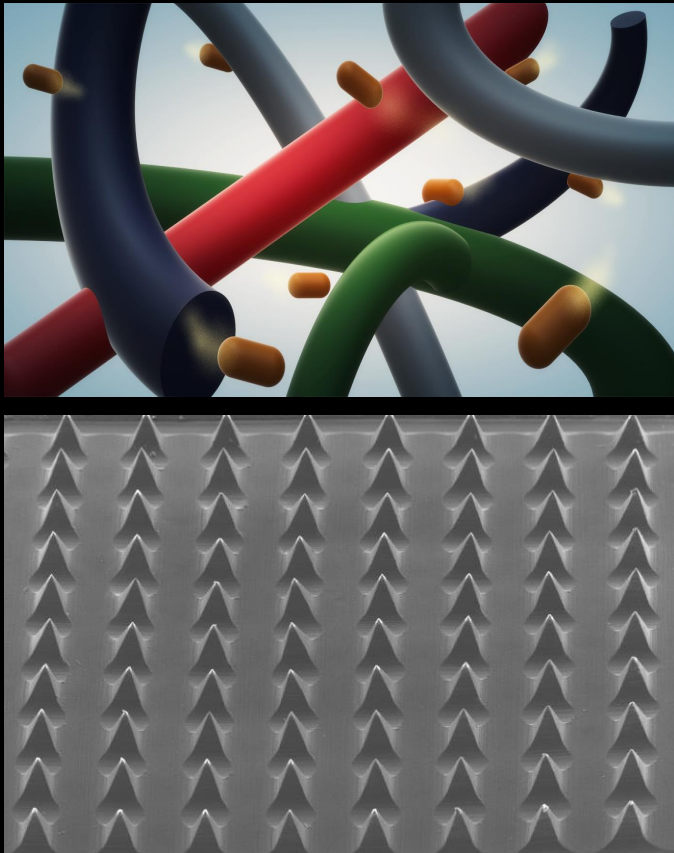
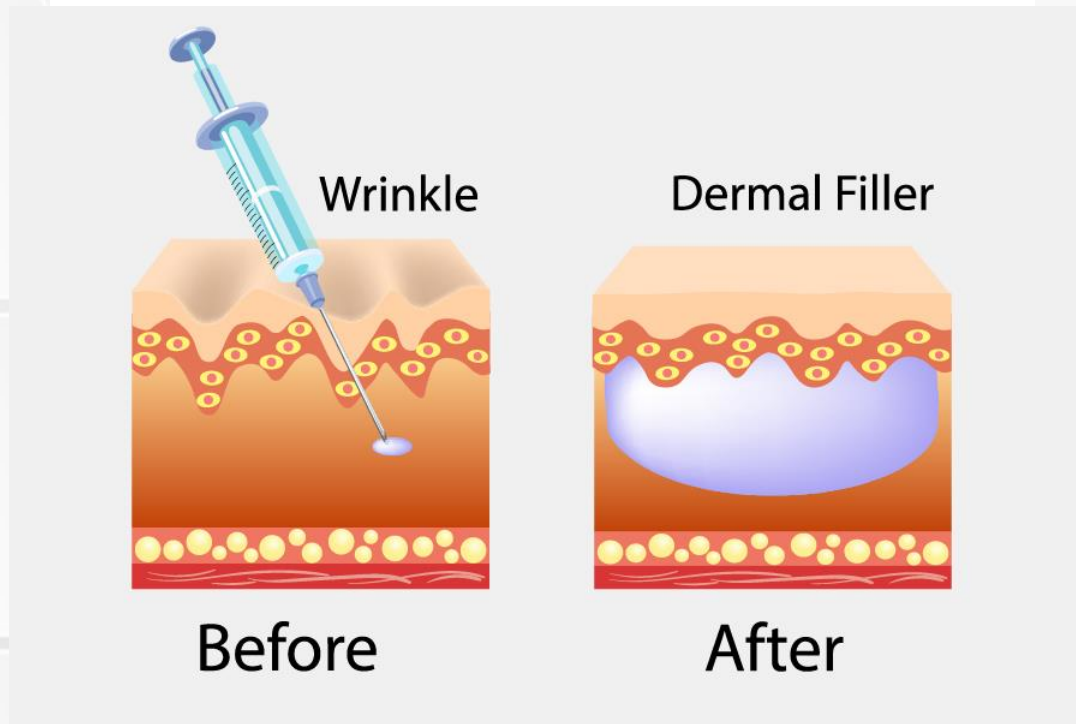




Living Delivery System for the Treatment of Skin Infections

Boaz Mizrahi,
CRS, Philadelphia, 2025

Shortcomings of topical formulations:



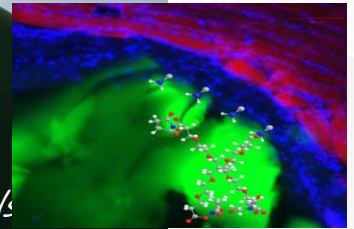
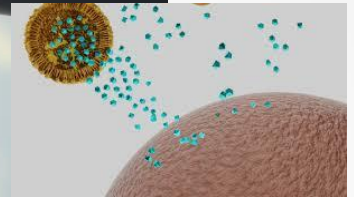
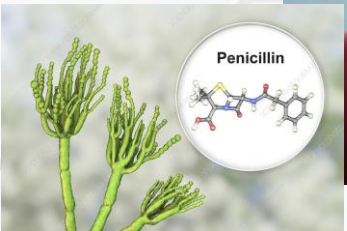
1. Low clinical efficacy

2. Low bioavailability

In Situ Bio-Inspired Materials

Living

Materials



(Hali et, al, Living Materials)

- Dynamic Response
- Self-growing Materials

(Adv. Mater., 30, 2018)

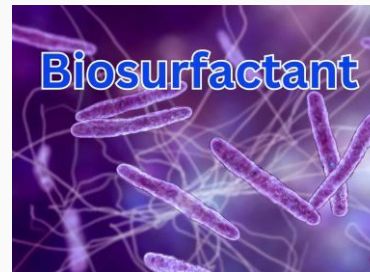
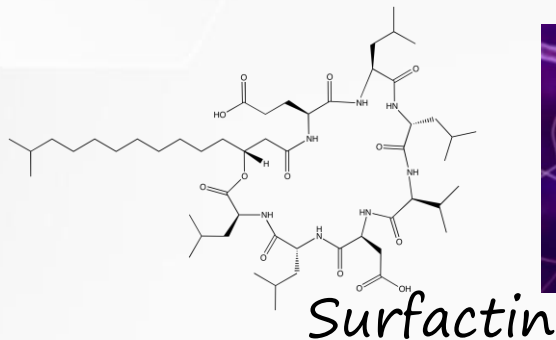
Living materials, a combination of live organism and traditional biomaterials, engineered living materials applying engineering principles to biology

Bacillus Subtilis

- Gram-positive bacteria
- Commonly found in soil/ on human skin
- Generally regarded as safe (GRAS)
- Produce and release antifungal/antibacterial compounds

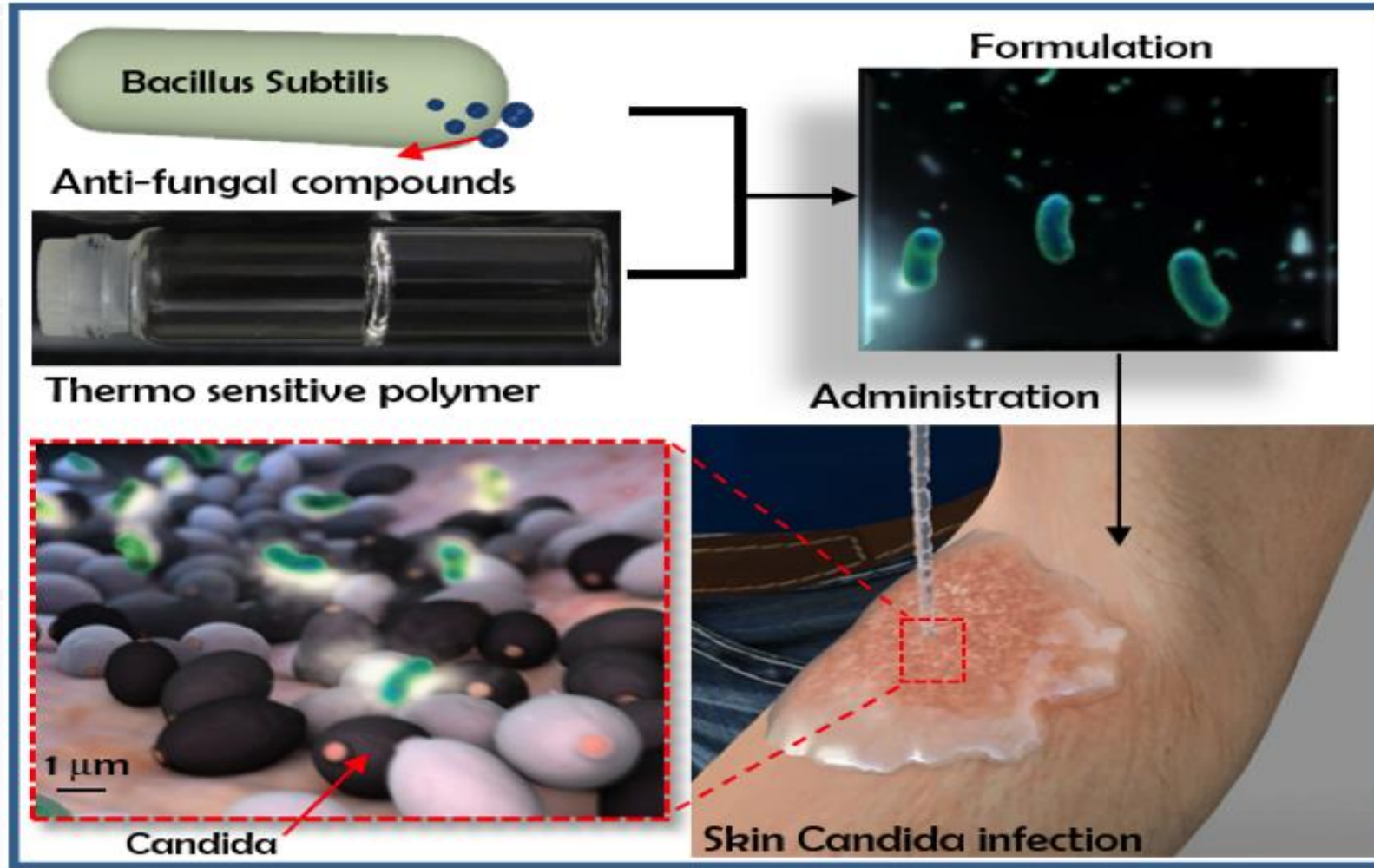


Bacillus Subtilllis



Biosurfactant

Our Hypothesis

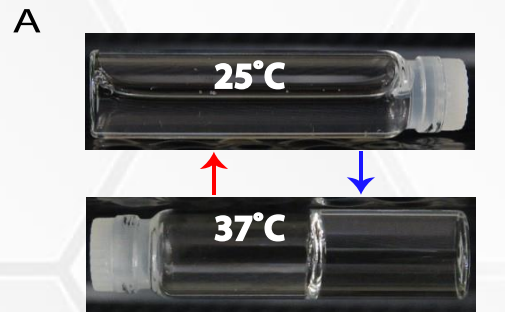


A live bacteria formulation that continuously produce and release anti-fungal agents

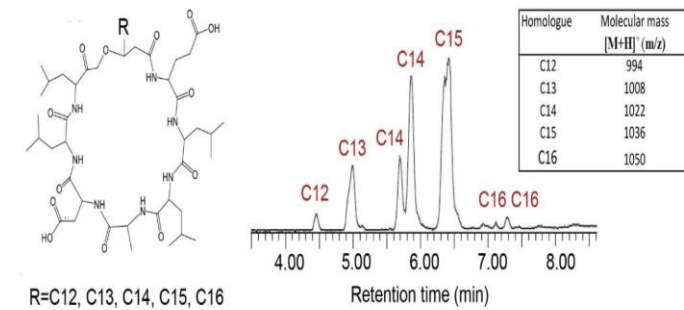
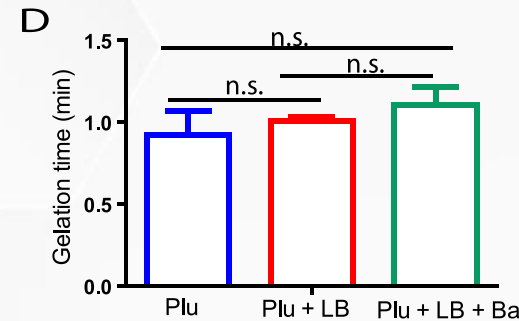
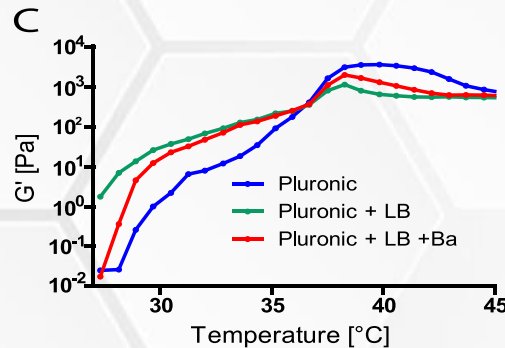
Bacteria / Gel Relationship

Bacteria had no effect on the gel

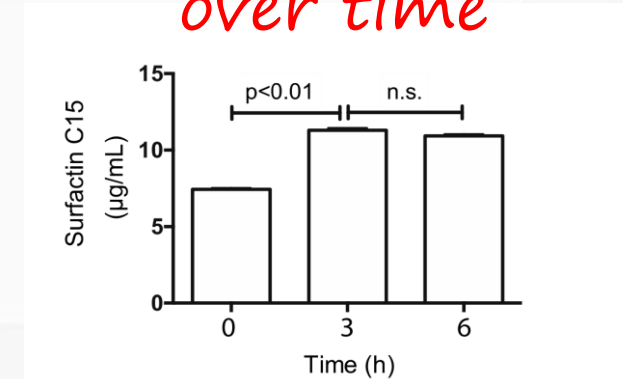
Gel had no effect on the bacteria



14 16 18 20
Concentration (%)



