles**
- **Various lengths of needles**
- **Various materials & APIs loading**



Microsystems & Nanoengineering
7:58 (2021)

Drug Delivery MNP (poke, and deliver)

Objective

Deliver active pharmaceutical ingredients (APIs) into skin in a non-invasive & effective way

Innovate & Substitute conventional drug delivery using MNP technology

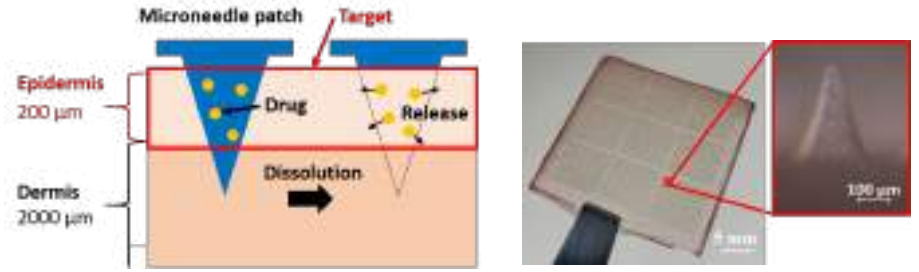
Keywords

Vaccine, sustained drug release, dissolvable MN, droplet-embedded MN

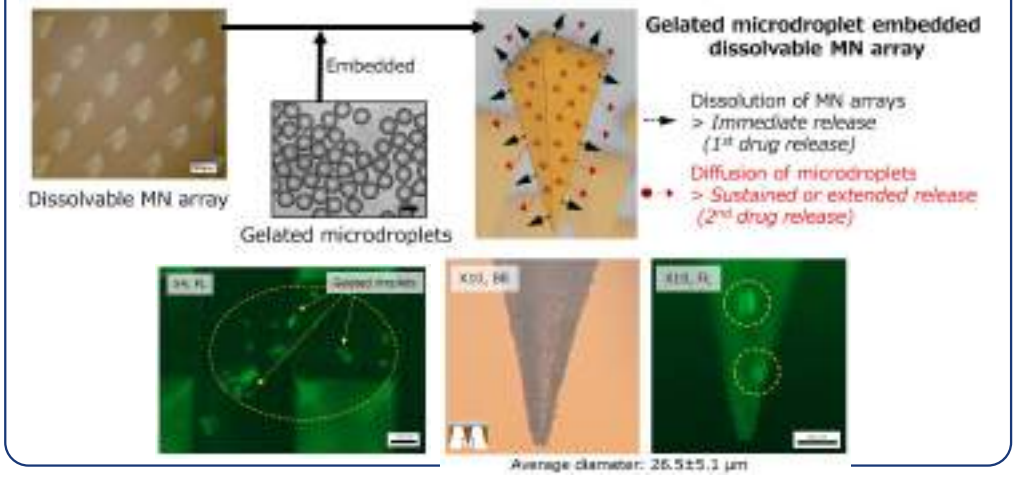
Current targets

COVID-19 & other vaccines, antibiotics, sclerosis, Keloid treatment with hepatocyte growth factor aptamer

COVID-19 Vaccine delivery MNP using vaccinia virus vector[1]



MNP with HA microdroplets embedded[2]



[1] The 13th Symposium on Micro-Nano Science and Technology, 15P2-PN-5 (2022), [2] JSPE Spring Meeting, G103 (2021)

For SARS-CoV 2 Vaccination Patch @ BS-TBS 4/28, 2021

2 min.

What is the limitation of current keloid treatment?

What is keloid?

- Fibroproliferative scars
- Altered growth factor regulation
- Long-term psychological & physical burdens

[1,2]

No single unifying hypothesis adequately explains keloid formation

Limitation of steroid tape & drugs:

- **Skin wrinkling**
- **Vasodilation**
- **Allergy**
- **Injection causes pain**

CORDRAN® Tape (Flurandrenolide, USP)

New alternatives instead of steroid tape are necessary

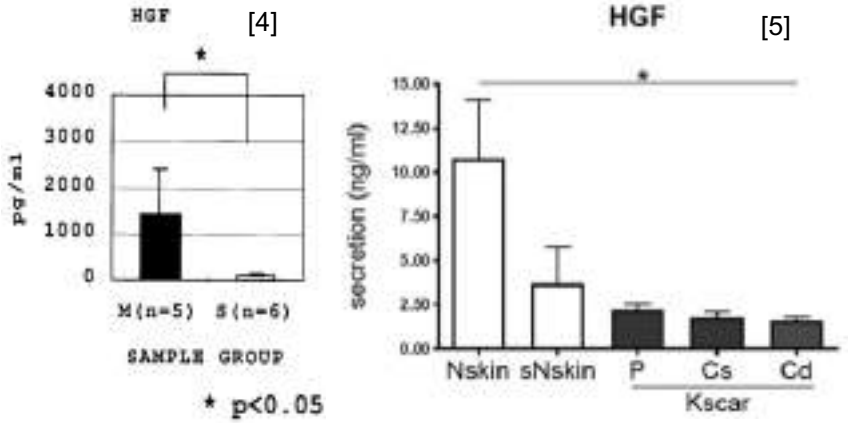
[1] R. Ogawa, DOI:10.5772/intechopen.84178 [2] Ali Al-Attar et al., DOI: 10.1097/01.prs.0000195073.73580.46

Previous research by collaborator, Prof. Okazaki

Keloid formation in buccal mucosa rarely occurs

HGF (Hepatocyte growth factor)

- Stimulate cellular functions
- Anti-fibrosis and Anti-inflammatory



High expression in oral mucosa & Low expression in keloid

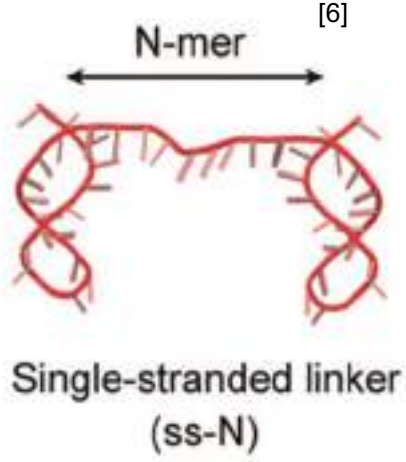
HGF treatment would be promising for keloid treatment

[3] M.F. Griffin et al, DOI: 10.1089/wound.2021.0038
[4] M. Okazaki, et al., Journal of Dermatological Science 30 (2002) 108/115
[5] G.C. Limandjaja et al., Archives of Dermatological Research (2018) 310:815–826, DOI: 10.1007/s00403-018-1873-1

Previous research by Lin and Cai in 伊藤大知研

HGF Aptamer-loaded Microneedles

Oligonucleotide mimetics of HGF developed by Sando Lab [6]



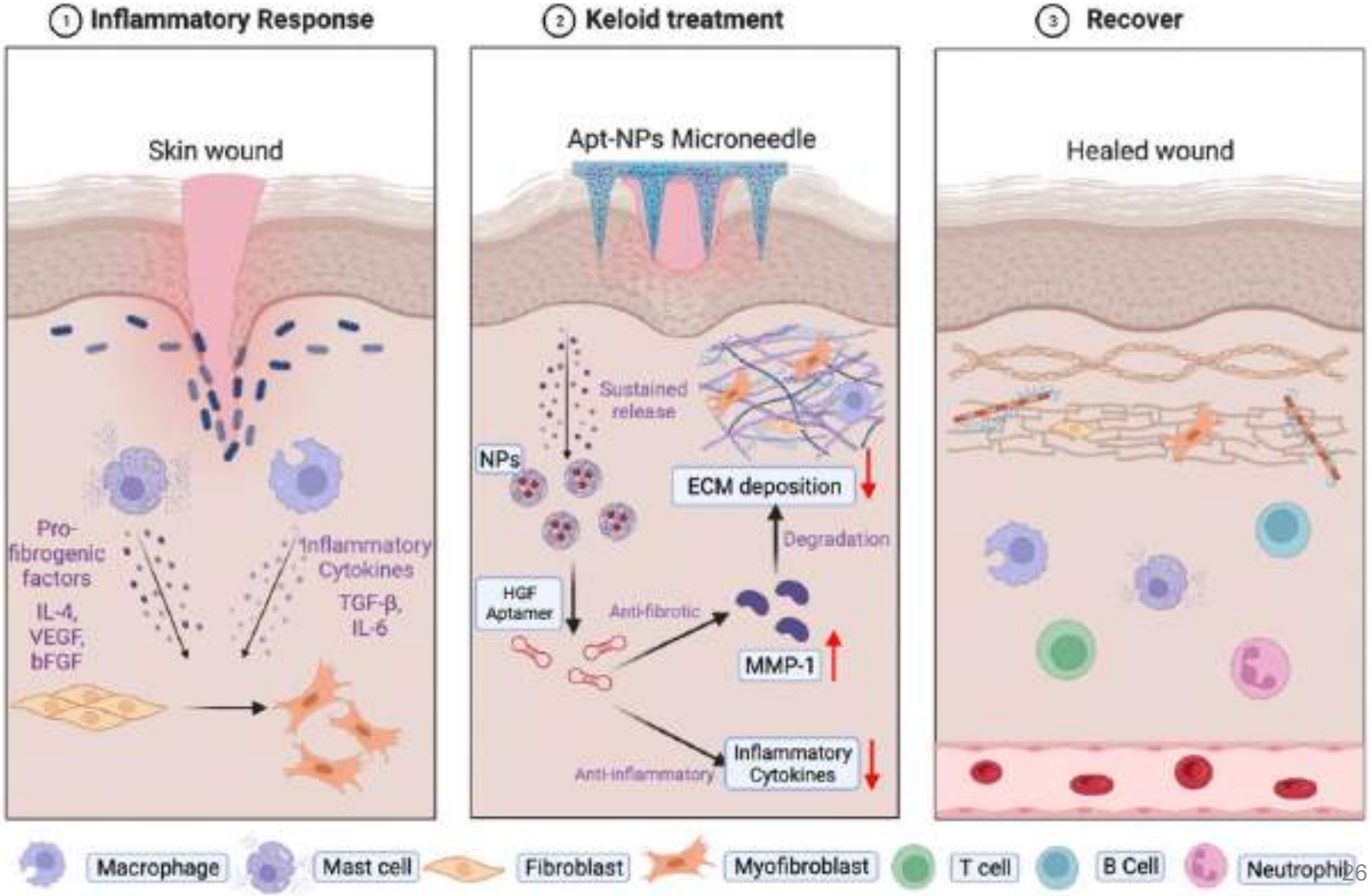
with Kim Lab

Successful administration of HGF aptamer and therapeutic effect for scleroderma model in mice.[7]

Our new technology would be promising for new keloid treatment

[6] Ueki et al, Sci. Adv. 2020; 6: eaay2801 [7] *Lin Cheyu, Master thesis in 2021 FY, Department of Bioengineering*

Objective

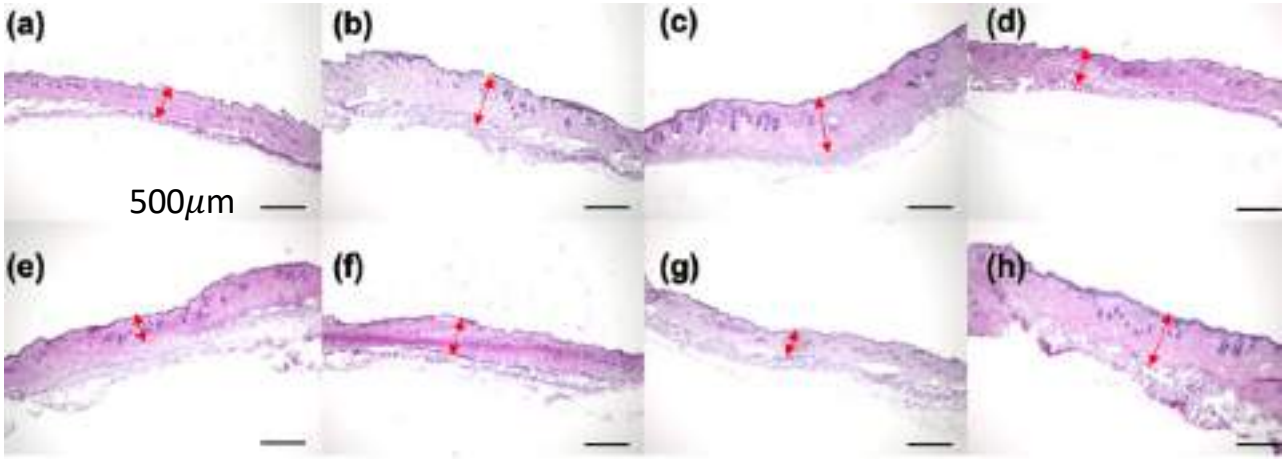

① Inflammatory Response
② Keloid treatment
③ Recover
Skin wound
Pro-fibrogenic factors
IL-4, VEGF, bFGF
Inflammatory Cytokines
TGF-β, IL-6
Apt-NPs Microneedle
Sustained release
NPs
ECM deposition
Degradation
HGF Aptamer
Anti-fibrotic
MMP-1
Anti-inflammatory
Inflammatory Cytokines
Healed wound
Macrophage
Mast cell
Fibroblast
Myofibroblast
T cell
B Cell
Neutrophil

Result 3-2

Group division

Group division

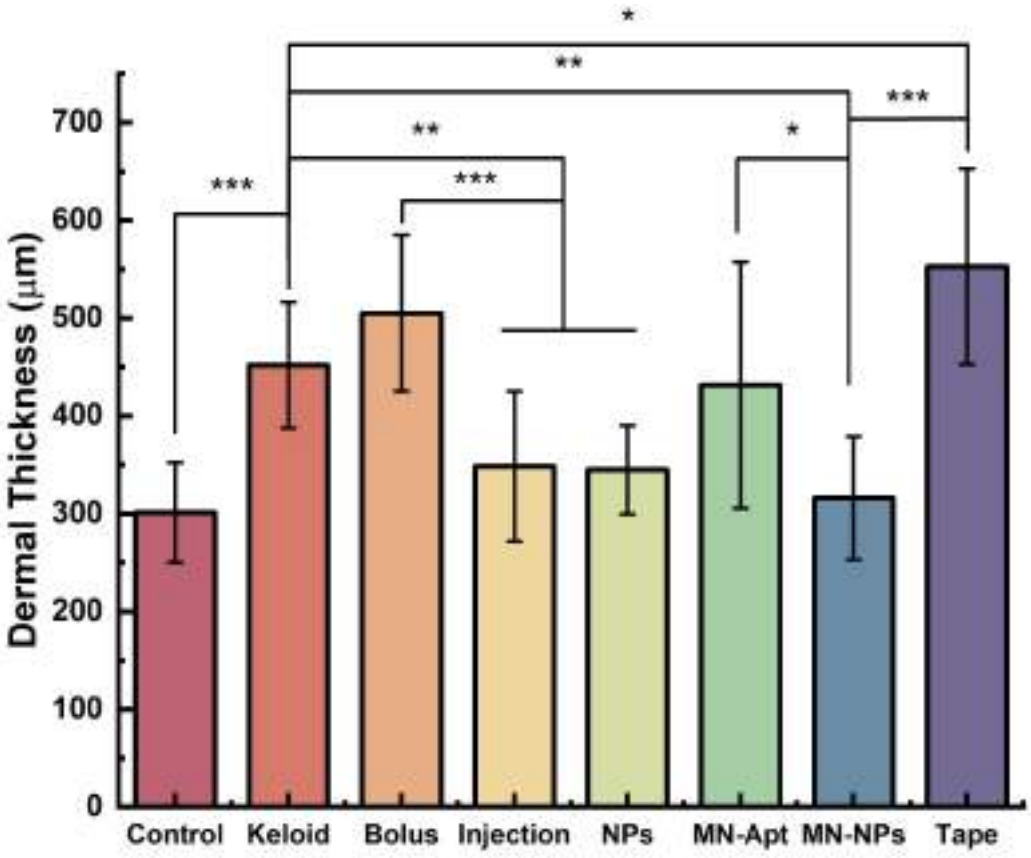
	Groups	Treatment	Instruction
A	Healthy mice	45μg/mice/day HGF apt	Control group (7 days)
B	Keloid model	200μL/mice/day Saline	Keloid model group (7 days)
C	Infection bolus	315μg/mice HGF apt	Negative control group (One shot)
D	Injection daily	45μg/mice/day HGF apt	Normal treatment (7days)
E	Aptamer-MN	315μg/mice/day HGF apt	Local delivery (One time)
F	Aptamer-NPs	200μg (10.0% E.E) HGF apt	Controlled release (One shot)
G	Aptamer-NPs-MN	200μg (10.0% E.E) HGF apt	Local + controlled release (One time)
H	Steroid tape	1cm*1cm tape (4 μg/cm^2)	Change everyday (7days)



Result 3-3

H&E staining

Dermal thickness



Direct administration ×

↓

Drug delivery system √

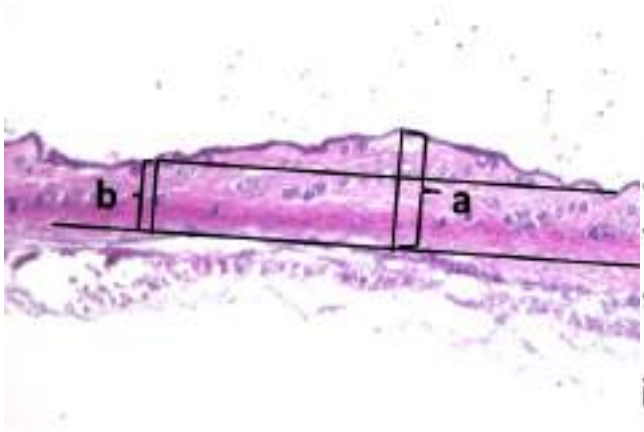
HGF aptamers utilizing DDS had shown therapeutic effect in mice model

Data are expressed as Mean ± SD(n=4), *p≤0.05.**p≤0.01.***p≤0.001, by One-way Anova

Result 3-4

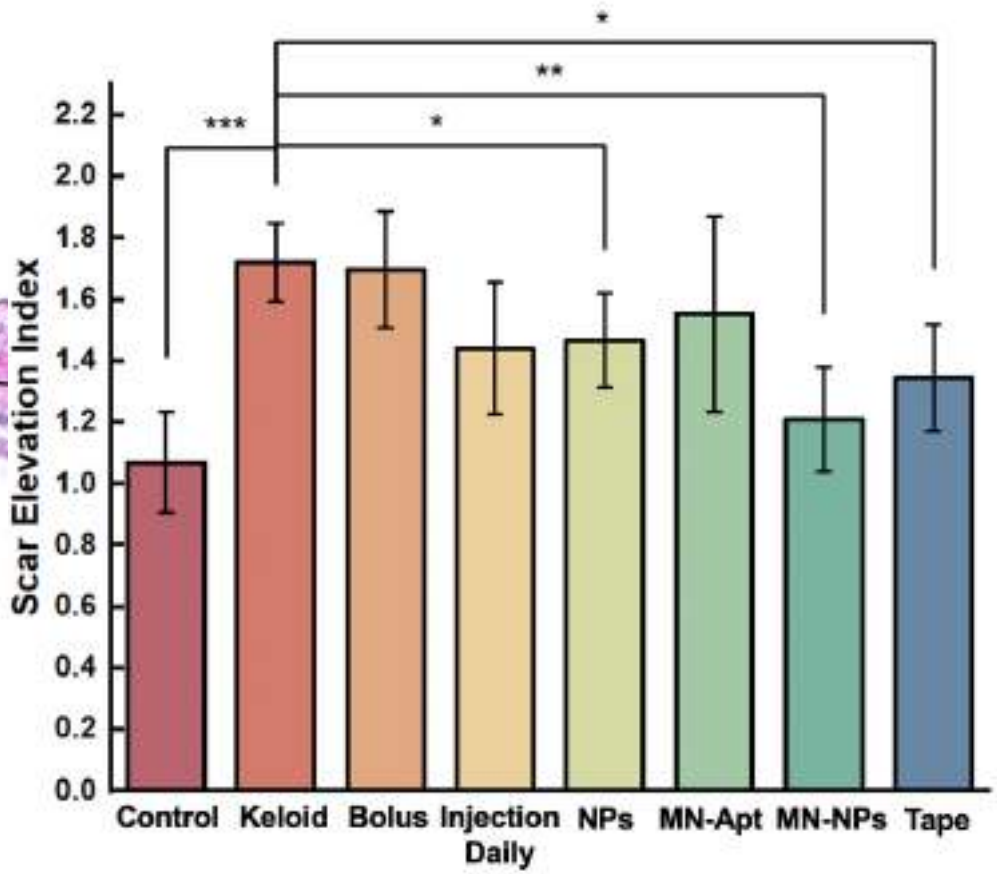
H&E staining

Scar Elevation Index[10]



$$SEI=\frac{a}{b}$$

MN-NPs performed best therapeutic efficacy



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[10] Z Yang, et al., Lasers in Medical Science (2019) 34:1317–1324, DOI: 10.1007/s10103-019-02716-5.

