

Bioinspired Peptide-Based Materials for Regenerative Therapies

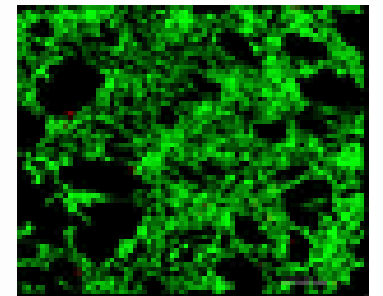
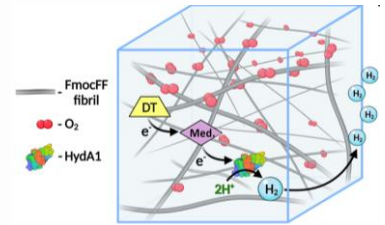
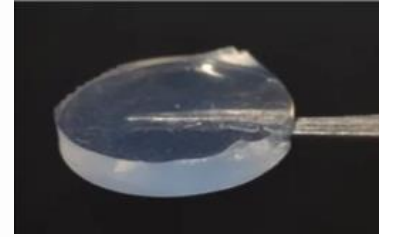
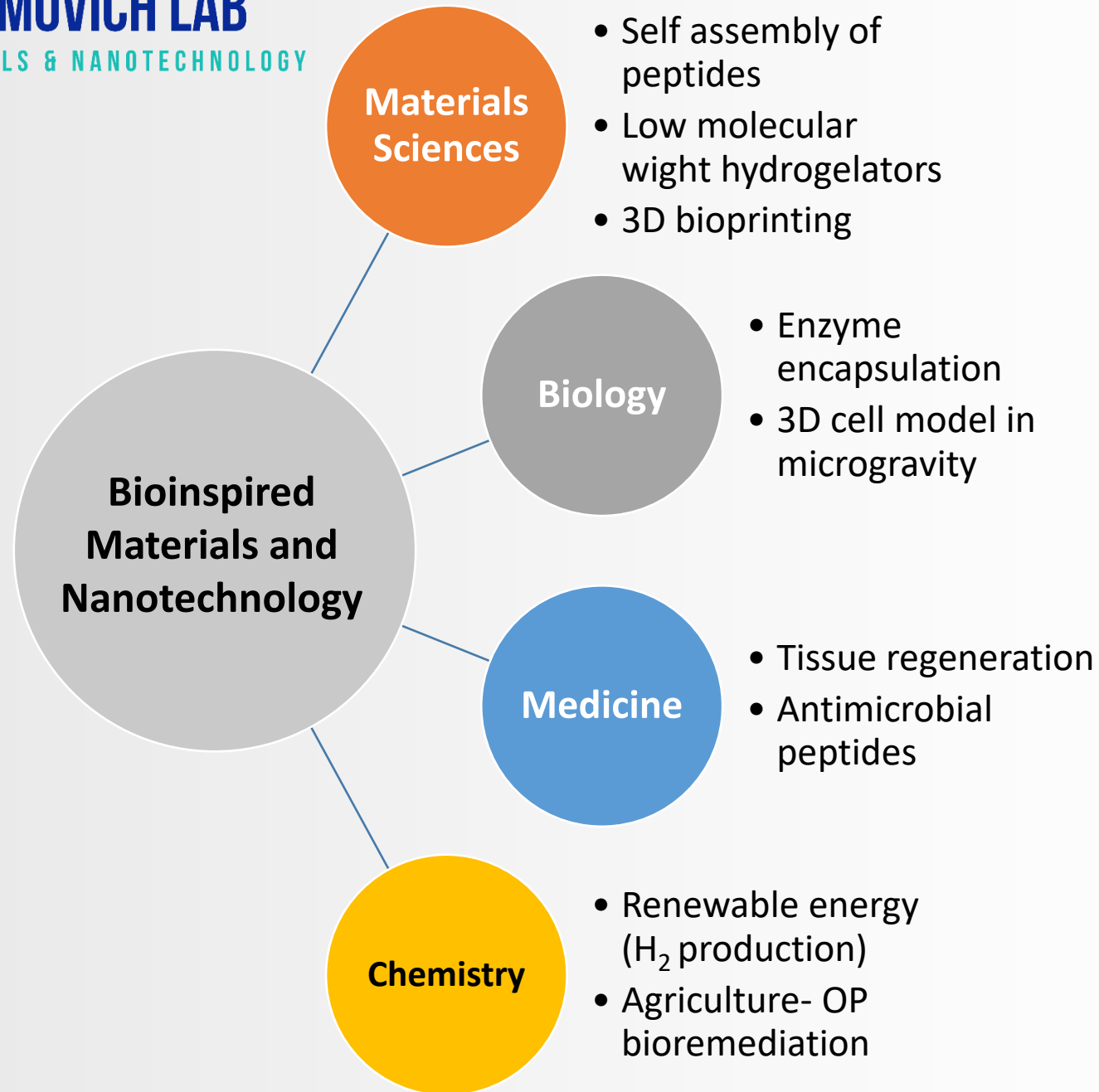


Prof. Lihi Adler-Abramovich

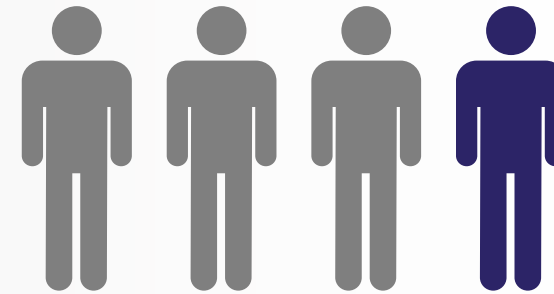
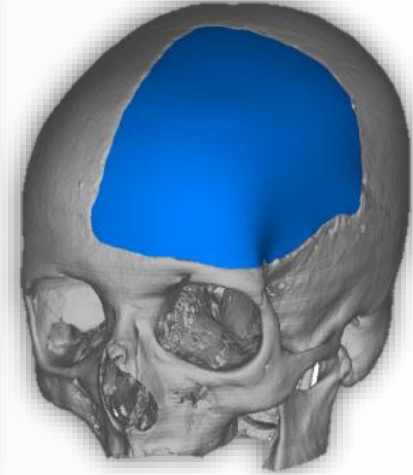
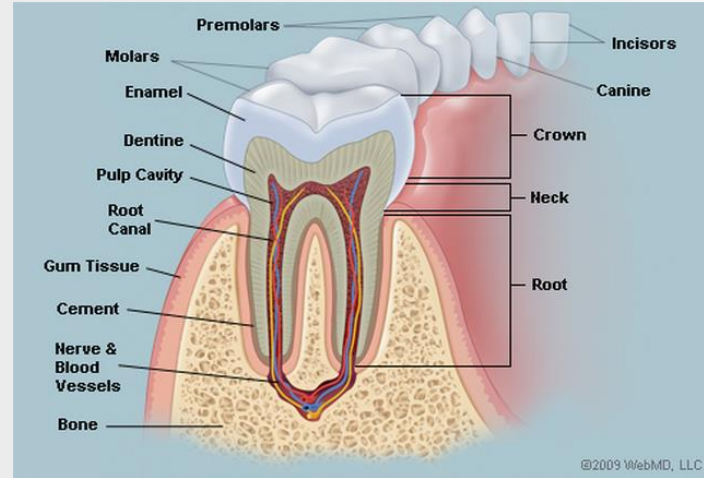
Chair, Department of Oral Biology, The Goldschleger School
of Dental Medicine, Gray Faculty of Medicine,
The Center for Nanoscience and Nanotechnology,
Tel-Aviv University, Tel Aviv, ISRAEL



CRS 2025 Annual Meeting
Philadelphia, PA, USA
July 14-18, 2025



The challenge: Bone Defects or a Bone Fracture



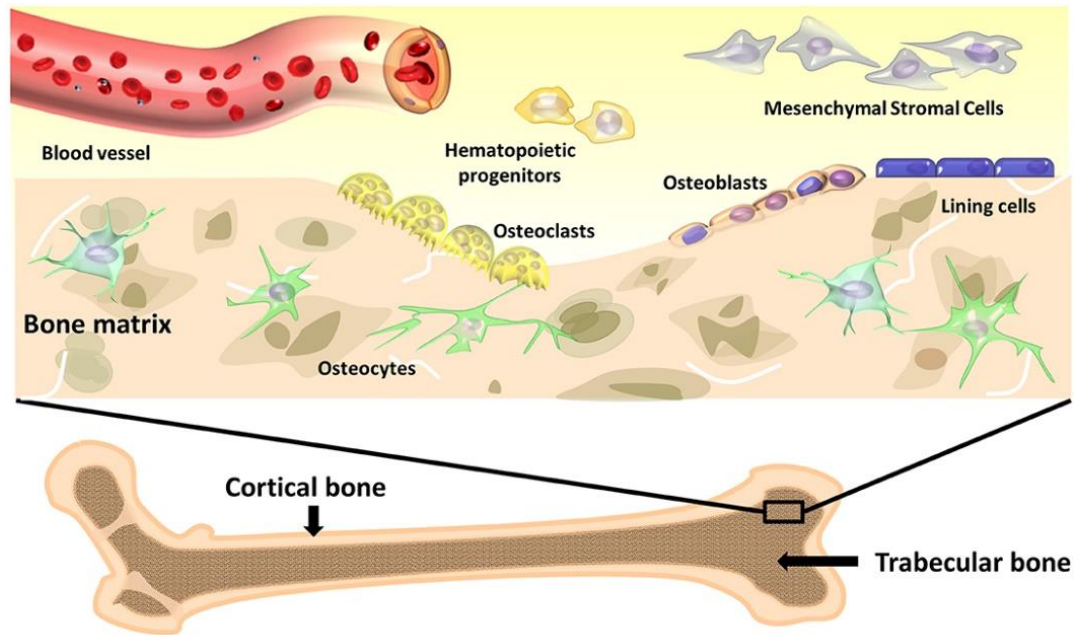
Periodontitis
Peri - implantitis

25% >74 years old
Full edentulous

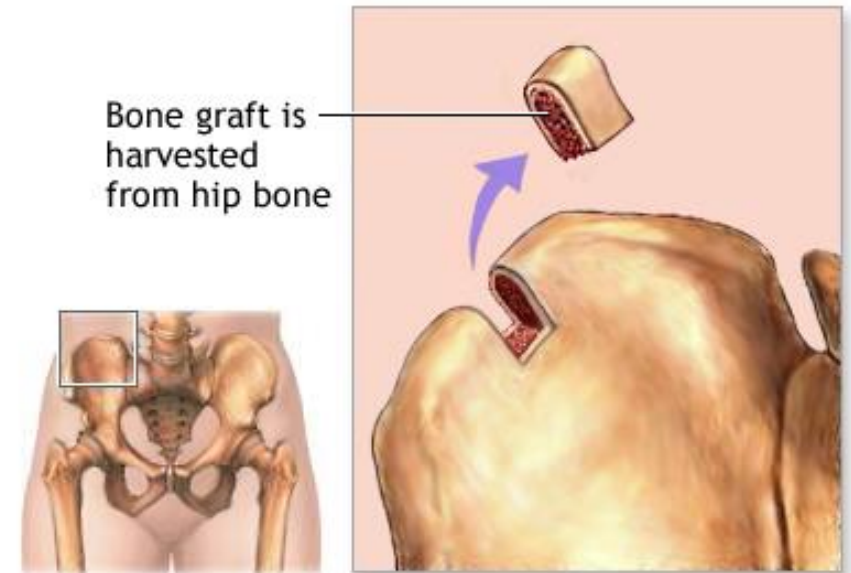
Bone Tissue Regeneration



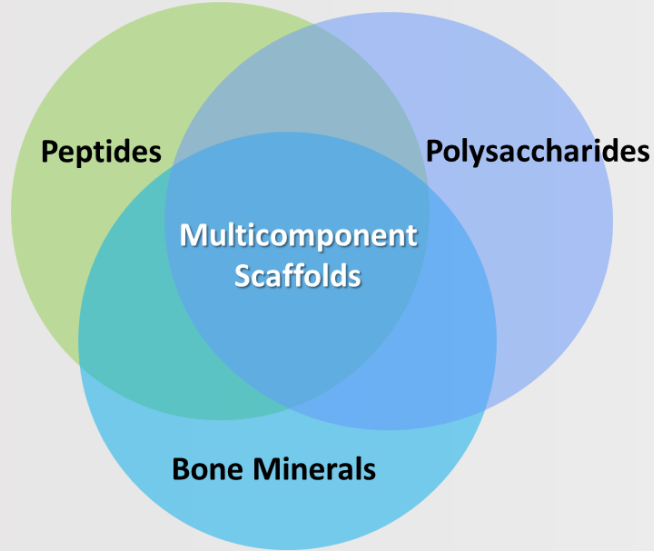
Bone can regenerate spontaneously



Current treatment: Auto-graft, allograft, xenograft, bone substitutes



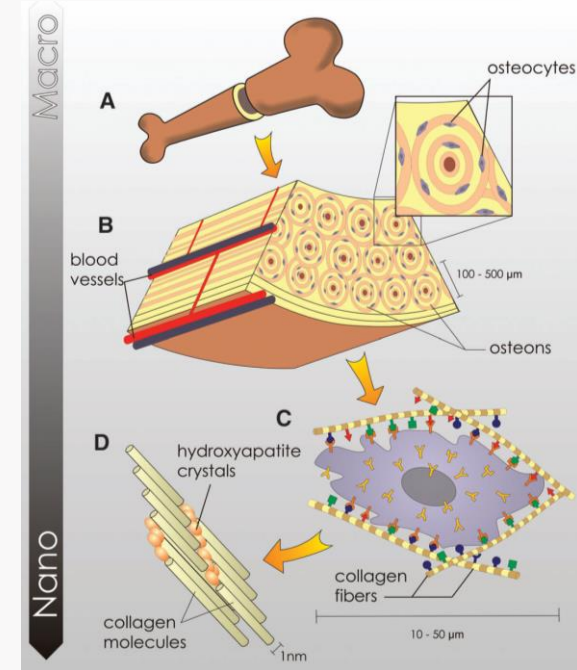
“Smart” Multicomponent Scaffolds



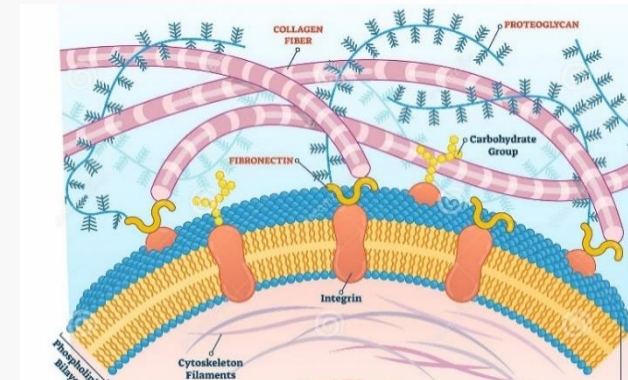
+ Growth factors
Osteogenesis → **BMPs** –
Bone Morphogenetic Proteins
Angiogenesis → **VEGF** –
Vascular Endothelial Growth Factor

Scaffold requirements

- Biocompatibility
- 3D support
- Adaptable to the defect shape
- Stiffness for mechano-sensing
- Space maintenance over time
- Controlled degradation rate
- Growth factors and drugs delivery



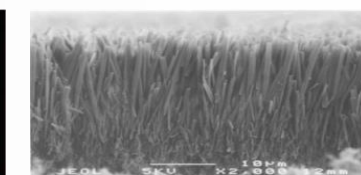
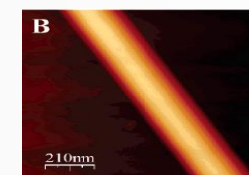
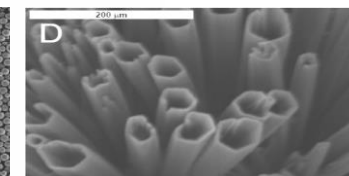
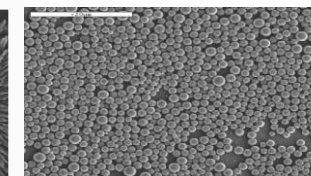
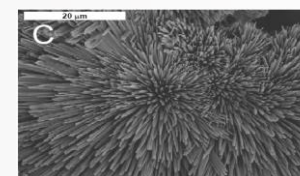
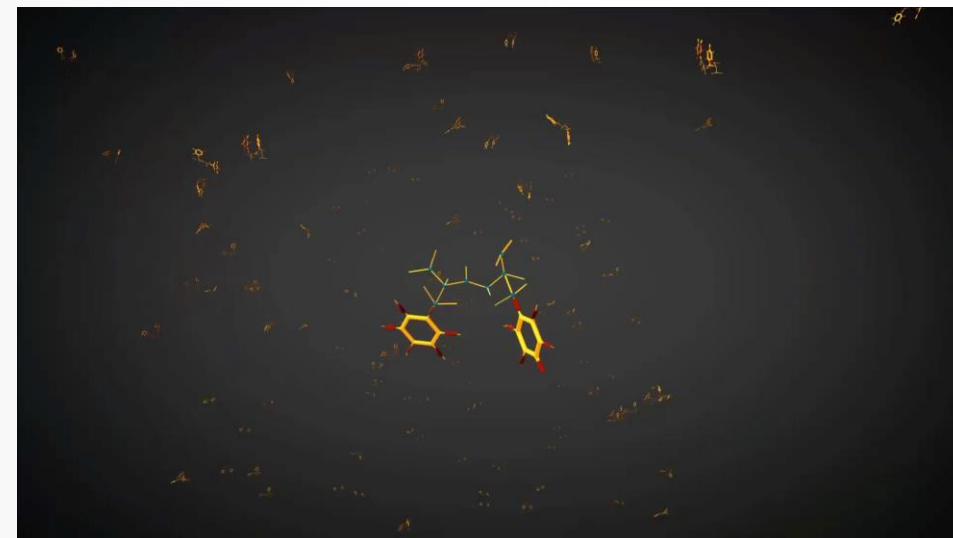
Stevens and George, Science 2005