Surfactin amount is increased over time

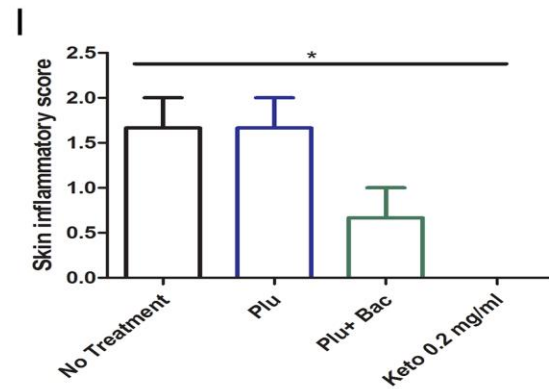
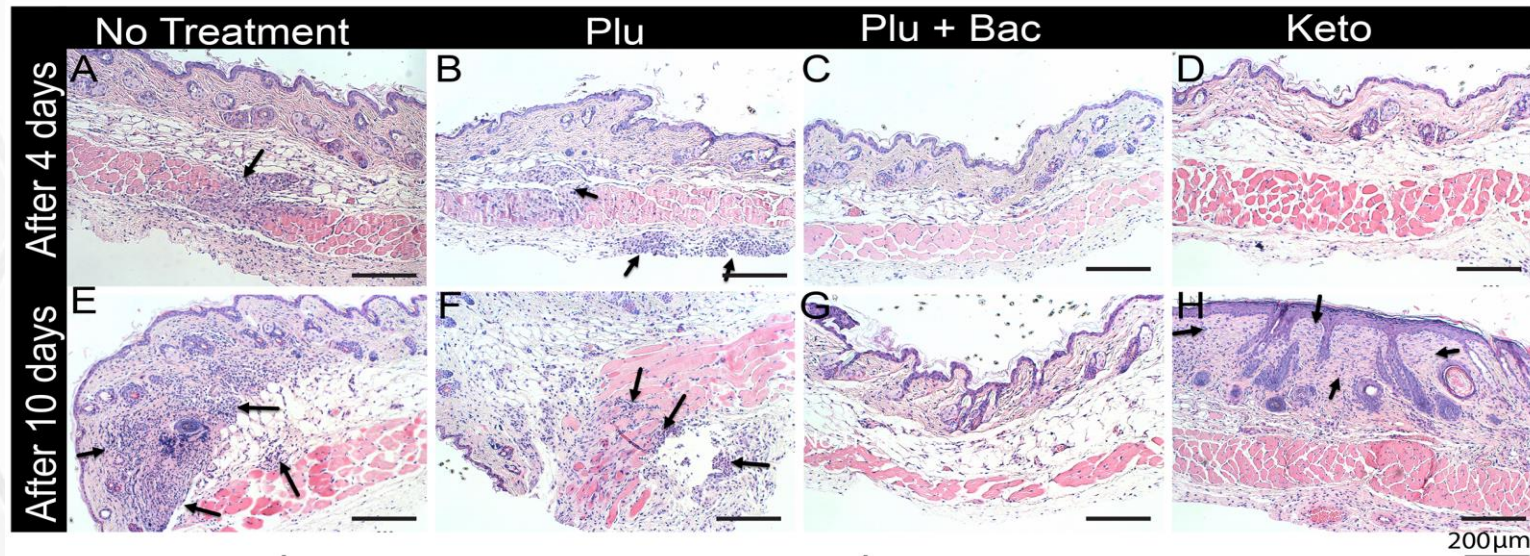


(Lufton et, al. *Advanced Functional Materials*, 2018)

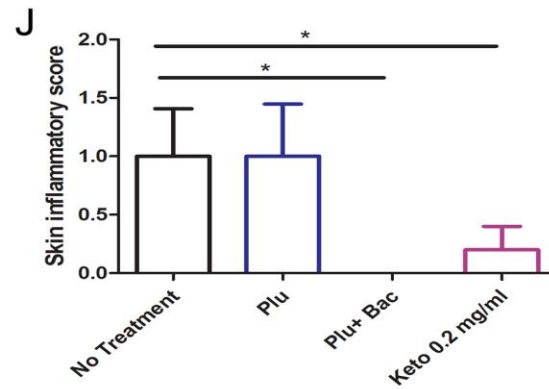


Candida infections are confined to the upper portion of the epidermis

Live skin for inflammation score reduces fungal infection ketoconazole



4 days

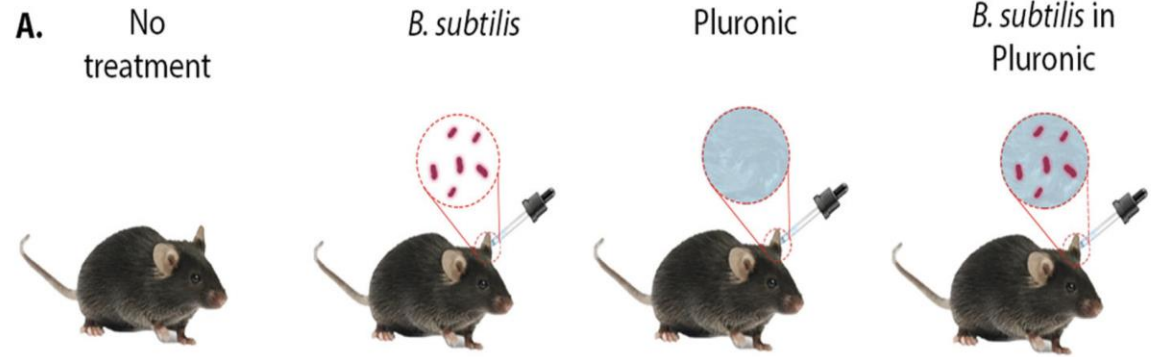


14 days

Live Formula for Treating Fungal Infection

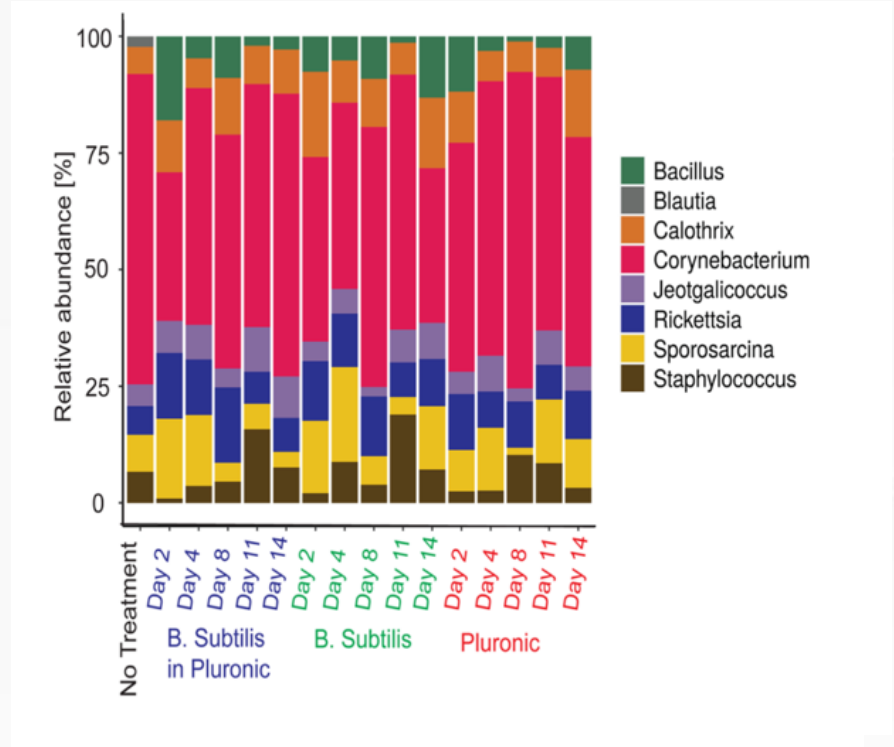


Microbiome is restored within 4 days



B. Experimental design

Day	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Formula application		✓	✓	✓	✓	✓	✓	✓							
Microbiome sampling	✓		✓		✓				✓			✓			✓



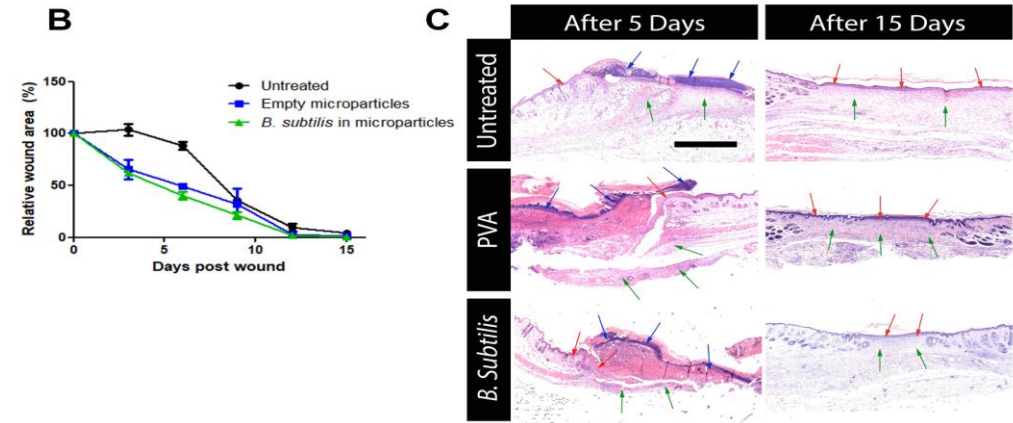
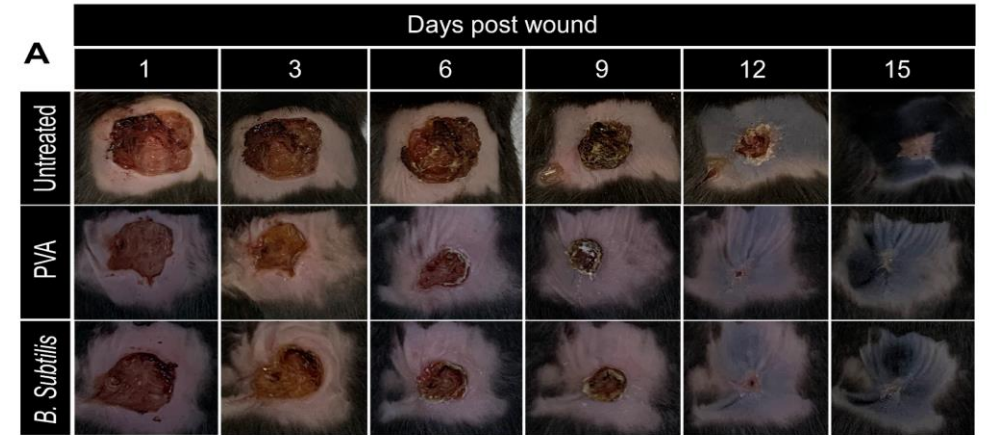
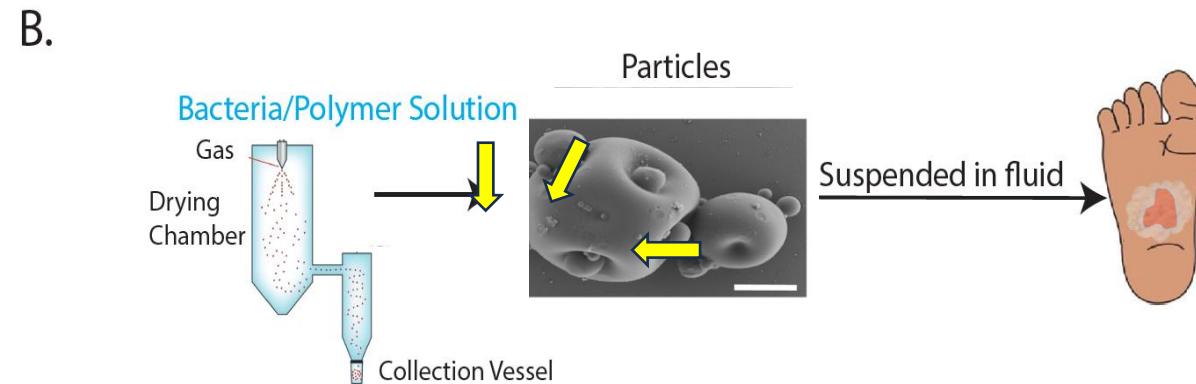
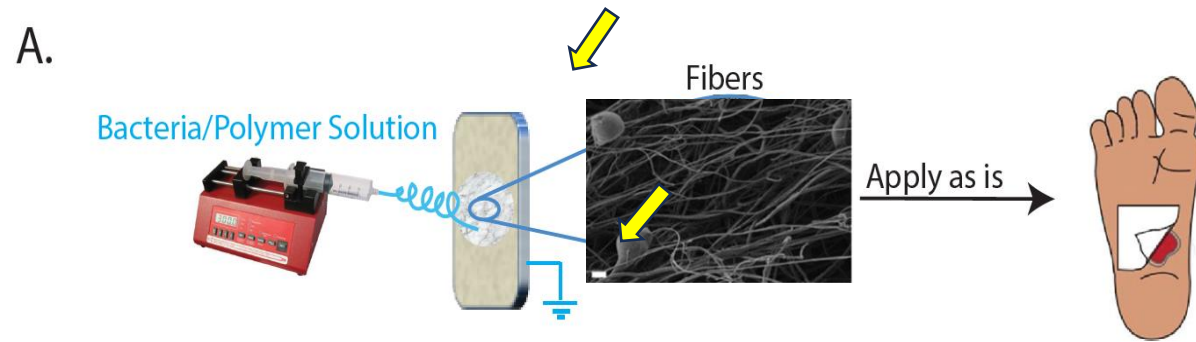
Four days after last application of the *B. subtilis* formulation, *B. subtilis* counts returned to its initial level.