2. Light Delivery for Care

MAPs for light therapy & new applications (poke, and irridiate)

Objective

MAPs are used to treat skin-related diseases directly

- **realize fast, simple, and low-cost treatment**
- **establish novel light therapy (Photodynamic Therapy, PDT) using MAPs**

Types of MAPs

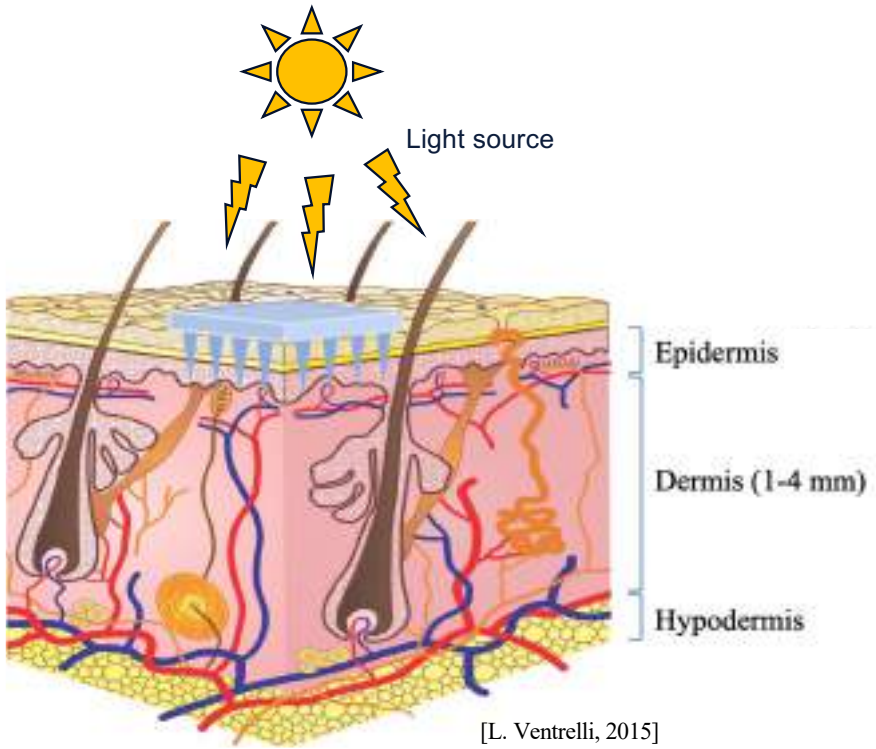
Solid (transparent) Optical MAP mainly, as a light guide

Target location & feasible applications

- Epidermis, dermis (with light exposure)
- Photodynamic therapy (PDT) for skin diseases (melanoma, acne, telangiectasia),
- hair removal

The other Types of MAPs

hemostasis, biotagging,…



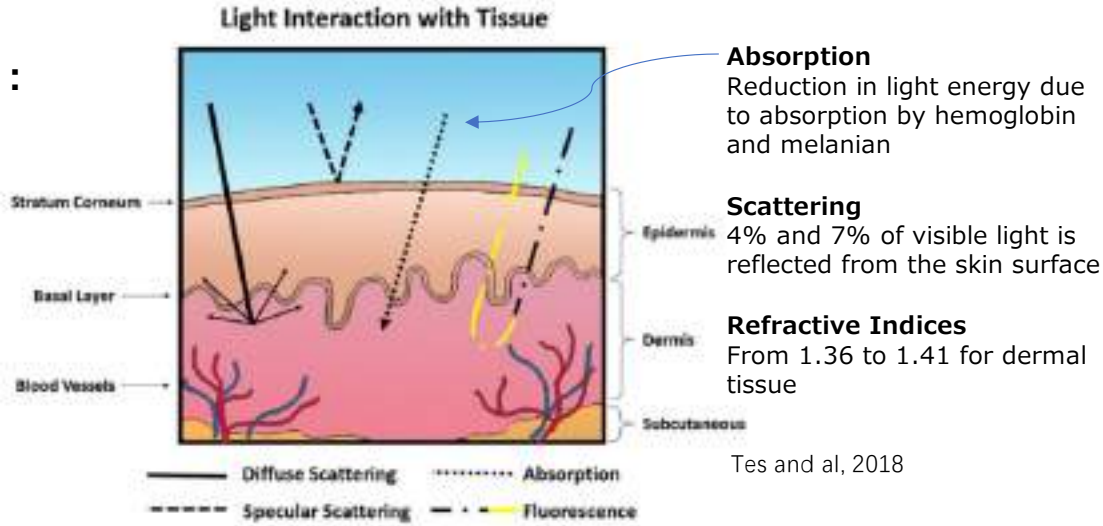
[L. Ventrelli, 2015]

Skin barrier limitation

PDT not effective against nodular and invasive forms :

- Stratum Corneum (SC) limits the entry of anticancer agents
- Light does not diffuse properly deep in the skin

➔ **Need for a medical device to resolve these limitations**



Absorption
Reduction in light energy due to absorption by hemoglobin and melanian

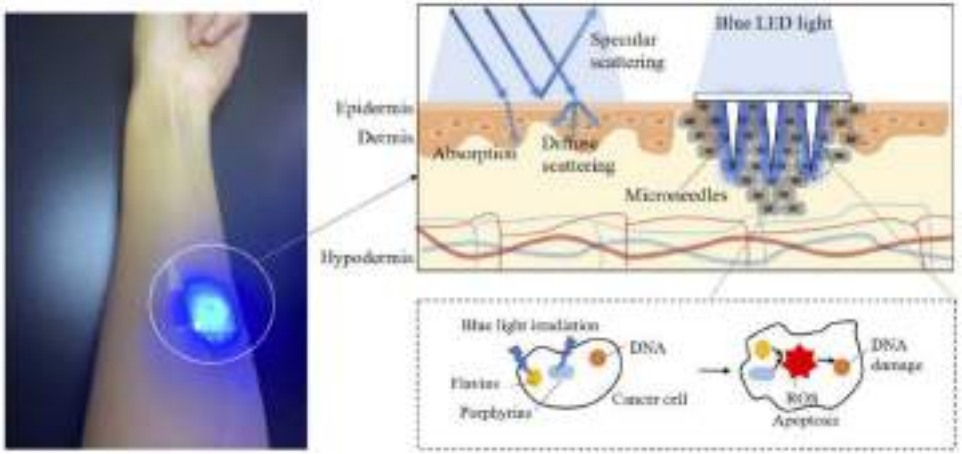
Scattering
4% and 7% of visible light is reflected from the skin surface

Refractive Indices
From 1.36 to 1.41 for dermal tissue

Tes and al, 2018

Optical Microneedles patches

- Delivery of molecules into deep layer of the skin
- Conduction of light over the dermis layer through the microneedles
- We develop optical microneedles patch that conduct light for treating skin diseases

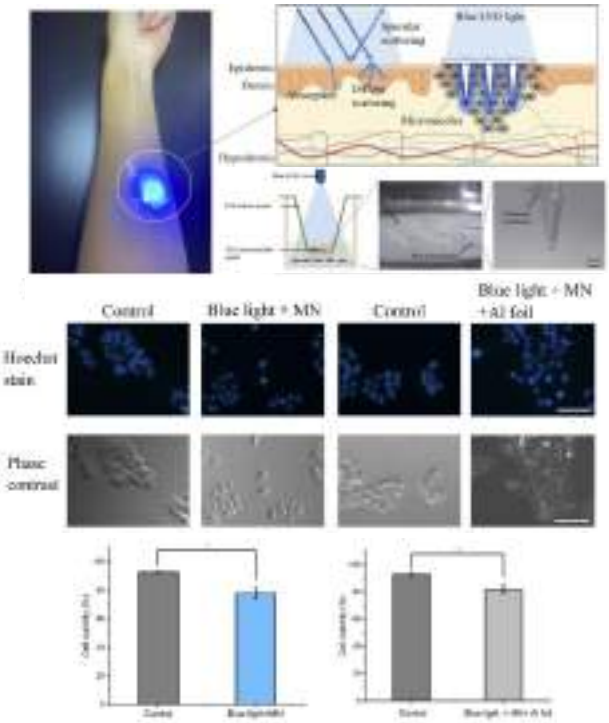


We *and al*, 2022

MAPs for light therapy & new applications

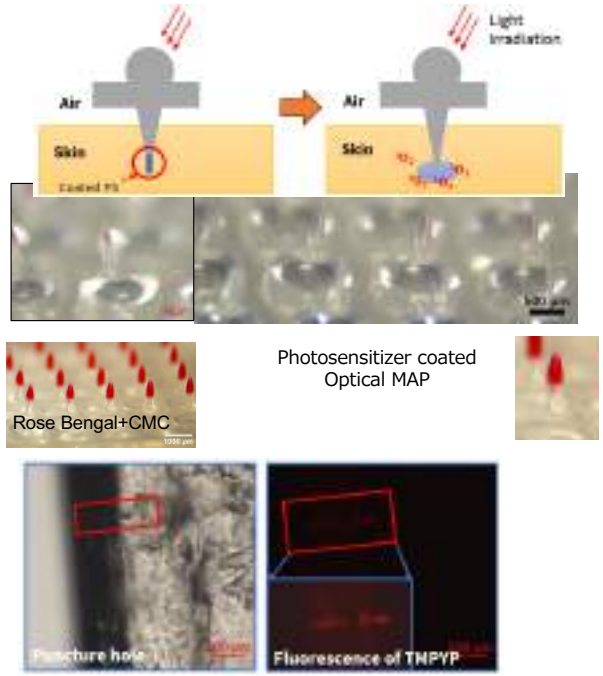
MAP to treat Skin cancer[1]

> Induces the apoptosis of melanoma cells by direct light delivery
> Blue light array (467 nm) as light source
> Light dose: 146.9 J/cm^2



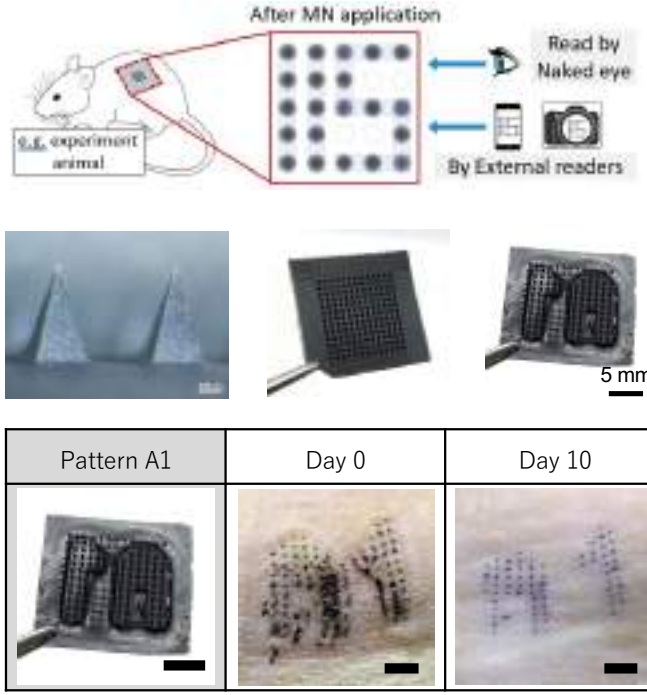
Coated MAP for Photodynamic therapy[2]

> Photosensitizer coated on optical MAP
> Kill non-melanoma cancer cells (e.g Basal Cell Carcinoma) by reactive oxygen species activated by light delivery



MAP for Biotagging[3]

> Biotagging for animals using patterned MAP
> Pattern formation for identification and its persistence over 1 month confirmed.



[1] ***Biomed. Opt. Express***, 13(2), 1045 (2022) [2] ***Micromachines***, 15, 6 (2024) [3] ***Scientific Reports***, 13, 22843 (2023)

MAP for Sensing

3. Extract for Diagnosis (Main talk)

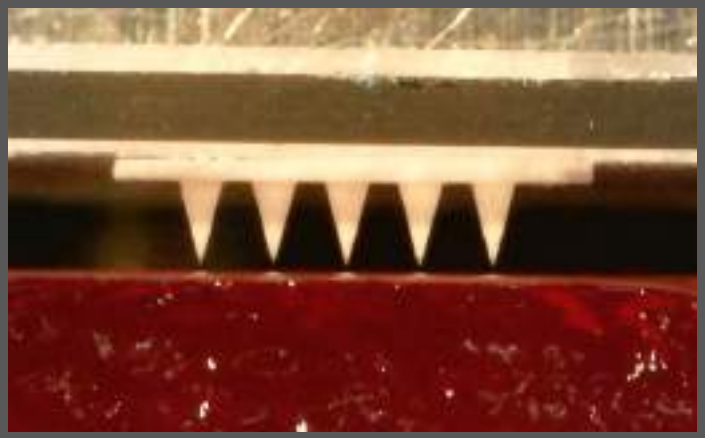
Our Mission

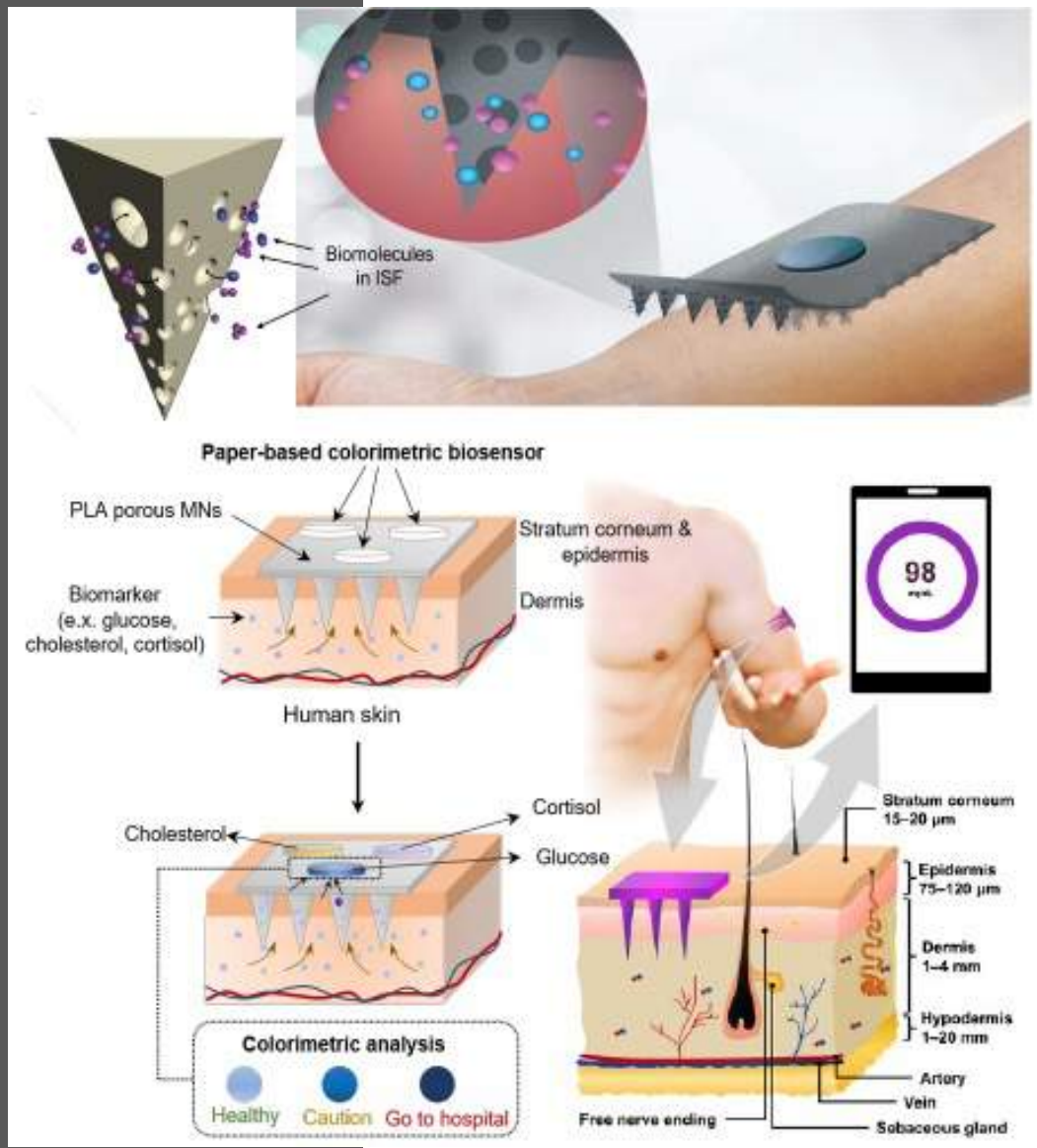
- We believe that prevention is better than cure.
- Preventive solution should be widely accessible, convenient, and accurate.

Preventive medicine
Regenerative medicine
▶ Successful Aging

Our Solution

We make self-monitoring sensors for everyone.

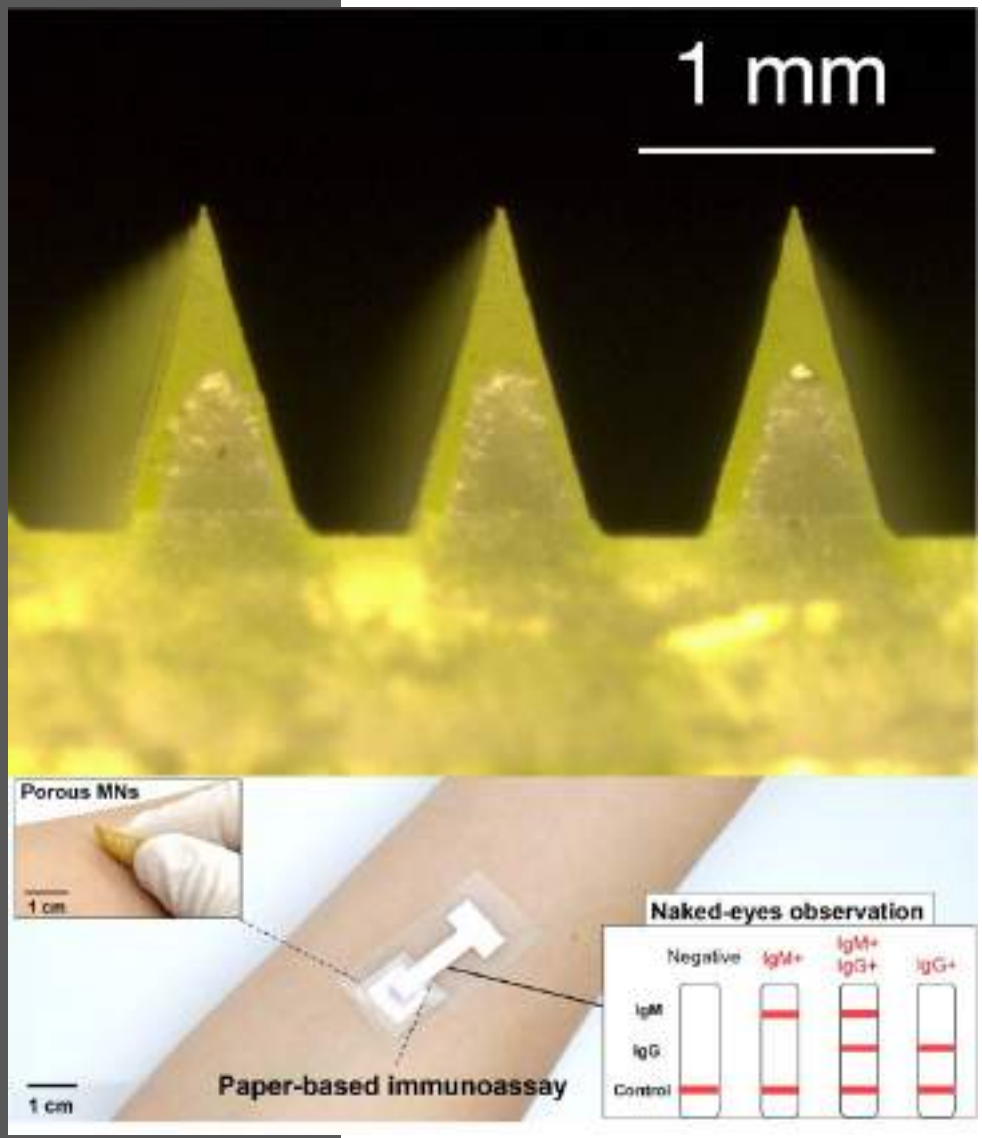




Porous Microneedles@B.J. Kim Lab.