Extracellular Matrix (ECM)

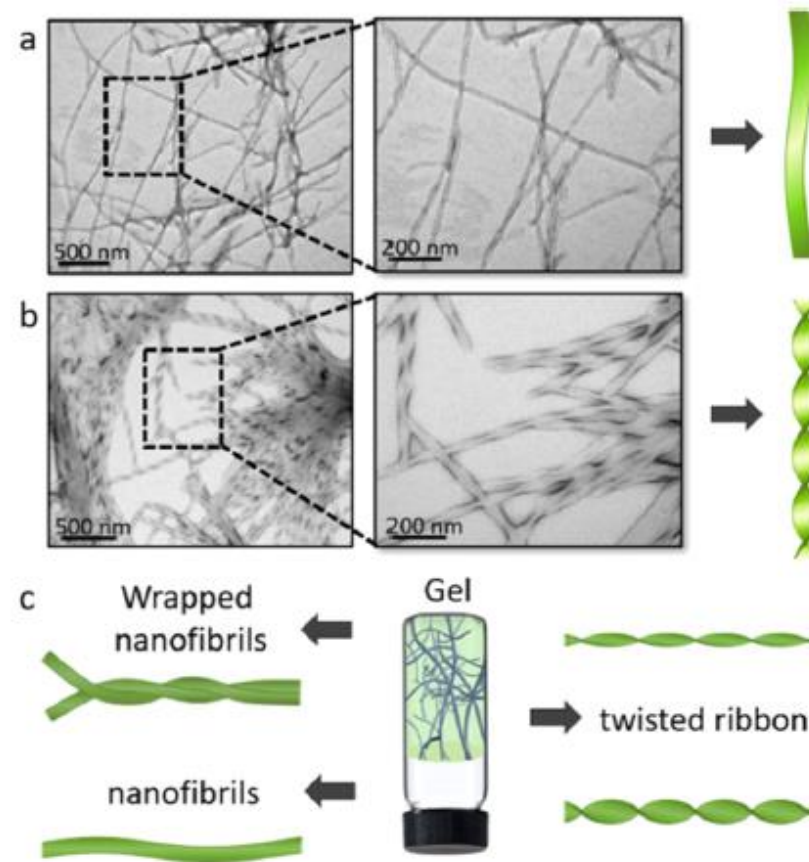
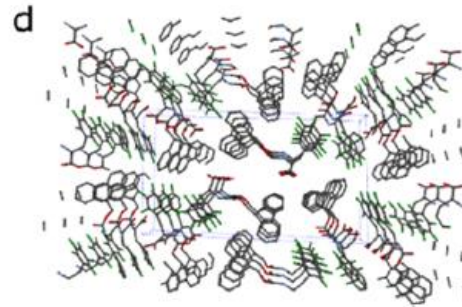
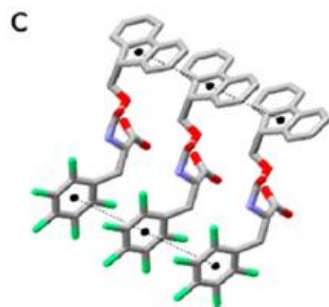
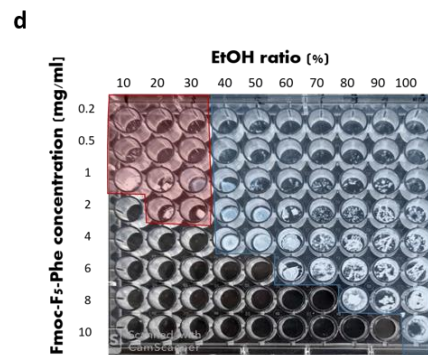
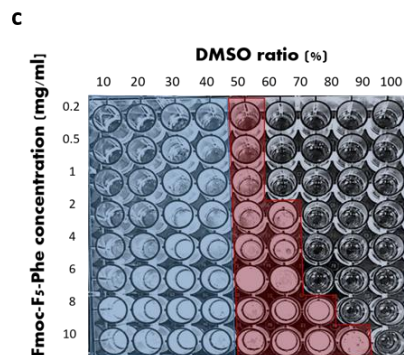
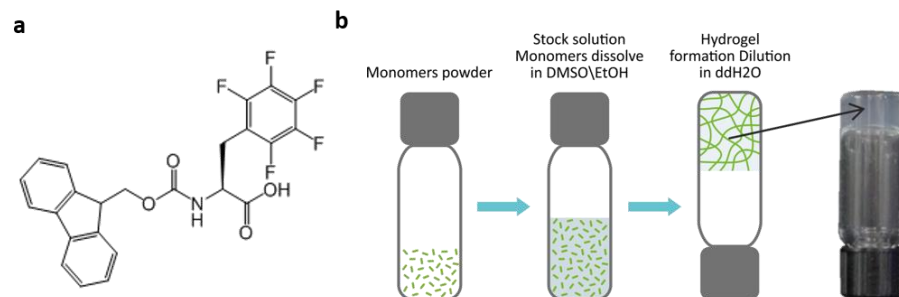
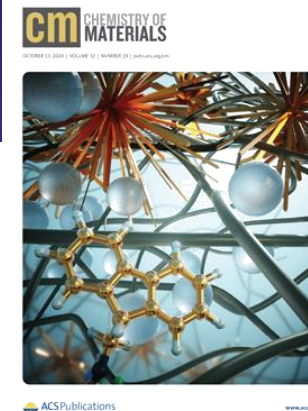
Aromatic Dipeptide Nanostructure Library

Compound name	Assemblies structured	Additional information
H-Phe-Phe-OH (FF)	Tubes, spheres, quantum-dots	Young modulus = 19–30 GPa, β -sheet
H-Phe-Phe-NH ₂	Nanotubes	
Ac-Phe-Phe-NH ₂	Nanotubes	
H-Phg-Phg-OH	Nanospheres	
H-Cys-Phe-Phe-OH	Nanospheres	
Boc-Phe-Phe-OH (Boc-FF)	Tubes, spheres	Young modulus = 140–275 GPa
Cbz-Phe-Phe-OH	Amyloid-like structures	
Cyclo-Phe-Phe	Tubular structures	α -Helix or β -turn
Fmoc-Phe-Phe-OH	Fibrous-hydrogel	$G' = 2 \times 10^4$ Pa, β -sheet
Fmoc-Phe-Gly-OH	Fibrous-hydrogel	
Fmoc-2-Nal-OH	Fibrous-hydrogel	β -Sheet
Fmoc-Gly-Phe-OH	Microtubes	
Fmoc-Phe-Arg-Gly-Asp-OH	Fibrous-hydrogel	β -Sheet
Fmoc-Arg-Gly-Asp-Phe-OH	Fibrous-hydrogel	β -Sheet
Fmoc-Arg-Gly-Asp-OH	Nanotubes	
Fmoc-Phe-Ser(<i>t</i> Bu)	Spheres	
Fmoc-Phe-Pro-OH	Spheres	
di-D-1-naphthylalanine	Tubular structures	
di-D-2-naphthylalanine	Tubular structures	Point stiffness ~ 1.25 GPa
H-(<i>p</i> -fluoro-Phe)-(p-fluoro-Phe)-OH	Tubular structures	
H-(pentafluoro-Phe)-(pentafluoro-Phe)-OH	Tubular structures	
H-(<i>p</i> -iodo-Phe)-(p-iodo-Phe)-OH	Fibrillar structures	
H-(<i>p</i> -nitro-Phe)-(p-nitro-Phe)-OH	Fibrillar structures and spheres	9
H-(4-phenyl-Phe)-(4-phenyl-Phe)-OH	Squared plates	
H-Phe-Phe-Phe-OH	Nanoplates	β -Sheet

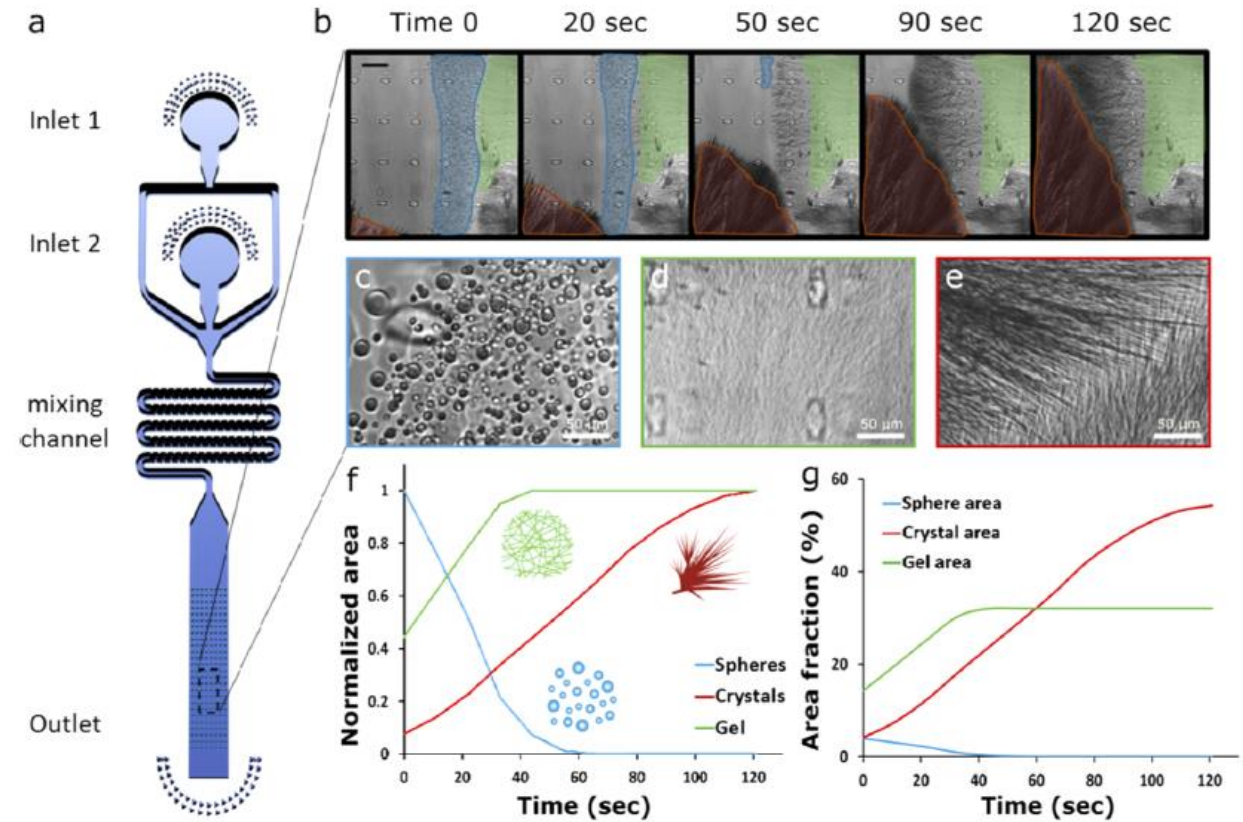
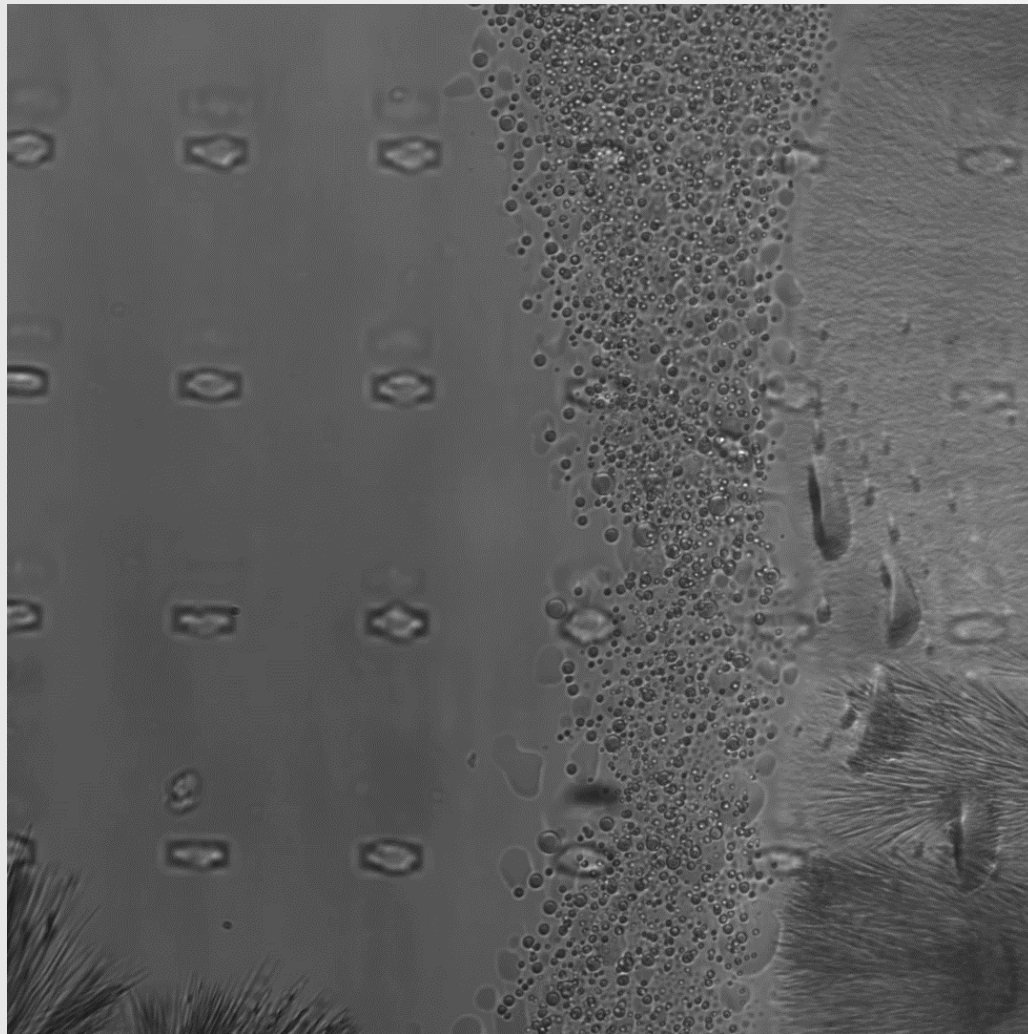


Adler-Abramovich and Gazit (2014) Chem. Soc. Rev.

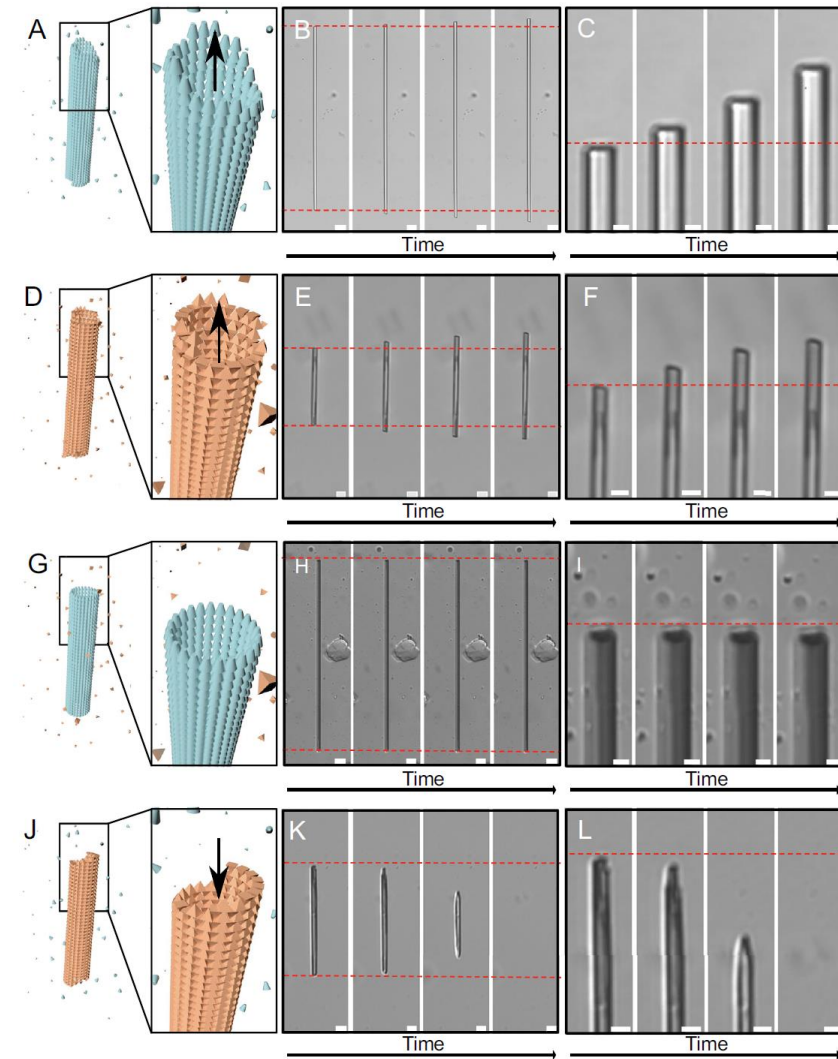
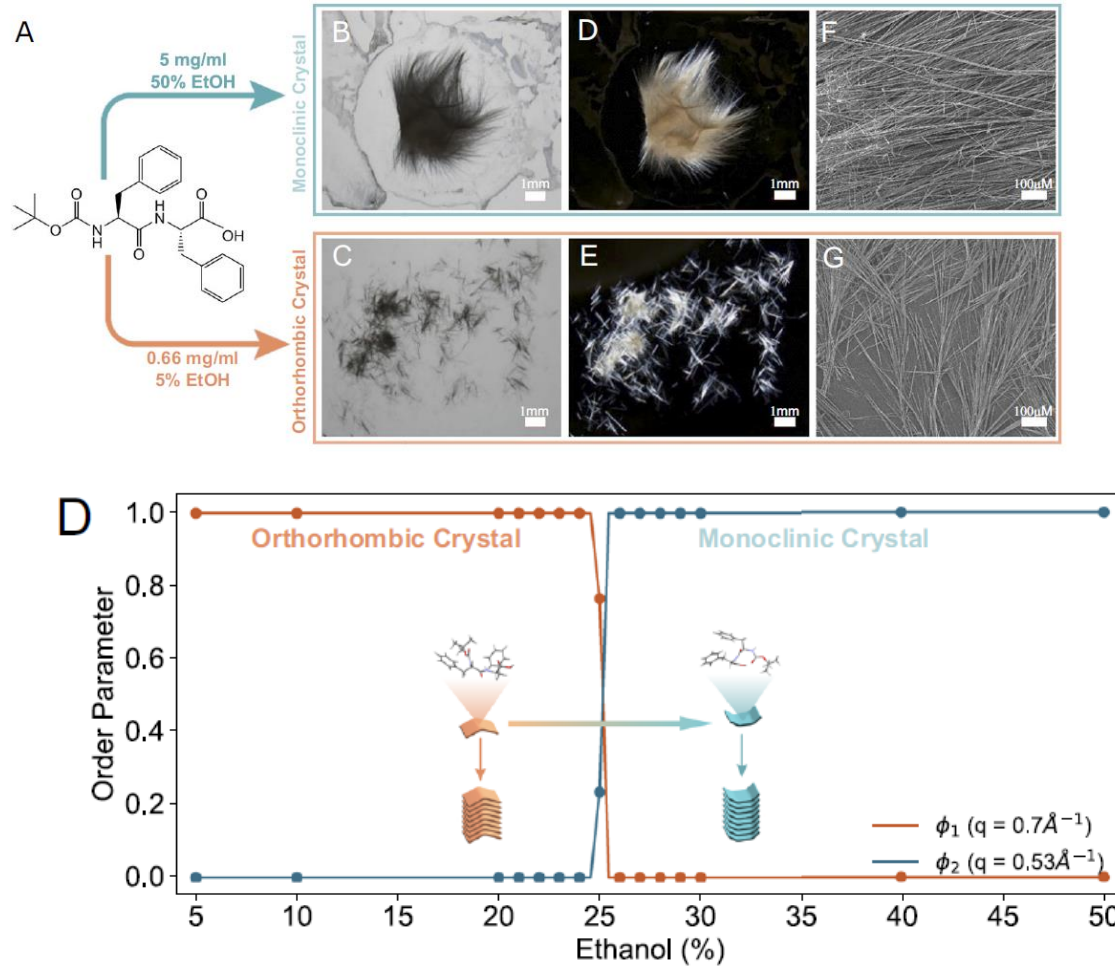
Phase Transition- The Solvent Effect