Moskovicz et al, Microorganisms, 2020

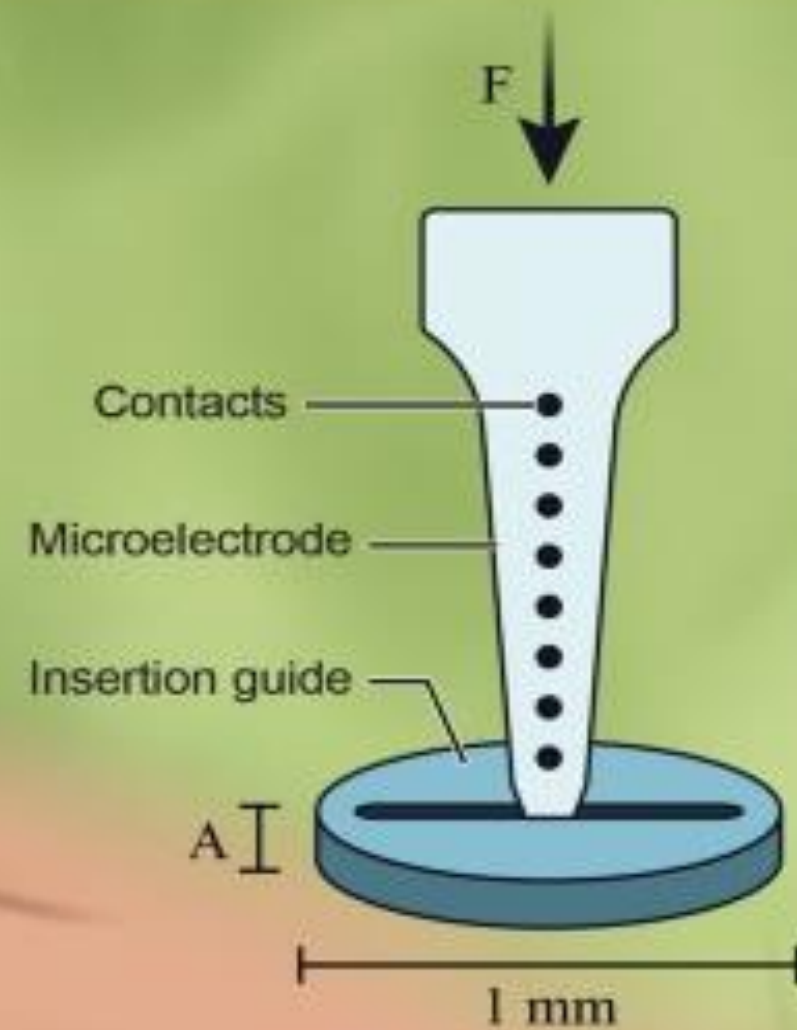
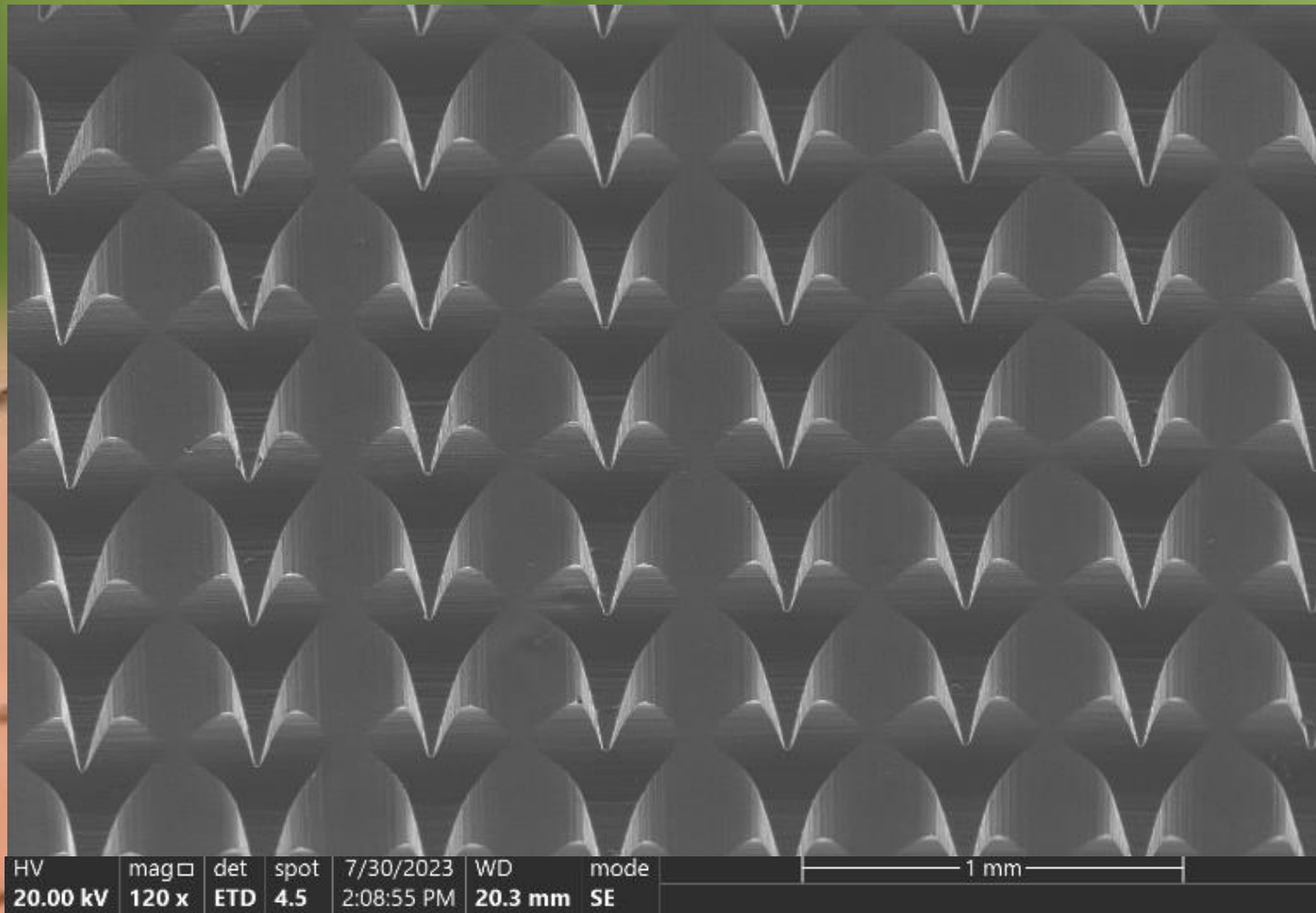
Moskovicz et al, BMC Microbiology, 2021

Treating Open Wounds With Living Materials

Bacillus Subtillis



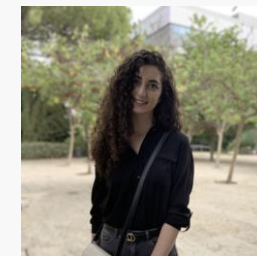
(Ben David et. al, ACS Omega 2020)



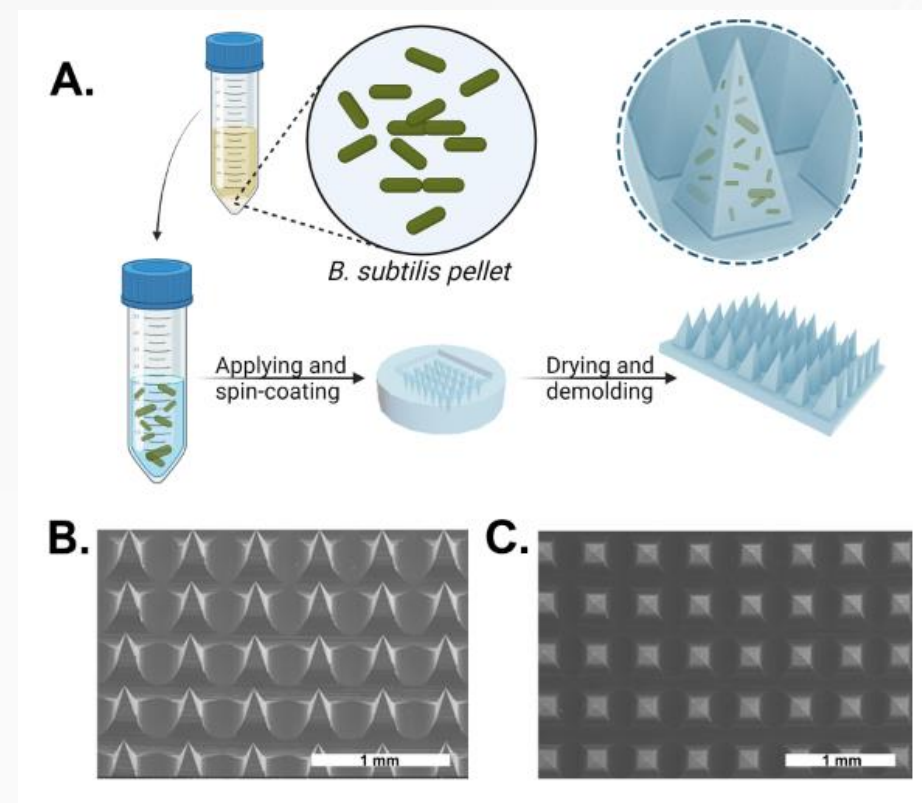
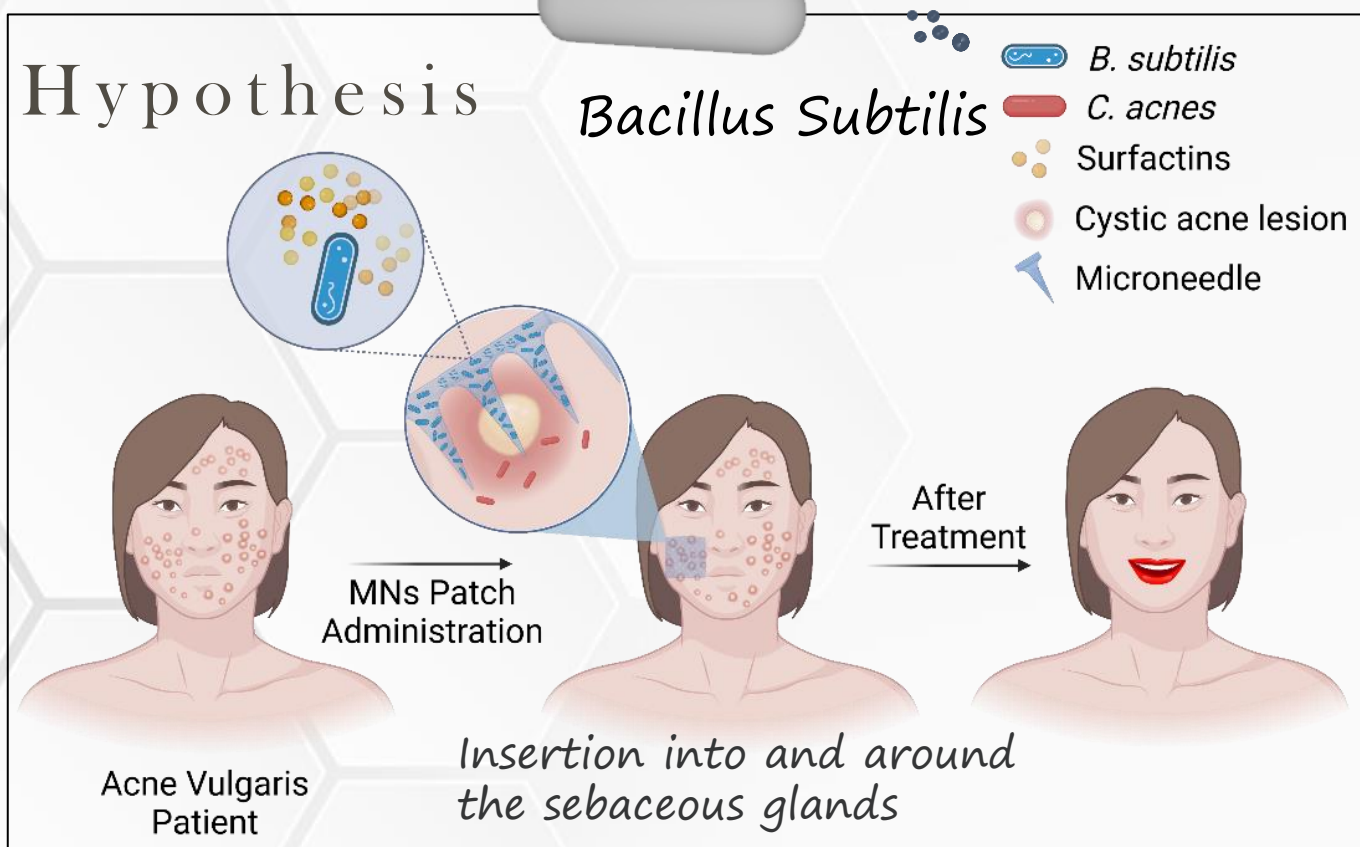
Mosquito bites

Microneedle: A patch compose of dozens of needles that can penetrate the skin painlessly

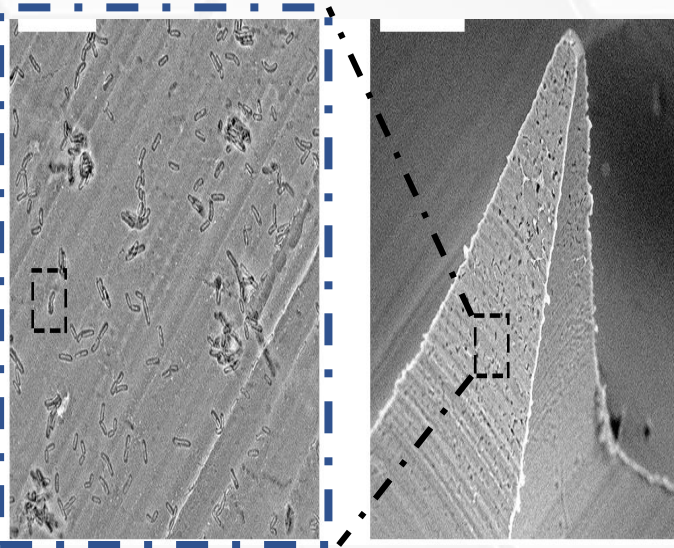
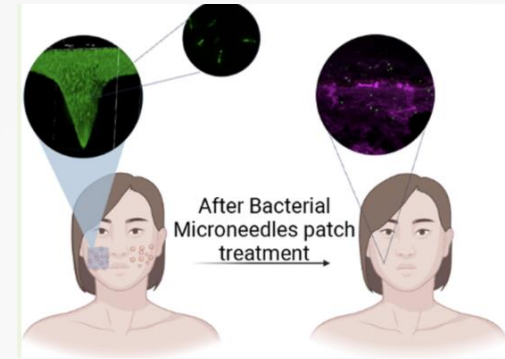
Living microneedles



