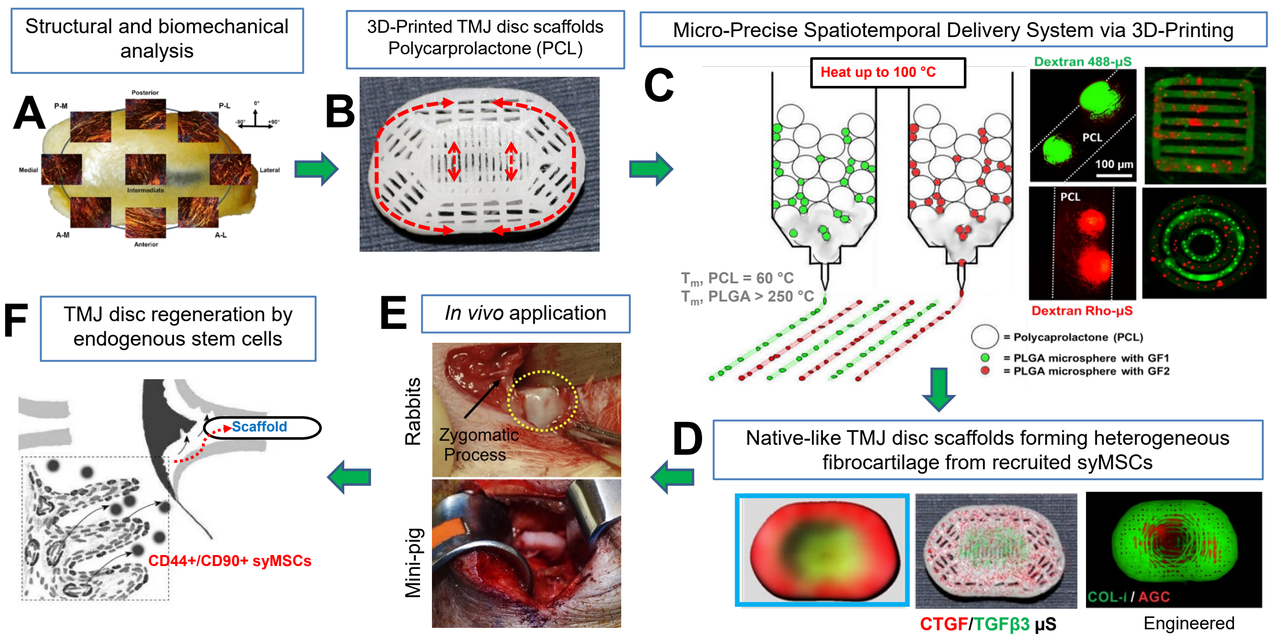
Fabrication of 3D Printed Scaffolds with Spatiotemporal Delivery of Small Molecules

Soomin (Shannon) Park, M.D. Sarker, Chang H. Lee
Center for Dental and Craniofacial Research, Columbia University, New York, NY

INTRODUCTION

- Over **10 million Americans** experience signs or symptoms of temporomandibular joint disorder (TMJD).
- TMJDs are the **second most commonly occurring musculoskeletal conditions** resulting in pain and disability (after chronic low back pain), with an **annual cost estimated at $4B.** About half to two-thirds of those with TMJ disorders will seek treatment. However, current treatment options are limited.
- We proposed a strategy for spatiotemporal-controlled delivery of bioactive cues by establishing precisely controlled micro-thin coating of hydrogel carriers on printed PCL layers using a multiple head extrusion system (MHES) integrated 3D Bioplotter.
- The research goal was to develop a reliable and reproducible spatiotemporal delivery system of small molecules as integrated with 3D printed scaffolds, with the main focus on obtaining:

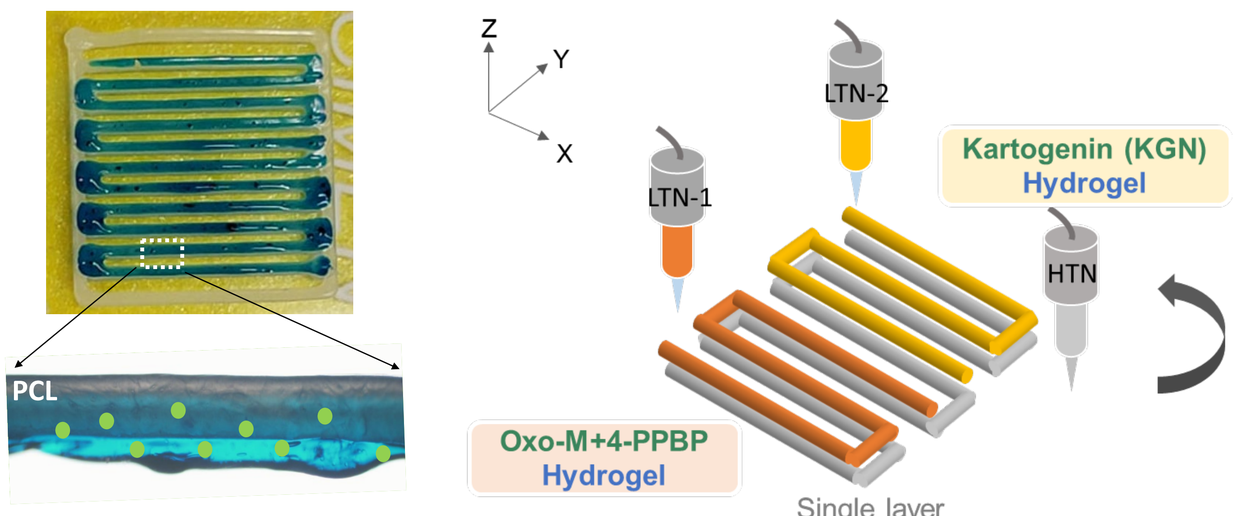
  Evenly distributed, homogenous, and spatially controlled coating of **hydrogel carriers** loaded with **small molecules**



METHODS & MATERIAL

- Hydrogel coating materials were extruded on top of PCL filaments using the MHES integrated 3D Bioplotter, with adjustments of multiple printing parameters.
- By controlling printing speed, feeding rate, and concentration of hydrogel layer, we have successfully achieved evenly distributed micro-coating of hydrogel carriers on PCL strands.
- To induce multi-phase fibrocartilaginous tissues, we applied Oxo-M and 4-PPBP, fibrogenic small molecules on one side and kartogenin, a chondrogenic cue, on the other side.

Fib: Fibrin, **Fib + Gen:** Fibrin cross-linked with genipin, **HA-MA:** methacrylate hyaluronic acid, **MDPs:** multidomain peptides, **Oxo-M:** Oxotremorine M, **4-PPBP:** PPBP maleate, **KGN:** Kartogenin

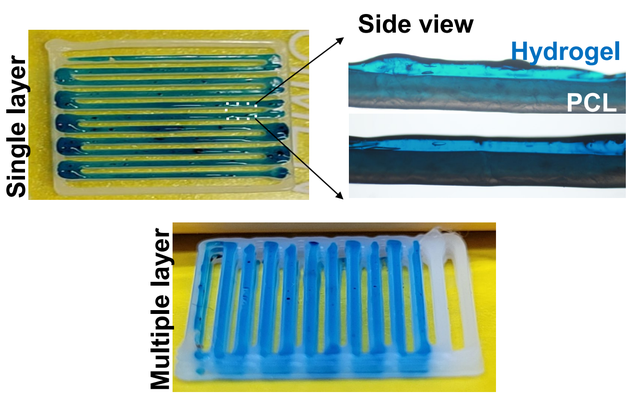


Hydrogel carriers: MDP, HA-MA, Fib / Fib + Gen
Small Molecules: Oxo-M, 4-PPBP, KGN

HTN = High-temperature nozzle
LTN= Low-temperature nozzle

RESULTS

Tuning of Hydrogel Printability



18% HA-MA (Alcian blue stained) + 3 mm/s needle speed (printable)

Fig. 1 Optimization of hydrogel concentration and needle speed

Coating Material Distribution

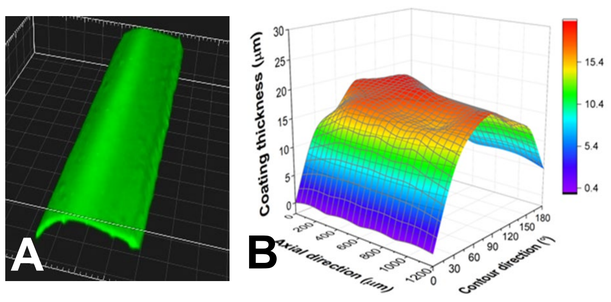


Fig. 2 (A) Confocal microscopic image of hydrogel coating (stained with FITC) on PCL strand (10x magnification, scale bar= 300 µm. (B) Coating distribution on PCL strand for 0.2 bar extrusion pressure.