Phase Transition in Real-Time using Microfluidics

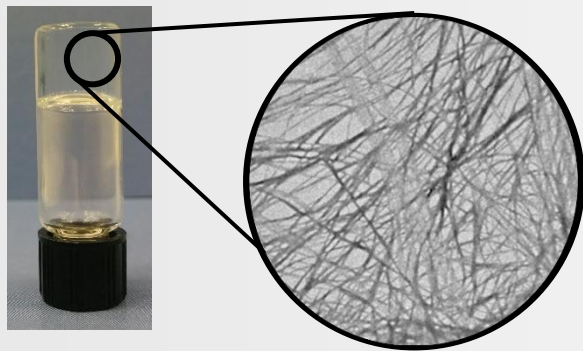


Even a 1% Change in Ethanol Concentration Can Determine the Crystalline structure

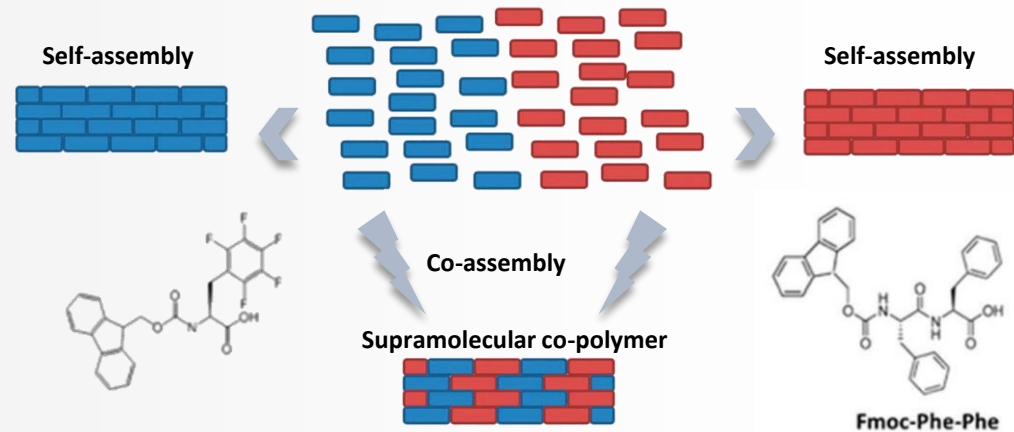


Extending the Peptide Based Materials Diversity

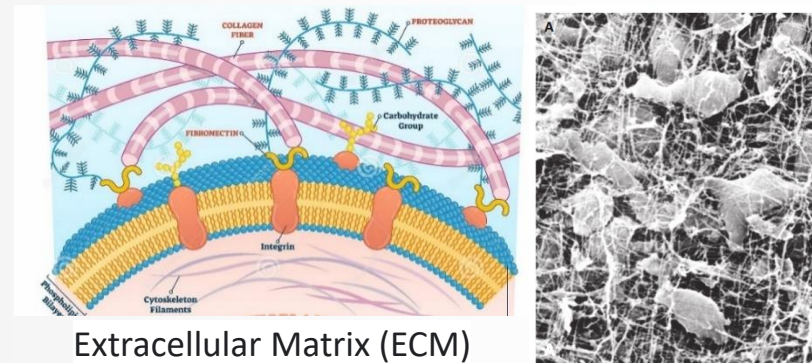
Self-assembling peptides



Hydrogel diversity by co-assembly



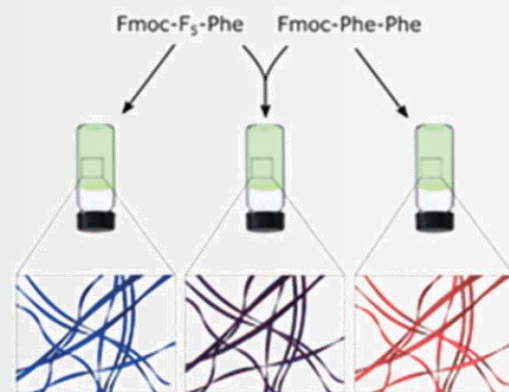
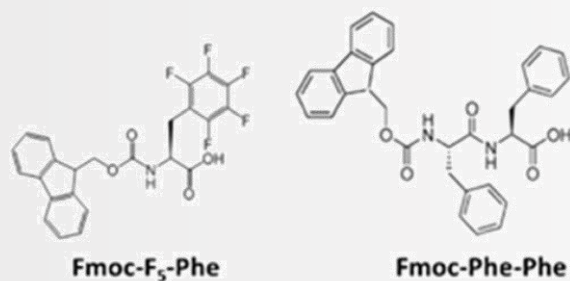
Mimicking complexed biological systems



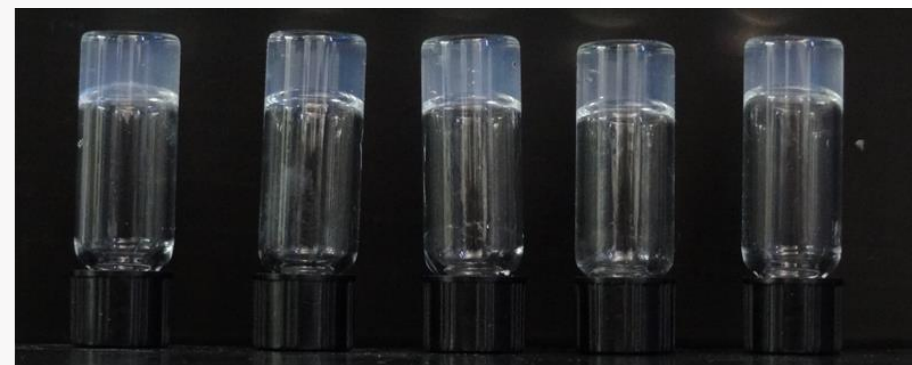
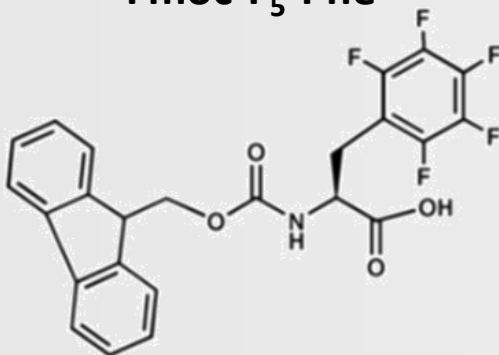
Pollard, *Cell Biology*, 3rd ed.

Adler-Abramovich *et al.* (2014) Chem. Soc. Rev.
Halperin...Adler-Abramovich (2017) Chem. Commun.
Ghosh... Adler-Abramovich (2017) Biomacromolecules

Stabilizing Hydrogels by Co-assembly



Fmoc-F₅-Phe



FmocFF

3:1

1:1

1:3

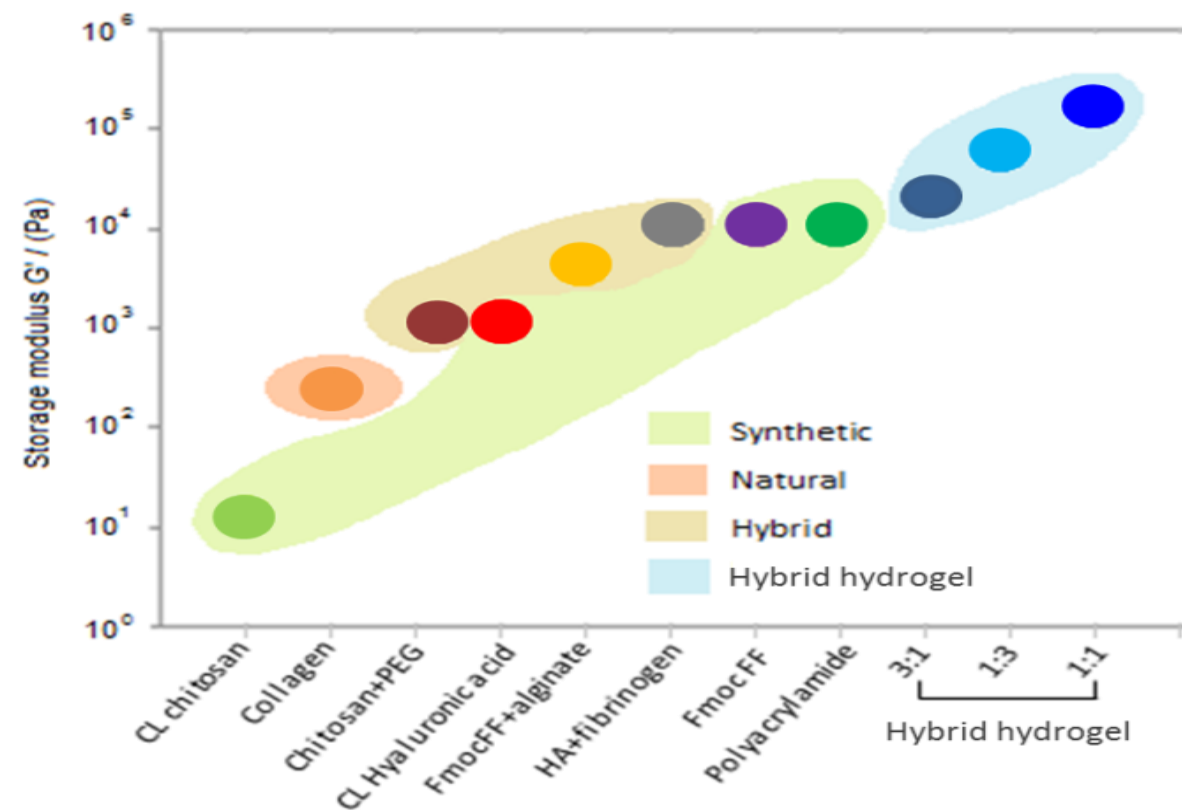
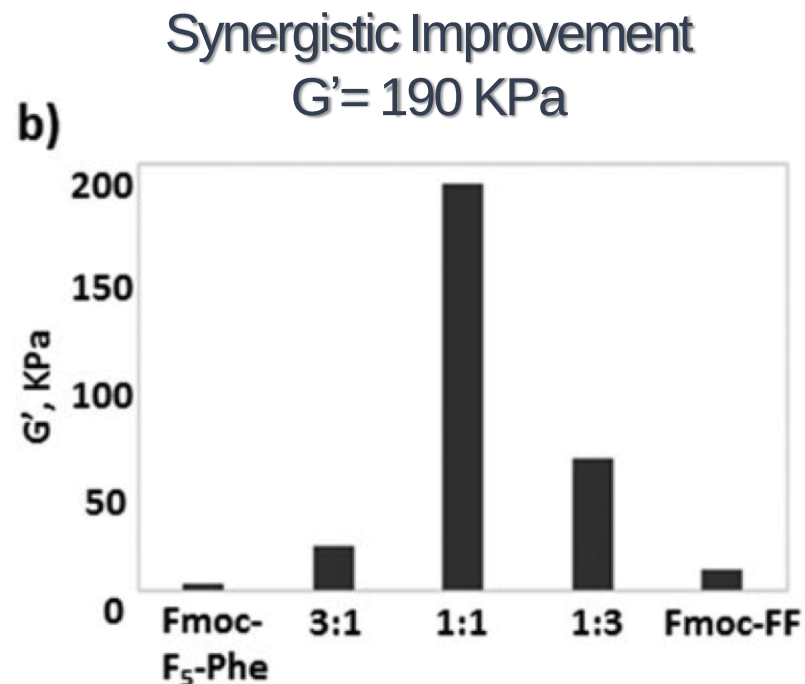
Fmoc-F₅-Phe