Sensor

– sampling by “Porous Needles”

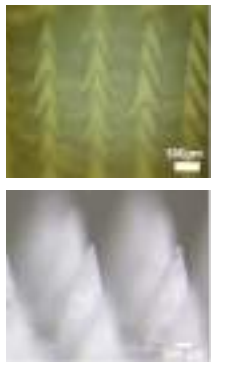


Scientific Reports, *12, 10693 (2022).*
https://doi.org/10.1038/s41598-022-14725-6

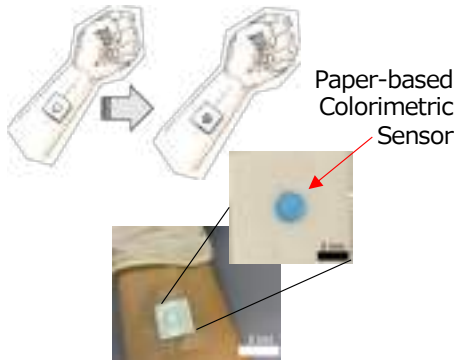
Biosensor MNP (poke, extract, and analyze)

Sensor group

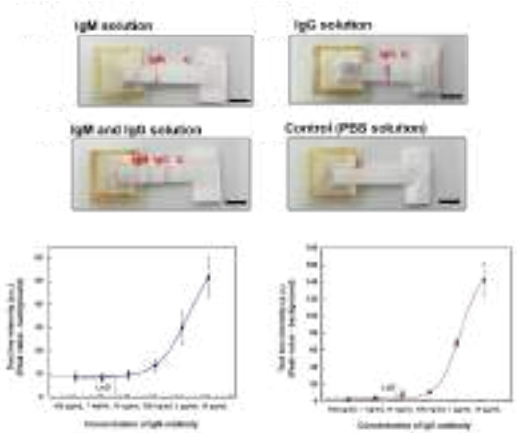
- **Objective**
  Develop MNP to **extract interstitial fluid (ISF)** & analyze ISF for sensing & monitoring the change of body functions >> Realize fast & simple diagnosis on site as healthcare device (instead of blood test)
- **Keywords:** porous MN, capillary action, interstitial fluid (ISF), colorimetric sensing
- **Current targets**: glucose, antibodies, cholesterol, cortisol, hormones, and so on



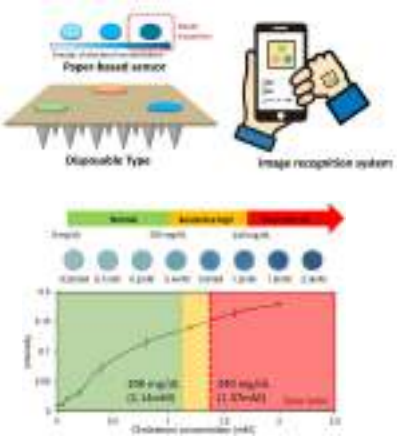
Porous MNP
(PLGA or PLA)



Glucose Sensing[1]



Sensing COVID-19
antibodies & concentration[2]



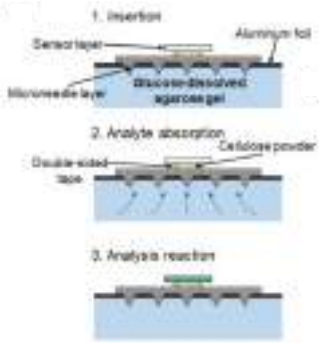
Sensing Cholesterol
Level[3]

[1] Medical Devices and Sensors, Vol.3, Issue 4, e10109 (2020), [2] Scientific Reports, Vol.12, 10693 (2022), [3] JSPE Autumn Meeting, G31 (2021)

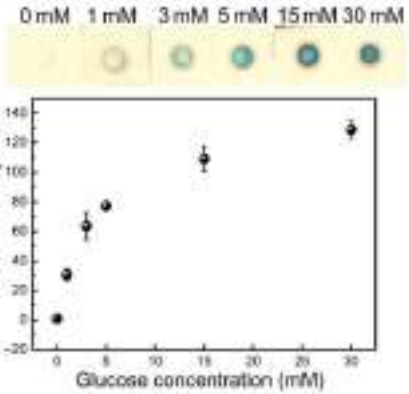
MAPs for diagnosis – Recent researches

MAP for Glucose assay[1]

> Integration with colorimetric assay
> LoD of glucose: 0.11 mM

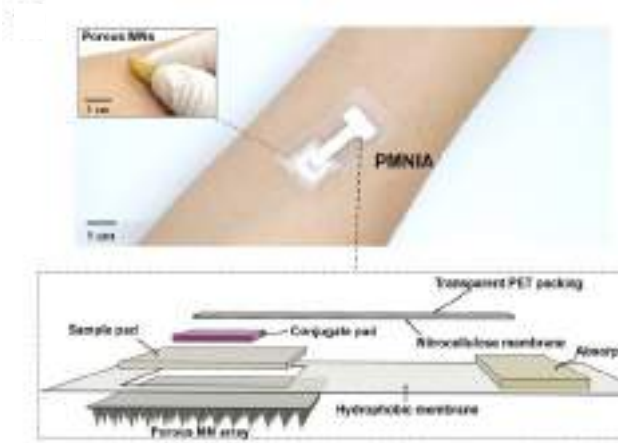


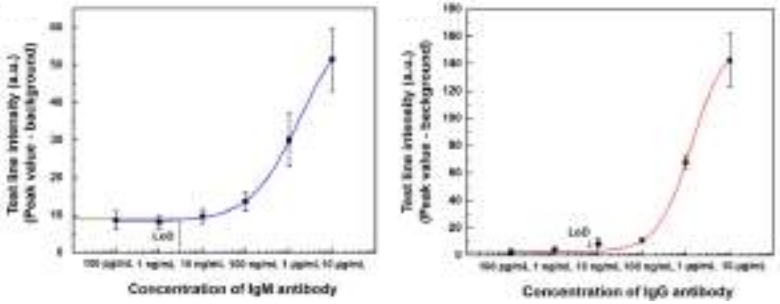
PLGA
Porous MAP



MAP to diagnose COVID-19 antibody[2]

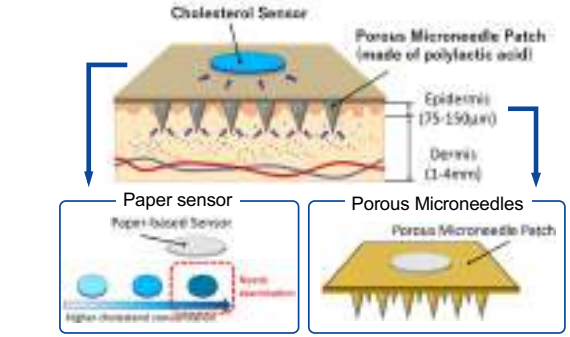
> Integration of porous MAP with lateral flow assay
> LoD for IgM & IgG antibodies: 3 ng/mL & 7 ng/mL

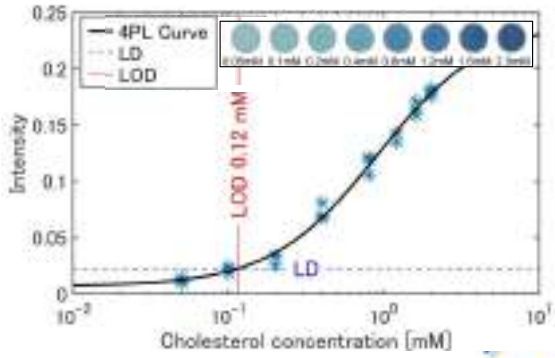




MAP to diagnose Cholesterol[3]

> Easy diagnosis using colorimetric assay
> LoD for cholesterol: 0.12 mM





[1] Med. Devices Sens., 3, e10109, 2020 [2] Sci. Rep., 12(1), 1–16, 2022 [3] uTAS2022, W150.f, 2022

NEWS RELEASE 14-SEP-2020

Painless paper patch test for glucose levels uses microneedles

Peer-Reviewed Publication

INSTITUTE OF INDUSTRIAL SCIENCE, THE UNIVERSITY OF TOKYO

Media Contact

Beomjoon

bjoonkim

Tokyo, Japan – Patches seem to be all t
rage these days. There are birth control
patches, nicotine patches, and transden
medicinal patches, just to name a few. N
a team of researchers led by Beomjoon K
at the Institute of Industrial Science, The
University of Tokyo have developed a pat
of needles connected to a paper sensor f
diagnosing conditions such as prediabete
Luckily, this patch doesn't multiply the pai
and discomfort of a single hypodermic
needle. In fact, these microneedles are
painless and biodegradable.

Researchers have been trying to develop a
practical way to use microneedles--tiny
needles less than 1 mm in length--for
routine do-it-yourself medical monitoring.
Microneedles are so short that they stay
within the skin and do not make contact
with any neurons, meaning that they cause
no pain. Rather than extracting blood, they d
important biomarkers that blood tests look fo
now, making a practical device that quickly an
overcome this problem by developing a way t
based sensors," says Kim. "The result is low-co
additional instruments."

To make the patch, the researchers first made t

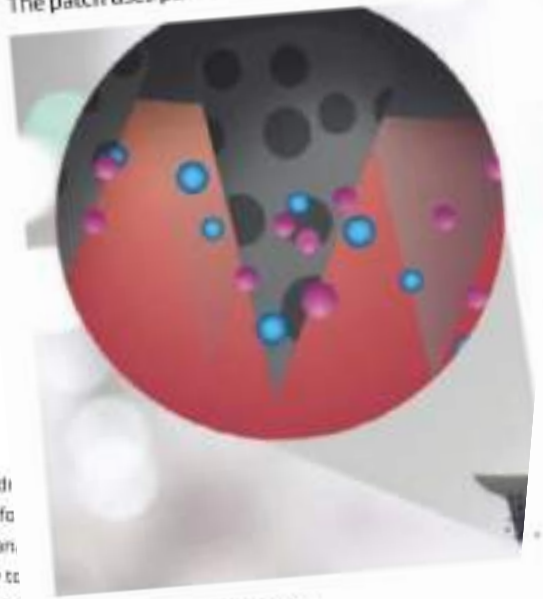
MENU

ELECTRONICS & SOFTWARE | PHOTONICS & IMAGING | MOTION CO

JANUARY 1, 2021 | MEDICAL | WEARABLES | MARKETS

Painless Paper Patch Tests Glucose

The patch uses painless, biodegradable microneedles.



University of Tokyo, Japan

Researchers have been trying to develop
1 mm in length — for routine at-home medical monitoring.
within the skin and do not make contact with any neurons, meaning that they
than extracting blood, they draw up fluid in the skin that contains most of the
look for. Several types of microneedles exist but until now, making

インフル

Research Highlights

New antibody detection method for coronavirus that does not require a blood sample

Researchers report a new, minimally invasive, antibody-based detection method for SARS-CoV-2 that could lead to the blood sample-free detection of many diseases.

Professor Beomjoon Kim

Doctor's Degree Program 3rd Lelia I Bae of Kim Lab

Despite significant and stunning advances in vaccine technology, the COVID-19 global pandemic is occurring. A key challenge in limiting the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is identifying infected individuals. Now, investigators from Japan have developed a new antibody-based method for the rapid and reliable detection of SARS-CoV-2 that does not require a blood sample.

The ineffective identification of SARS-CoV-2-infected individuals has severely limited the global response to the COVID-19 pandemic, and the high rate of asymptomatic infections (16%–38%) has exacerbated this situation. The preferred sample detection method is to collect samples by swabbing the nasal and throat tissues. However, the application of this method is limited by its long detection time (4–6 hours), high costs, and requirements for specialized equipment and medical personnel, particularly in resource-limited countries.

An alternative and complementary method for the confirmation of COVID-19 infection involves the detection of SARS-CoV-2-specific antibodies. Testing serum based on gold nanoparticles are currently in widespread use for point-of-care testing in many countries. They produce sensitive and reliable results within 10–30 minutes, but they require blood samples collected via a finger prick using a lancing device. This is painful and increases the risk of infection or cross-contamination, and the used lancing components present a potential biohazard risk.

Lead author Lelia Bae from UTokyo-IIS, explains, "To develop a minimally invasive detection assay that would avoid these drawbacks, we explored the idea of sampling and testing the interstitial fluid (ISF), which is located in the epidermis and dermis layers of human skin. Although the antibody levels in the ISF are approximately 10%–20% of those in blood, it was still feasible that anti-SARS-CoV-2 IgM/IgG antibodies could be detected and that ISF could act as a direct substitute for blood sampling."

After demonstrating that ISF could be suitable for antibody detection, the researchers developed an innovative approach to both sample and test the ISF. First, we developed biodegradable polymer microneedles made of polylactic acid that draws up the ISF from human skin," explains Beomjoon Kim, senior author. "Then, we constructed a paper-based immunoassay biosensor for the detection of SARS-CoV-2-specific antibodies." By integrating these two elements, the researchers created a compact patch capable of an on-skin detection of the antibodies within 3 minutes (result from in vitro tests).

This novel detection device has great potential for the rapid screening of COVID-19 and many other infectious diseases that is safe and acceptable to patients. It holds promise for use in many countries regardless of their wealth, which is a key aim for the global management of infectious diseases.

Reference

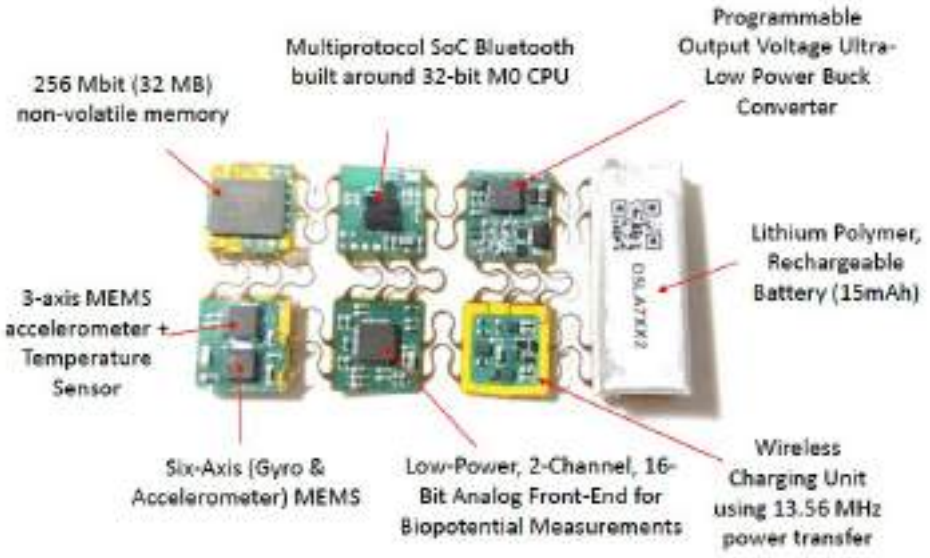
Wearable sensors as “electronic device”

Motion-Tracking sensors

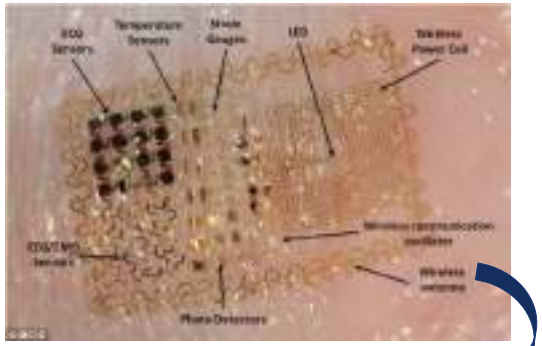
- Accelerometer, Gyro, Magnetometer
- GNSS(GPS, Galileo, Beidou, GLONASS)

Bodily Function sensors

- Heart rate, Pulse Oximetry
- Temperature
- Chemical/electrical: RF communication



@MC10 BioStamp



Bio markers -> Fluidic Biomarkers for smart bandages

	Measurement	Input Needed	Connection	Continuous
Temperature	Electrical	Voltage	Skin Contact Electrodes	Yes
Electrocradiogram	Electrical	Passive	Adhesive Electrodes	Yes
Photoplethysmograph	Optical	Light	Adhesive Sensor	Yes
Electrolytes	Potentiometry	Wicked Sweat/Blood	Wick	Yes
Blood Gasses	Amperometry	Capillary Blood	Microneedle	Yes
DNA Markers	DNA	Nucleic Acid Amplification/Fluid Sample	Swab/Tissue Sample	No
Protien Markers	Eletrochemical/Optical	Swabbed Blood/Sweat/Urine/Sweat	Swab	Maybe

Biomarkers examples

- Neuropeptides (NpY, Orexin A..), Catecholamines
- Cytokines, Corticosteroids
- PSMA/Antigens
- Glucono Lactone (glucose oxidase)
- Saccharide (boronic acid)

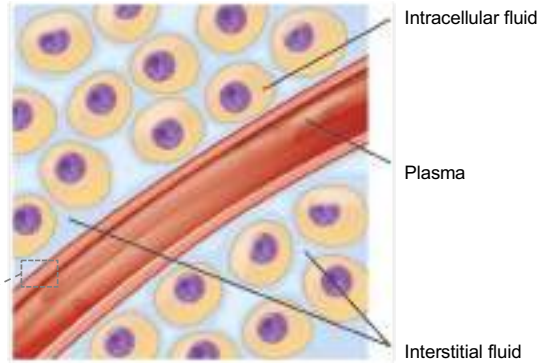
Good Point-of-Care Testing
For real diagnostics

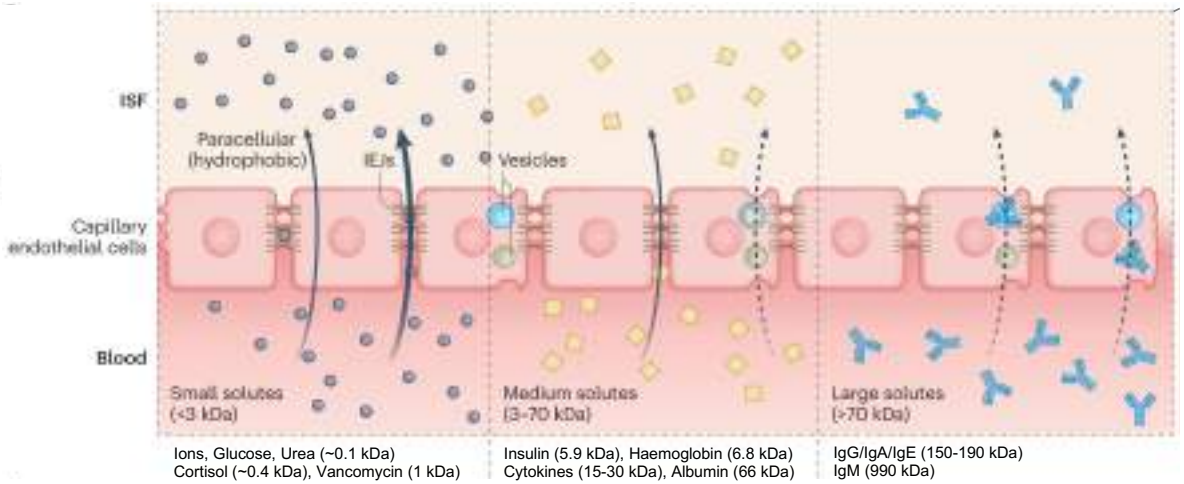
1. Motivation: Interstitial fluid (ISF) sampling for medical diagnosis

Dermal ISF: Potential bodily fluid for medical diagnosis

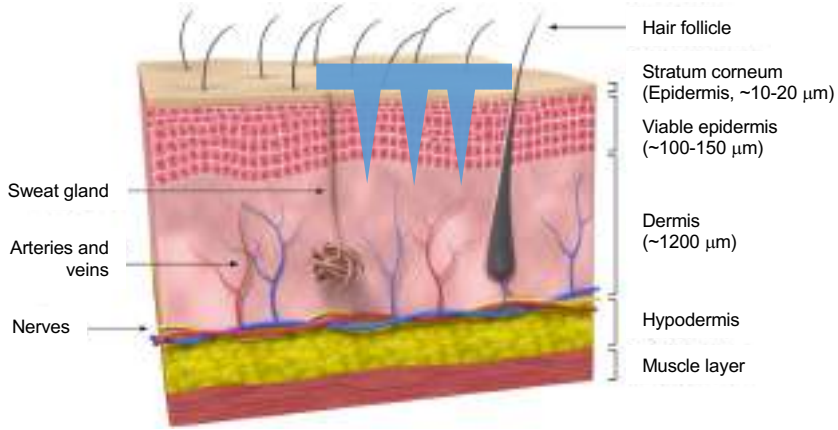
Interstitial fluid (ISF) is a bodily fluid naturally produced via trans-capillary blood exchange that surrounds cells within tissues.

Dermal ISF, ISF within the skin, is commonly thought to be roughly equivalent to blood in terms of biomarker composition. Because it is present near the skin's surface, it could enable easier access to biomarkers without the pain or clotting associated with blood draws.