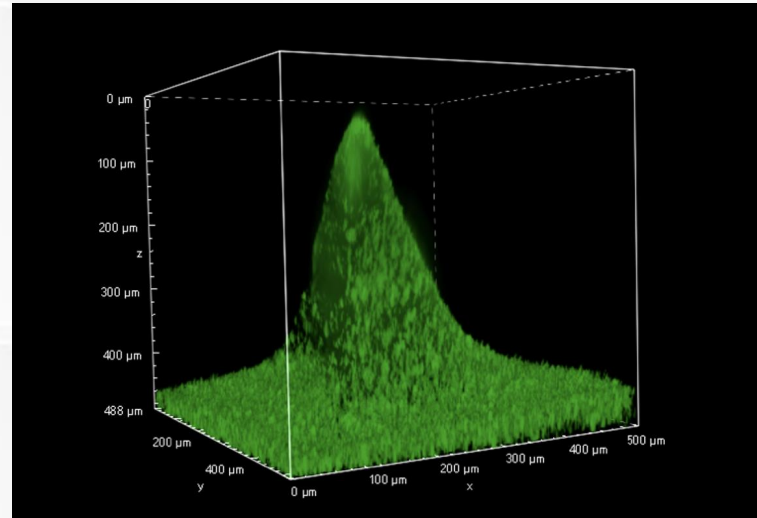
Caroline Hali



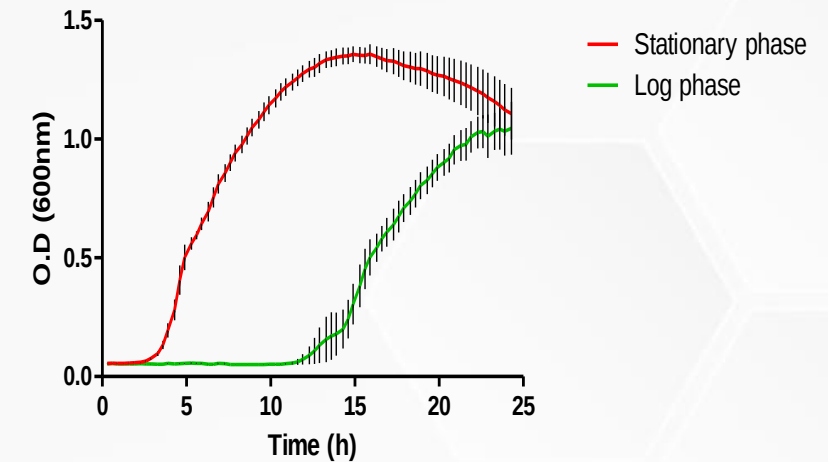
Living Microneedles



Bacillus Subtilis
In needles



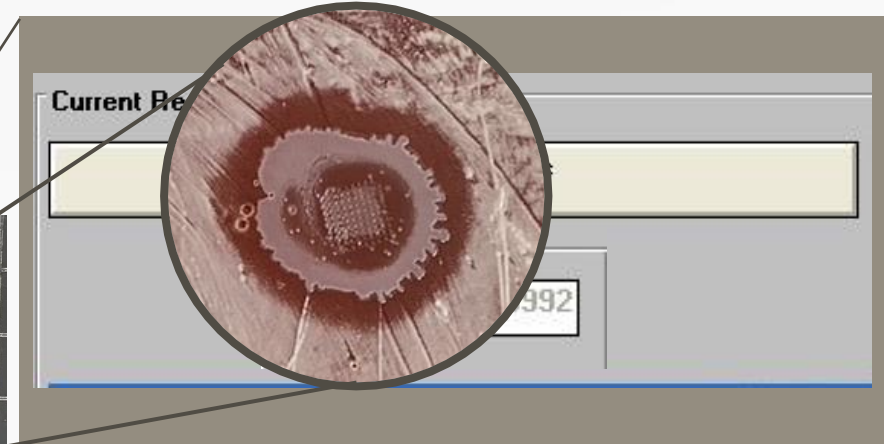
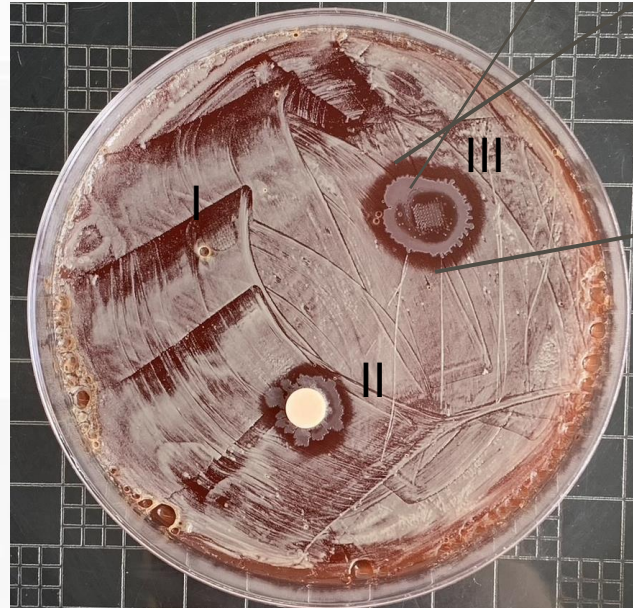
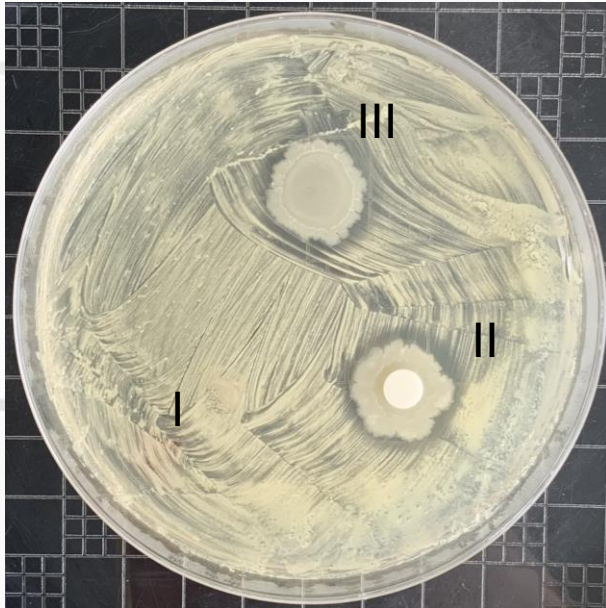
Spinning disc
confocal microscopy
showing fluorescent
Bacillus Subtilis



Recovery times of *Bacillus Subtilis* compared to free bacteria (N=4)

B. subtilis microneedles inhibits *C. acnes* growth

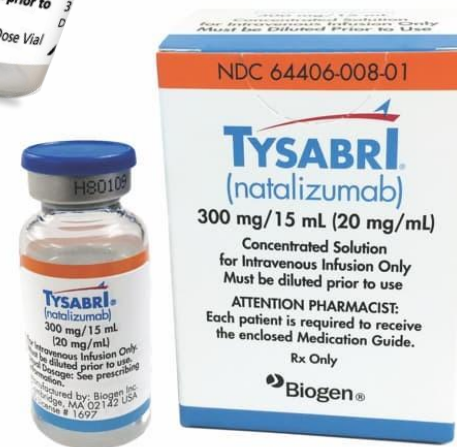
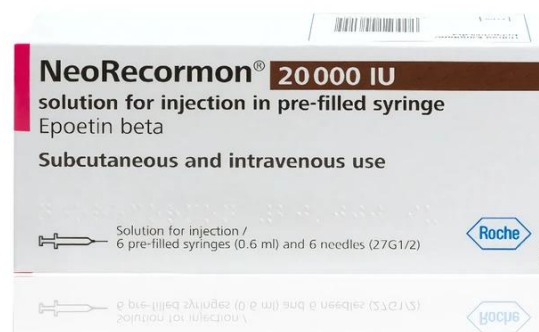
C. acnes



- I – Empty MN patch
- II – *B. subtilis* disc
- III – Living MN patch

Protein therapeutics

Challenges



Poor tissue penetration

Low stability

Pathogenic contaminations

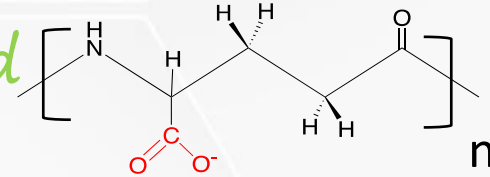
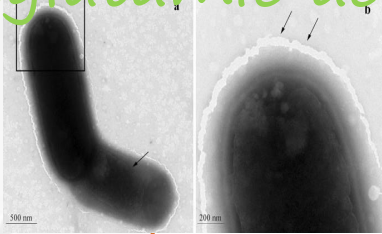
High production cost



A new route of administration is needed

Poly- γ -glutamate System

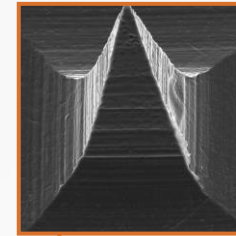
Polyglutamic acid



The living component

Bacillus paralicheniformis

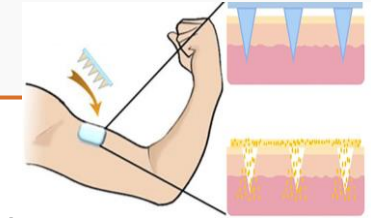
- Gram positive
- Naturally found in soil
- Qualified presumption of safety (QPS by EFSA)
- Polyglutamic acid (γ -PGA) producer



The material component

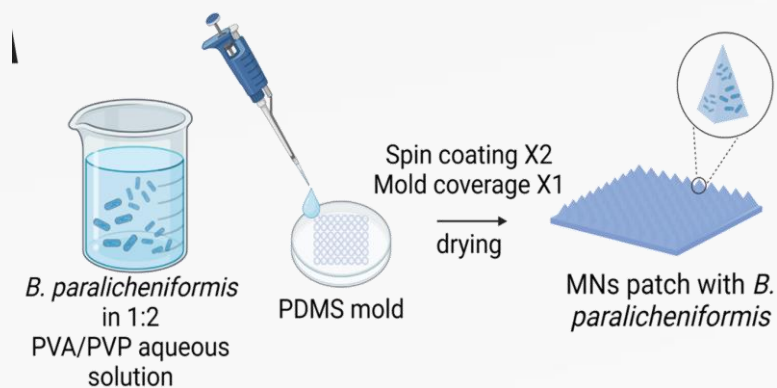
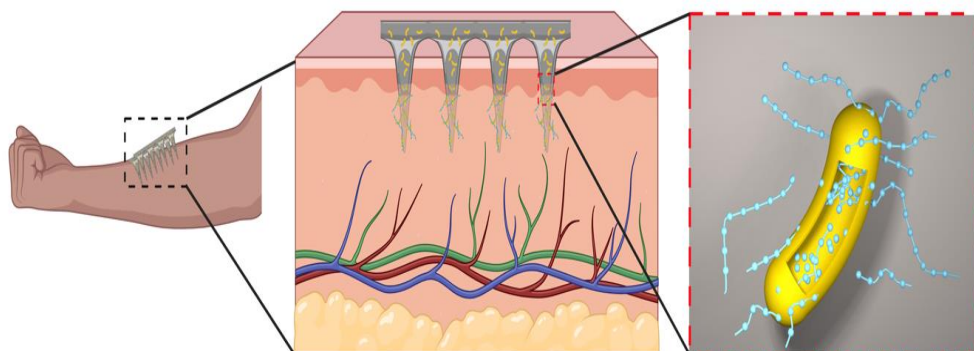
Dermal delivery system

- Micron-sized dissolving needles patch (PVA/PVP)
- Dermal delivery of bacteria and PGA
- Painless
- At-home use

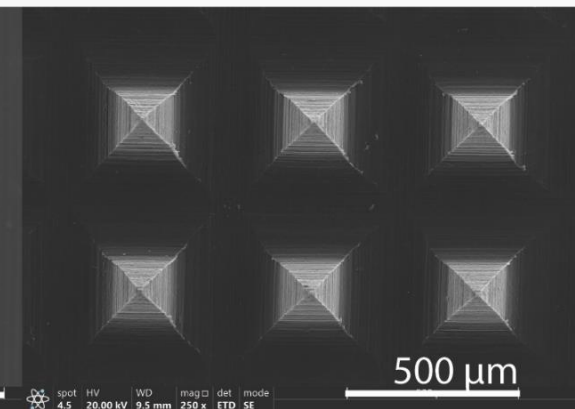
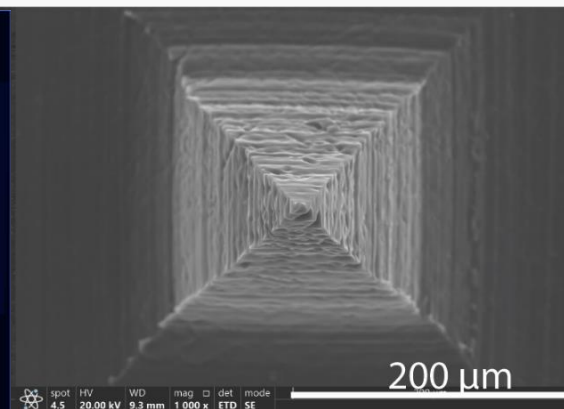
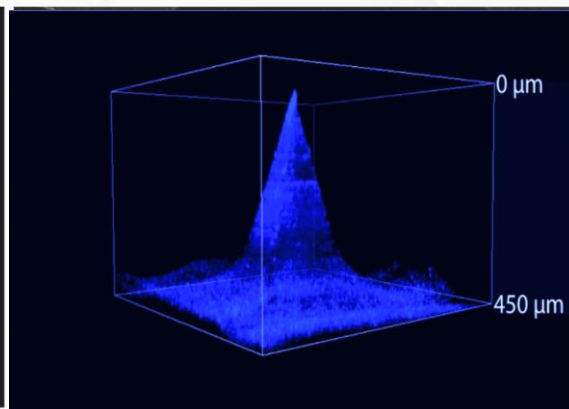


Yang et al., APSB, 2017

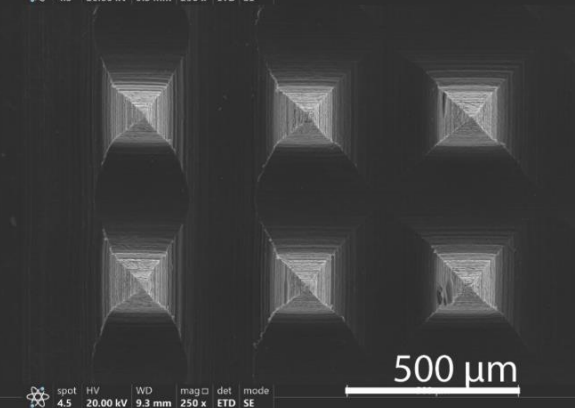
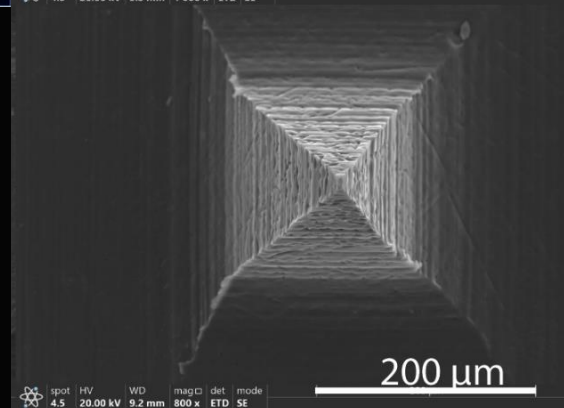
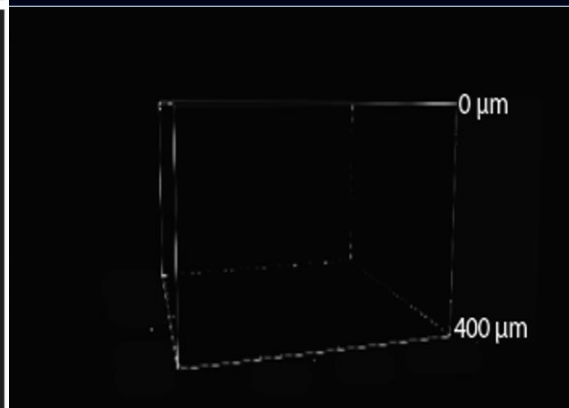
In-situ production of therapeutic polymers may overcome some of the challenges