After 20 days

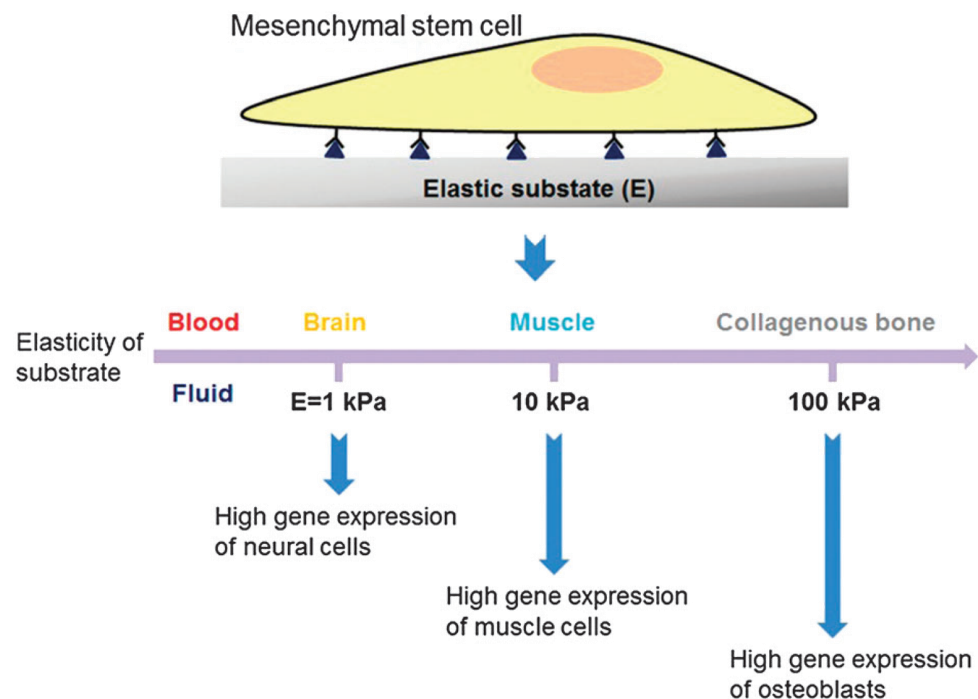


Fmoc-F₅-Phe **1:1**

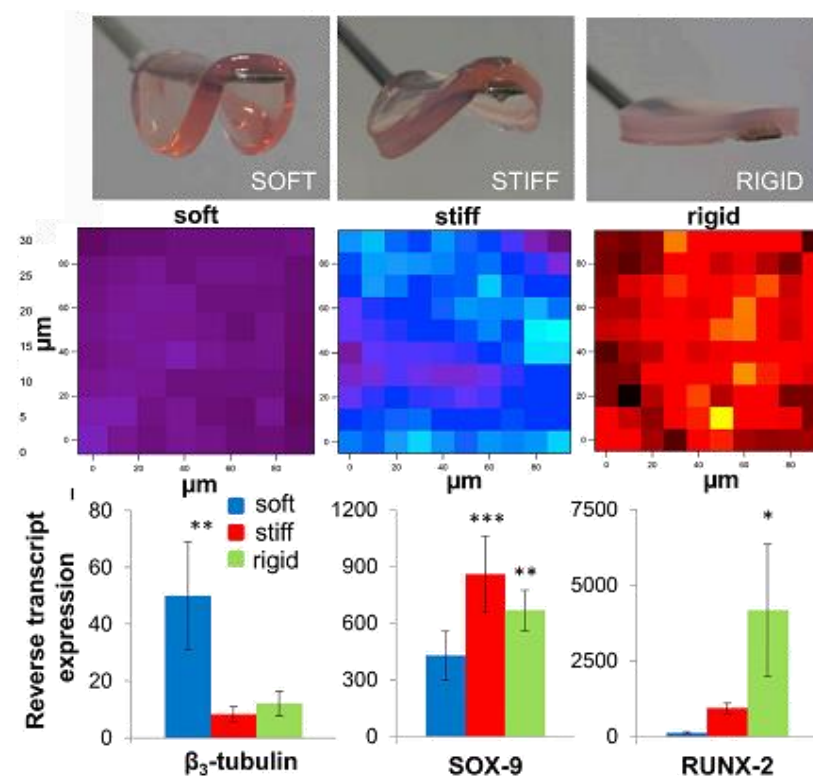
Exceptionally Rigid Hydrogels



Stem Cell Differentiation and Mechano-Sensing

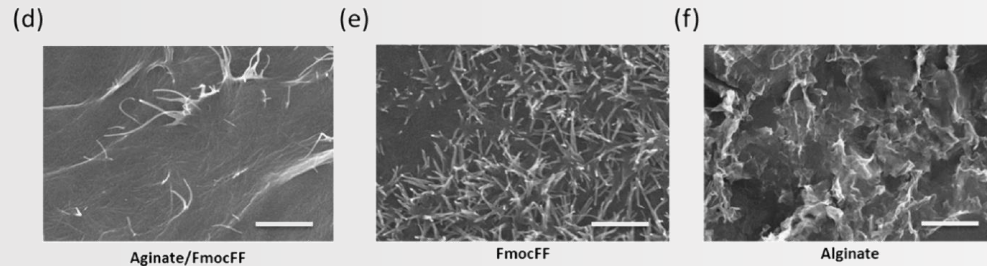
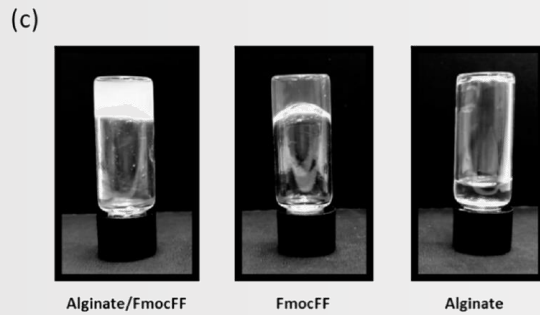
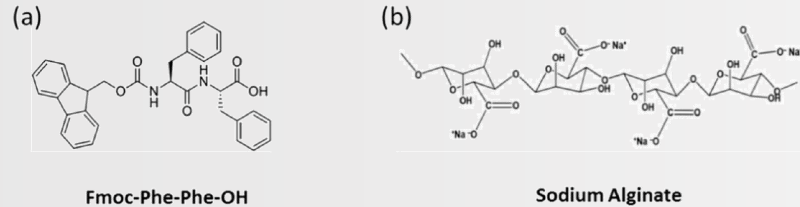
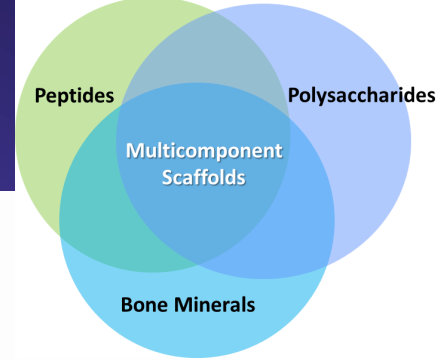


Engler *et al.* Discher. (2006) Cell
Higuchi *et al.* (2012) Chem. Rev.

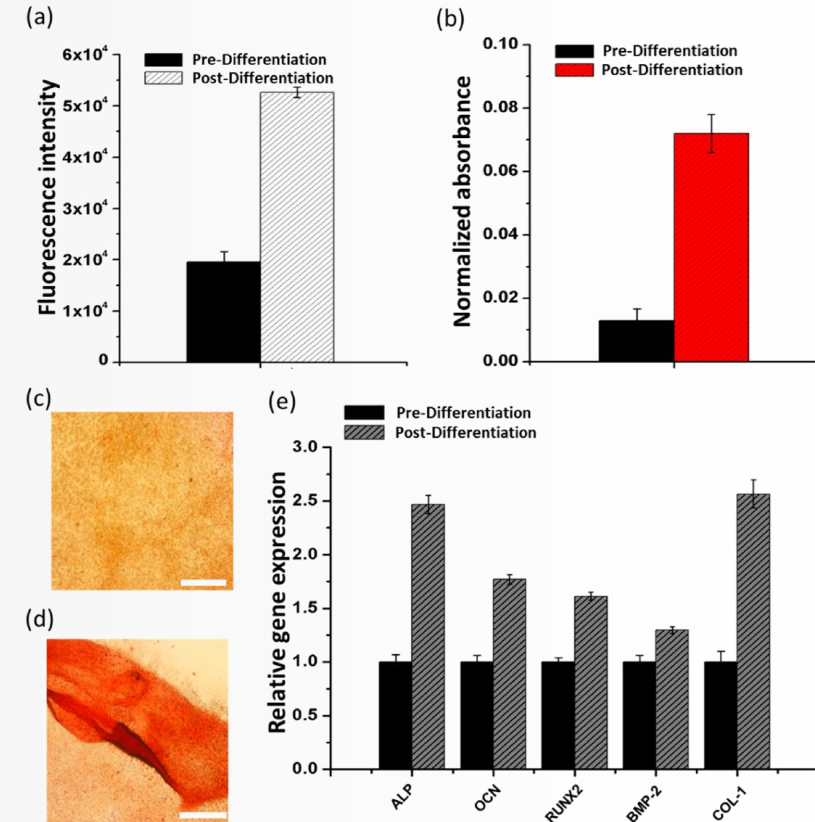
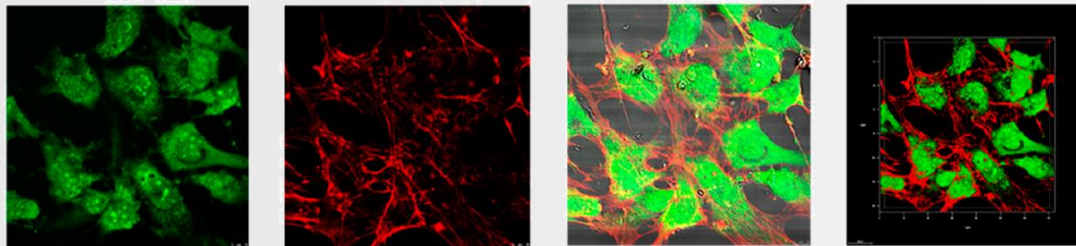


Alakpa...Ulijn (2016) Chem

Alginate-Peptide Composite Hydrogel



MC3T3-E1 cells on
Alginate/FmocFF
Composite gel



Hyaluronic Acid in Medical Use

Orthopedics



EUFLEXXA® is injected into the knees of osteoarthritis patients to improve movement and reduce pain

Cosmetics treatments

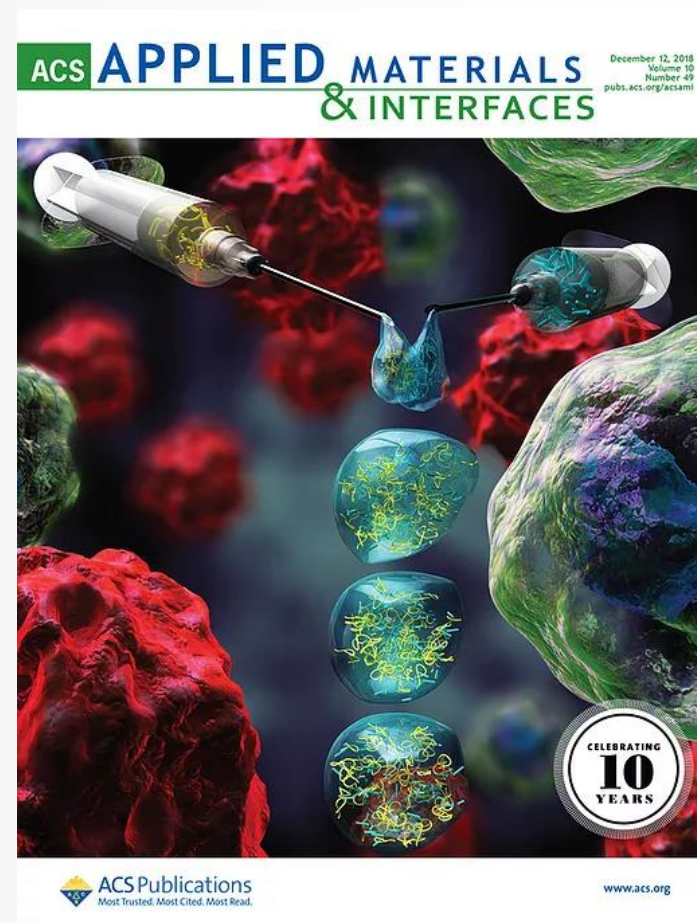
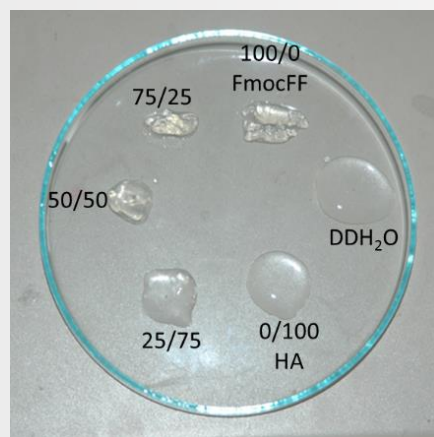
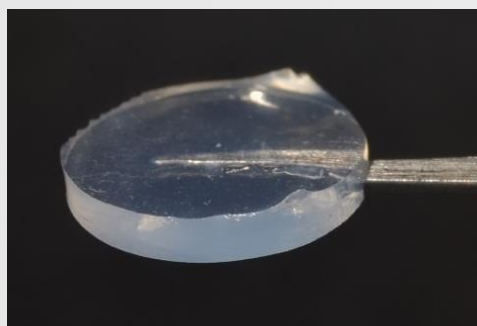
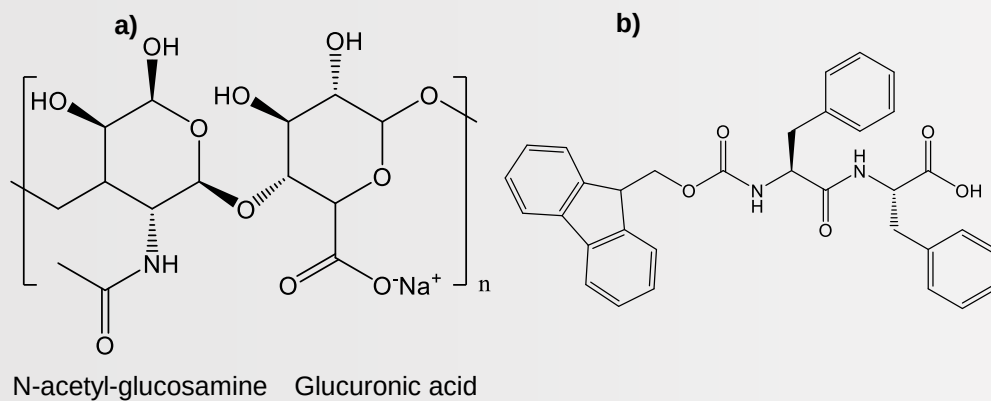


- ButaneDiol Diglycidyl Ether (BDDE) crosslinking
- Residual BDDE < 2 ppm (FDA limit)
- Storage modulus, G' up to 1,000 Pa

The problem: limited durability

Control of Hydrogel Rigidity and Durability

FmocFF/hyaluronic acid composite hydrogel

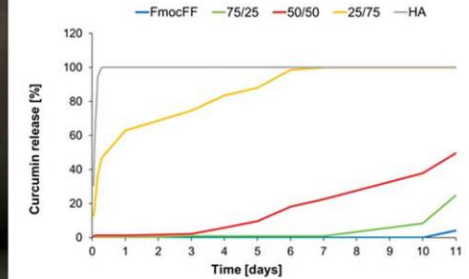
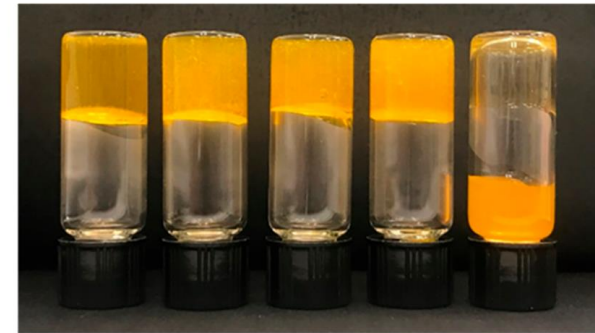


Injectable Dermal Filler for Soft Tissue Repair

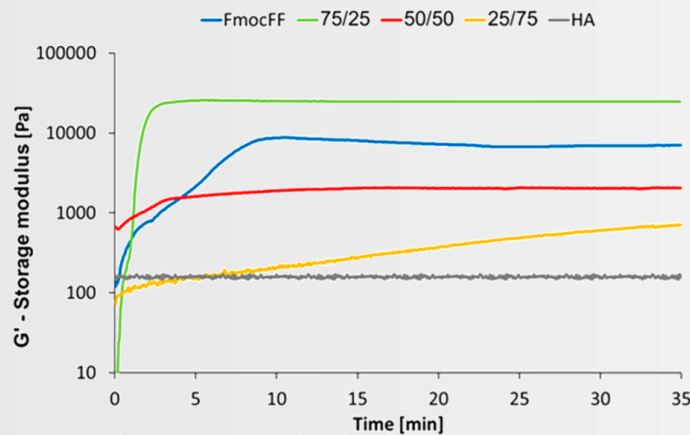
Injectable hydrogels



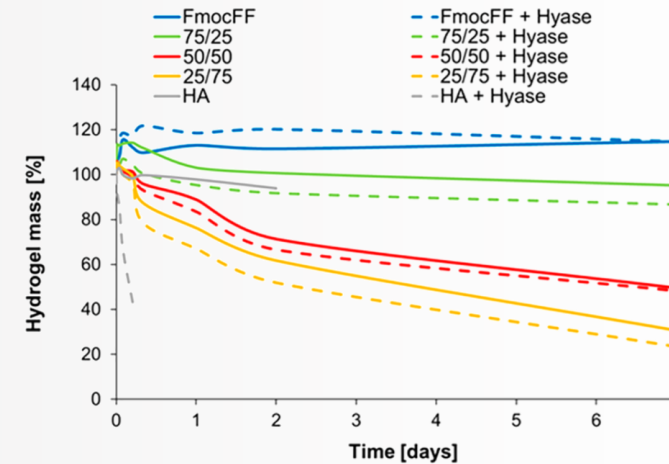
Slow release of Curcumin



Mechanical properties



Hydrogel stability against hyaluronidase

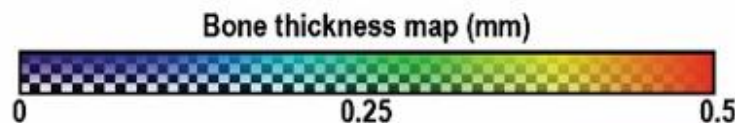
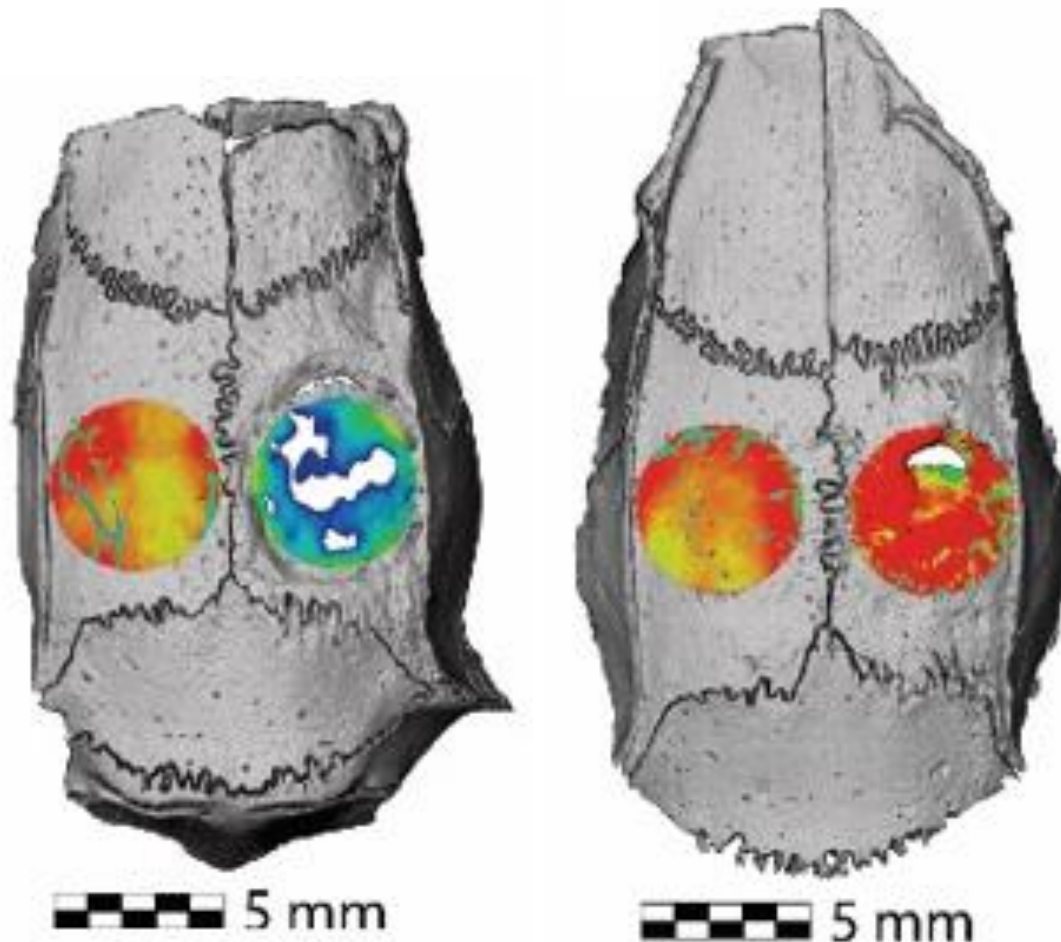


