Shear-thinning, Nanoparticle-based Hydrogels as an Injectable Delivery Platform for Repair of Chronic Diabetic Skin Wounds

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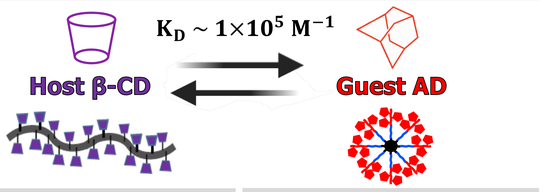
Introduction

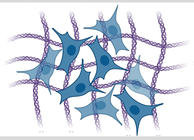
Injectable biomaterials are a promising therapeutic delivery platform for small molecule drugs and therapeutic stem cells, for tissue regeneration and repair applications.[1, 2]

SHEAR-THINNING HYDROGELS

formed by non-covalent interactions mediating physical crosslinking show promise as **injectable delivery platform**.[3]



Hyaluronic Acid is Biologically Active ECM



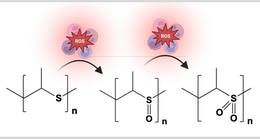
HA Provides

Enzymatic degradation

Repair and regeneration of damaged tissue[1]

Retention of therapeutic cells[2,3]

Synthetic Nanoparticle is ROS-Responsive



NP Provides

Oxidative degradation[4]

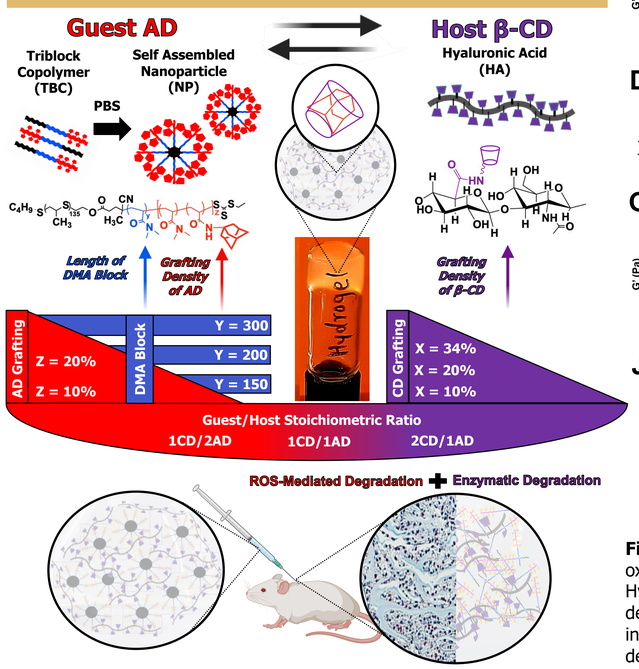
Antioxidant behavior

ROS-responsive release of small molecule drugs[4]

Overall Objective

Develop NP/HA shear-thinning hydrogel as an injectable, wound-filling platform for sustained delivery of small molecules and retention of therapeutic stem cells to promote repair of chronic diabetic skin wounds

NP/HA Shear-thinning Hydrogel



Results

Self-Assembly of Stable NPs Grafted with AD

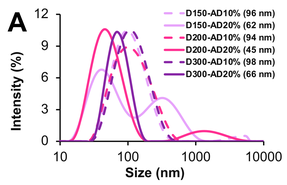
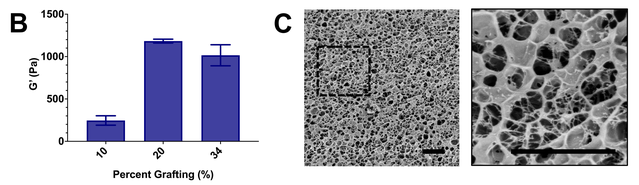


Figure 1. (**A**) DLS measurements demonstrate self-assembly of TBCs with varying block length and AD grafting density to form stable NPs. (**B**) Grafting density of 20% for HA-CD results in highest mechanical strength of final NP/HA hydrogel. (**C**) Cryo-SEM imaging of final NP/HA hydrogel illustrates interconnected porous 3D crosslinked network. Scale bars are 2 μm.