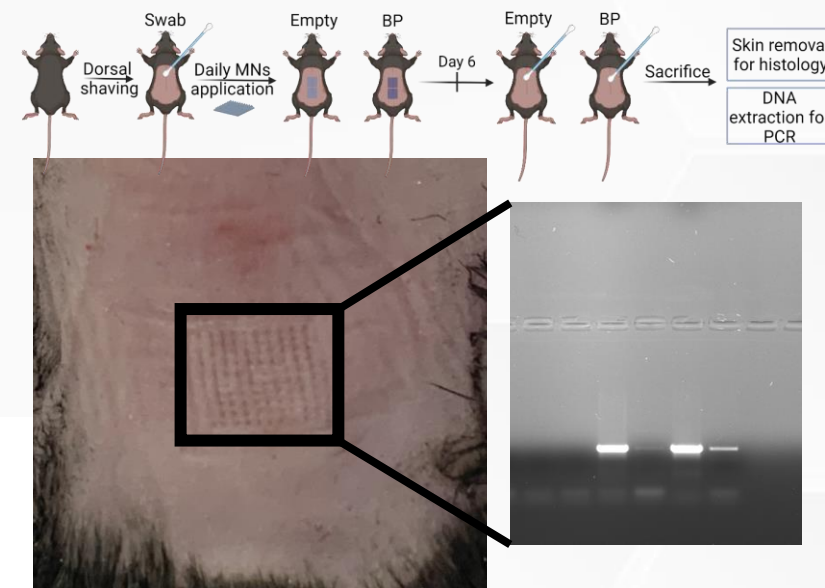
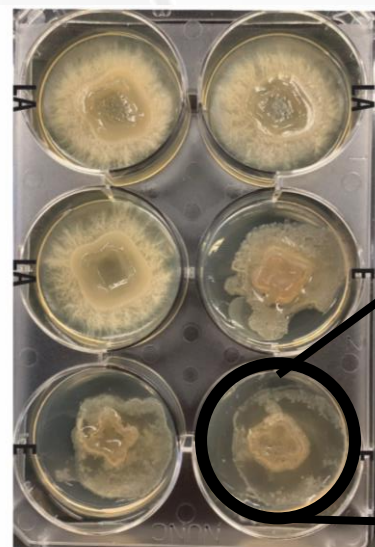
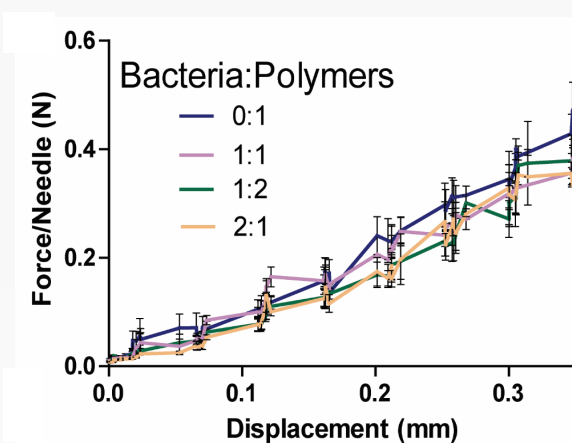
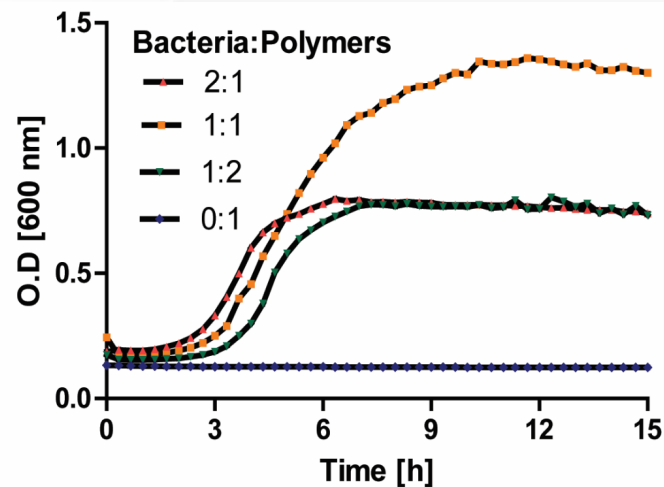
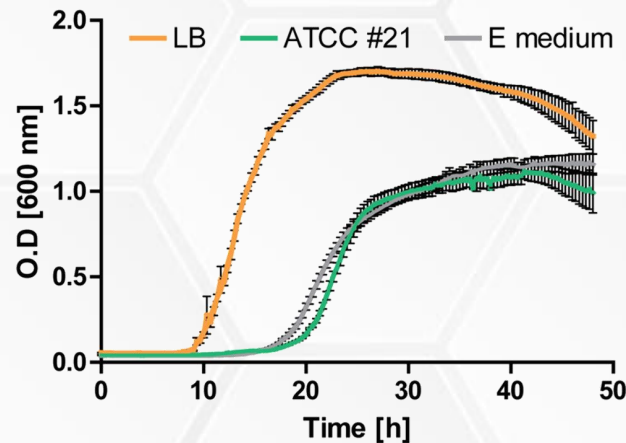


MNs with bacteria



MNs W/O bacteria

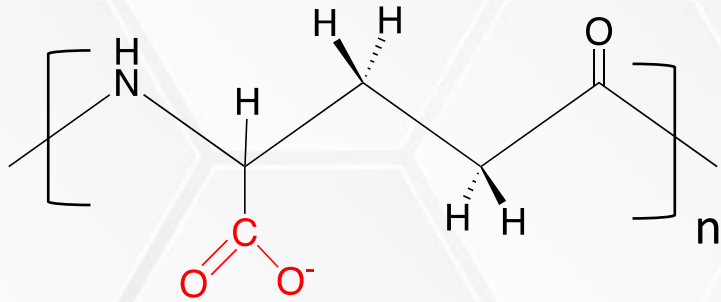




Running Experiments: Living Microneedles

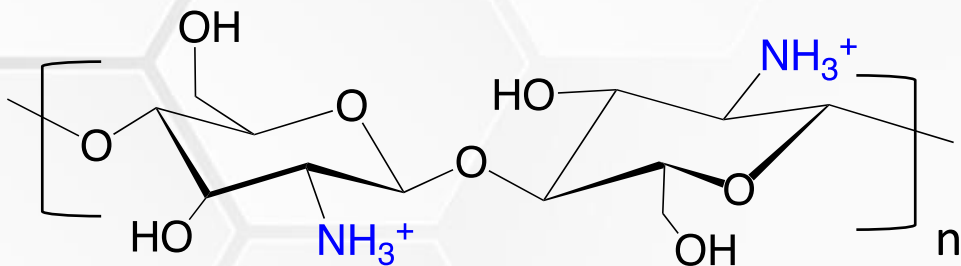


Gali Cohen Gadol

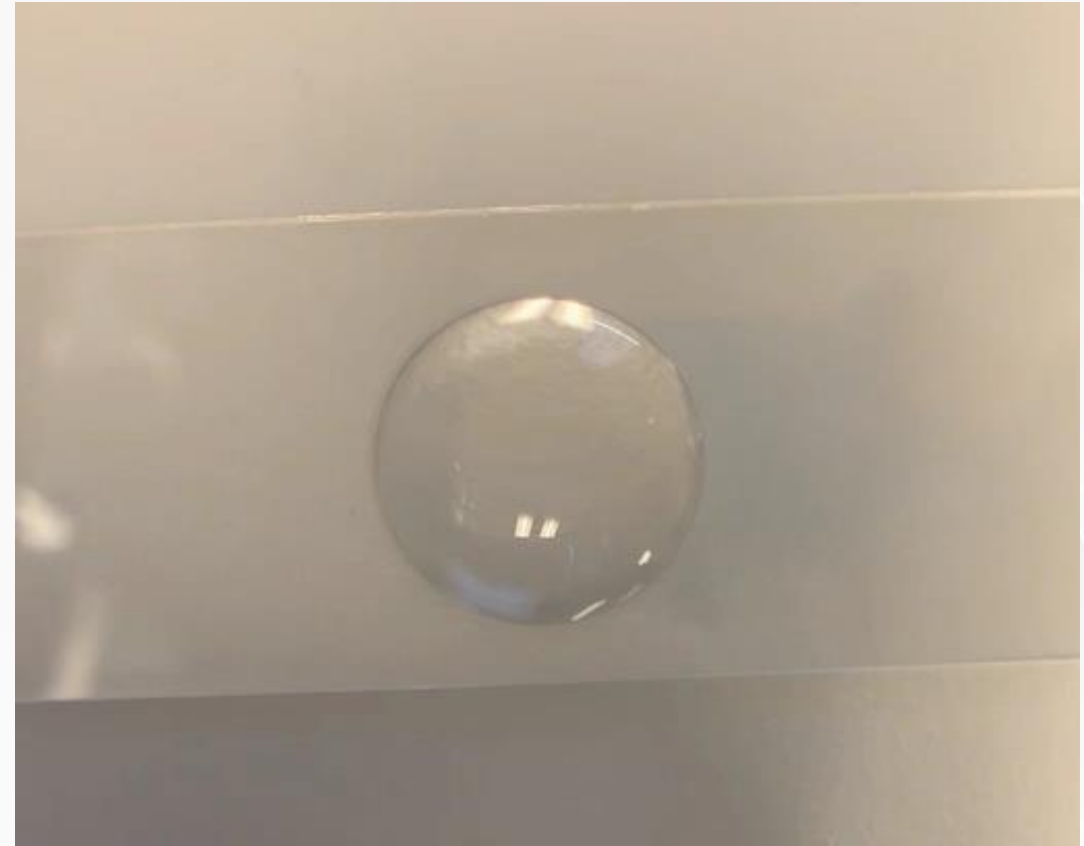


Polyglutamic acid (*negatively charged*)

+



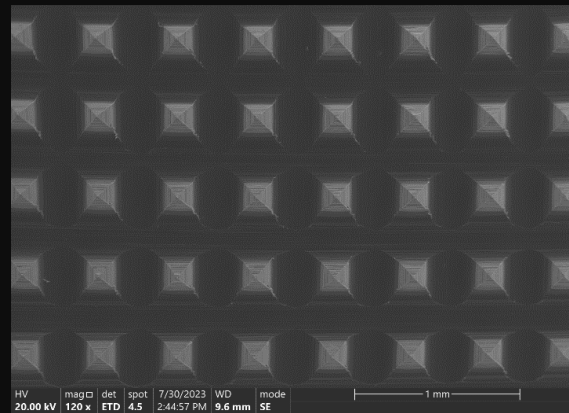
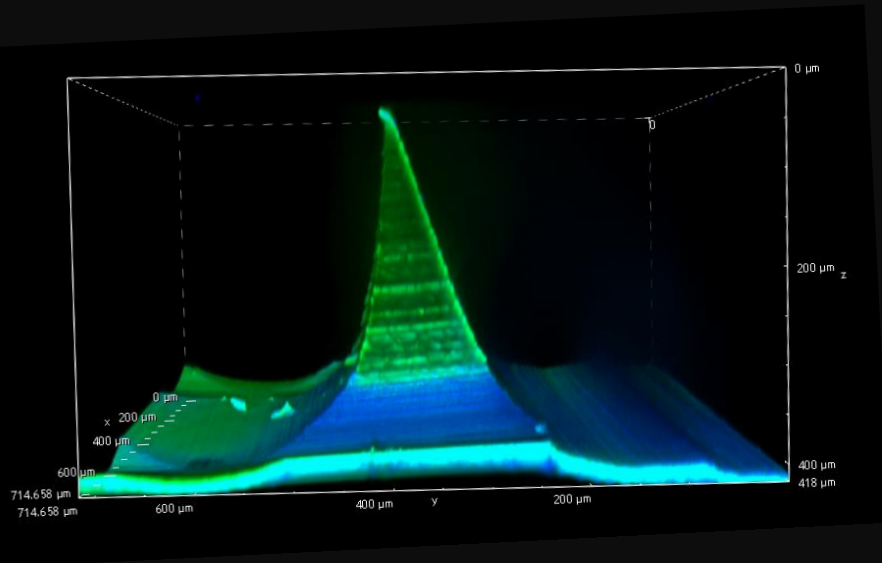
Chitosan (*positively charged*)





PVA/PVP
B.paralicheniformis

Chitosan/PVA



THANKS!

Dr. Adi Gross
Noa Ben-David
Neta Shimony
Eden Perle
Gali Cohen
Leonid Galperin
Anastasia Shapiro
Caroline Hali
Chagay Schechter



רשות החדשנות
Israel Innovation
Authority



Russell Berrie Nanotechnology Institute
TECHNION – ISRAEL INSTITUTE OF TECHNOLOGY
המכון לננוטכנולוגיה ע"ש ראסל ברי
הטכניון-מכון סטנדורד לירושלם

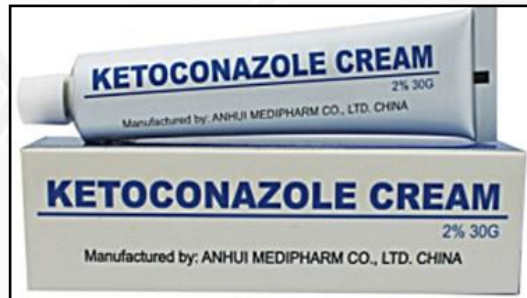
boazmizrahi.technion.ac.il



@boaz_mizrahi

Current Treatments

Local



- Inefficient
- Poor compliance
- Recurrence

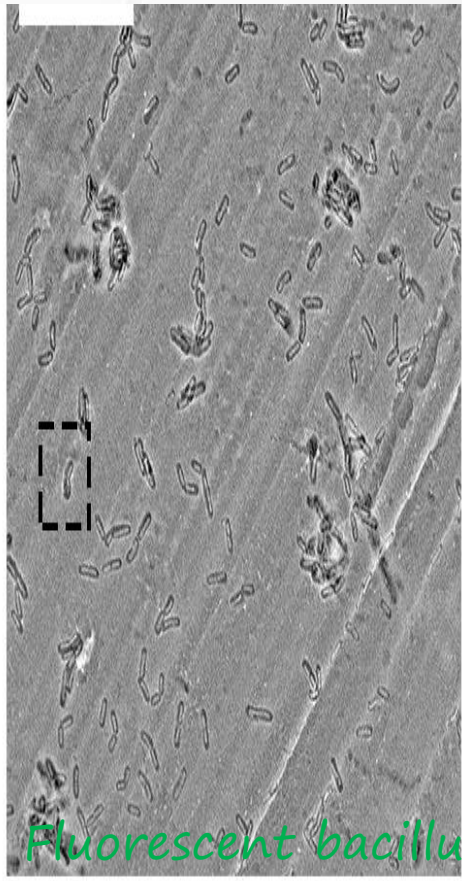
Systemic



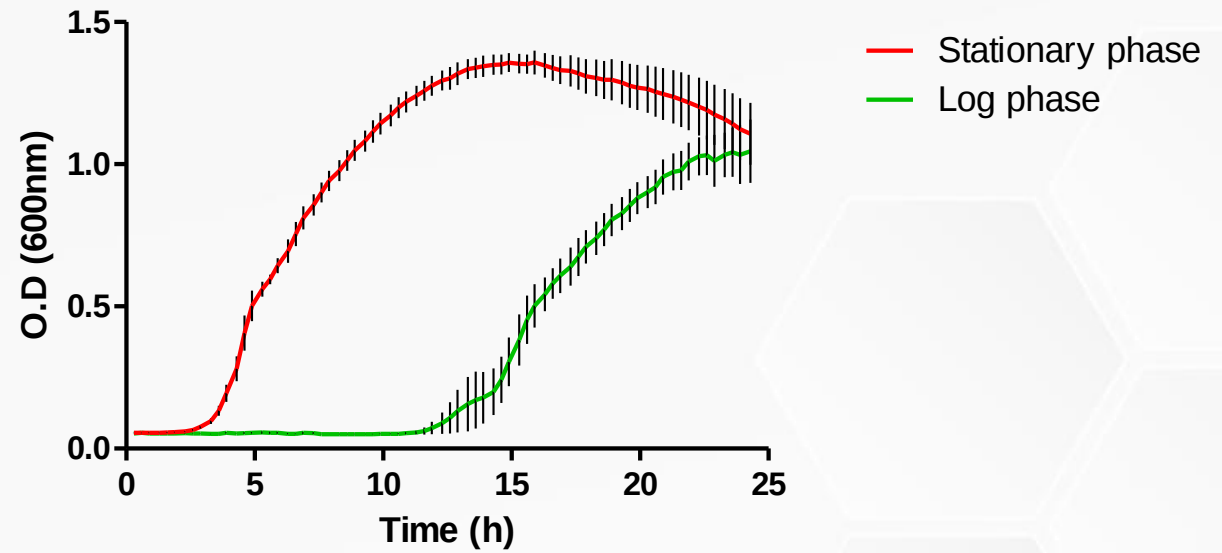
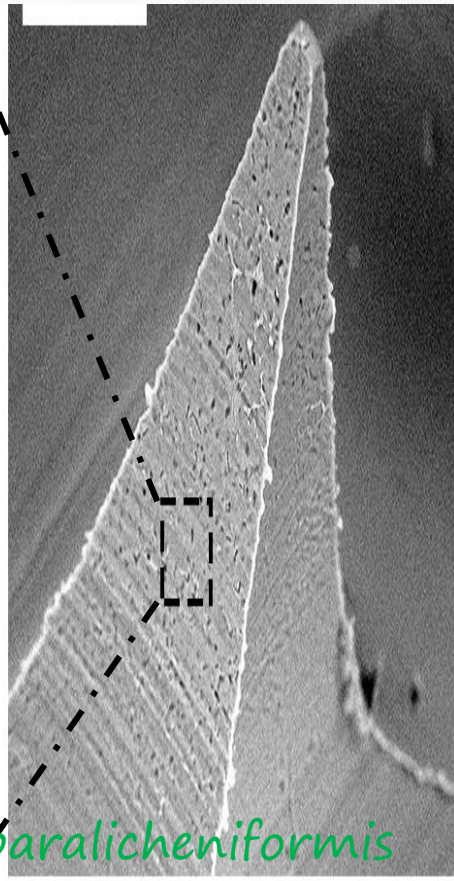
- Fever, chills and headache
- Significant liver and kidney toxicities
- Recurrence