Injectable Hydrogel for Bone Regeneration

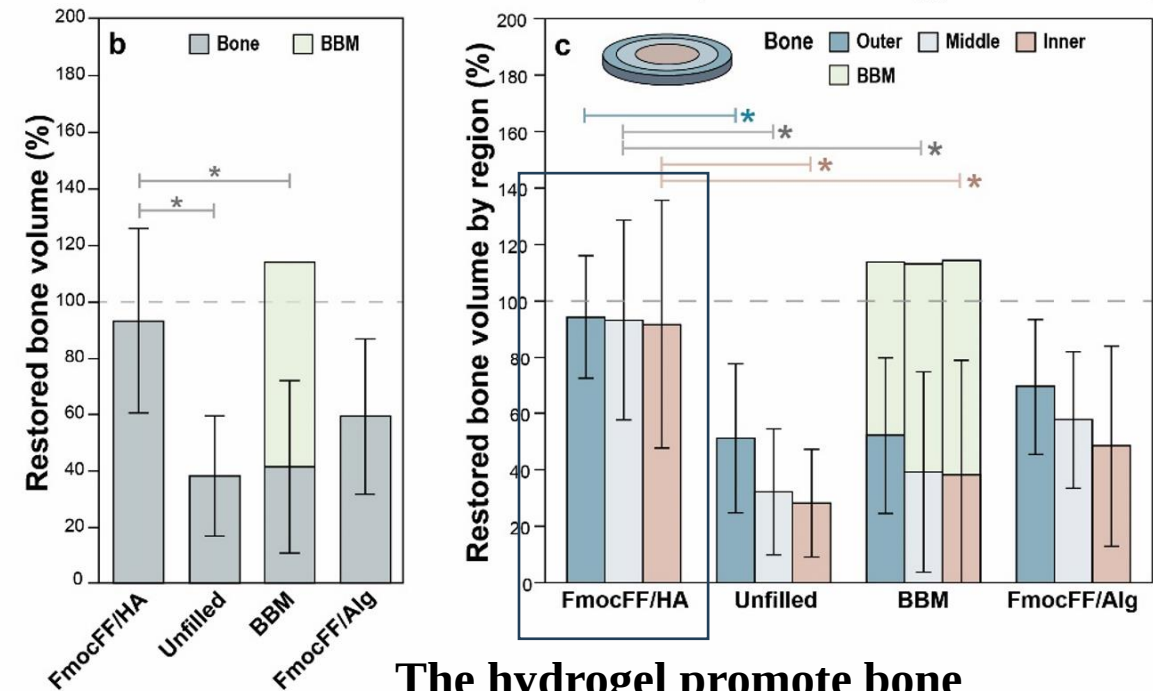
In collaboration with Prof. Rachel Sarig

Sham

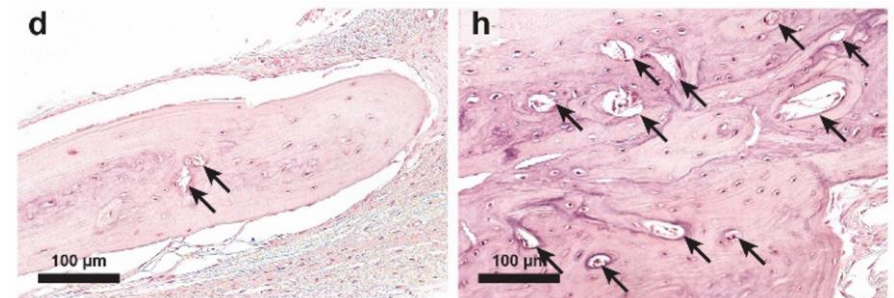
Hydrogel



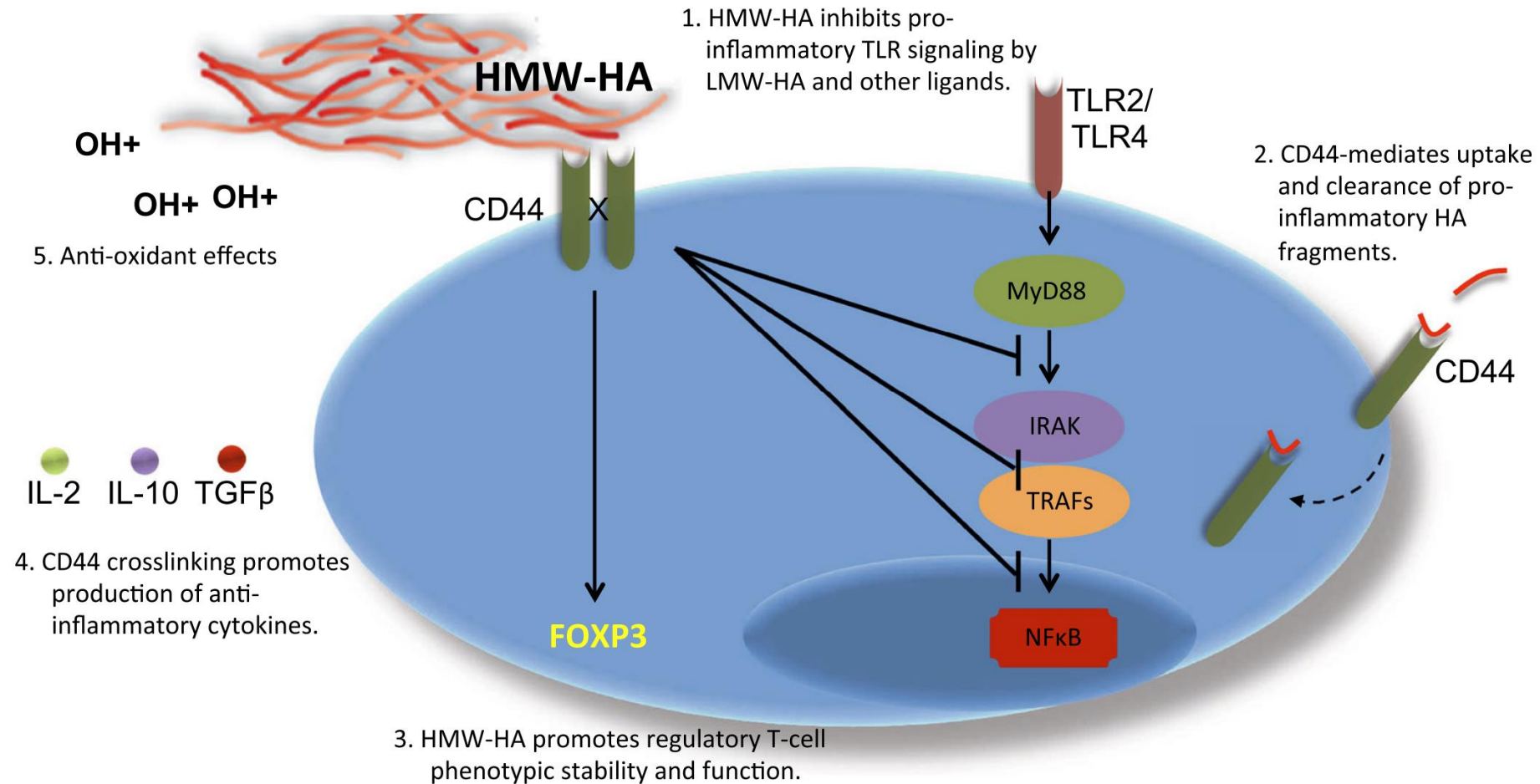
The hydrogel treatment resulted in approximately 93% bone restoration



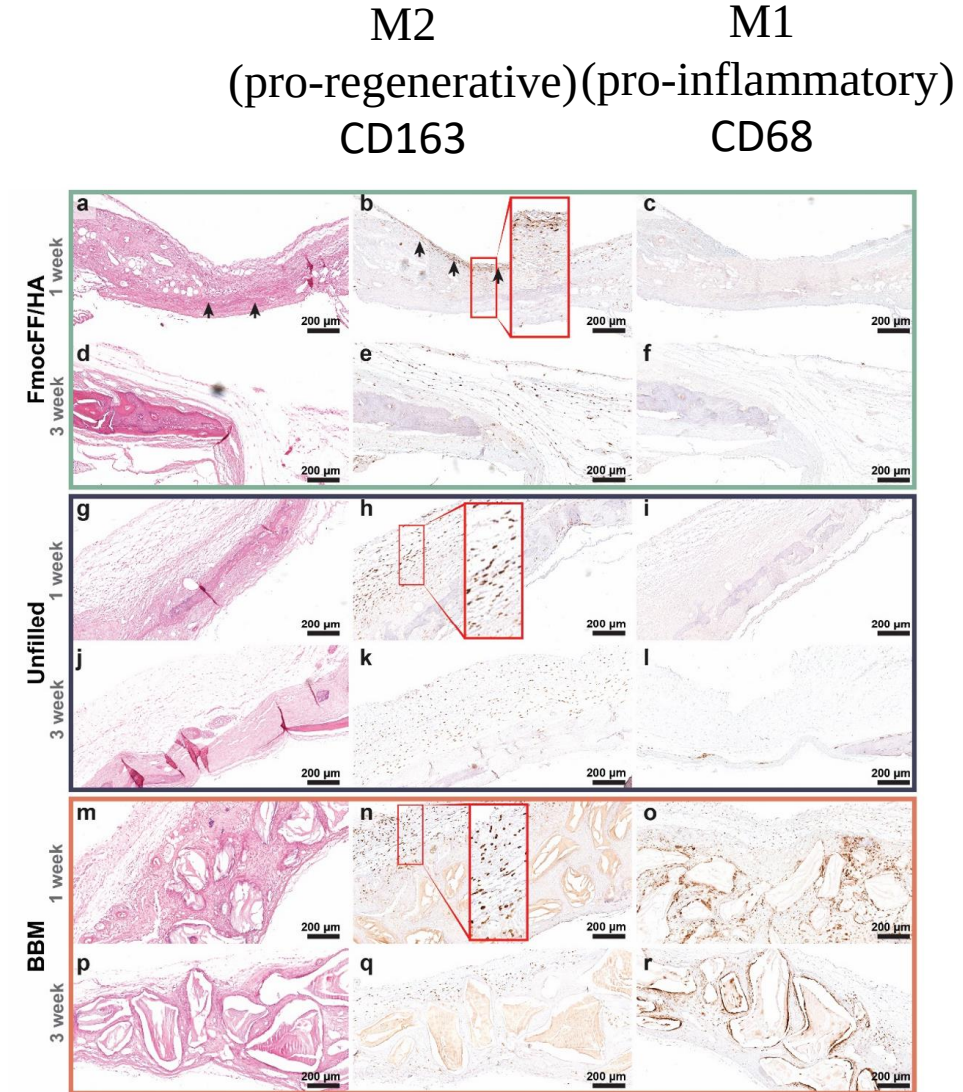
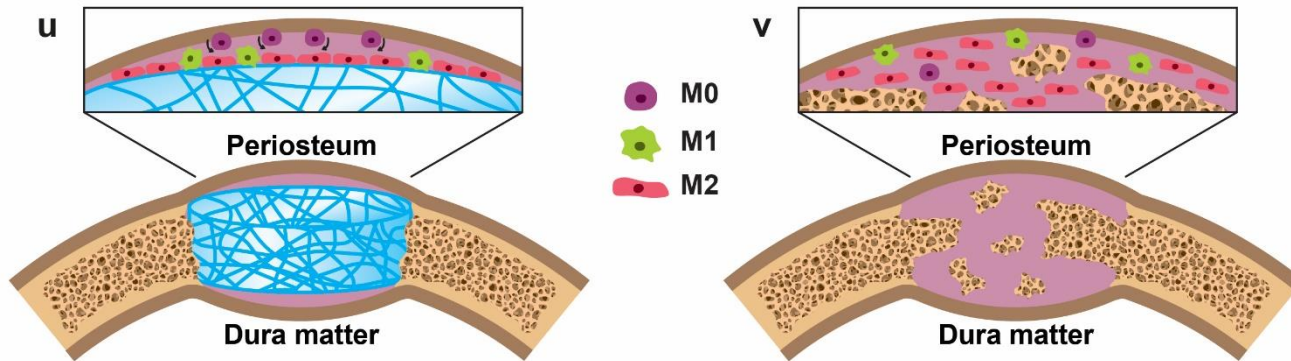
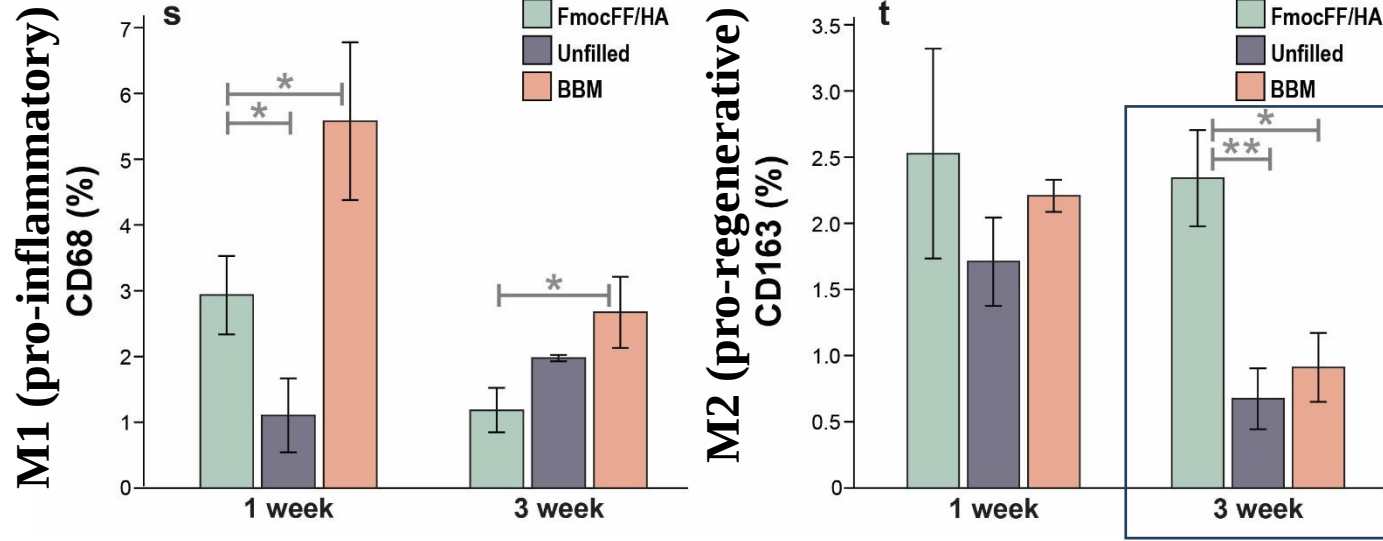
The hydrogel promote bone regeneration in the middle of the defect



High Molecular Weight HA Interacts with CD44 Receptor and Promotes Production of Anti-inflammatory Cytokines

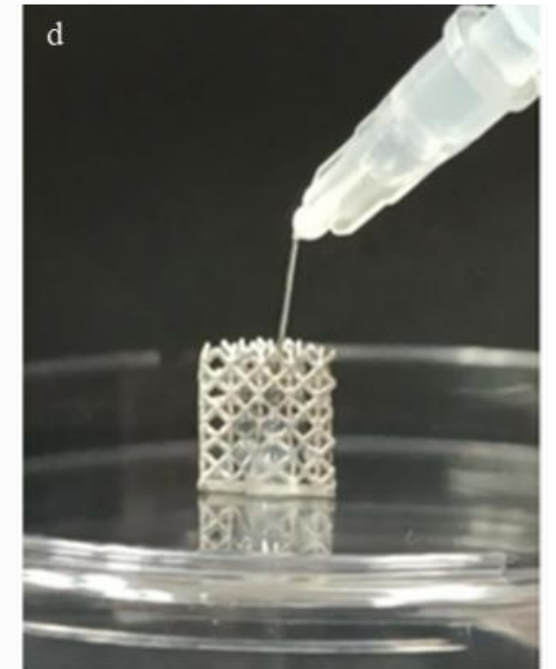
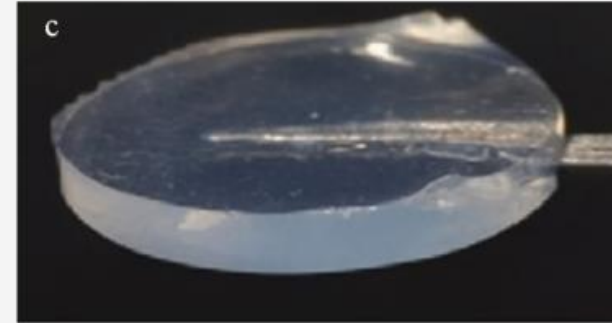


The Biomaterials cause Macrophages Immunomodulation- M1 (pro-inflammatory) to M2 (pro-regenerative)