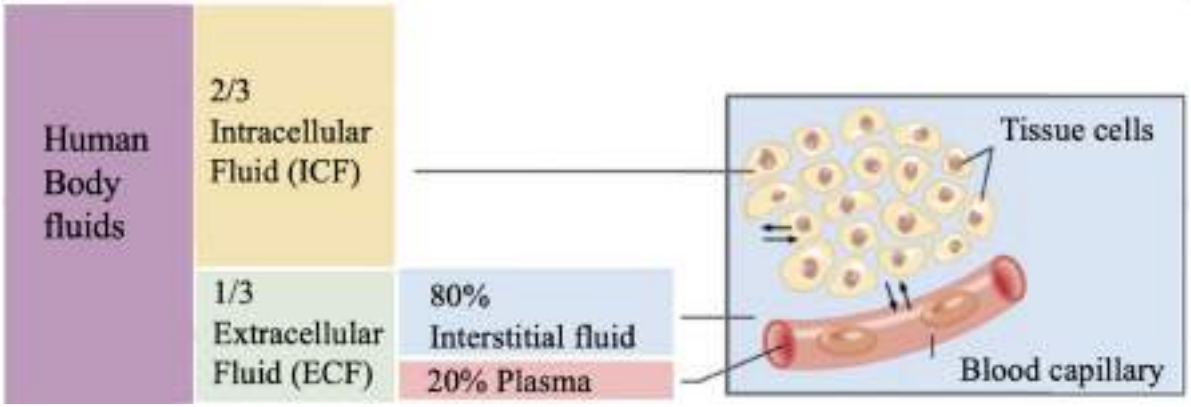


Microneedles for dermal ISF sampling



Nature Biomedical Engineering, 2023, 7, 1541-1555. *Trends in Analytical Chemistry*, 2021, 135, 116148.

Interstitial fluid (ISF) for biomarker analysis



The **interstitial fluid** (ISF) refers to the human body fluid surrounding cells and tissues that accounts for about 80% of extracellular fluid, serving as bridge between blood and cells for biomarker exchange.

	Na^+	Lactate	Glucose	Cortisol	Drugs	Cytokines	Antibodies
Blood plasma	135-145 mM	0.5-10 mM	4.1-6.9 mM	Tens of nanomolar	Related to dose	Picomolar to nanomolar	Varies
ISF	Similar to plasma	Similar to plasma	Similar to plasma	Similar to plasma	Similar to plasma	80% of plasma	15-25% of plasma
Saliva	Tens of millimolar	Tenths of millimolar	~1% of plasma	Similar to plasma	Similar to plasma	Local dominates	Local or diluted
Sweat	Tens of millimolar	~5-10 mM	~1% of plasma	Similar to plasma	Similar to plasma	<0.1% of plasma	Local or diluted

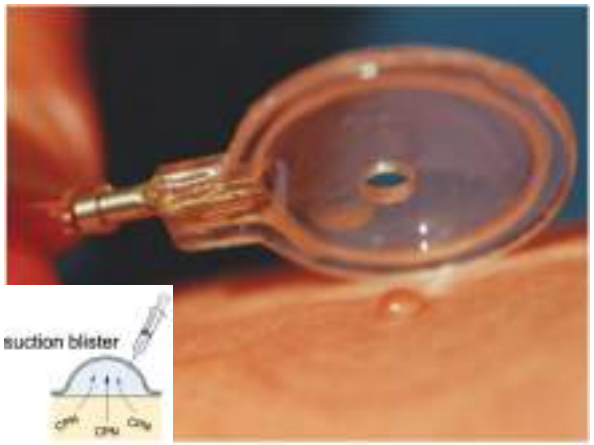
- ➢ Similar biomarker composition with blood
- ➢ Related concentration to blood
- ➢ Distinct proteins present in ISF

Concentration range of Glucose
blood plasma: 2- 40 mM
ISF : 1.99-22.2mM
Saliva : 0.008-1.77mM
Sweat : 0.01-1.11mM
Tears : 0.05-5mM

https://www.lecturio.com/concepts/body-fluid-compartment/
Heikenfeld, J., Jajack, A., Feldman, B. et al. Accessing analytes in biofluids for peripheral biochemical monitoring. Nat Biotechnol 37, 407–419 (2019).

Conventional ISF sampling methods

Access to ISF from skin dermal layer



Suction blister

Open flow microperfusion

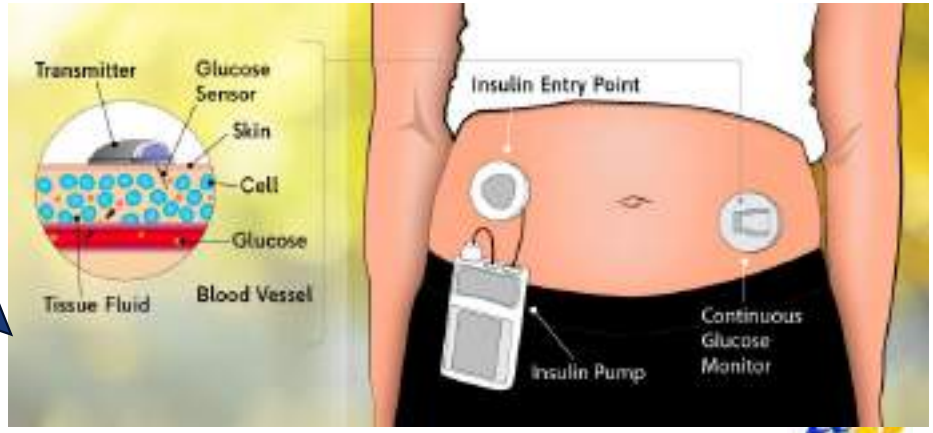
- Complex components and process
- Require for medical expert
- Tissue damage and skin injuries

Ventrelli L, Marsilio Strambini L, Barillaro G. Microneedles for transdermal biosensing: current picture and future direction. ***Advanced healthcare materials***, 2015, 4(17): 2606-2640.
https://kennedylab.med.umn.edu/skin-blister-device
https://www.joanneum.at/en/health/infrastructure/open-flow-micro perfusion

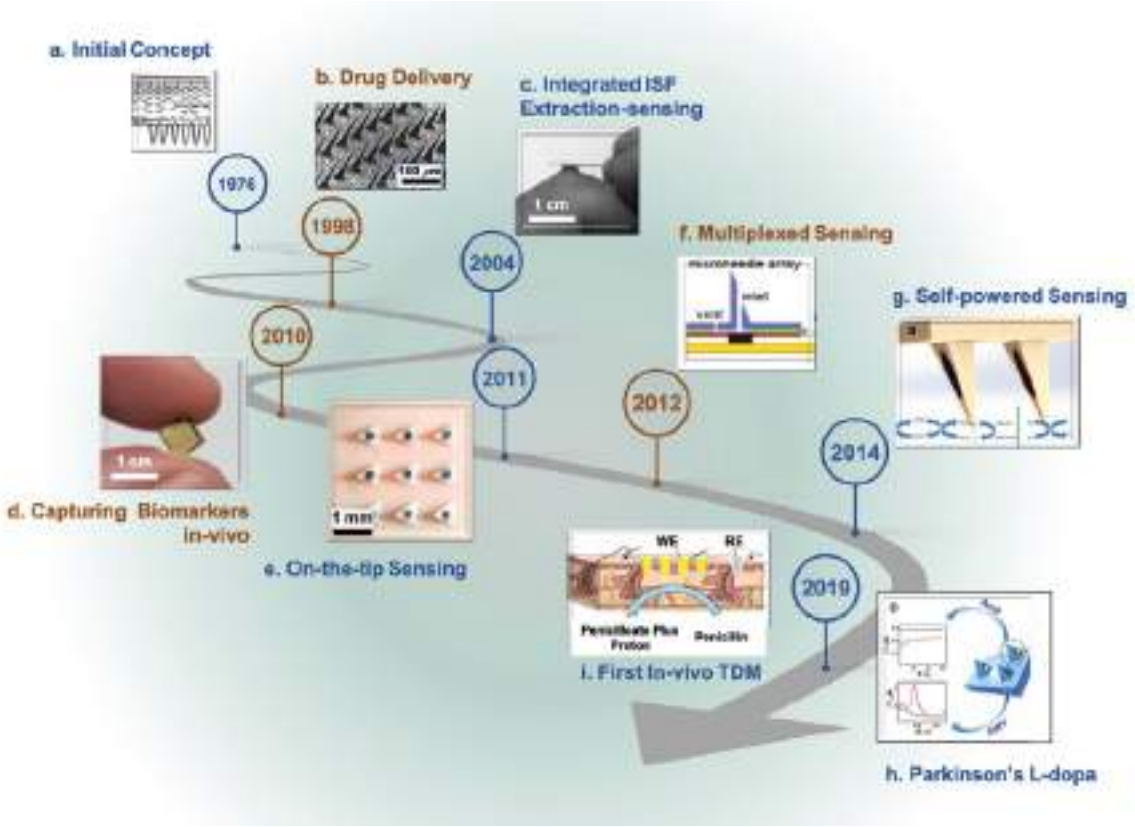
Currently one example

CGM
(Continuous Glucose Monitoring)

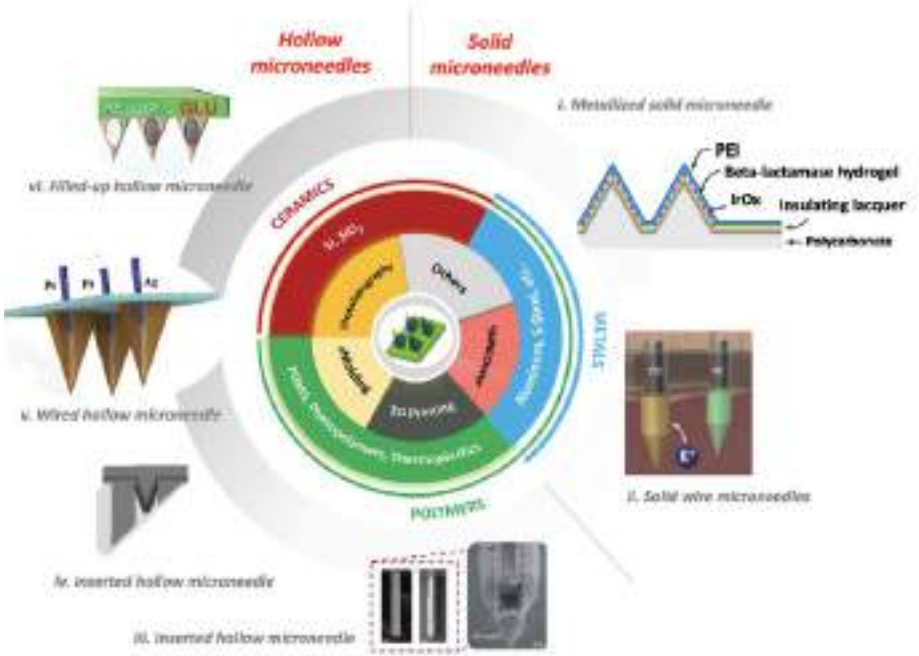
©Abbott.



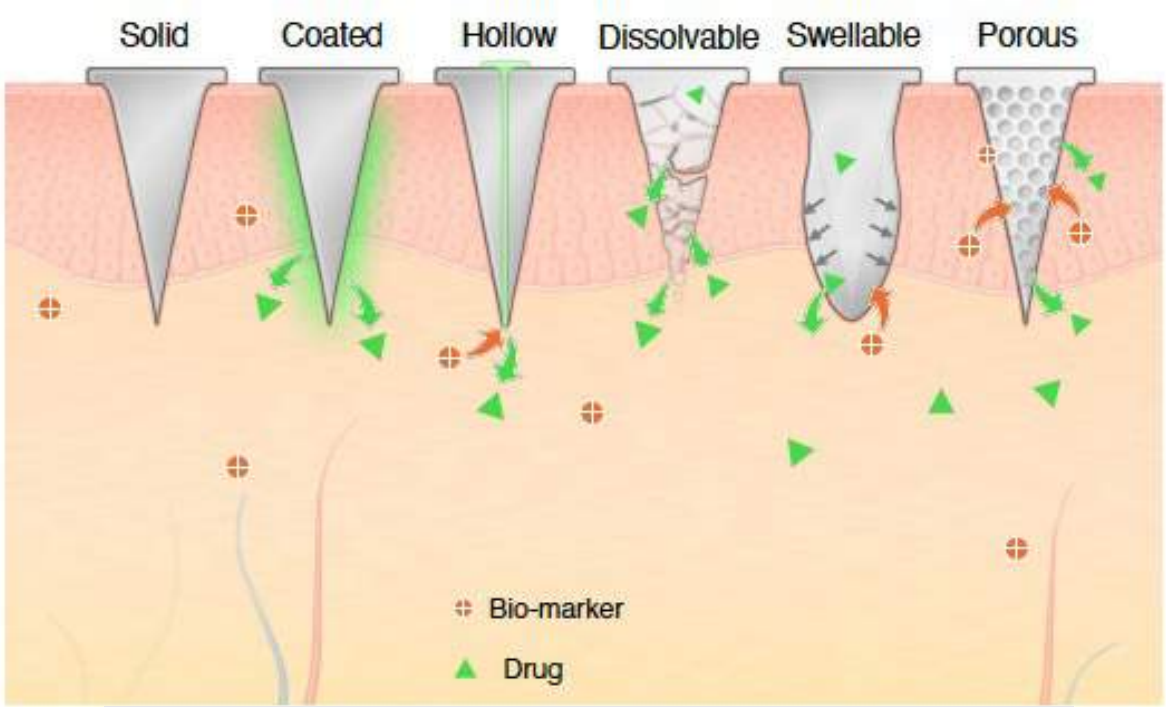
Major accomplishments in history of MAP, with focus primarily on sensing applications



H.Teymourian, et al. ***Adv. Healthcare Mats.***, 2021



ISF sampling via microneedles (MNs)



- **No need** for medical expert during usage
- **Simple** and **low-cost** access to dermal ISF
- **Minimal invasive** manner

Hollow MNs

- Cumbersome fabrication process
- Channel congestion
- Non biodegradable material

Swellable MNs

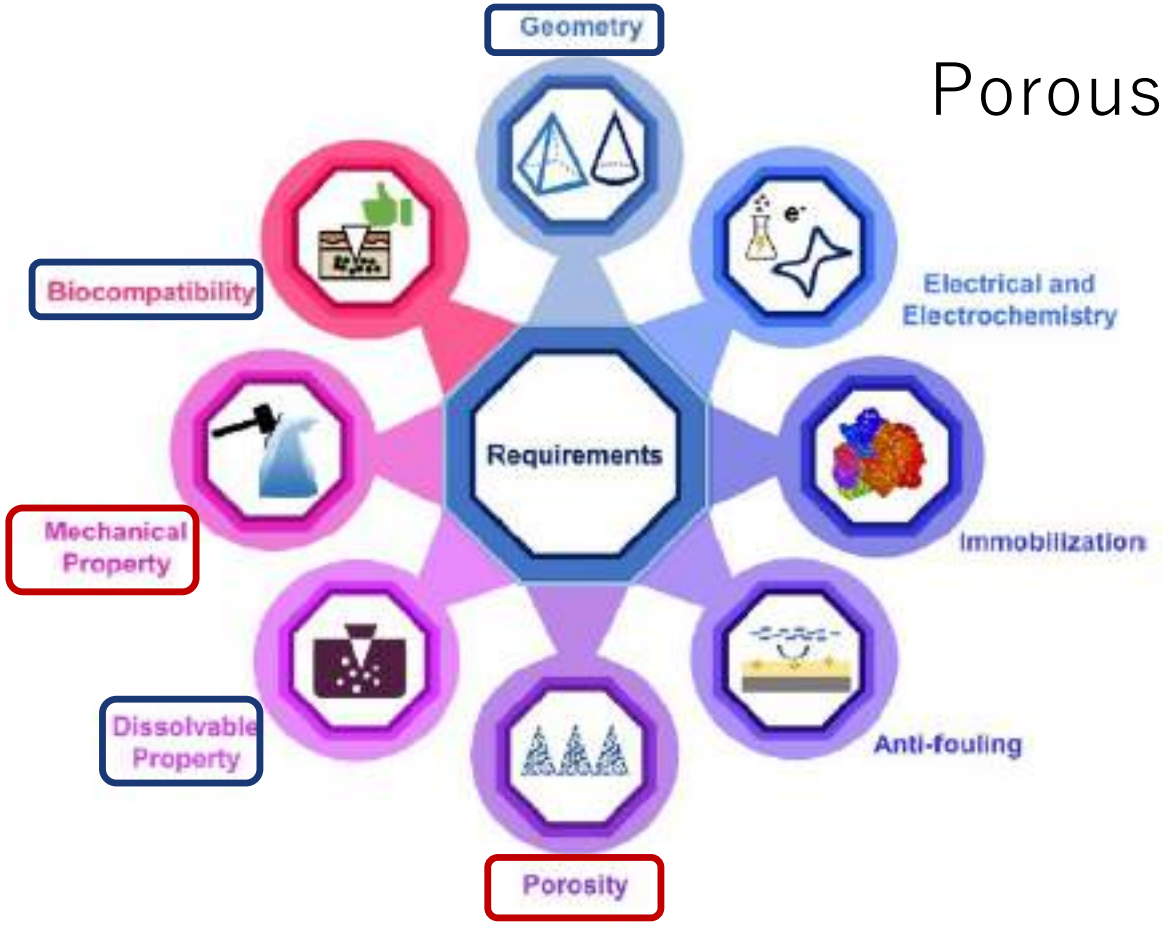
- Post processing and sample recovery
- Medical expert or laboratory analysis

Porous MNs

- **ISF extraction with capillary force**
- **Biodegradable polymer material**
- **Biosensor integrated onto MN substrate**

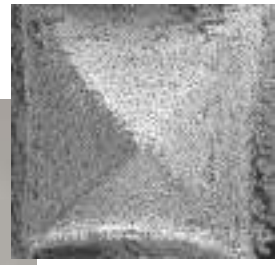
Bao, L., Park, J., Bonfante, G. et al. Recent advances in porous microneedles: materials, fabrication, and transdermal applications. ***Drug Deliv. and Transl. Res***. 12, 395–414 (2022).

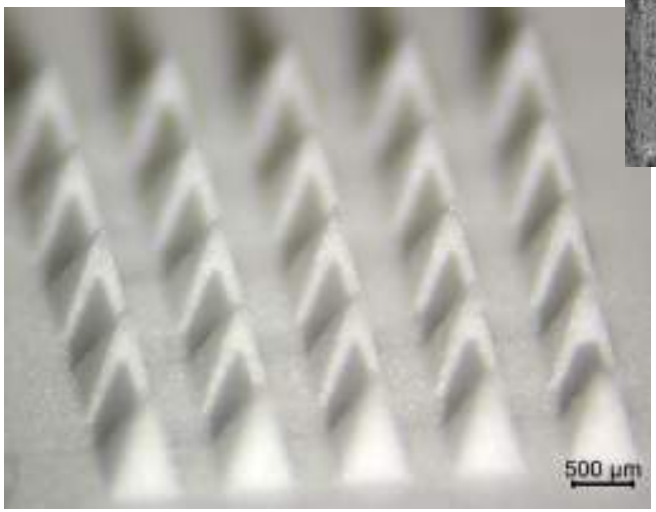
Requirements



H. Abdullah, et al. ***Microchimica Acta***., 2022

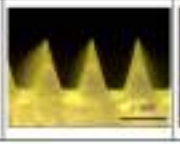
Porous MAP

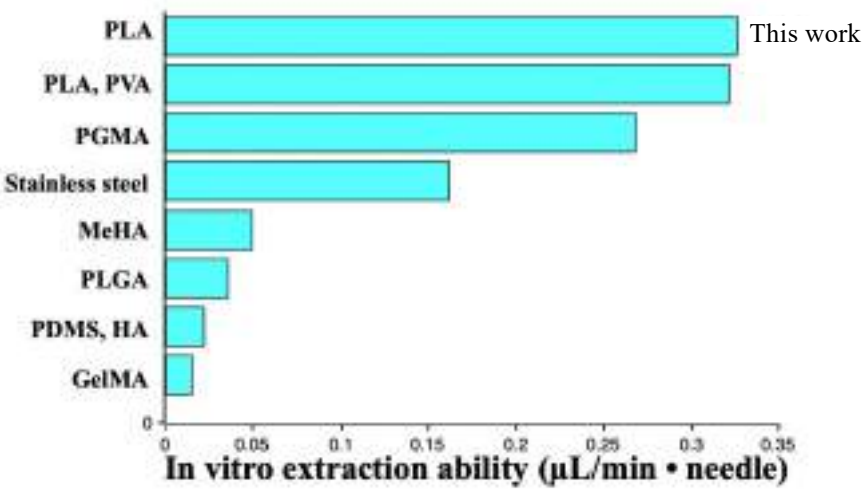




Biodegradable PLA porous MN array patch

Several Porous MAPs in KimLab

Fabrication technique	Hot embossing	Porogen leaching			Single emulsion	Microfluidic
Material	Stainless steel	PDMS,HA	PLGA	PGMA	PLA,PVA	PLA
Failure force (N)	0.52	0.34	0.34	1.35	0.93	0.19
Porosity (%)	36	**60~80**	**30~65**	**36~49**	23.4	53
Pore size (μm)	2.22	30-60	5-15	1		**6.6~16.8**
In vitro extraction (μL/ min • needle)	0.162	0.022	0.036	0.268	0.322	0.326
Optical Microscopy						



➢ Porous MN array extraction ability increased by regulating pore size distribution under same porosity when using microspheres of different sizes for MN fabrication.