Resistant candida species have already been discovered

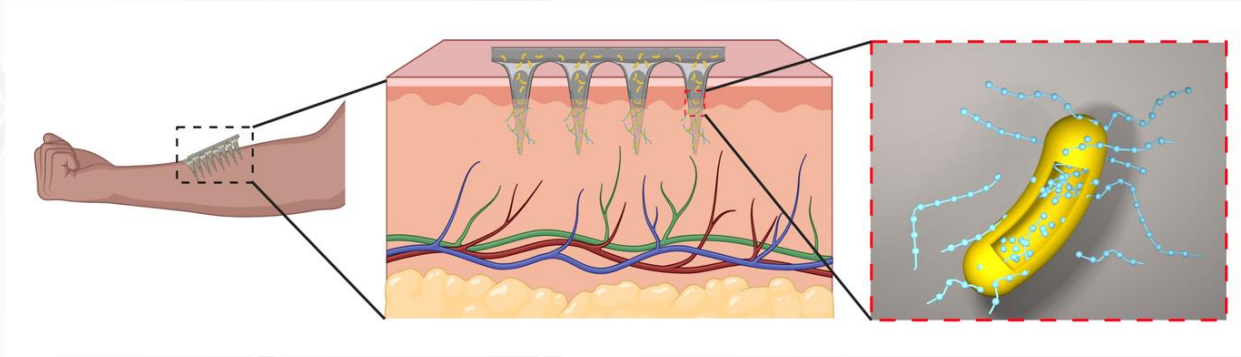
Current research: *Living Microneedles*



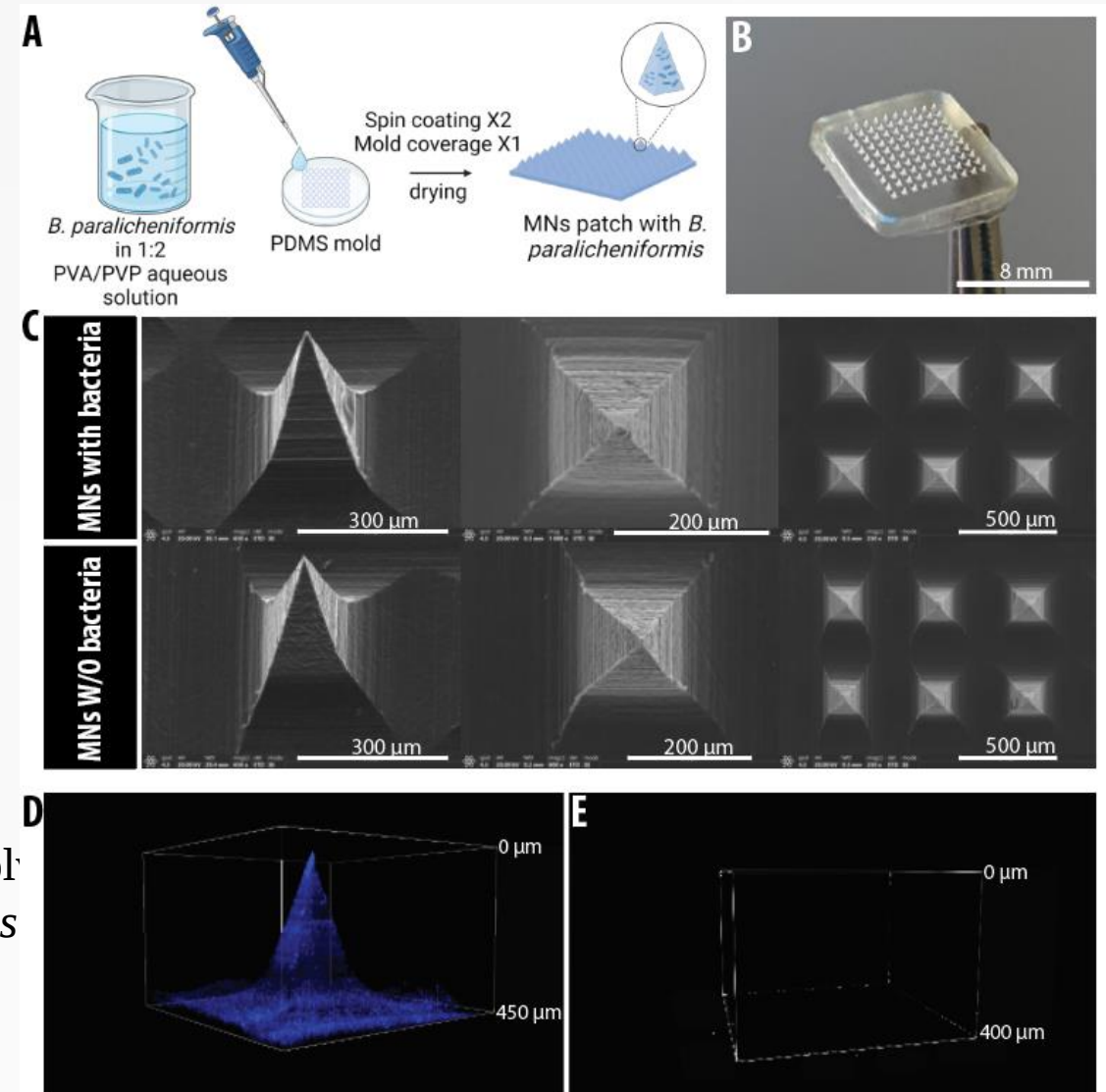
Fluorescent bacillus paralicheniformis



Recovery times of bacteria released from MNs comparing the initial states of bacteria (logarithmic Vs. stationary phase) N=4.

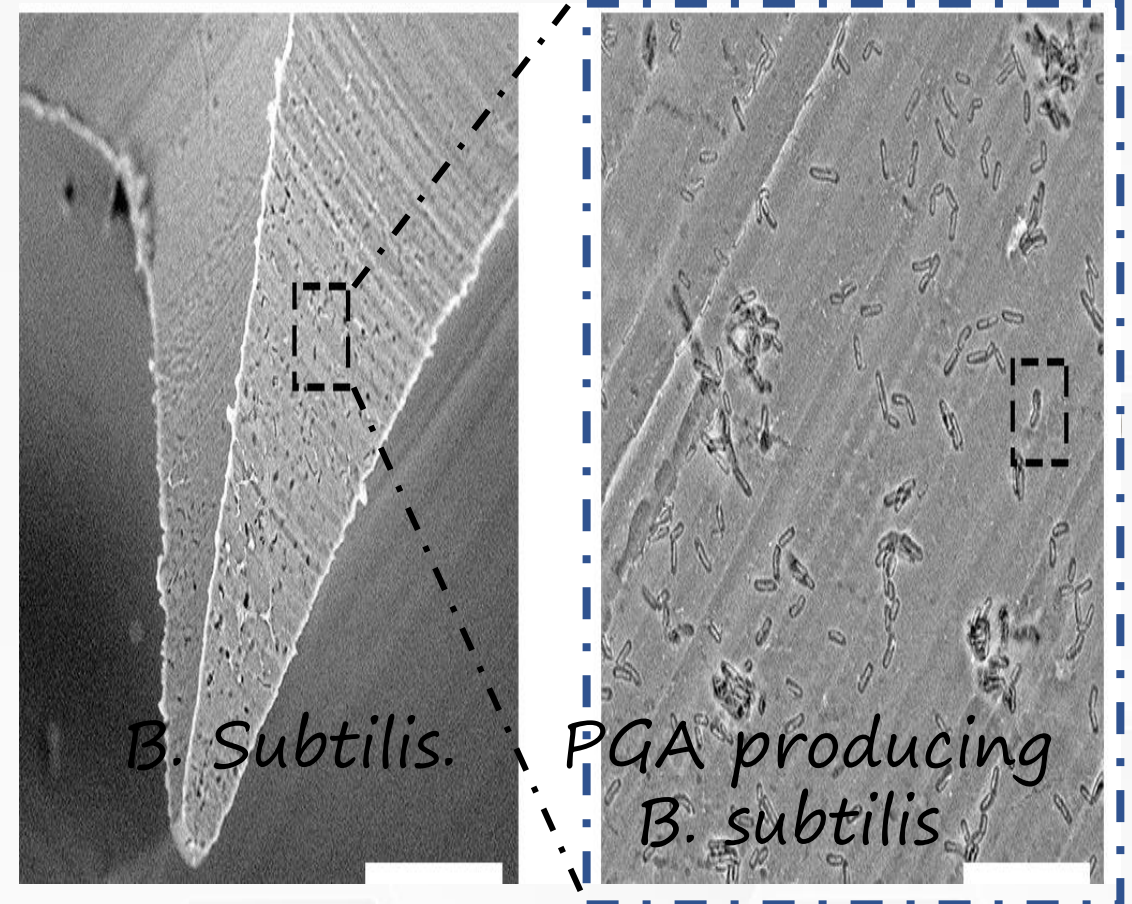
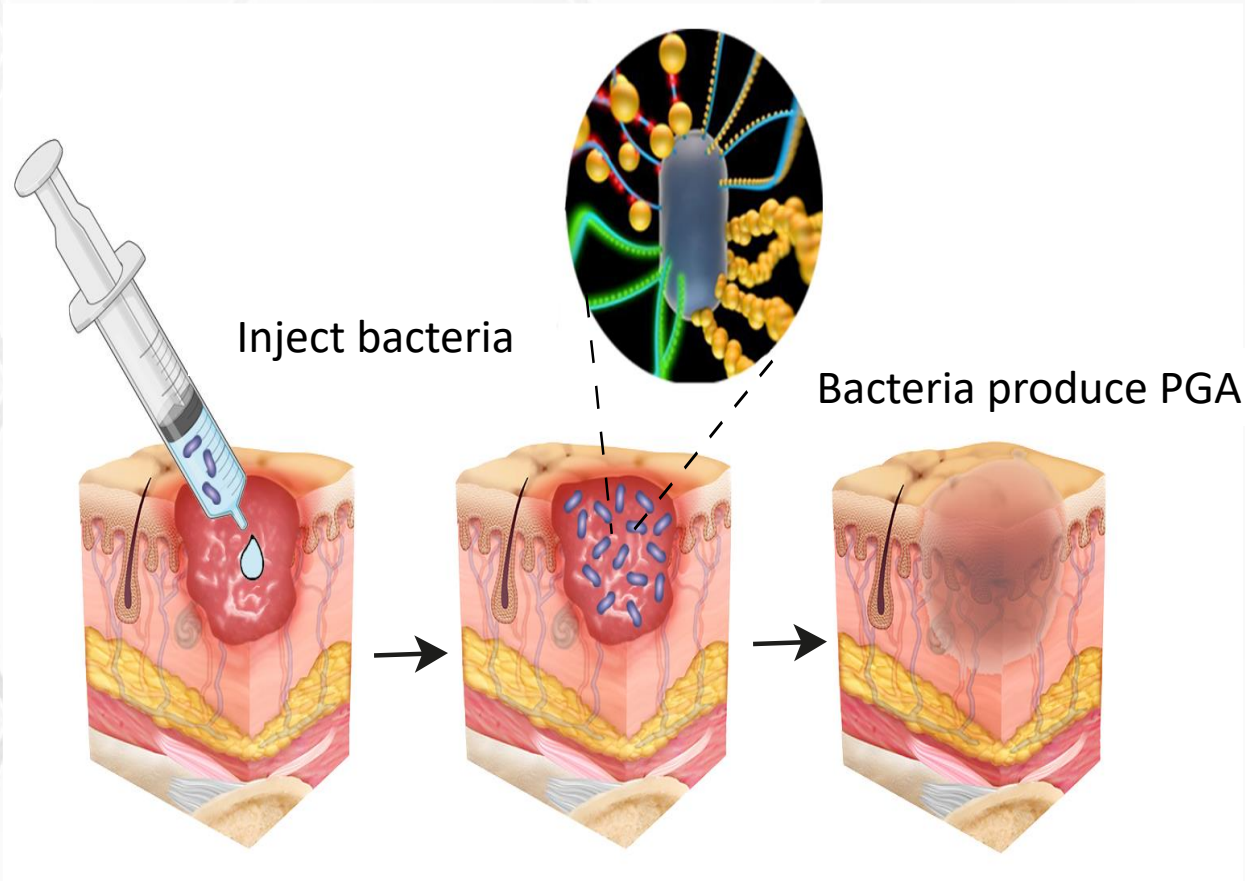


MNs array administration. The polymers comprising the device dissolve bacterial cargo onto the skin. This allows *B. paralicheniformis*