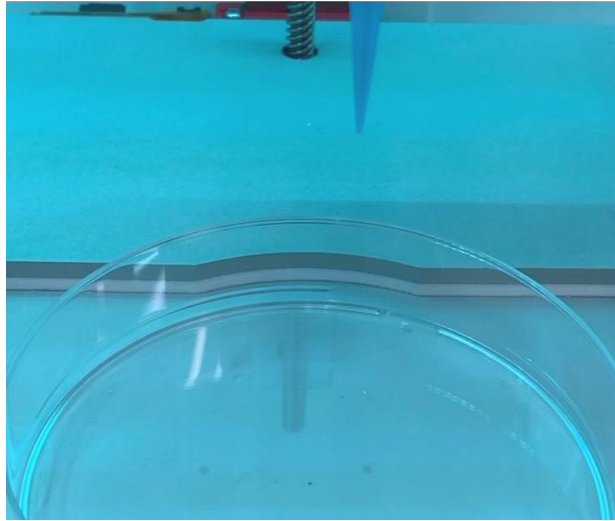


Bioactive Patient-specific Titanium “Cage” Implants

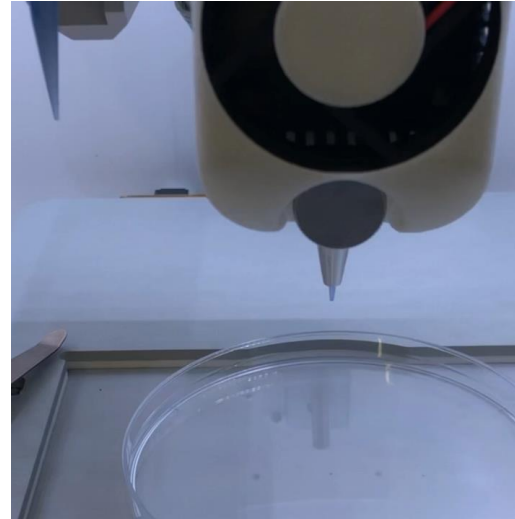
In collaboration with Dr. Solomon Dadia, the Levin Center for 3D Printing and Surgical Innovation, Tel Aviv Sourasky Medical Center



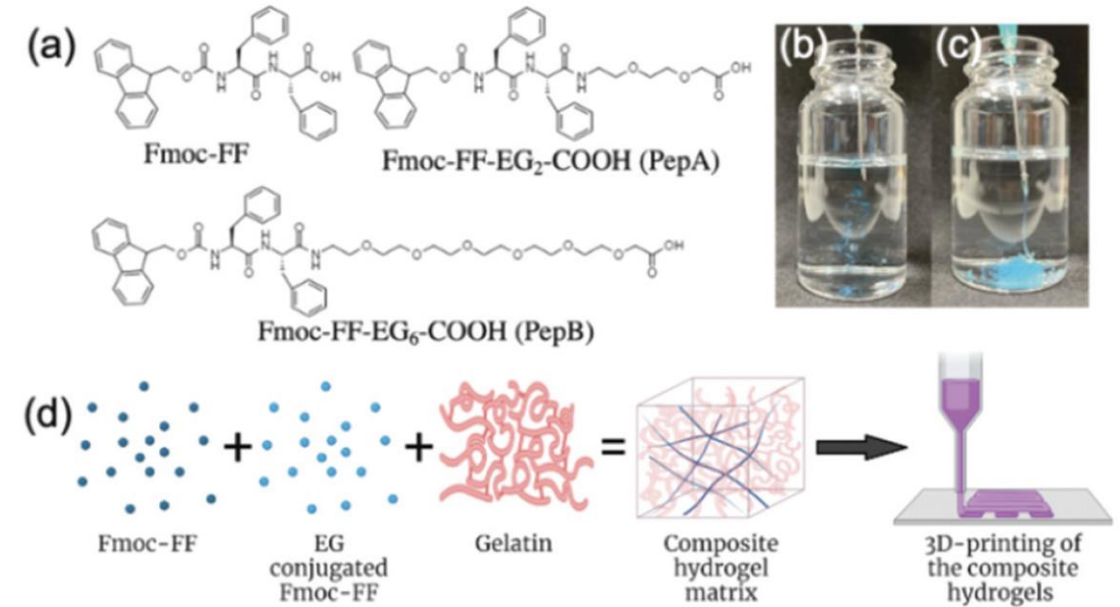
3D Printing of the Scaffolds



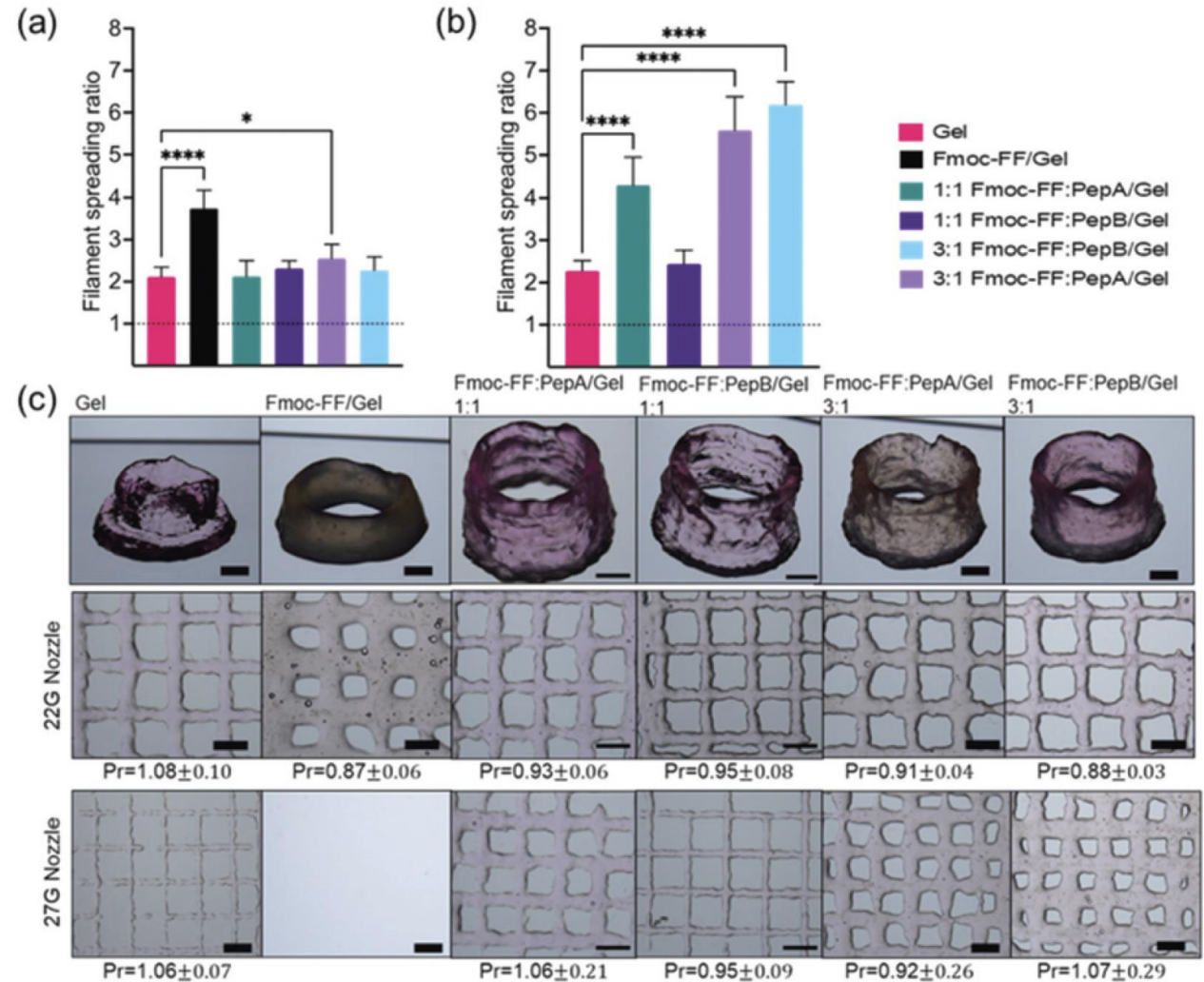
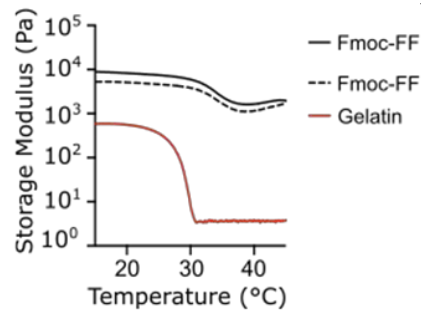
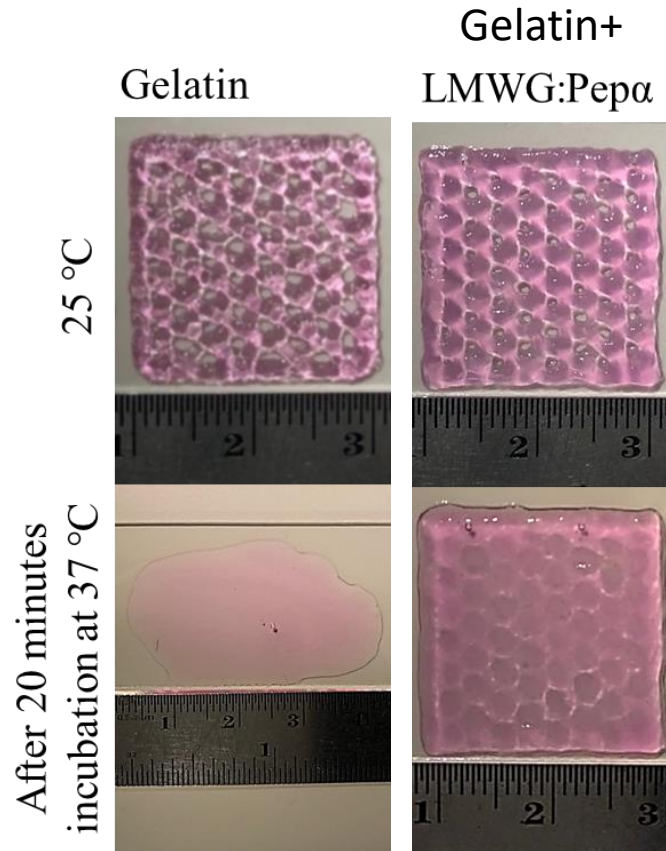
1:1 Fmoc-FF:Pep β
Hydrogel



1:1 Fmoc-FF:Pep β /Gelatin
Hydrogel

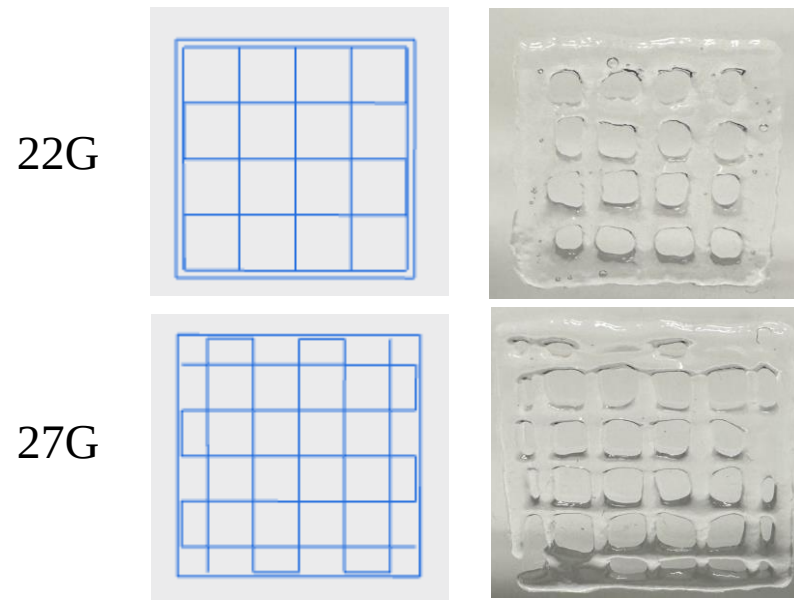


Ethylene-Glycol Conjugated Peptide Hydrogels

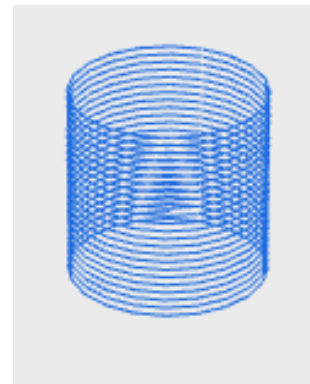


Bioink 3D-printability

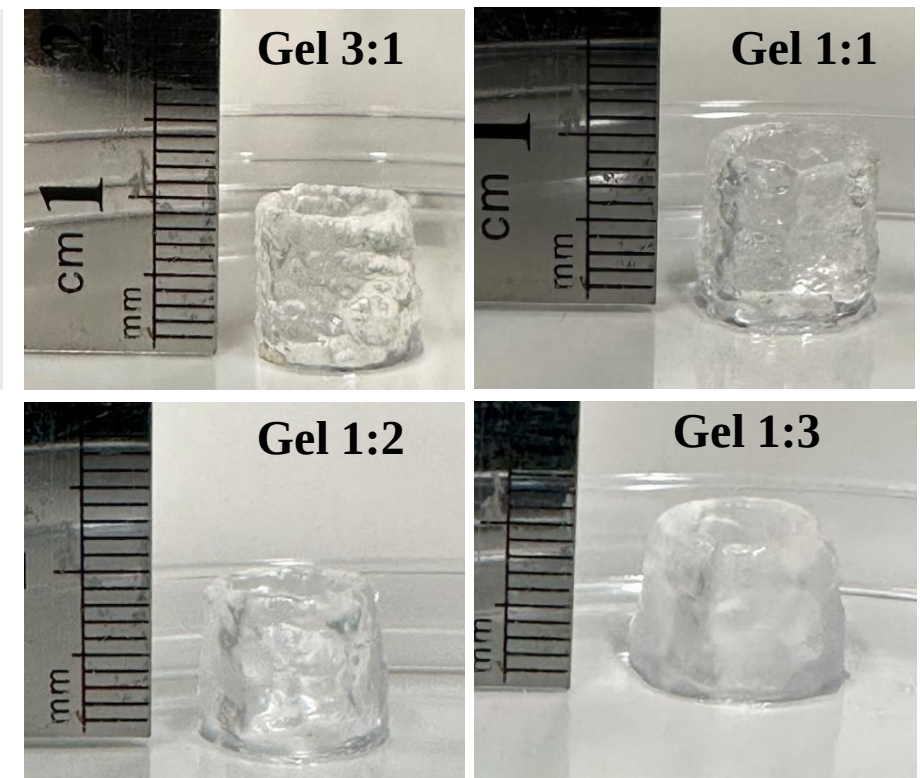
Testing different gauge capacity



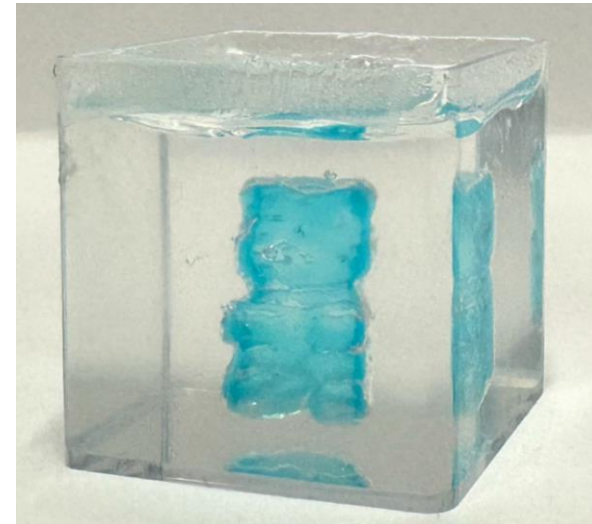
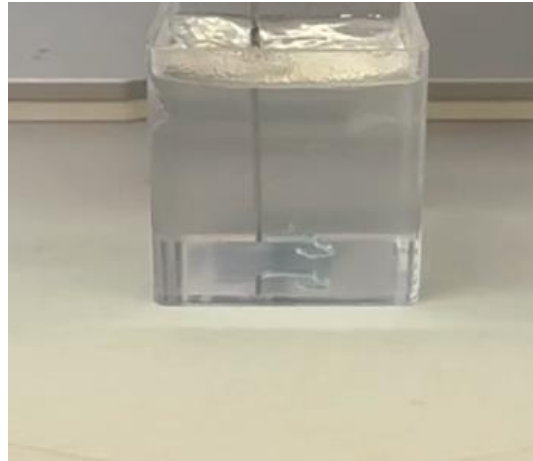
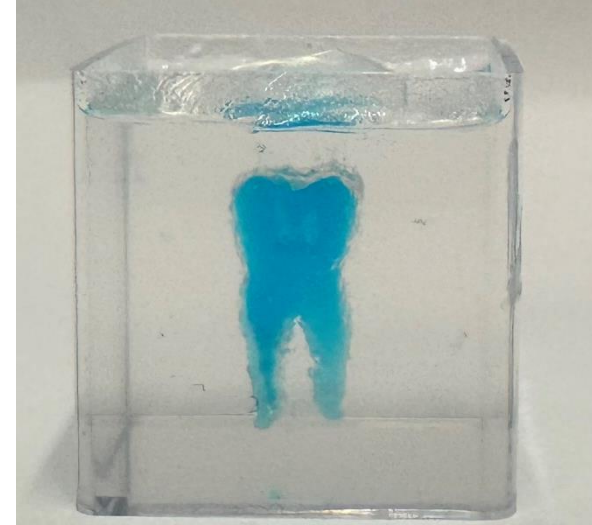
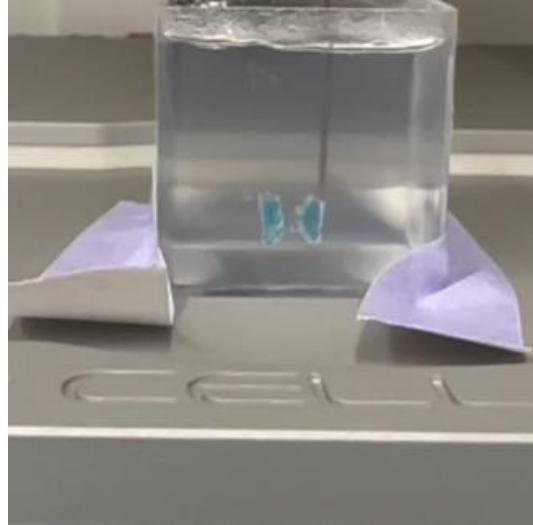
24 layers