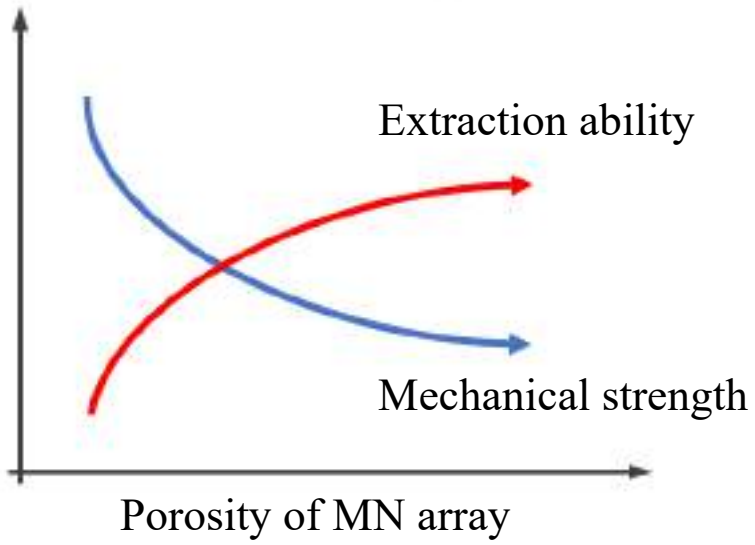
Further Tasks

- Porous MN extraction ability improvement using smaller microspheres or surface modification.
- In vivo extraction ability test on rat dorsal skin for practical application.

Current fabrication and problem of porous MNs

High extraction ability required for porous MNs based biomarker analysis → Increase extraction ability by regulating **porosity** → Tradeoff problem between extraction ability and mechanical strength

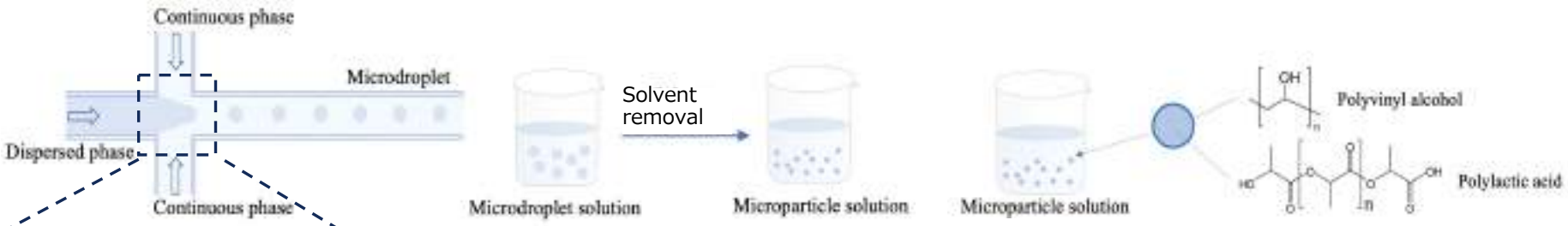
Fabrication method	Material	Porosity (%)	Pore size (μm)
Hot embossing	Stainless steel	36	2.22
Porogen leaching	PDMS	**60 ~ 80**	30-60
	PLGA	**30 ~ 65**	5-15
	PGMA	**36 ~ 49**	1
	PGMA		0.26
Phase inversion	CA	**40 ~ 90**	
	PSF-PDA-PEG		6.8
Single emulsion	PLA, PVA	23.4	

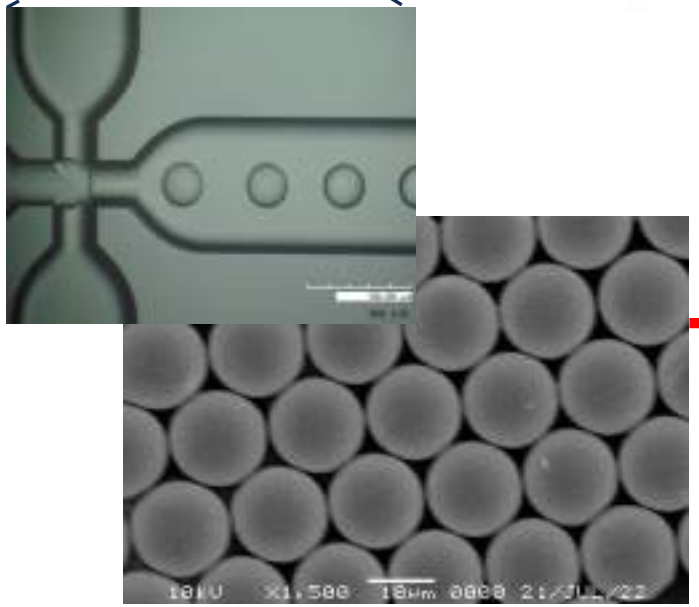


Porous MN array made with different materials for ISF sampling

Biosensor MNP (Porous MN details)

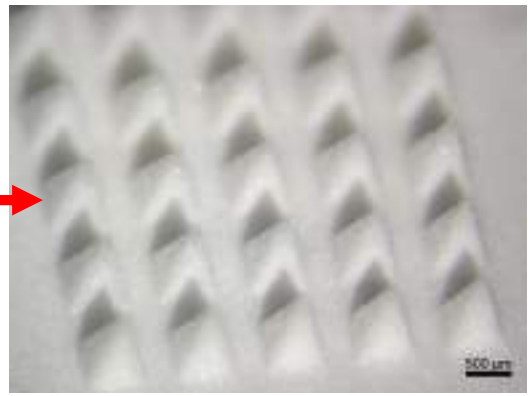
Microparticle preparation using Shear Flow focusing microfluidic technology

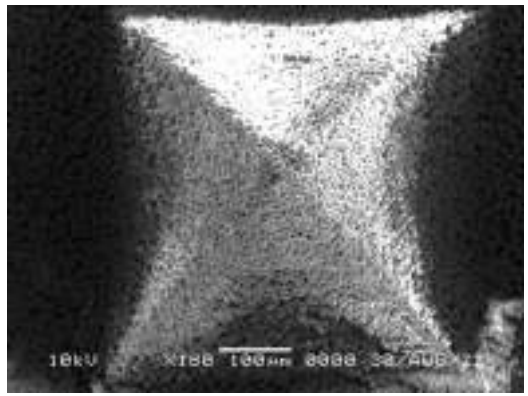




Fabricated PLA microparticles

Micro molding

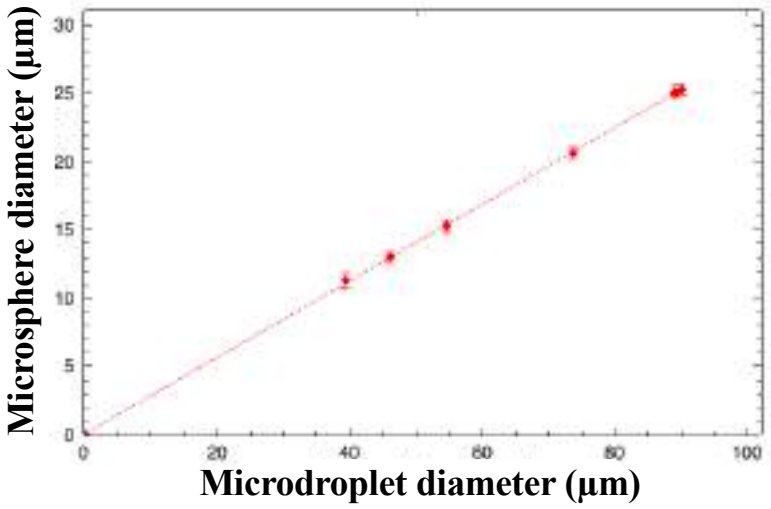


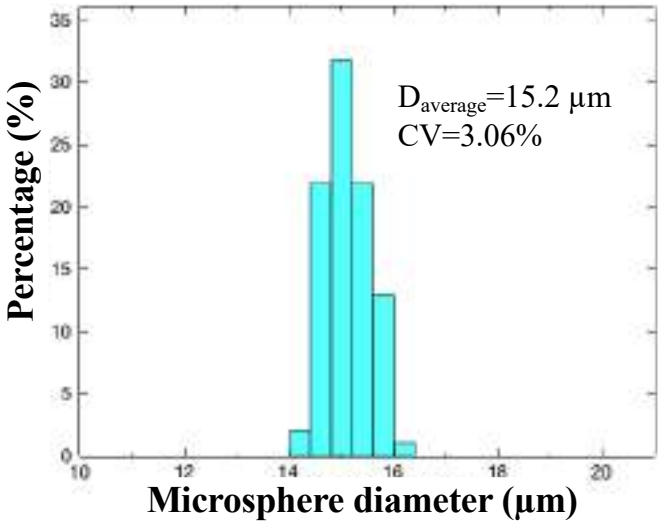


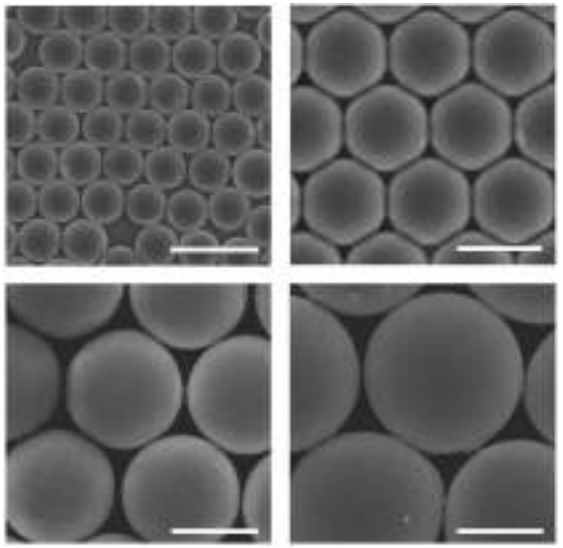
PLA porous MNP composed of bonded microparticles

Microsphere production

Microsphere characterization







Monodisperse microspheres of different sizes.
Scale bars: 20 μm

Shrinkage ratio = D_s / D_d = 28.05%

(R^2 = 0.99 , 1% PLA/DCM)

D_s : Microsphere diameter (μm)

D_d : Initial microdroplet diameter (μm)

(variable by changing dispersed phase concentration)

CV = σ / D = 2-6 %

CV : Coefficient of variation

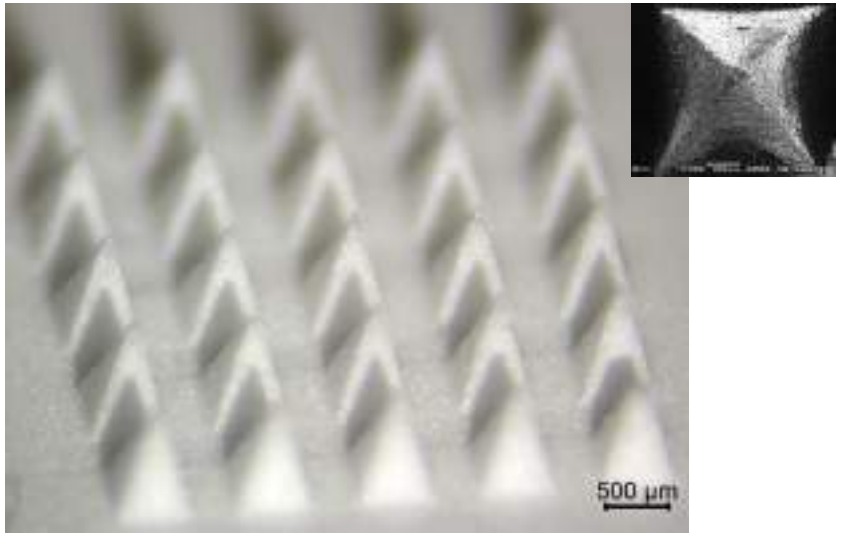
σ : Standard deviation of microsphere diameter (μm)

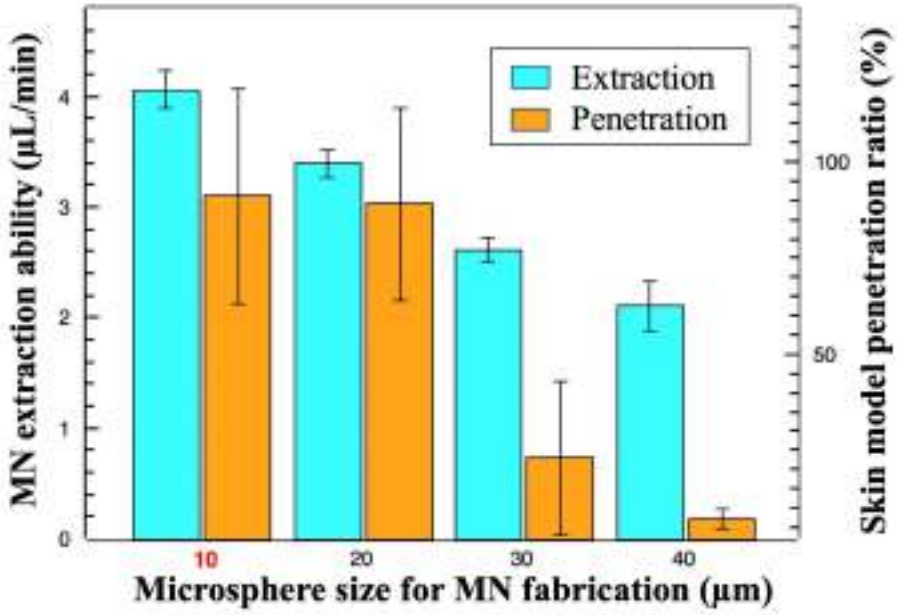
D : Mean diameter of microspheres (μm)

➢ Monodisperse PLA microspheres with controllable diameters from 10 μm to 50 μm

Experiments and results

Microneedle array optimization and evaluation





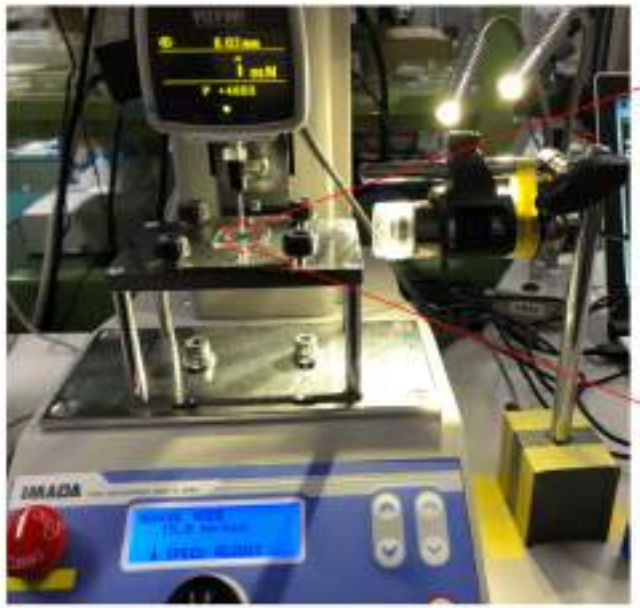
Microneedle array dimension

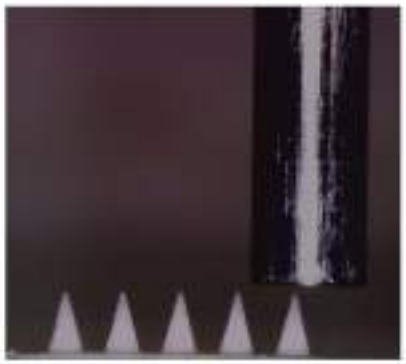
- Height : 1060.6 ± 12.4 μm
- Base width : 596.8 ± 19.4 μm
- Tip diameter : 26.1 ± 6.1 μm

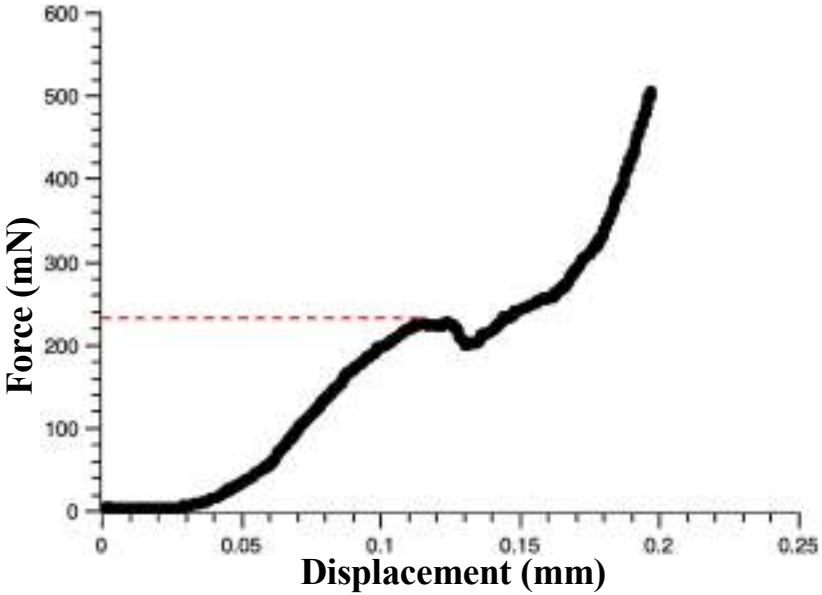
➢ Porous MNs fabricated using 10 μm microspheres had better extraction ability and mechanical strength than that of 20 μm microspheres.

Experiments and results

Microneedle array optimization and evaluation



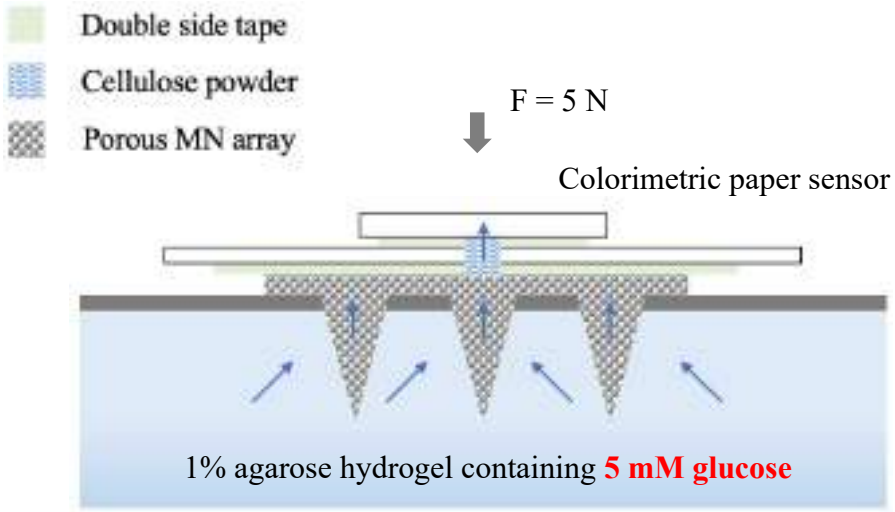




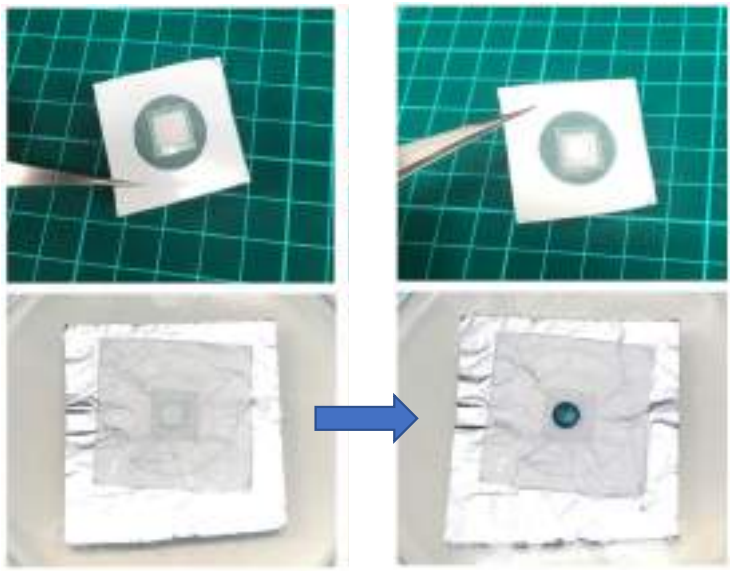
- Average failure force of porous MNs made with 10 μm microspheres was 189.4 mN, larger than the force required for human skin insertion (58 mN).
- Average failure force of porous MNs made with 10 μm microspheres larger than that of 20 μm microspheres (137.7 mN).