Living Microneedles

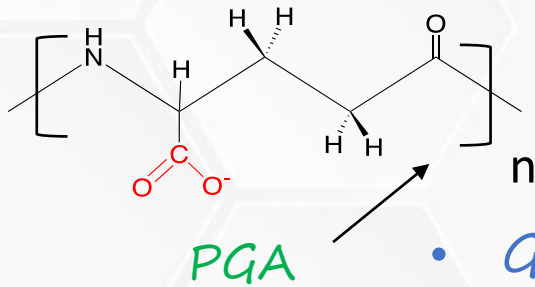
Living bacteria in microneedle



B. Subtillis producing polyglutamic acid on the skin

Bacillus paralicheniformis

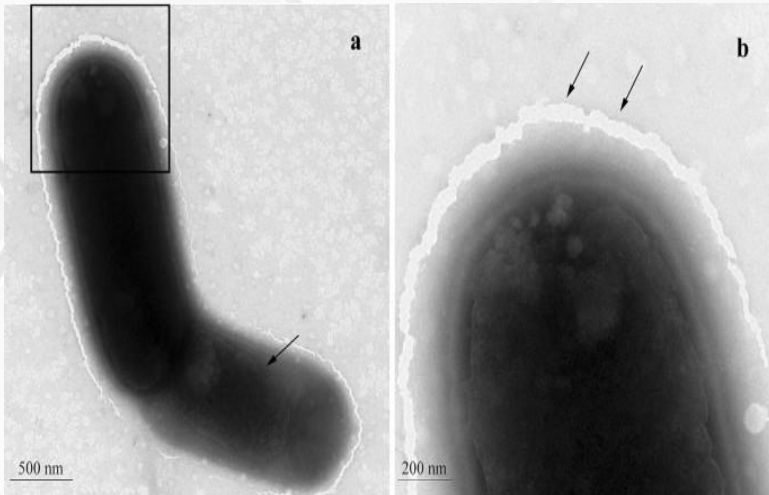
Polyglutamic acid

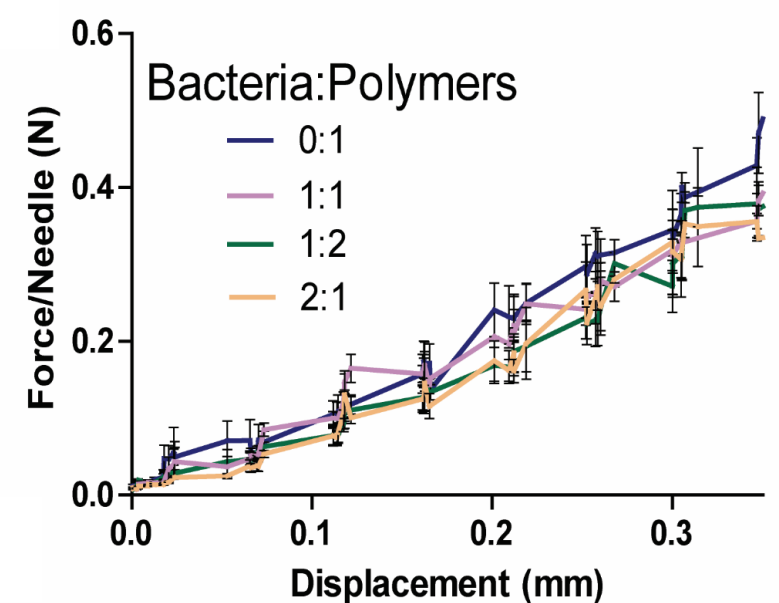
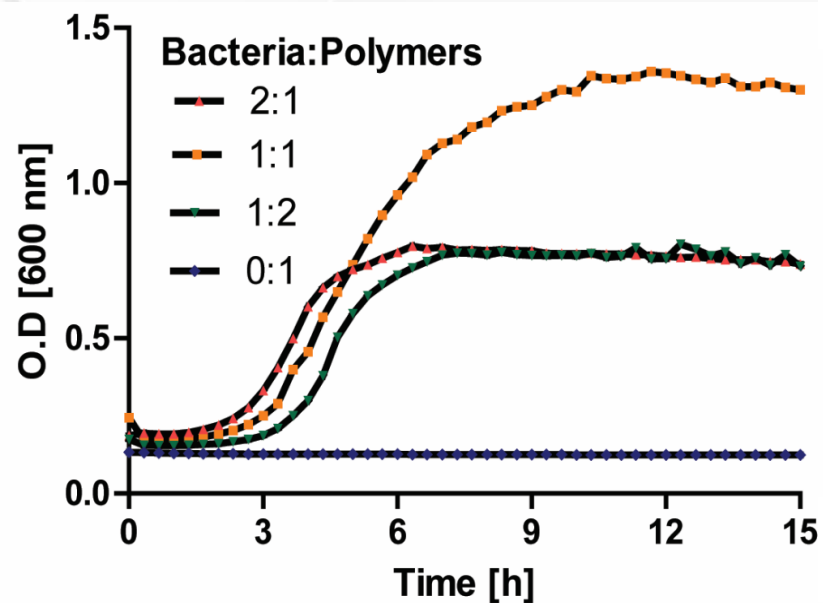
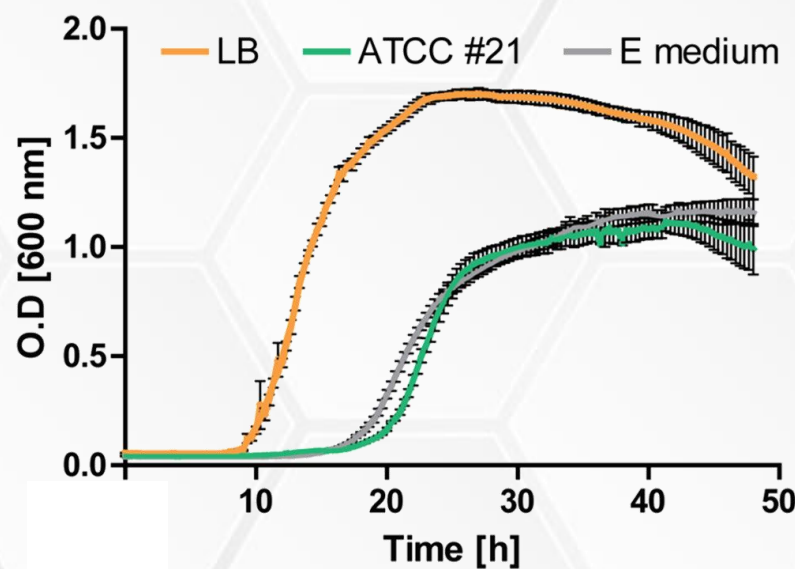


- Gram positive
- Naturally found in soil
- Qualified presumption of safety (QPS by EFSA)
- γ -PGA producer
- Hyaluronic acid like polymer

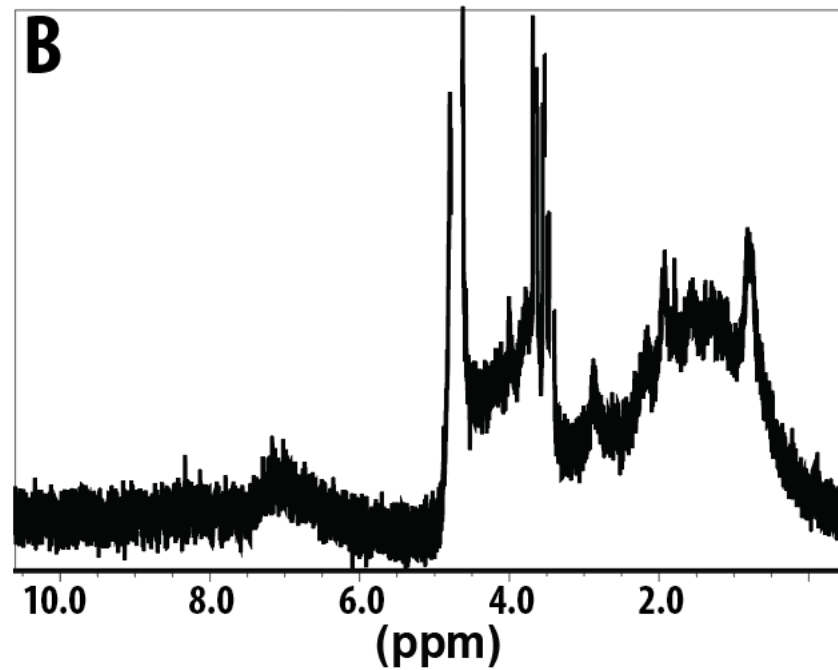
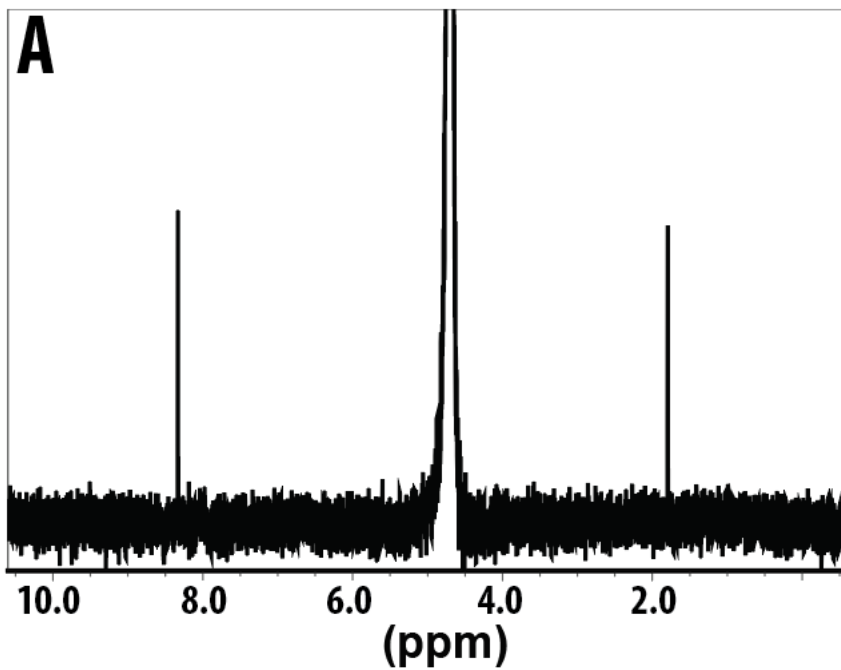
Research hypothesis

Long lasting in-situ production of therapeutic polymers onto the skin can overcome some of these challenges

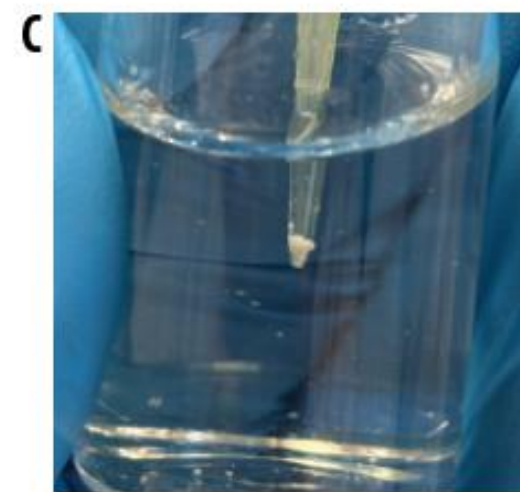
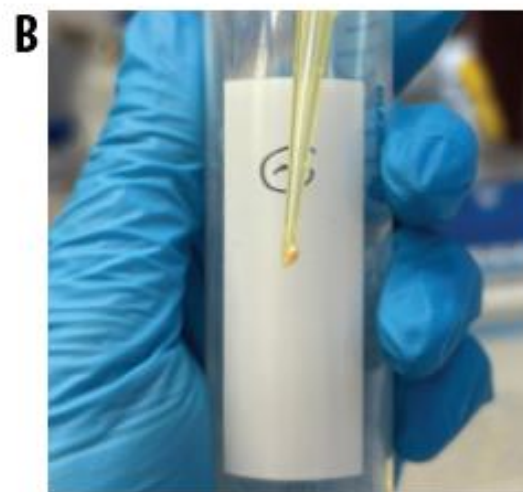
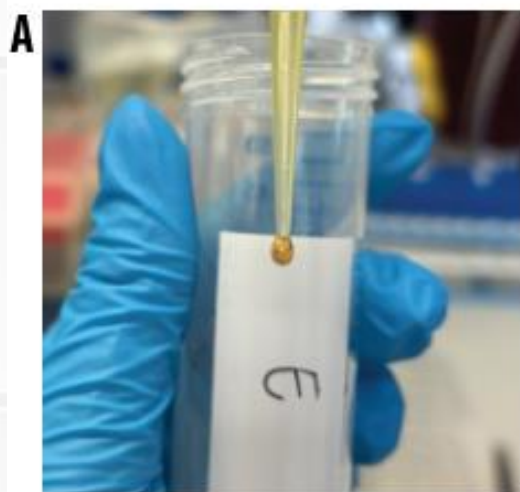