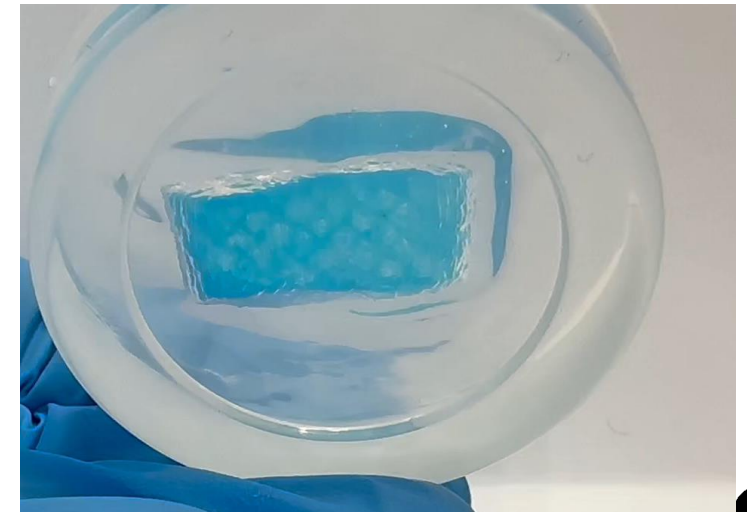
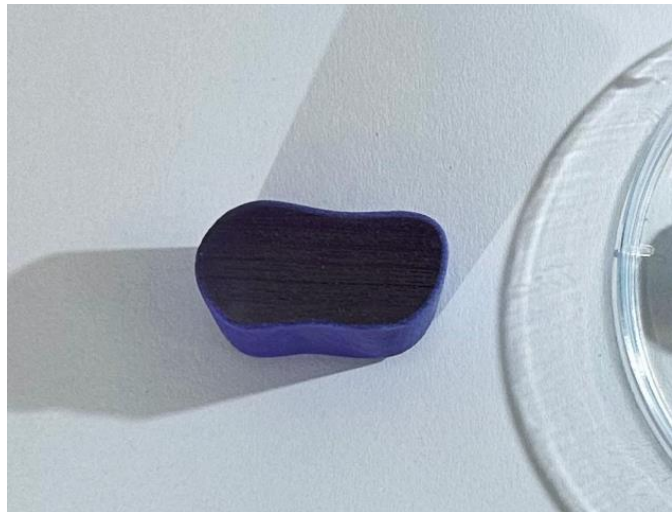
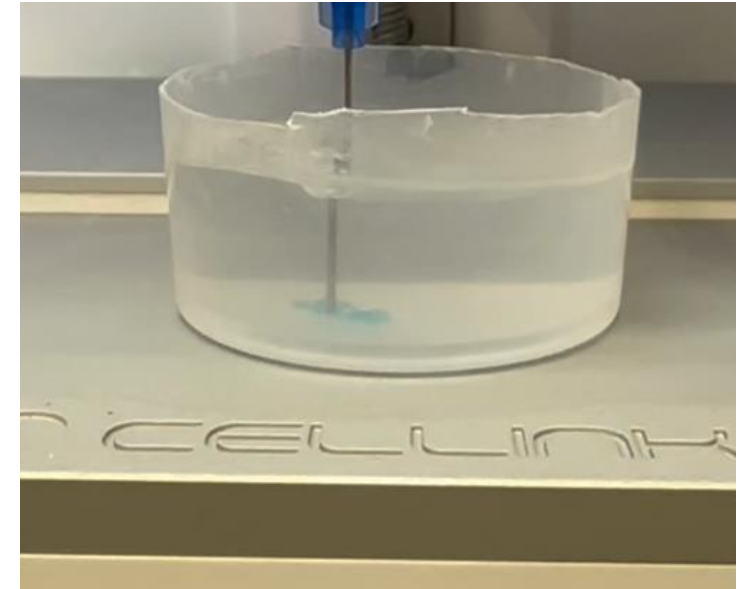
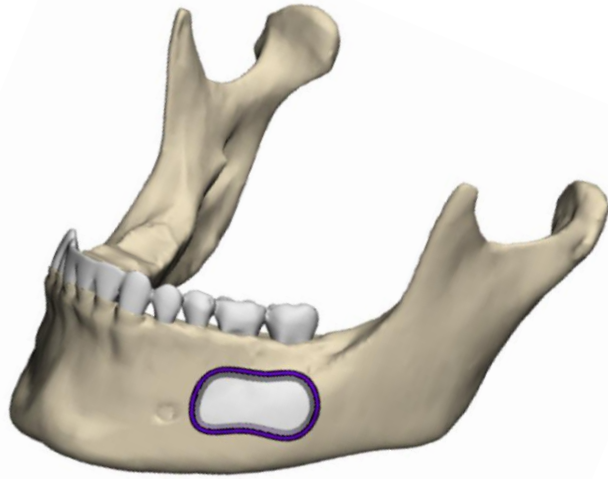
Testing self support properties



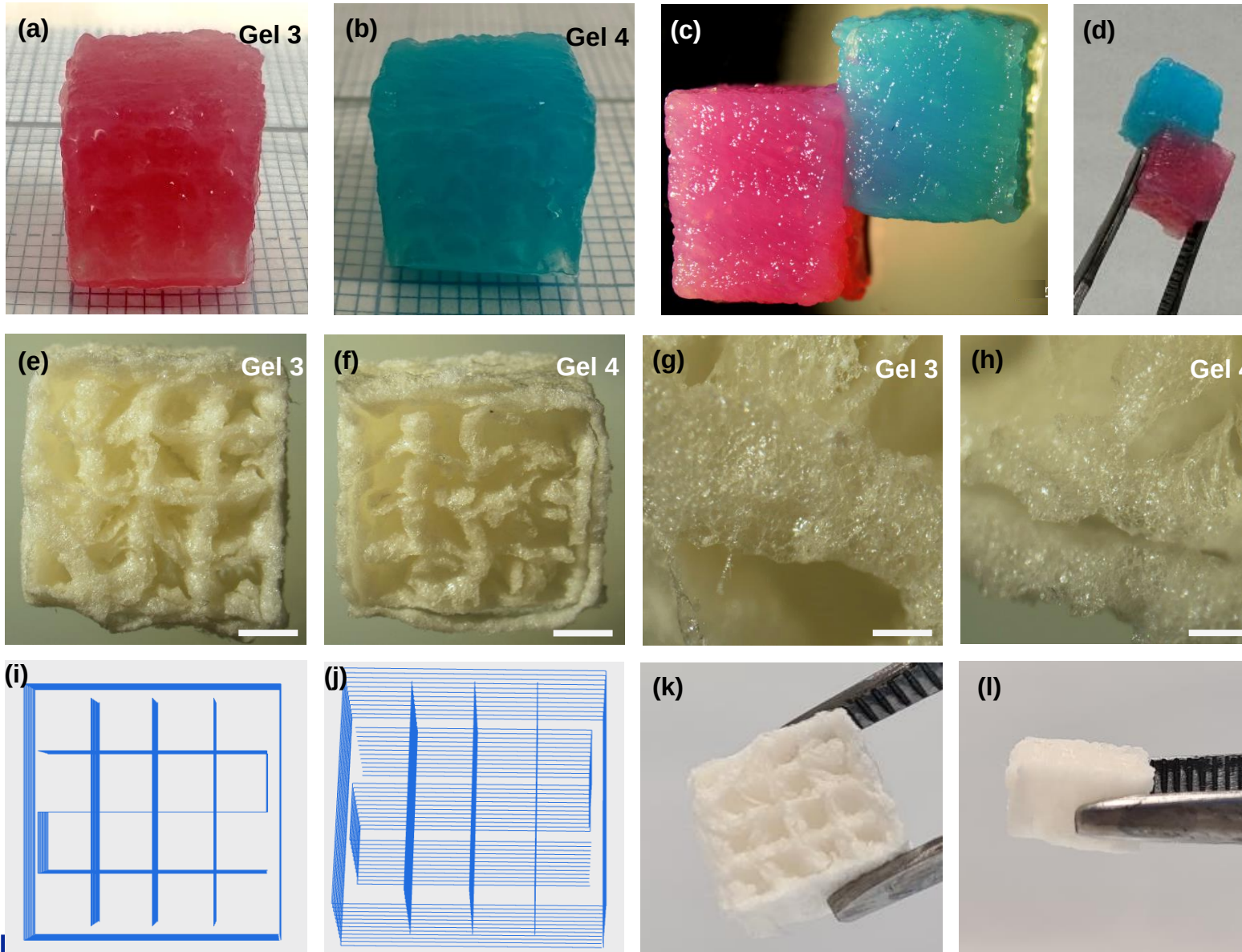
3D printing of more complex constructs in suspension media



3D printing of a mandible defect

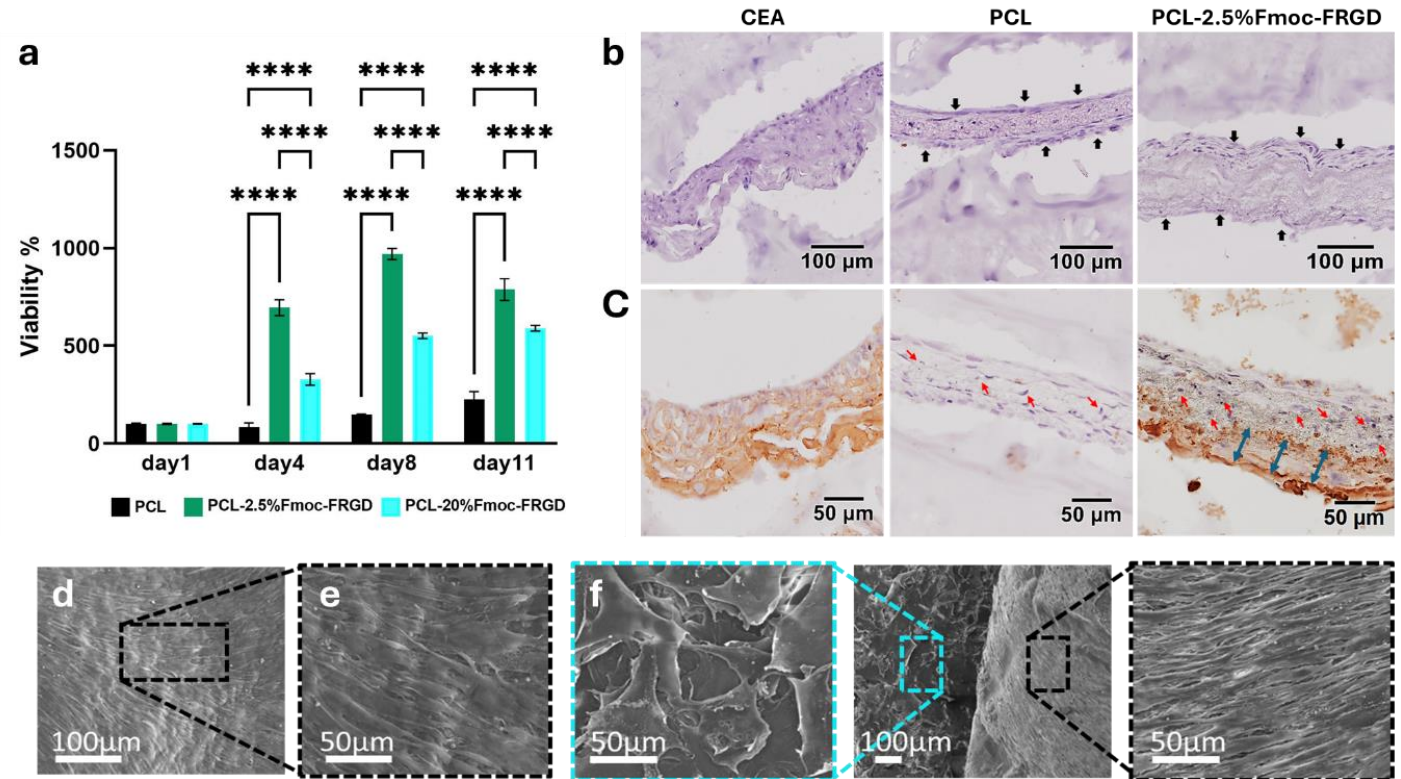
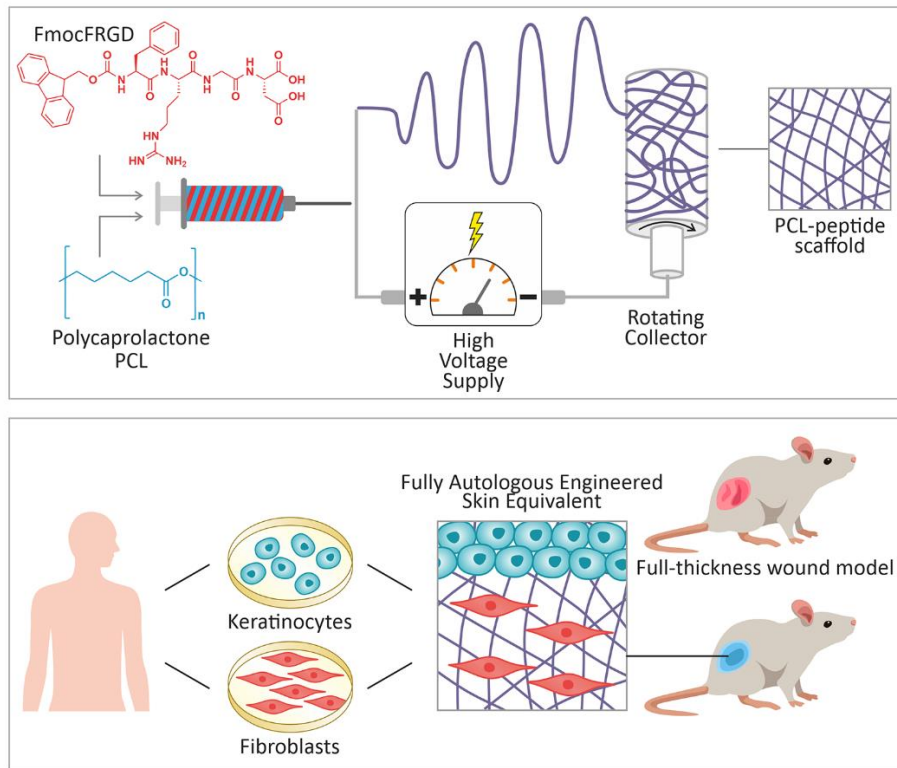


3D-printability and Self Assembly of Antimicrobial Peptides



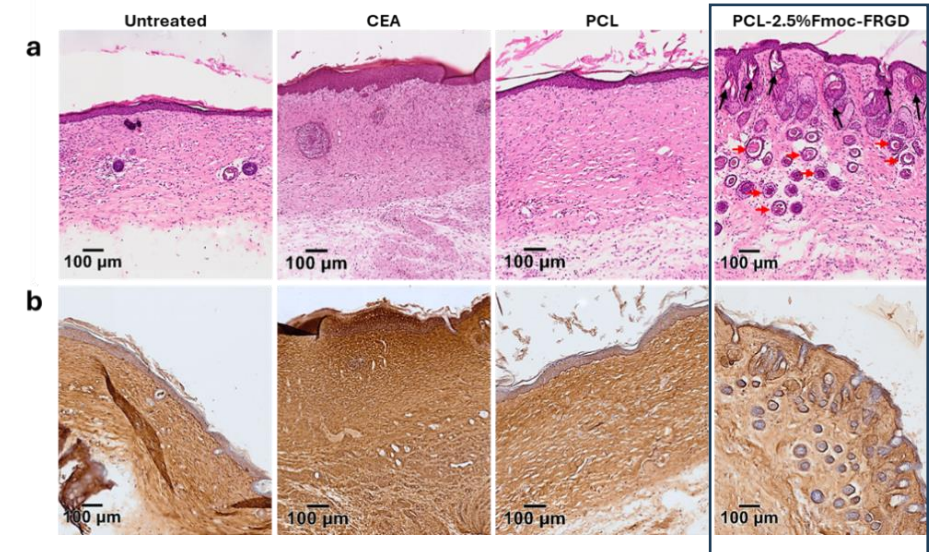
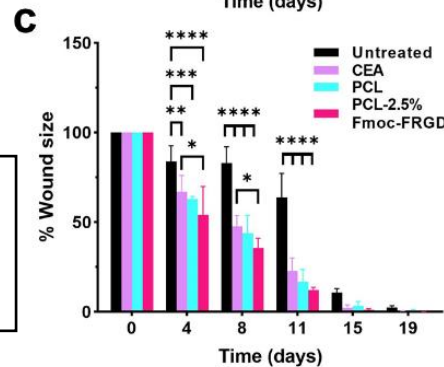
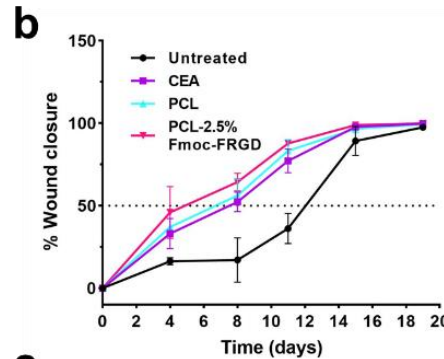
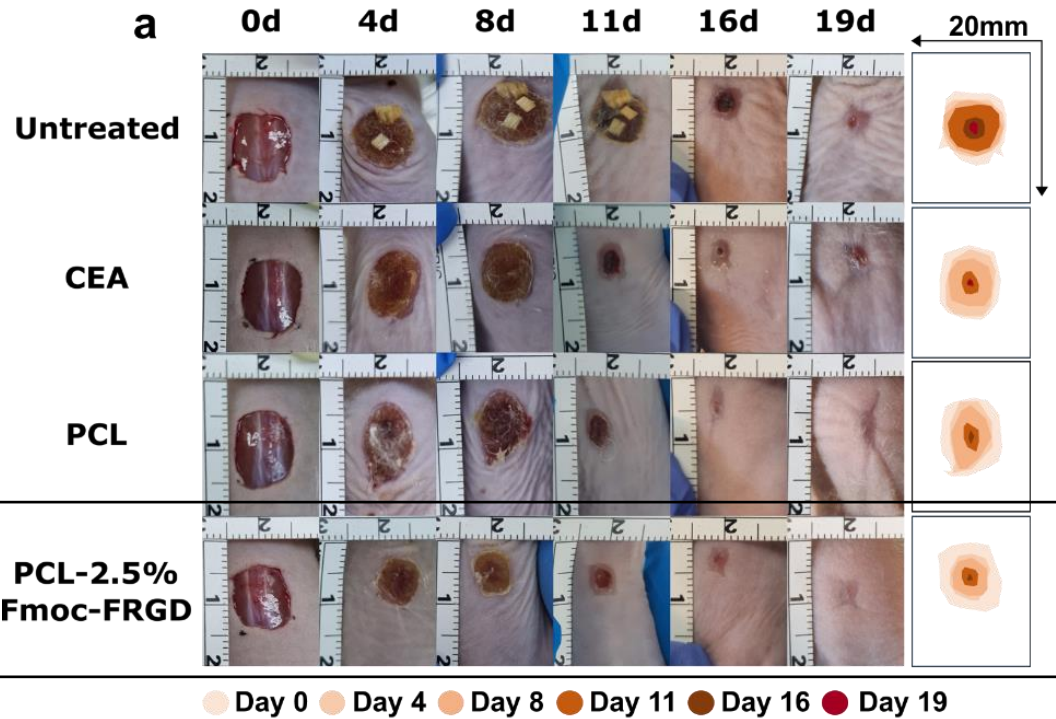
Autologous Electrospun Polymer-Peptide Skin Equivalent for Severe Burn Injuries