Experiments and results

Microneedle array optimization and evaluation



Porous MN array integrated sensing system for glucose detection

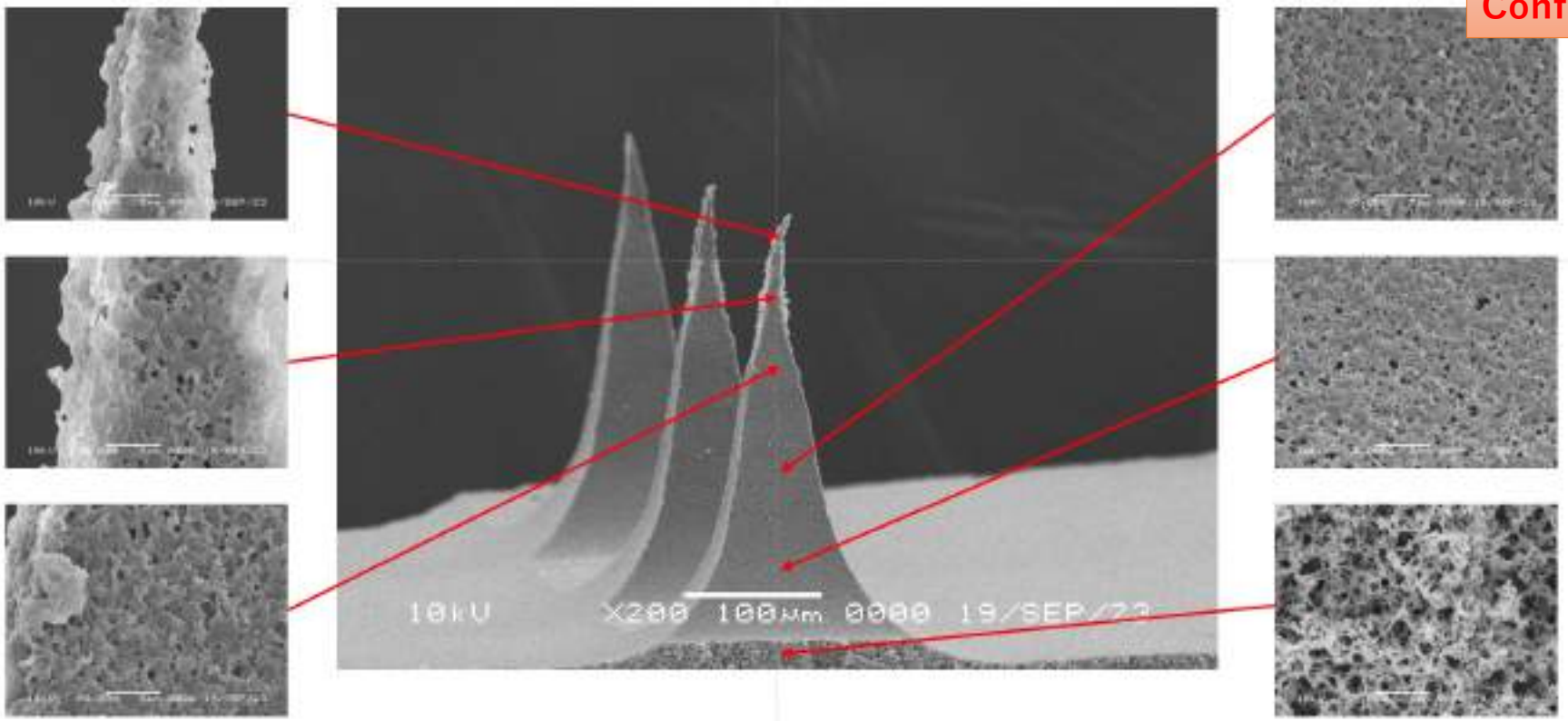


Right after MN application 3 min after application (color change)

- Porous MNs made with 10 μm microspheres could extract 8.14 μL sample fluid from human skin model in 1 min and saturated within 3 min when pressed with 5N (0.326 μL/min for each needle).
- When integrated to glucose sensing system with sensor on the back of MN array, the colorimetric paper sensor started to change color after 2 min and saturated within 10 seconds.

New Porous MAP by using Nonsolvent-induced Phase Separation Method (NIPS)

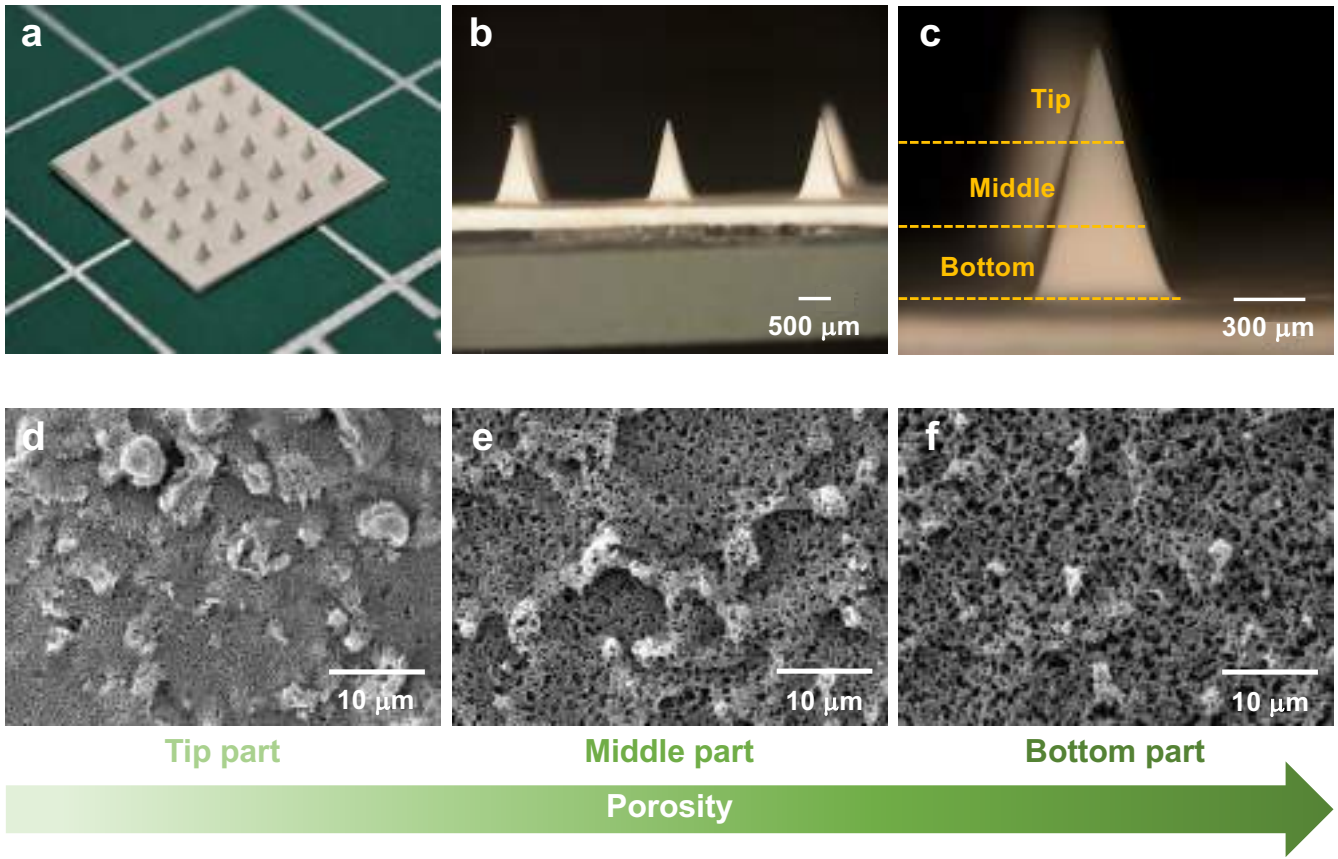
Confidential



・ニードル先端部から底部まで，気孔率が大きくなる傾向を示す
・基板の気孔率が大きいことがわかる

Patent 特願 2024-074962
Nano Select 2024 In printing

3. Morphology of porous PGA microneedle array patch (MAP)



MN length: avg. **~1069 μm**

Base length: avg. **~601 μm**

Array: **5×5**

Substrate thickness: avg. **~267.5 μm**

Patch dimension: **12 mm×12 mm**

Gradient distribution property of micropores on porous PGA MNs.

Fig. 2 Morphology of the fabricated porous PGA microneedle array patch (MAP).

4. Porosity and mechanical property of porous PGA microneedle array patch (MAP)

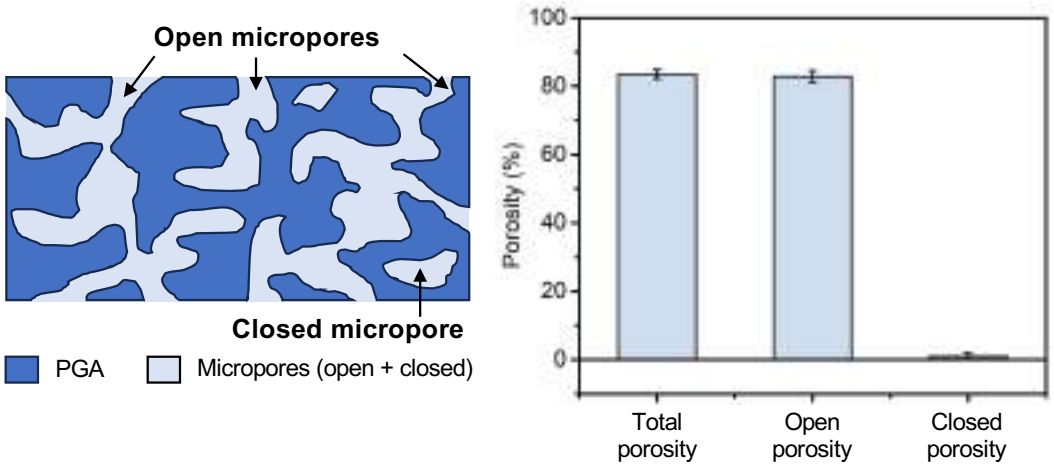


Fig. 1 Porosity evaluation of the porous PGA MAP based on Archimedes' principle.

- **The open porosity and total porosity** of the porous PGA microneedle array patch (**without filter paper**) are **82.79 ± 1.73%** and **83.50 ± 1.33%**, respectively, exhibiting a **high porosity.**
- **Majority of micropores** formed on porous microneedle array patch are **well interconnected** according to **1.91 ± 1.00% of the closed porosity (i.e., the difference between the P_{open} and P_{total})**.

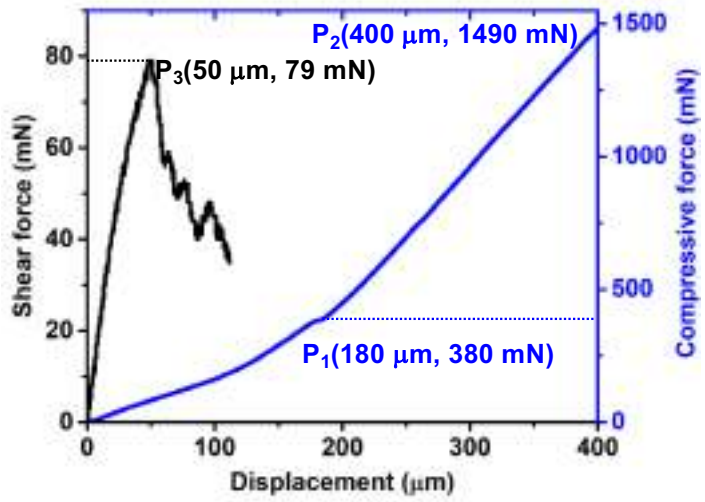
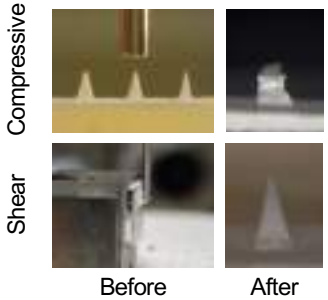
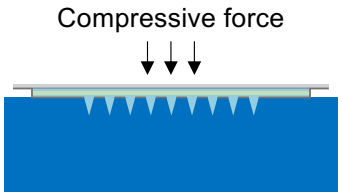


Fig. 2 Mechanical property of the porous PGA microneedles



The porous PGA microneedles have the **failure force** of **380 mN** and **79 mN** in **vertical** and **shear** direction, respectively, which are large enough for piercing skin (> **58 mN**) and sampling dermal ISF.

5. Extraction evaluation of porous PGA microneedle array patch (MAP)



Glass sheet Double-side tape

Porous PGA MAP Filter paper

Aluminum foil: 12 μm-thickness

Agarose gel: 1% methylene blue, 1% agarose

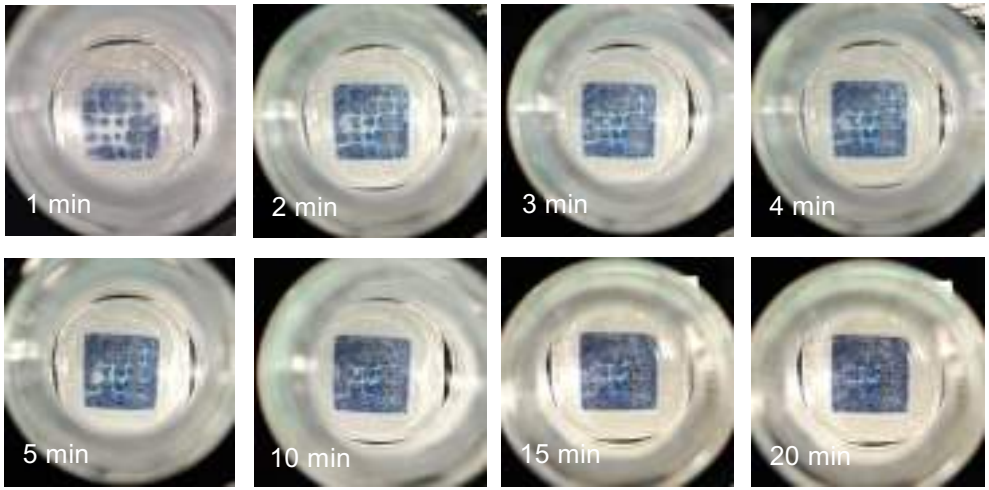
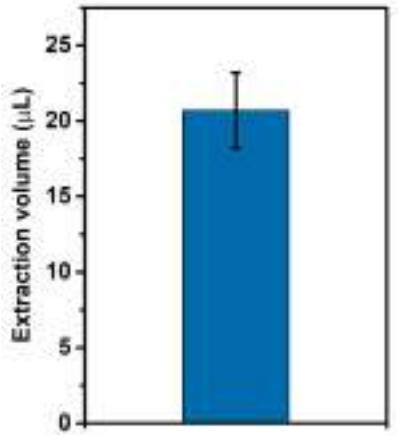
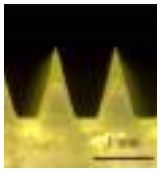
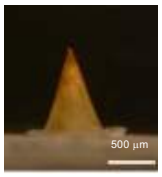
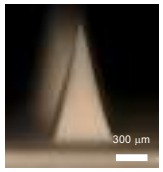


Fig. 1 Back side-view of extraction process.



Result 1: The porous PGA MAP (with filter paper) can extract **20.69±2.50 μL-liquid under 0.2 N-force in 20 min.**

Table 1 Comparison in extraction ability of the porous PGA MAP with others (all Kimlab. porous MNs)

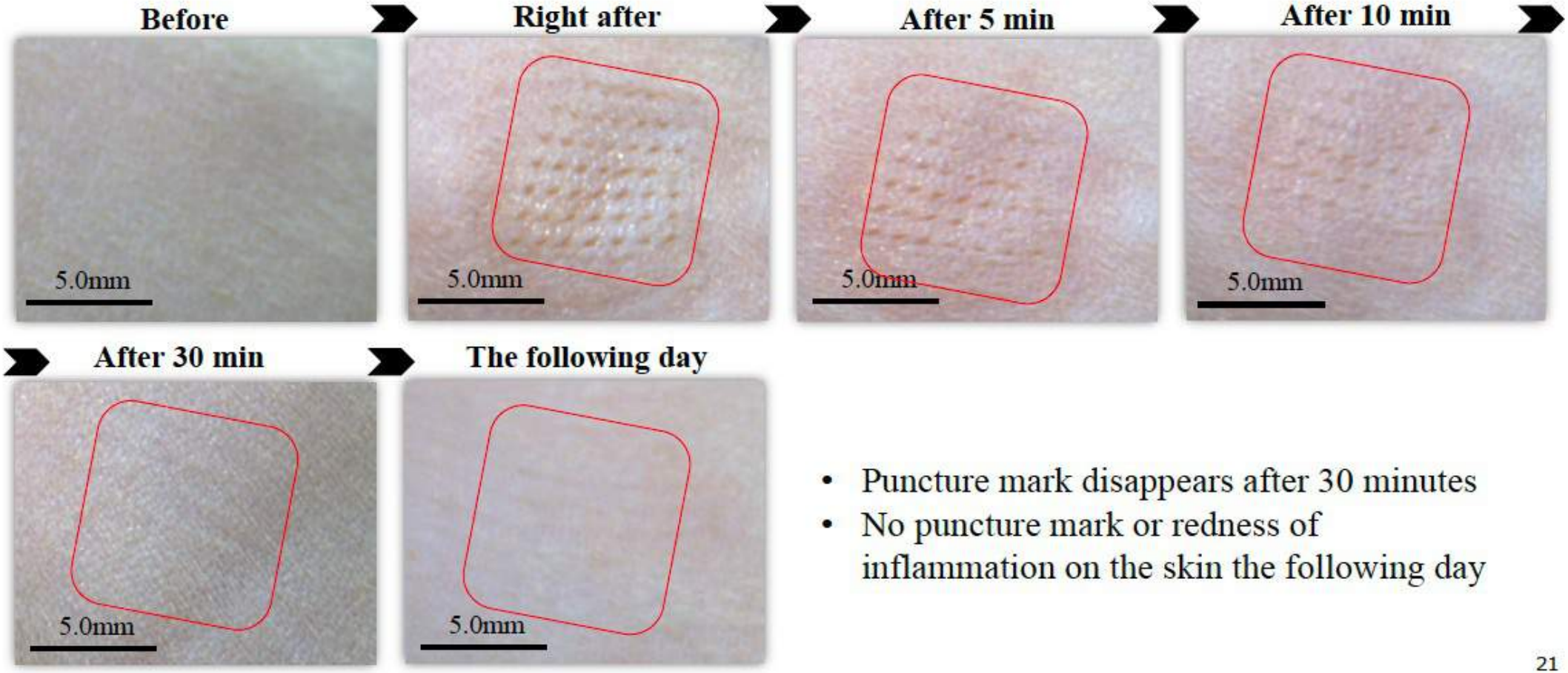
Material	PDMS, HA	PLGA	PGMA	PLA, PVA	**PGA**
Porous MAP sample					
Rate (μL/min·needle)	0.022 1st. generation	0.036	0.268	0.322	**0.693**

Result 2: The porous PGA MAP has the **highest liquid extraction rate** than others.