RESULTS

Evaluation of Mechanical Strength and Drug Release Profile

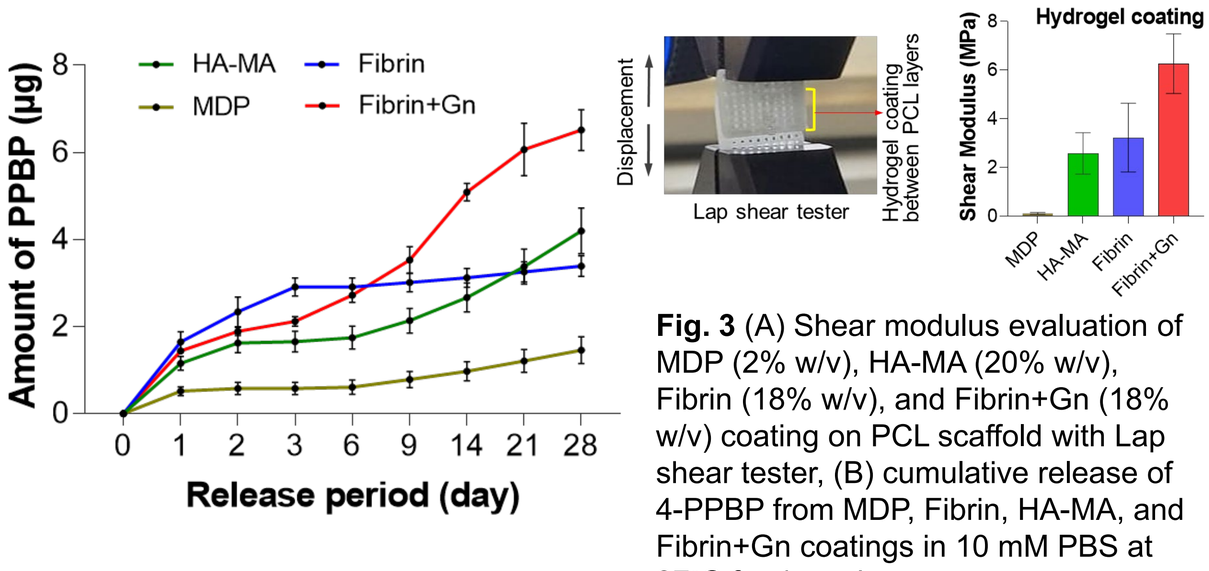


Fig. 3 (A) Shear modulus evaluation of MDP (2% w/v), HA-MA (20% w/v), Fibrin (18% w/v), and Fibrin+Gn (18% w/v) coating on PCL scaffold with Lap shear tester, (B) cumulative release of 4-PPBP from MDP, Fibrin, HA-MA, and Fibrin+Gn coatings in 10 mM PBS at 37°C for 4 weeks.