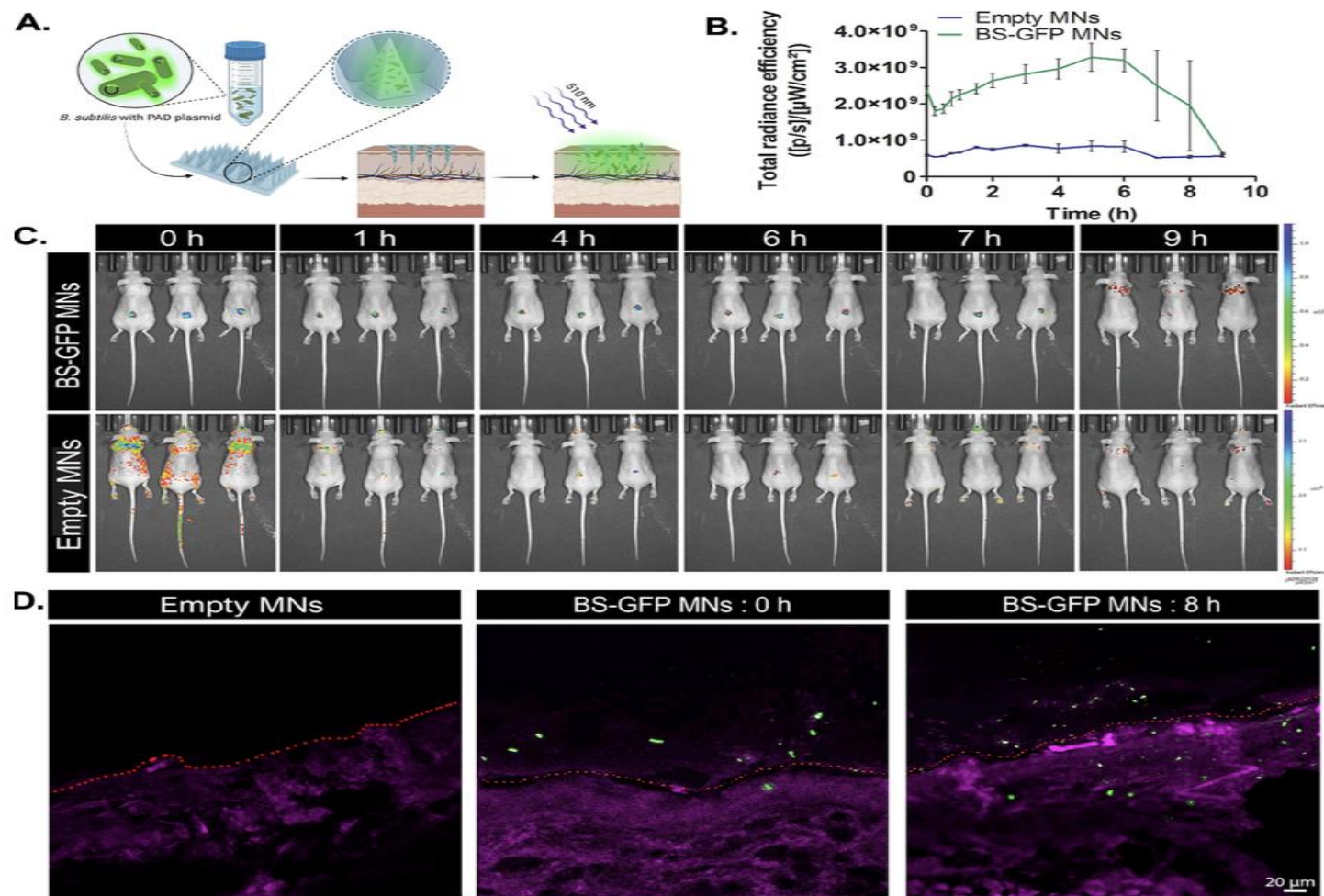


Empty M N s



BP M N s



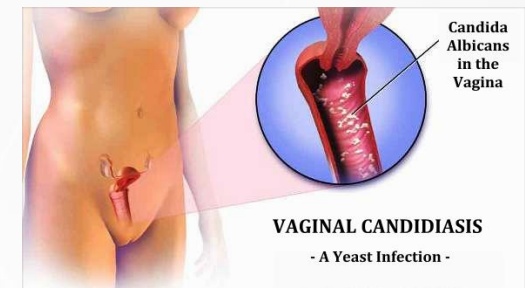
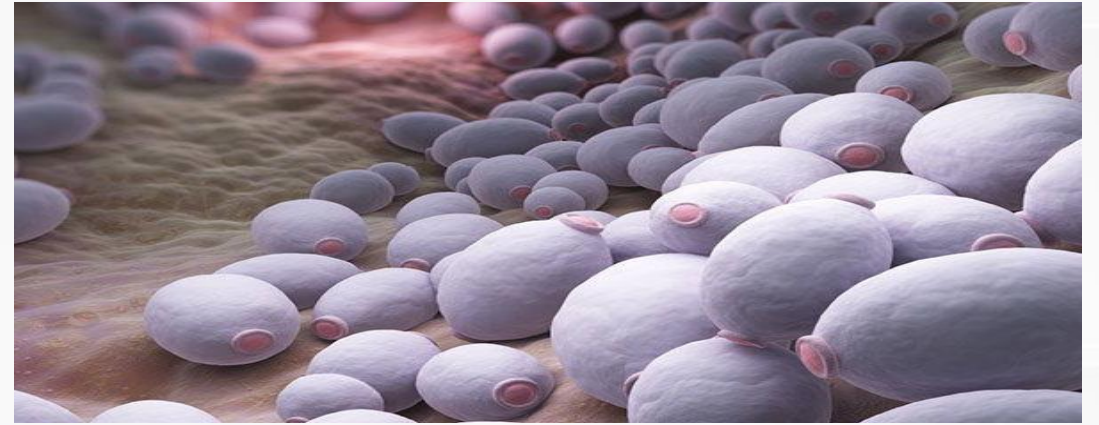


(Alperovitz, Ben David et. al, *ACS Biomat. Sci. and Eng.* 2025)

Fungal Infections:

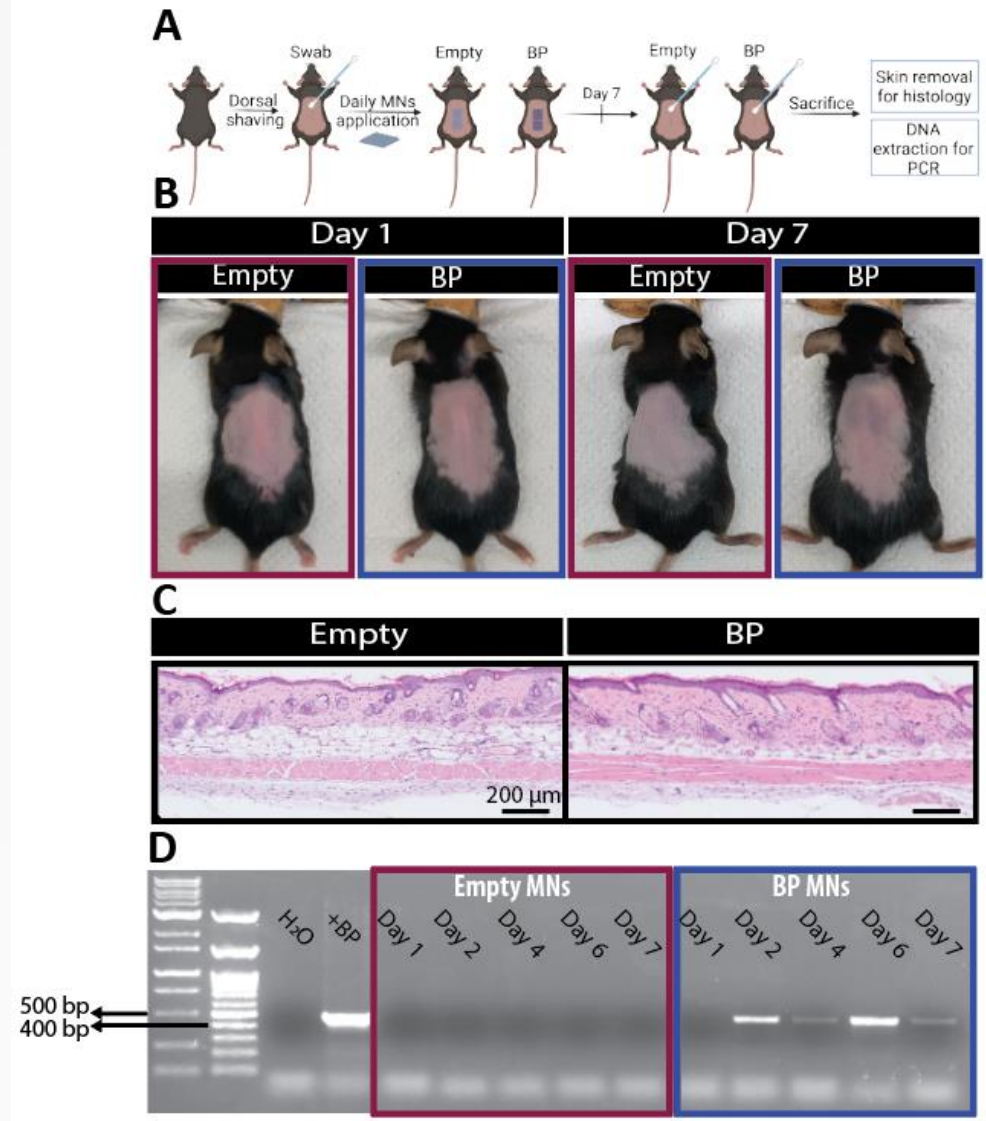
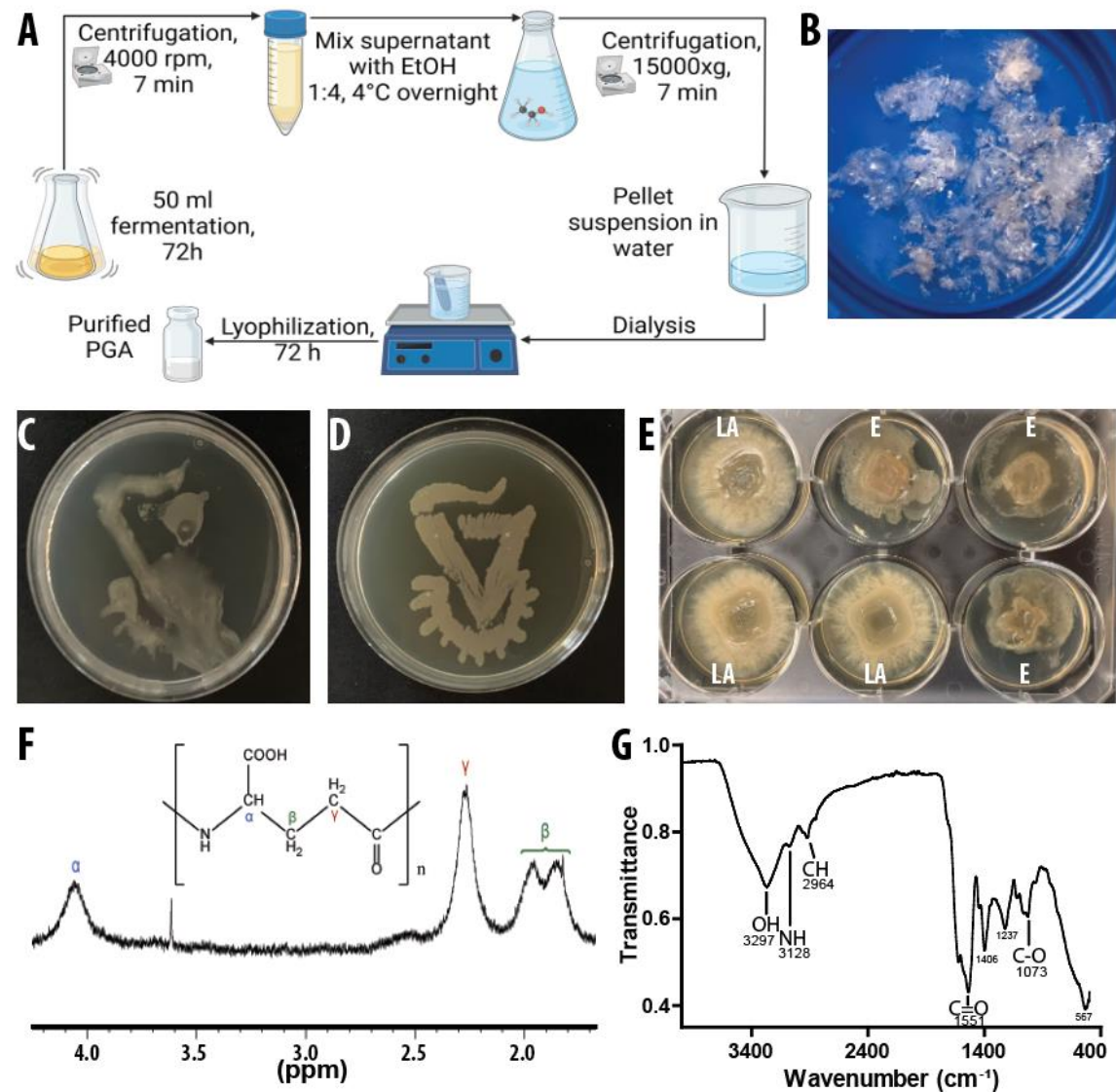
Fungal Infections:

- Yeast infection
- Eczema/Skin lesions/Rash
- Ringworm
- Athlete foot infection/Sunspots
- Candidiasis

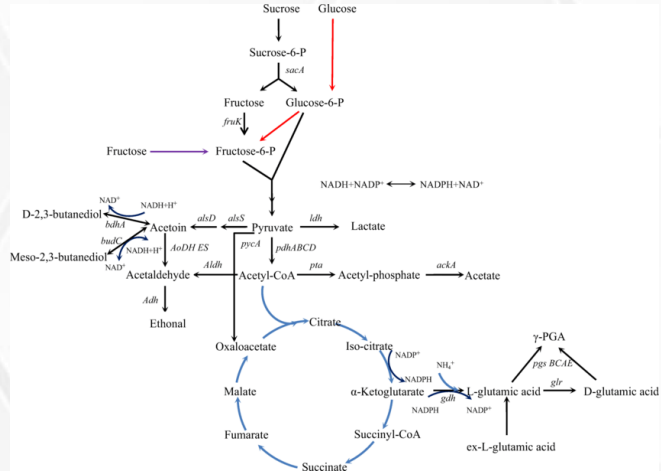


Problem - Fungal Infection

1.7 billion world wide



Caroline



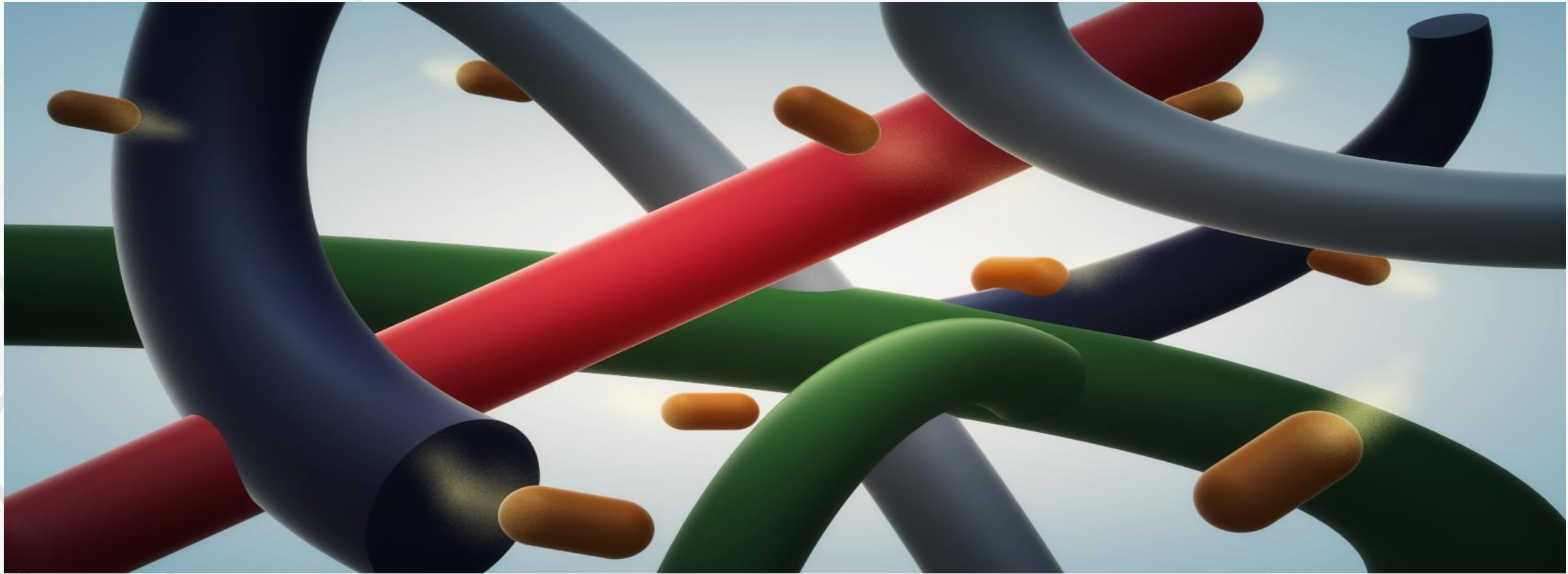
B. paralicheniformis



B. paralicheniformis +
100 μ l of 2% chitosan layer



Living Bio-Materials



Lufton et al, *Adv. Funct. Mater.*, 2018; Ben-David et al, *ACS Omega*, 2021; Rogev et al, *Toxicol. Pathol.*, 2019;
are based on the ability of the organisms to synthesize complex molecules. Moskopitz et al, *BMJ Microbiology*, 2021

(Hali et, al, *Living Materials*, Springer Book chapter, 2023)