(PGA:1 N-force for 1 min; others: 5 N-force for 1 min)

4. RESULT

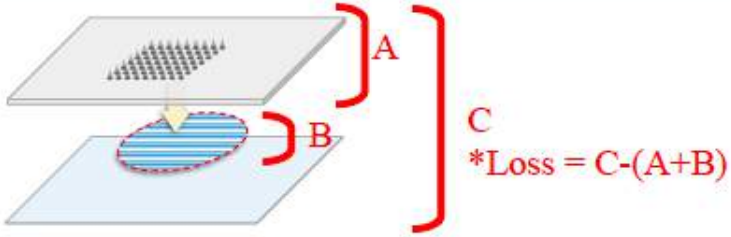
III. In vivo: with animals

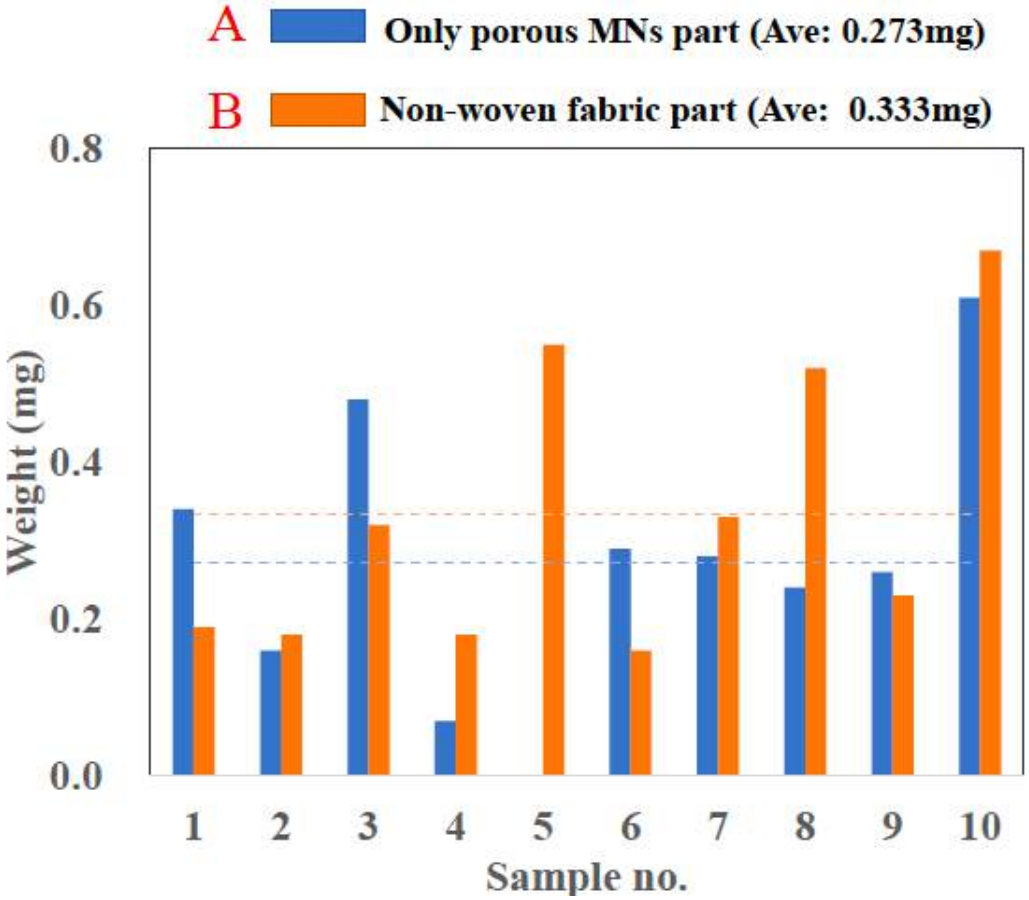


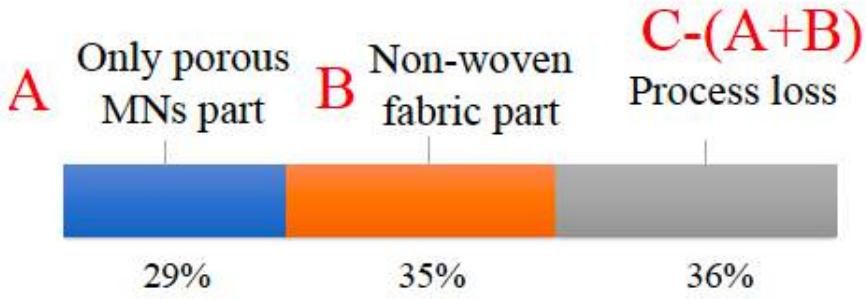
- Puncture mark disappears after 30 minutes
- No puncture mark or redness of inflammation on the skin the following day

4. RESULT

III. In vivo: with animals







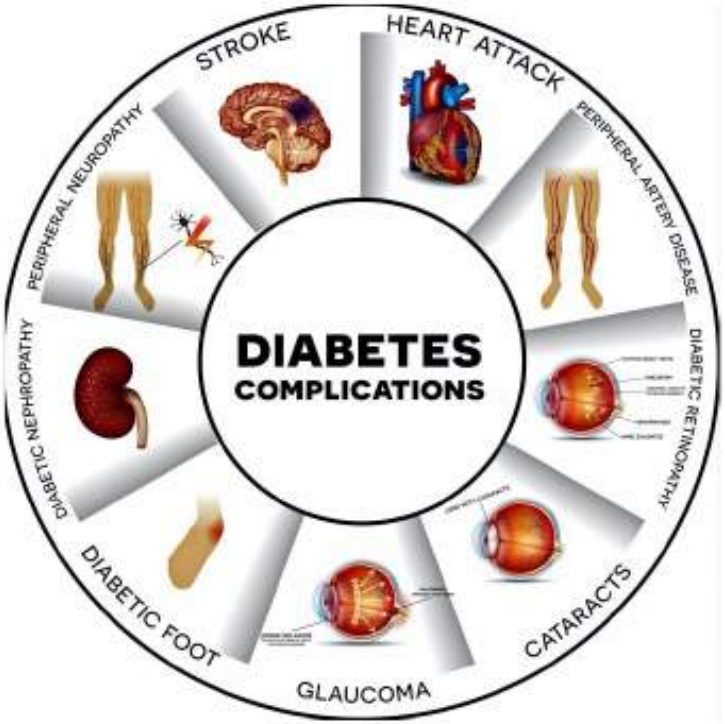
- B absorption decreased and losses increased. (Loss ratio:26→36%)
- Variation from sample to sample
- Less absorption than agarose gel

Diabetes Mellitus

1 in 11

It is estimated that 415 million people are living with diabetes in the world.

Diabetes is a leading cause of death and disability worldwide.



GROWING DANGER

Type 2 diabetes increasing in every country every year.
78,000 children develop type 1 diabetes every year

GOVERNMENT NEEDS

Diabetes caused at least 465 billion USD in healthcare
expenditures in 2011.
(11% total healthcare expenditures in adults)

More Problems

LIMITED DIAGNOSTIC SOLUTIONS

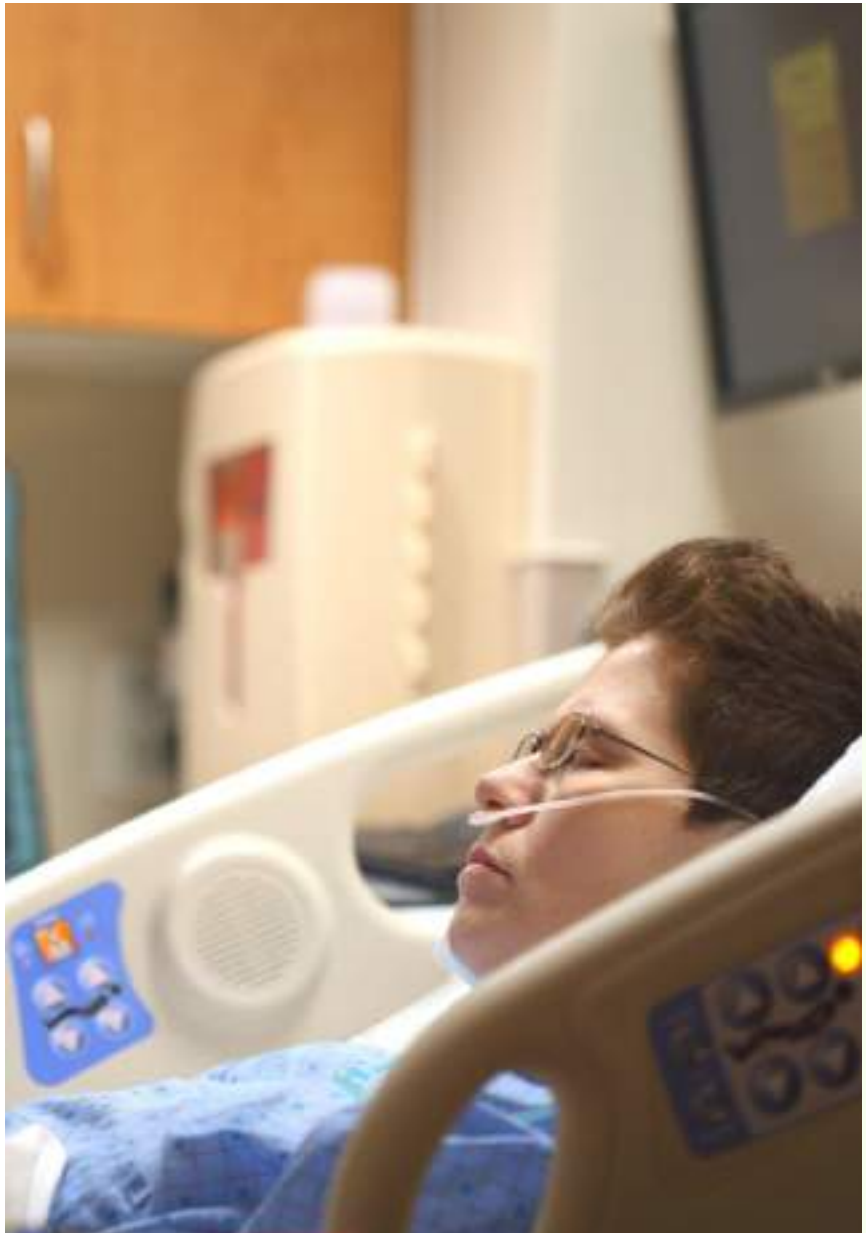
Current devices are expensive and obtrusive for pre-diabetes and diabetes patients. The blood collecting process is painful, requires administration, and nobody has the time for it these days.

80% ARE NOT AWARE

Approximately 88 million American adults—more than 1 in 3—have **pre-diabetes**. Of those with pre-diabetes, more than 80% don’t know they have it.

80% CAN'T AFFORD

Nearly 80% of people with diabetes live in low and middle-income countries. Current mass glucose monitoring solutions are expensive for governments .



Why Now?

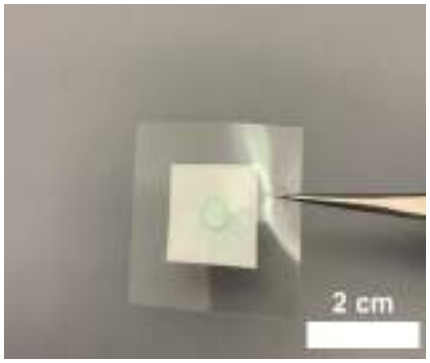
ACT BEFORE IT'S TOO LATE

Worldwide diabetes can be treated and its consequences avoided or delayed with diet, physical activity, and medical treatments but most importantly: Regular Diagnostics.

Application of device

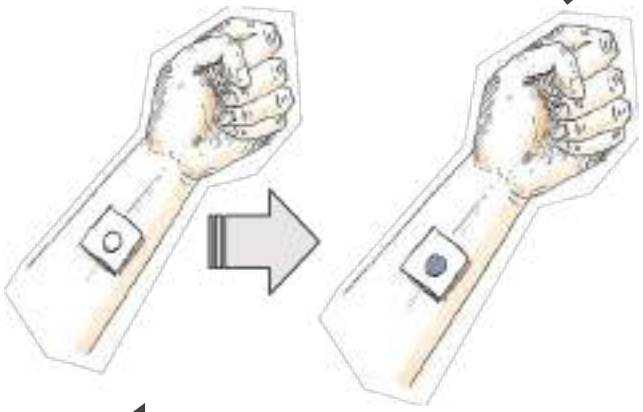
Preparation

With adhesion tape



Attachment to the skin

Attach and analysis

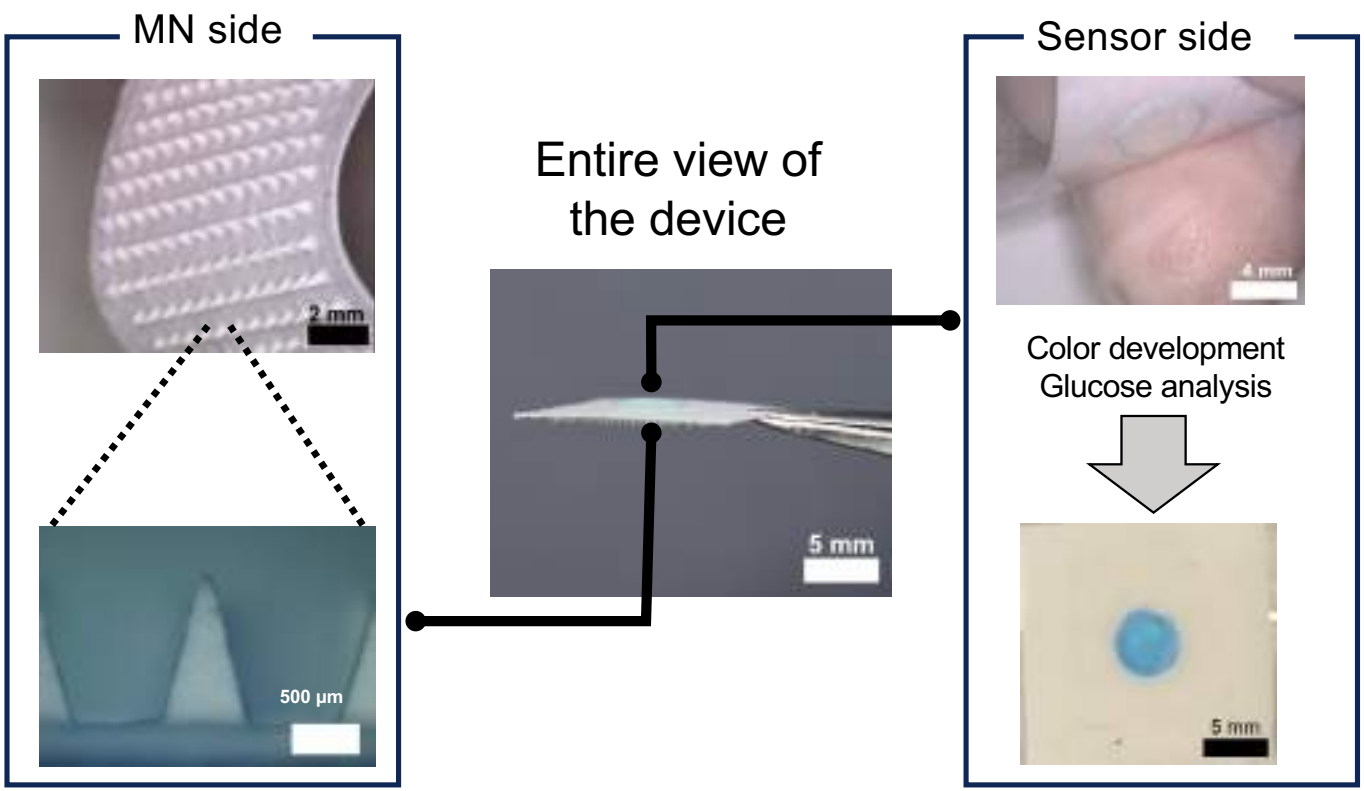


Alert to the user

Disposal

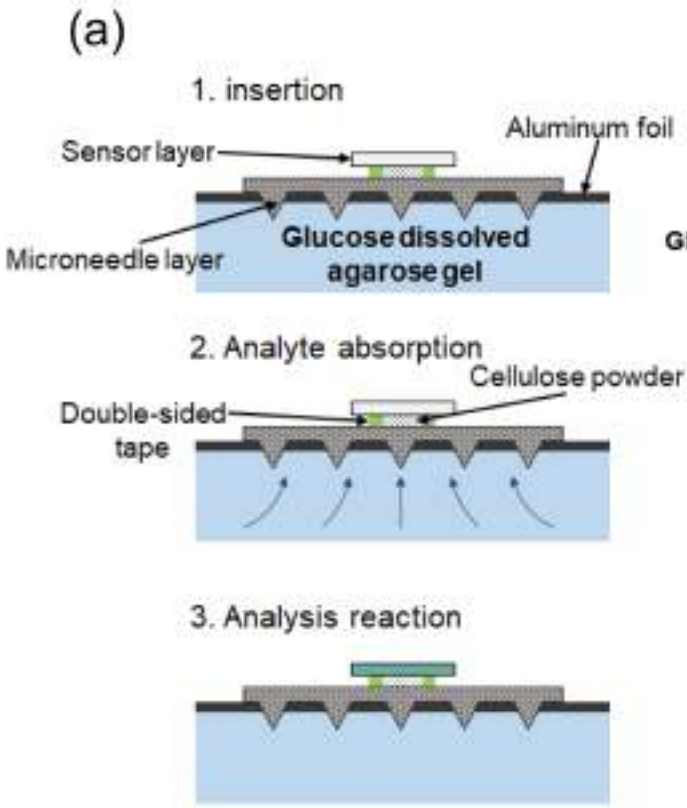
Release from the skin

Results of fabrication



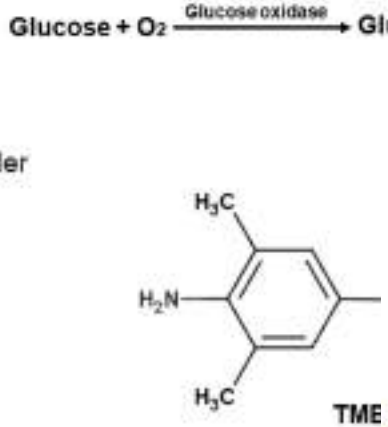
Research object 1 : porous MN
Research object 2 : PLGA biodegradable polymer

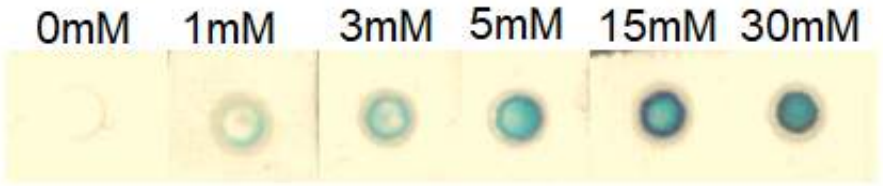
Research object 3 : Integration with paper-based sensor