Histology of Hydrogel-coated PCL Scaffolds Cultured with hBMSC

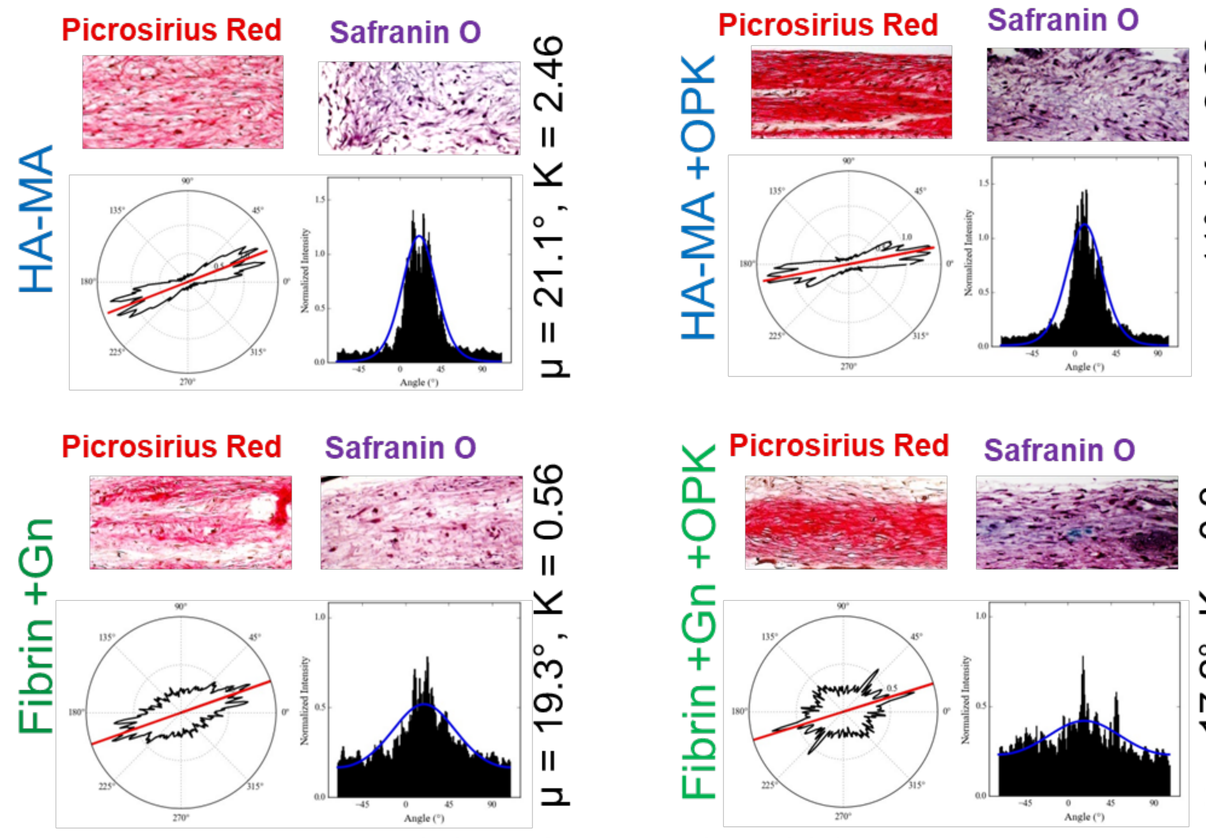
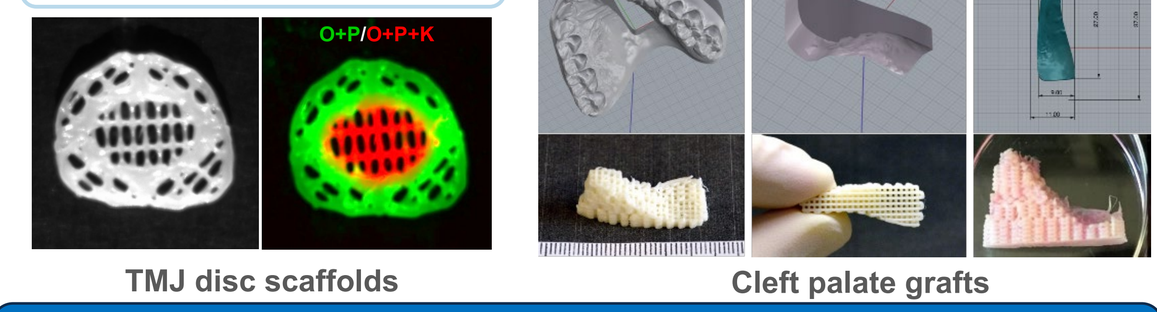


Fig. 4 Picrosirius Red and Safranin O staining of hBMSC for 6 weeks culture in the PCL scaffold coated with hydrogel alone and OPK loaded hydrogel. Ellipse fit and semicircular Von Mises fit were shown for each coating to present the ECM fiber orientation distribution, where µ= mean orientation of fibers, K = fiber dispersion parameter (anisotropy).

DISCUSSION & CONCLUSION

- Our data suggest that the chemical properties of the hydrogel and the crosslinking agent affect the mechanical strength of various coating materials and release properties of small molecules.
- With MSC culture, micro-coating of Fib-Gen loaded with Oxo-M, 4-PPBP, and Kartogenin promoted multi-phase fibrocartilaginous tissue formation.
- ***Spatial temporal delivery of small molecule is critical for enhanced cellular regeneration.***
- Ongoing works include scaling up the micro-coated 3D-printed scaffolds for regeneration of various musculoskeletal tissues, PDL and cementum regeneration, alveolar bone defect regeneration, and cleft lip palate regeneration

Application for Regeneration of Complex Tissues



ACKNOWLEDGEMENT

Supported by CDM Summer Research Fellowship Program and NIH/NIDCR R01DE029321 to C.H.L.