In collaboration with Amit Sitt and the Kaufman-Green Skin Graft Engineering Center in Sheba Hospital



Autologous Electrospun Polymer-Peptide Skin Equivalent for Severe Burn Injuries

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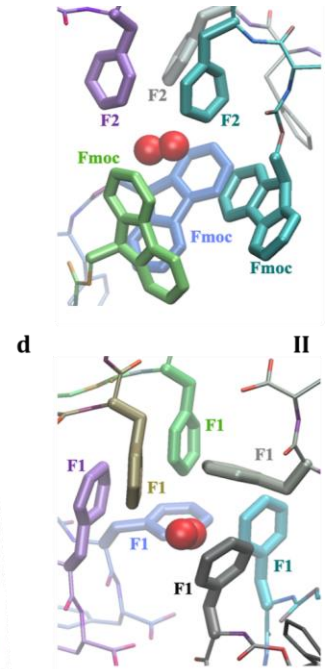
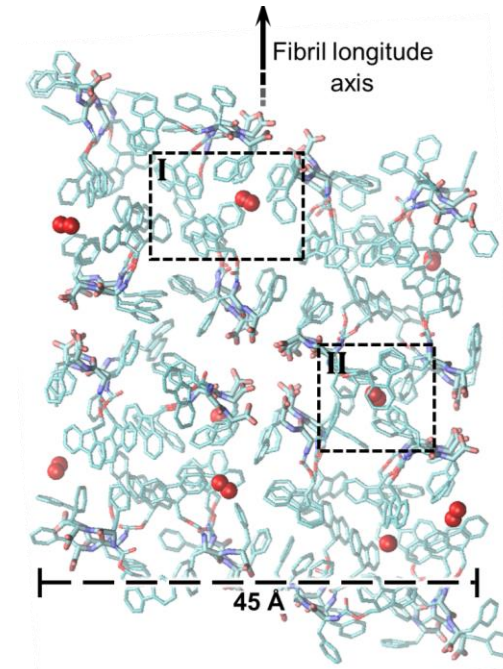
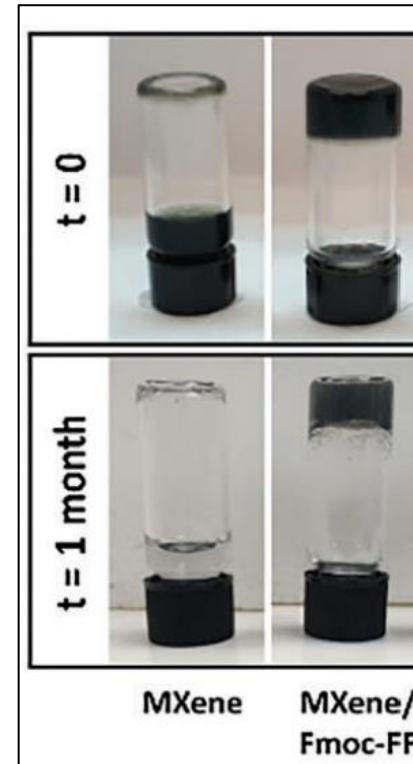
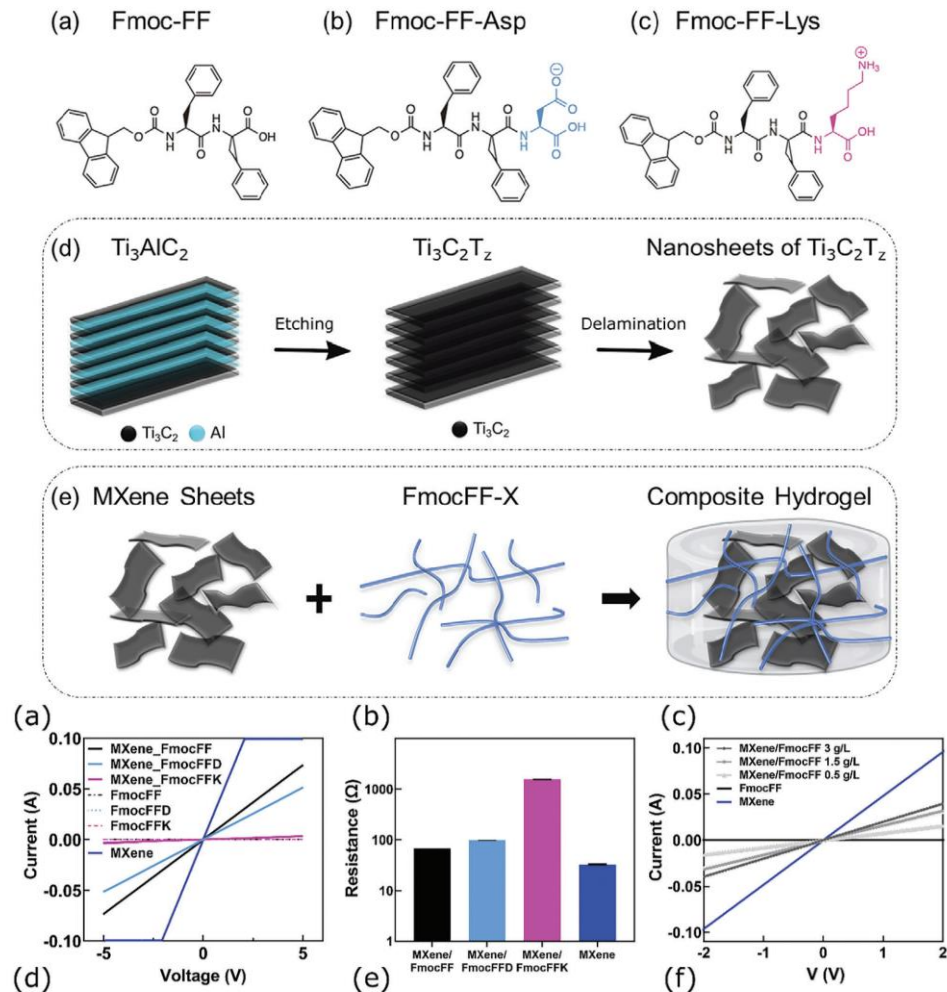


T_{50} =12 days was improved to T_{50} =4 days

Conductive Peptide-Based MXene Hydrogel as a Piezoresistive Sensor

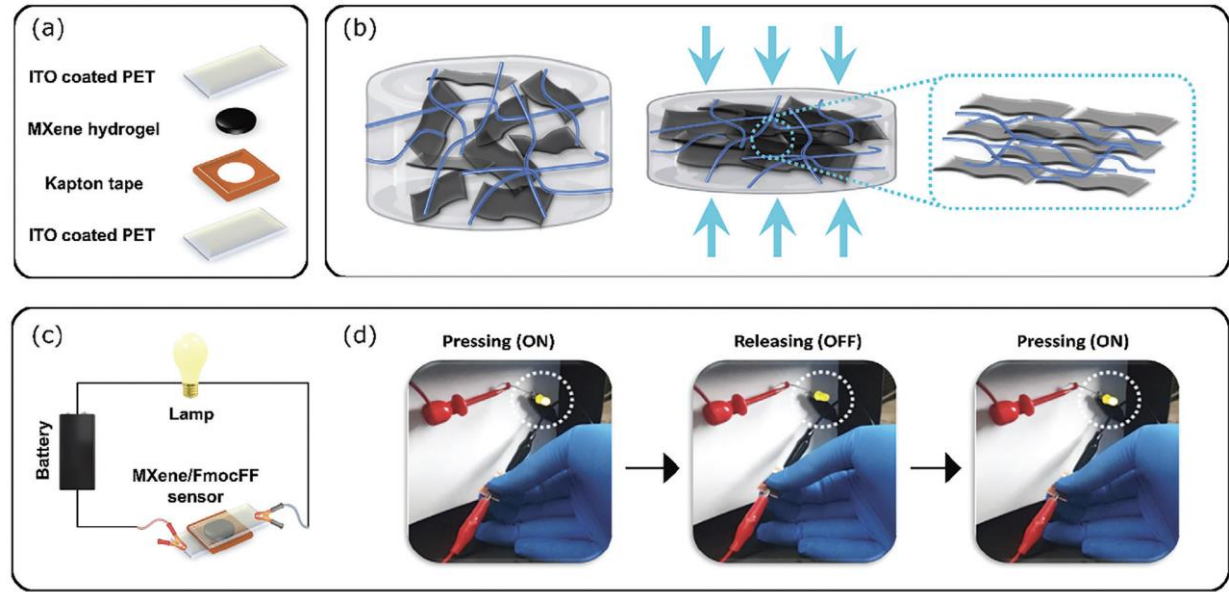
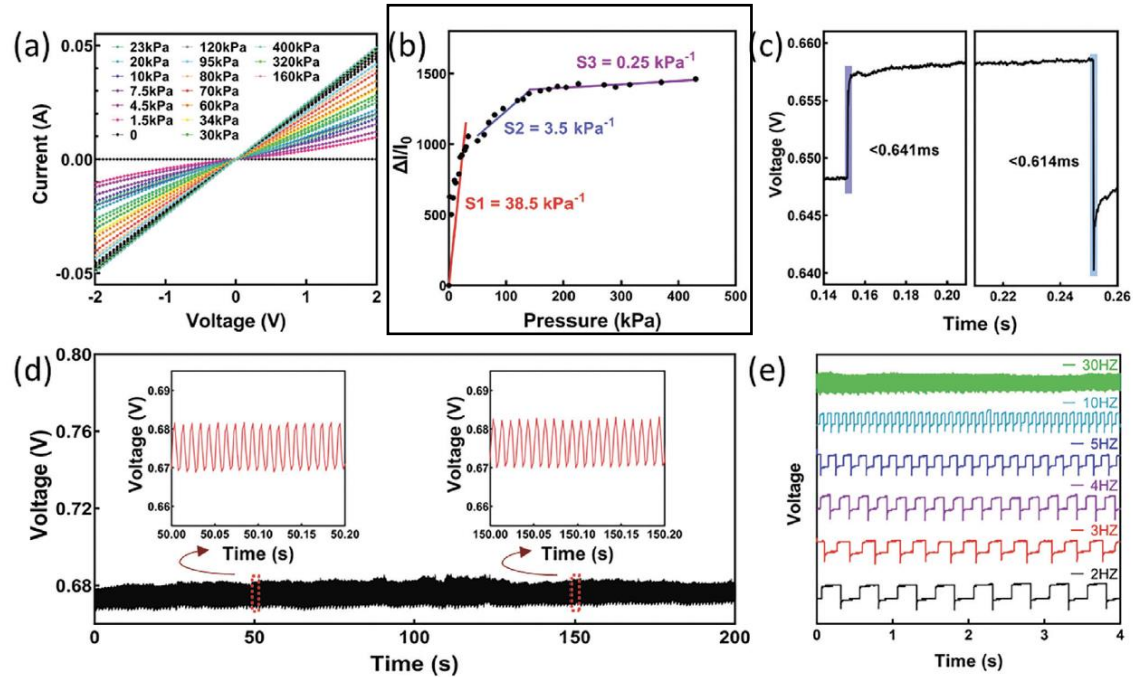
In collaboration with Maxim Sokol (TAU)

In collaboration with Phanourios Tamamis
Texas A&M

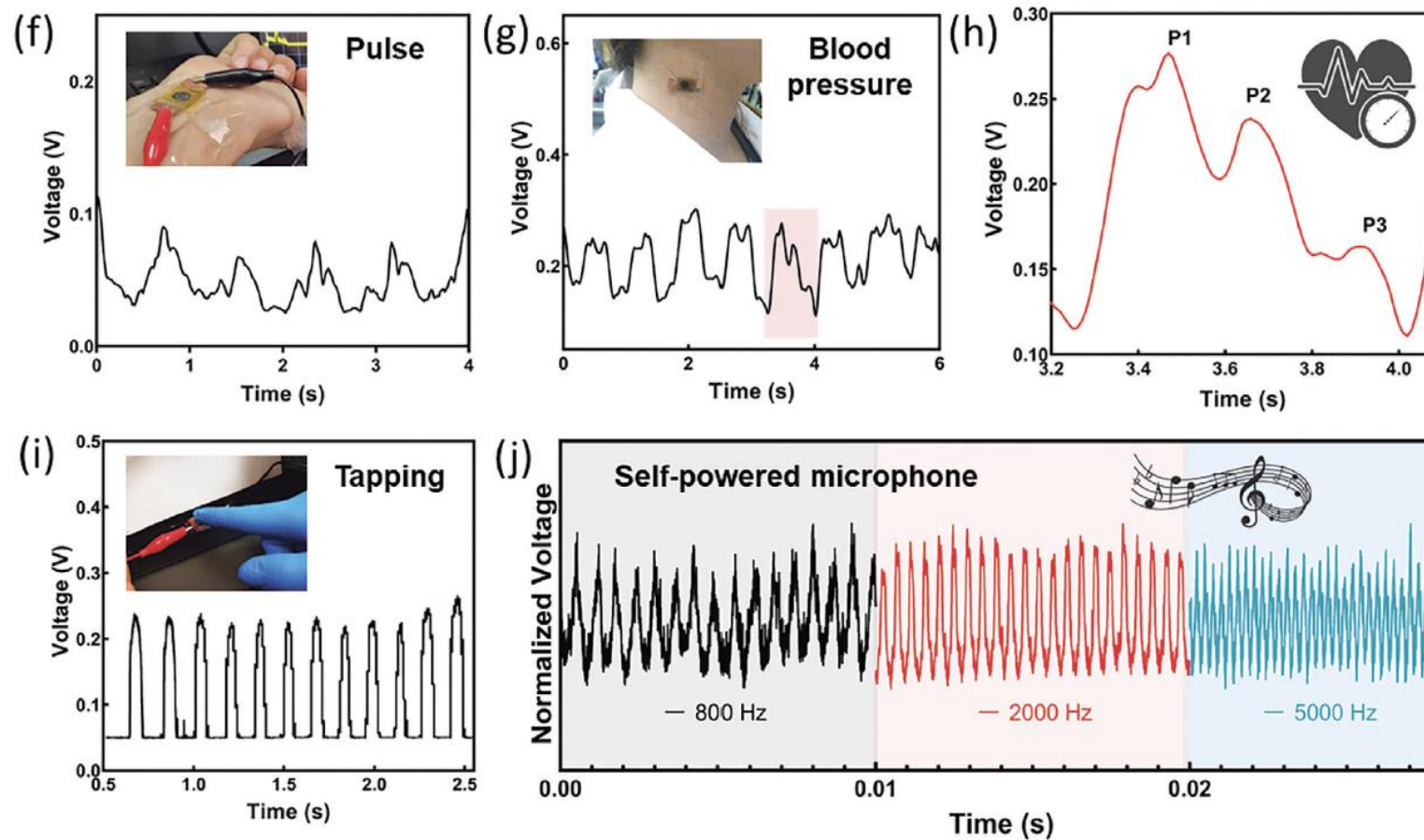


Ben-Zvi*, Grinberg* et. al. ACS Nano 2021, 15, 6530

Conductive Peptide-Based MXene Hydrogel as a Piezoresistive Sensor

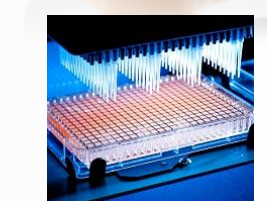
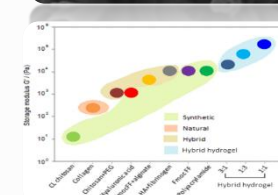
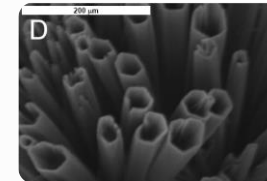


Conductive Peptide-Based MXene Hydrogel as a Piezoresistive Sensor



Summary

- ✓ We designed various peptides that can self-assemble into nanostructures as well as hydrogels with notable physical properties
- ✓ To extend the diversity of the nano-materials, we used a co-assembly approach
- ✓ We demonstrated bone regeneration and immunomodulation *in vivo*
- ✓ We combined gelatin with modified peptide to allow precise 3D printing
- ✓ We designed and fabricated electrospun polymer-peptide skin equivalent for severe burn injuries
- ✓ We incorporated MXene in the hydrogel to fabricate a piezoresistive sensitive sensor



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LAA Group Members

- Dr. Moran Aviv
- Dr. Sigal Rencus-Lazar
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- Dr. Livnat Afriat-Jurnou (Migal)



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- Prof. Ehud Gazit
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- Dr. Eyal Rosen
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