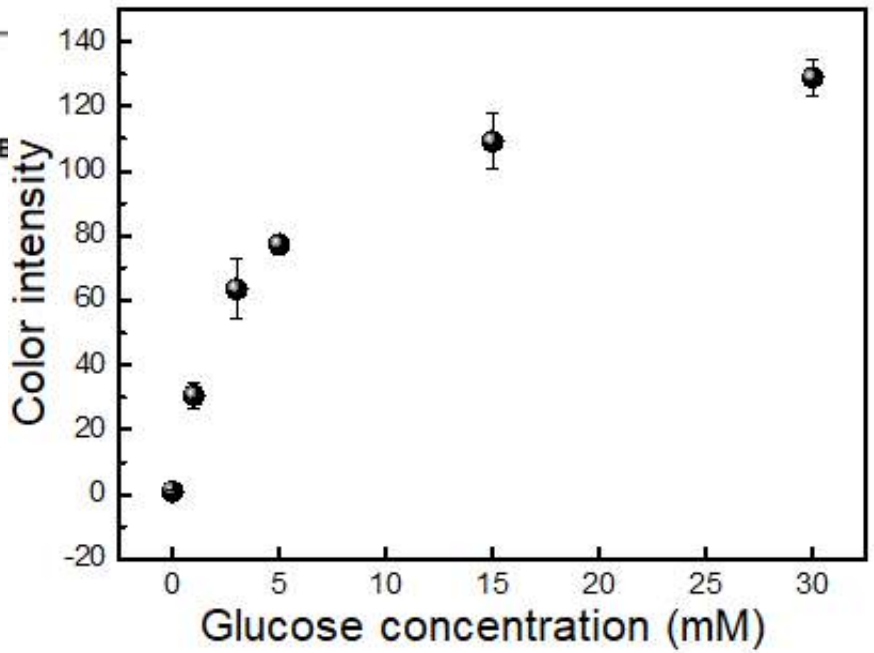


既に動物実験に

Glucose oxidase, peroxidase (2 enzyme) and TMB dye



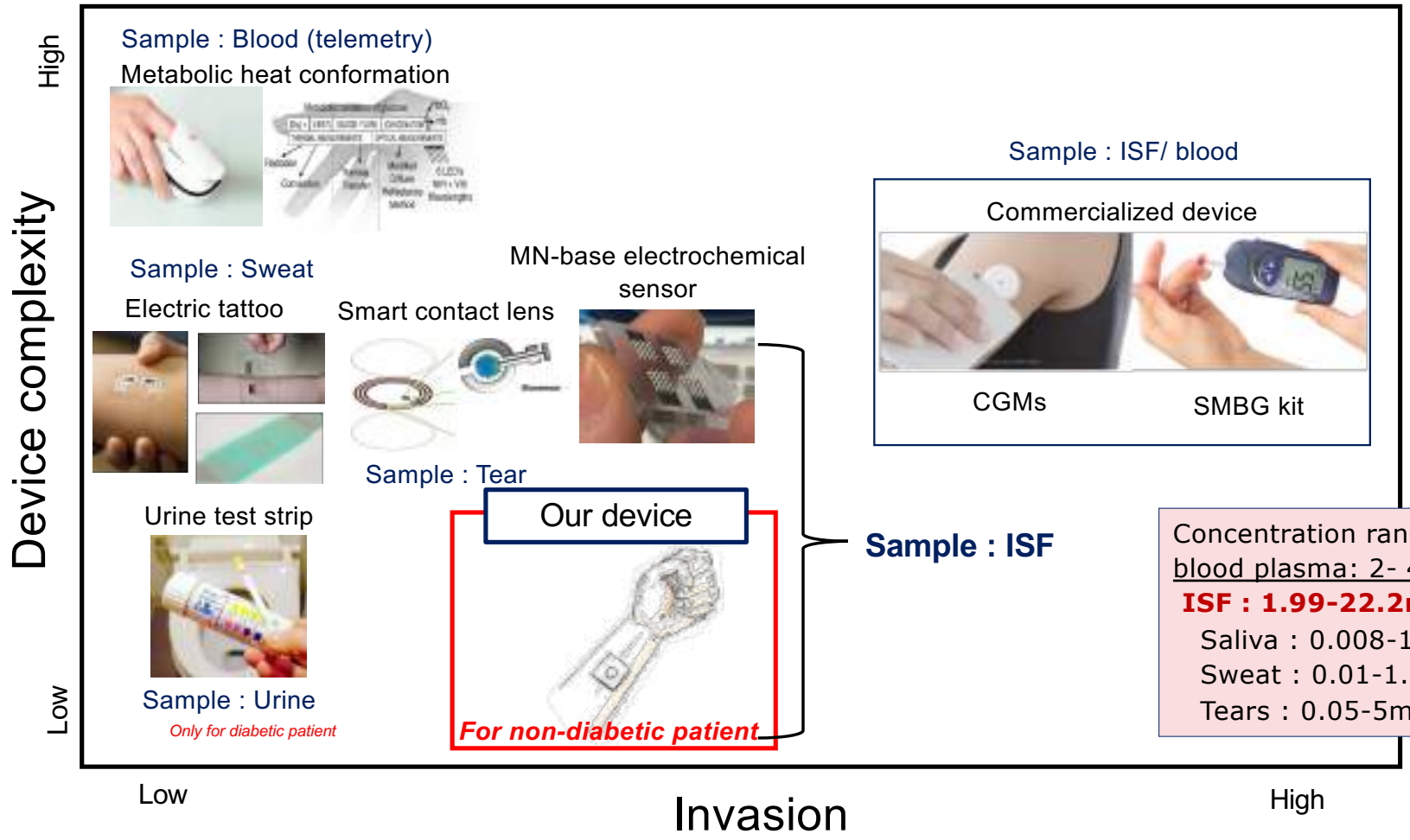




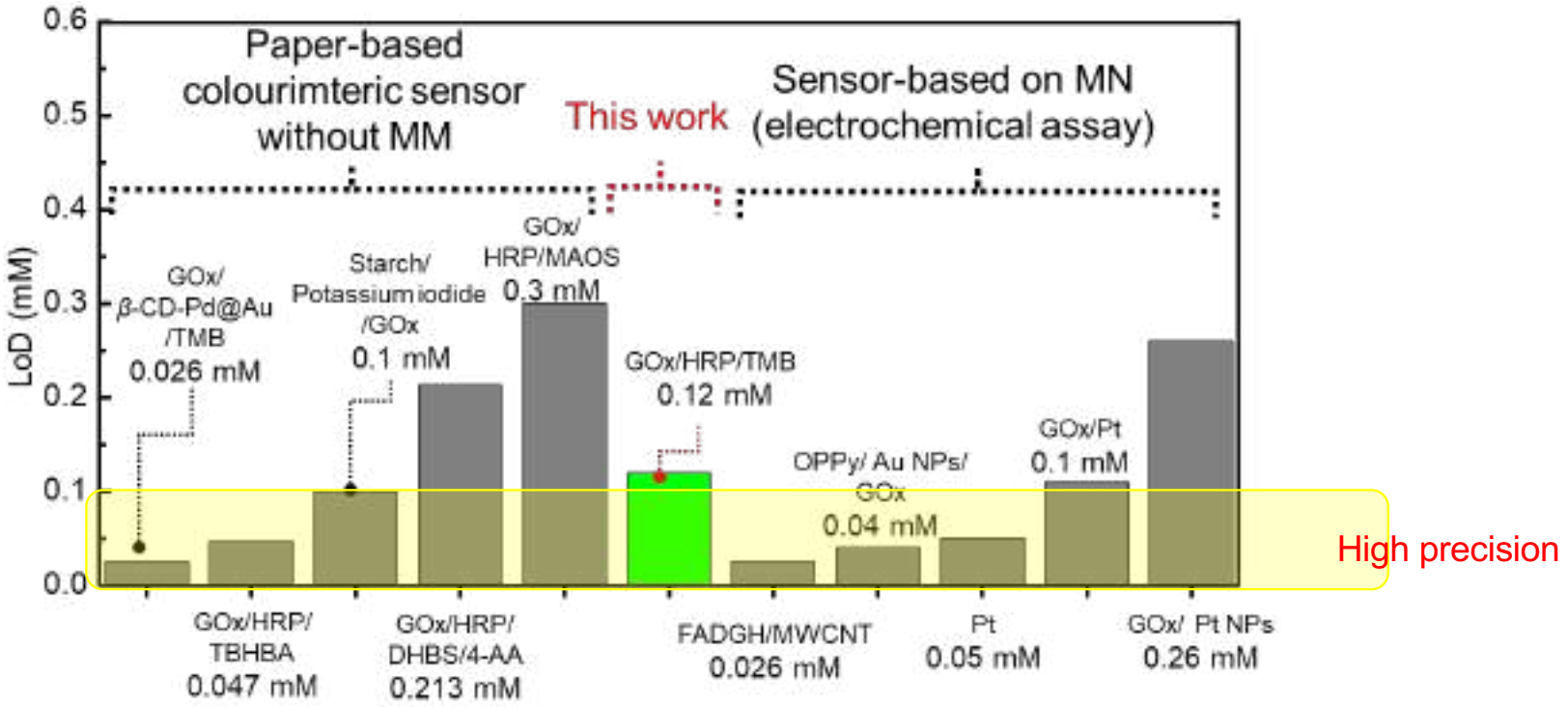
- Capillary driven(毛細管力)- 35 nL /min./一本
- Within 2 min.

Medical Devices & Sensors **2020** *(July)*
Collaboration with Minami Lab.

Comparisons with previous study on glucose monitoring



Comparison of with previously developed glucose sensor

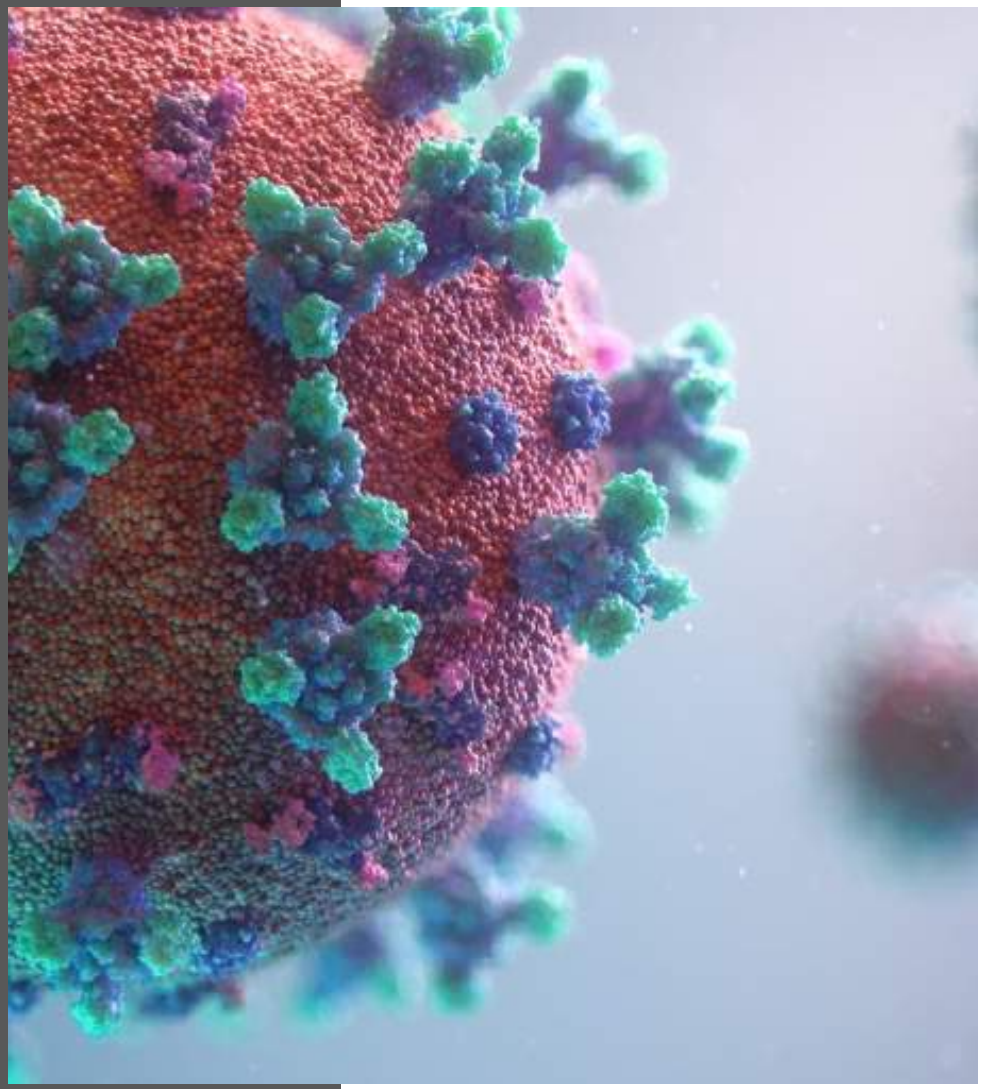


- The fabricated and applied sensor in this work has a satisfying LoD compared to previous research
- The device proposed in this work has as an advantage in usability compare to other sensor

Porous Microneedles

Diagnosing COVID-19

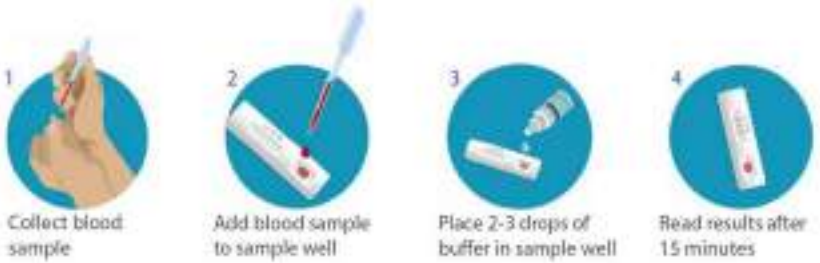
Tool for Painless, Rapid Detection



Scientific Reports, 10.1038/s41598-022-14725-6, 2022

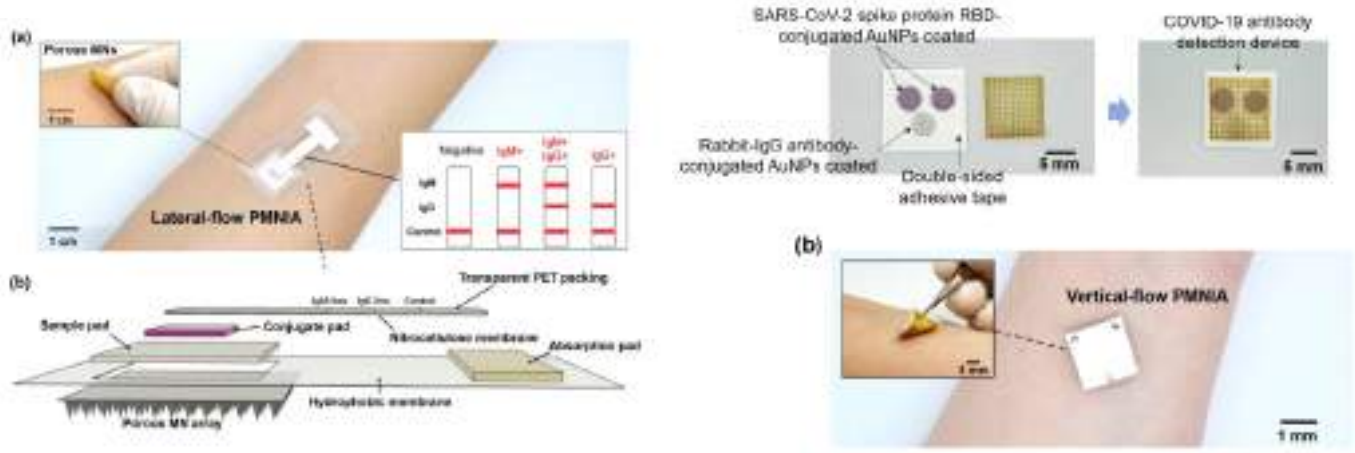
2．マイクロニードルパッチの展開: 新型コロナウイルス抗体検査パッチ

従来の検査キット
(ラテラルフロー)



➡ 採血

マイクロニードル抗体検査



- 従来の検査デバイスをパッチ内に実装（動物実験成功）
- 測定原理は免疫学的検定→将来の感染症にも有効

Evaluation of lateral-flow PMNIA

Anti-SARS-CoV-2 IgM & IgG detection

(a) IgM positive

(b) IgG positive

(c) IgM & IgG positive

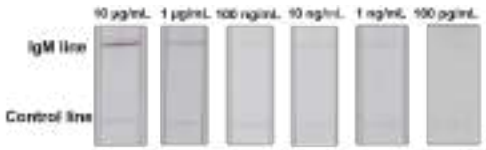
(d) Negative

a. 5 μg/mL anti-SARS-CoV-2 IgM antibody; **b.** 5 μg/mL anti-SARS-CoV-2 IgG antibody;
c. mixture of 5 μg/mL anti-SARS-CoV-2 IgM and IgG antibody solution; **d**. PBS solution

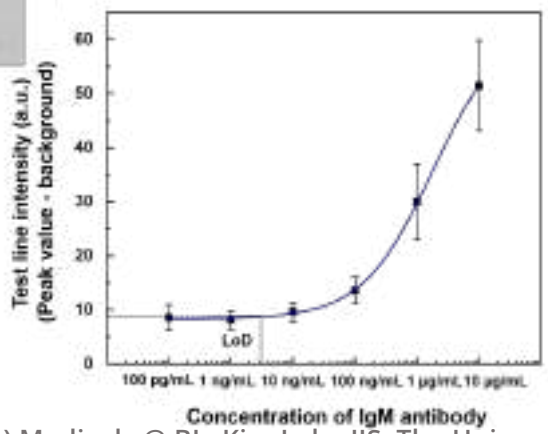
* Scale bar: 5 mm

Limit of Detection (LoD)

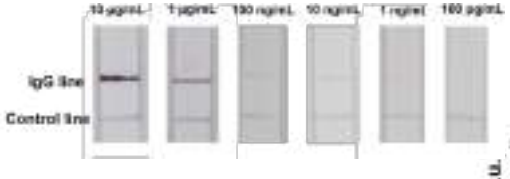
LoD for anti-SARS-CoV-2 IgM (n=3)



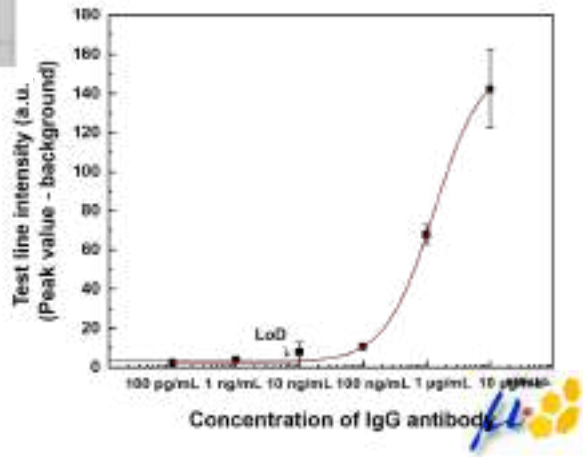
LoD: 3 ng/mL



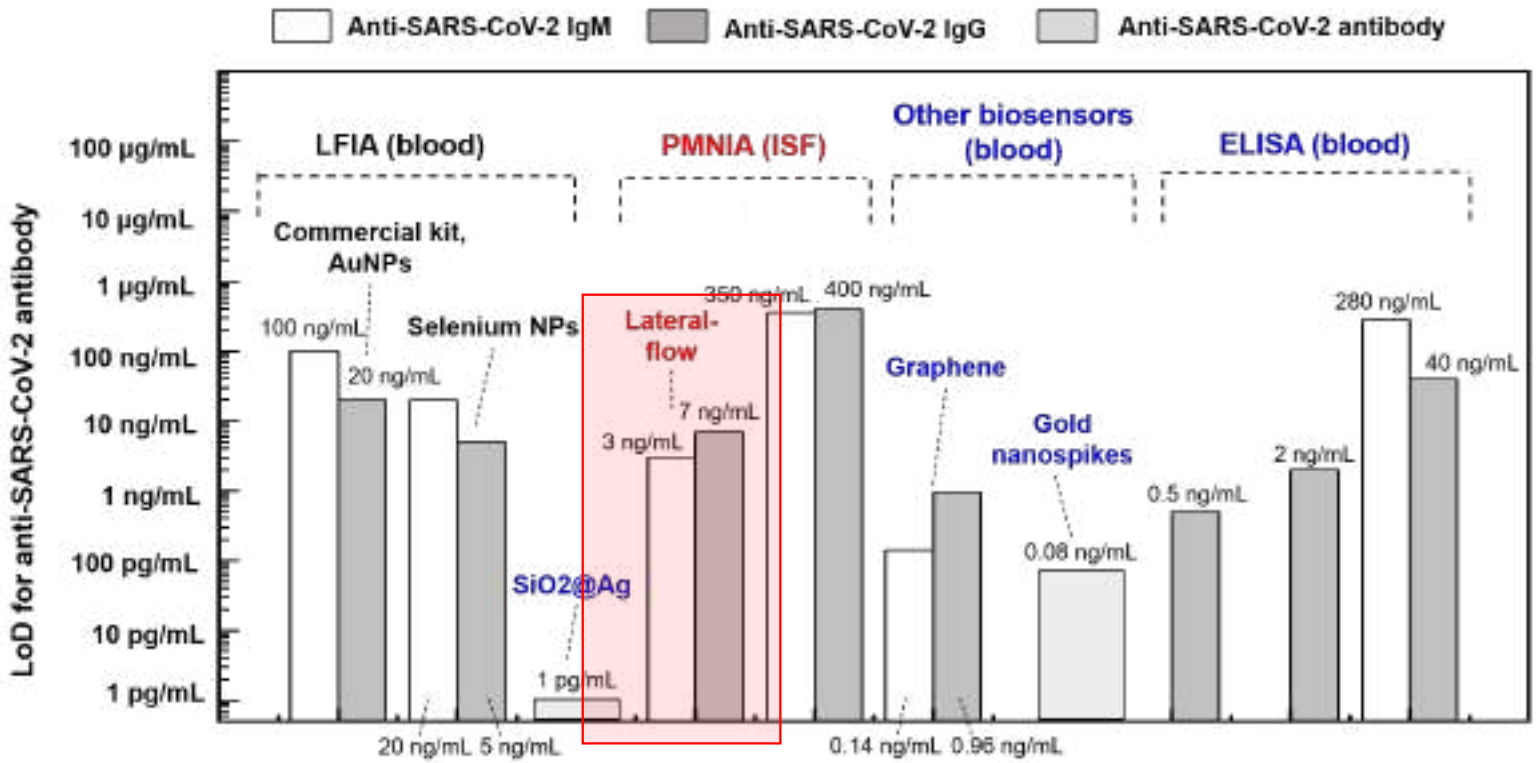
LoD for anti-SARS-CoV-2 IgG (n=3)



LoD: 7 ng/mL



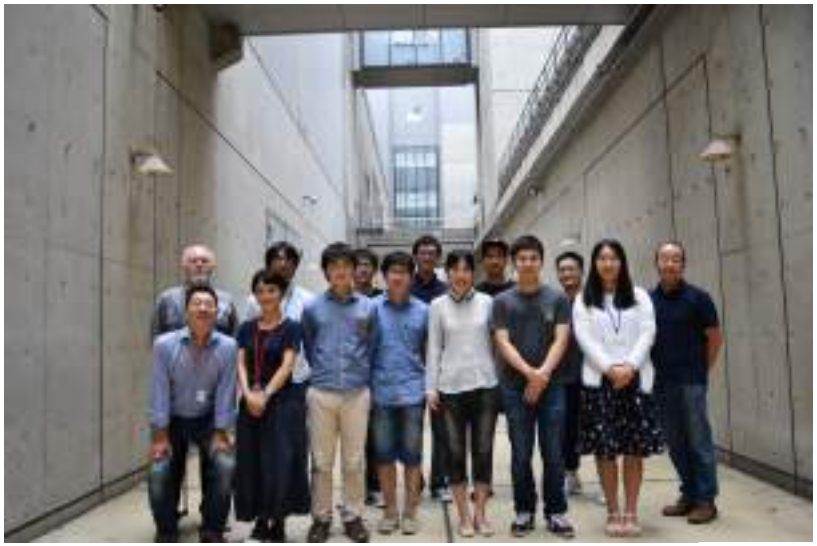
Comparison with previous researches (LoD)



Comparable or higher sensitivity than currently available commercial kit

>> Demonstrated that the proposed lateral-flow PMNIA can be a promising device for painless detection of SARS-CoV-2-specific antibody in ISF

Thank you for your attention!



Please, click here!