Synthesis of HA Grafted with β-CD



NP/HA Hydrogel Demonstrates Range of Mechanical Strengths and Shear-thinning Behaviors

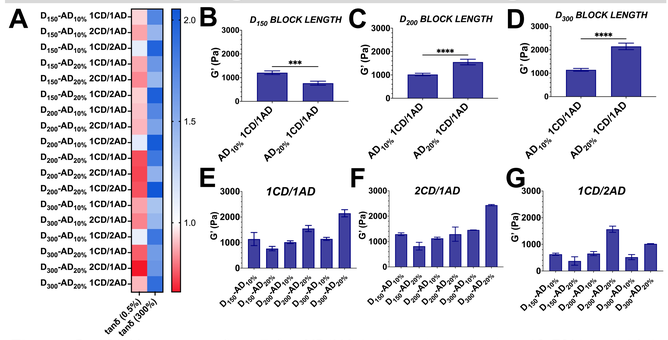


Figure 2. (**A**) Heat map of tanδ for NP/HA hydrogels under low (0.5%) and high (300%) strain confirms shear-thinning behavior. Effect of AD grafting on G′ of NP/HA hydrogel with increasing DMA blocks **(B)** 150 units, **(C)** 200 units, and **(D)** 300 units. Effect of CD/AD ratio on G′ of NP/HA hydrogel with increasing DMA blocks and mixed at **(E)** 1CD/1AD, **(F)** 2CD/1AD, and **(G)** 1CD/2AD.

NP/HA Hydrogel Provides Injectable Delivery of Cells and Protection from Shear Stress

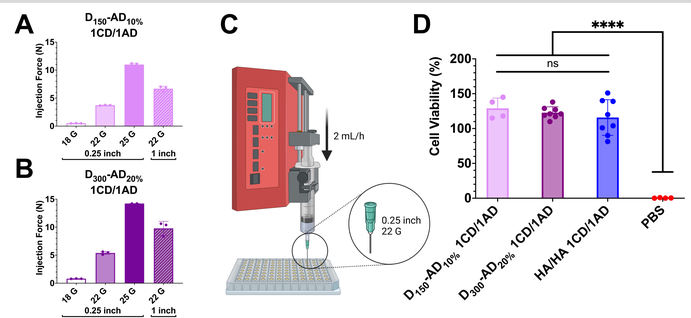


Figure 4. (**A-B**) Injection force required to pass NP/HA hydrogels through needles of varying gauges and lengths remains below forces acceptable for clinical translation. (**C-D**) Viability of encapsulated mMSCs following injection at constant flowrate maintained by a syringe pump indicates that NP/HA hydrogels protect cells from shear stress during injection compared to injection of cell suspension in PBS.

NP/HA Hydrogel is Susceptible to Oxidative and Enzymatic Degradation

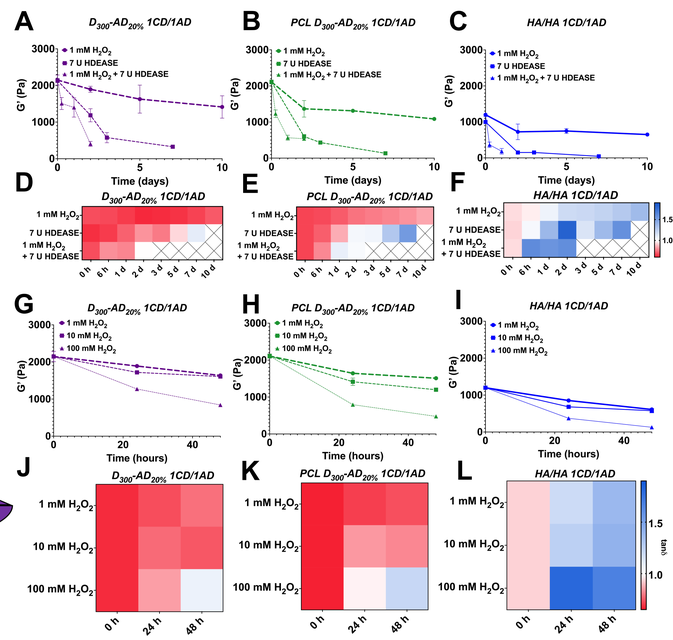


Figure 3. Comparison of (**A-C**) G′ and (**D-F**) tanδ of hydrogels subjected to oxidative (H_2O_2), enzymatic (Hyaluronidase), and combined degradation (H_2O_2 + Hyaluronidase) shows NP/HA hydrogels are susceptible to both modes of degradation. Comparison (**G-I**) G′ and (**J-L**) tanδ of hydrogels subjected to increasing levels of oxidative degradation (H_2O_2) demonstrates ROS-responsive degradation of PPS NP/HA hydrogels.

NP/HA Hydrogel is Capable of Cellular Encapsulation and Protection from ROS

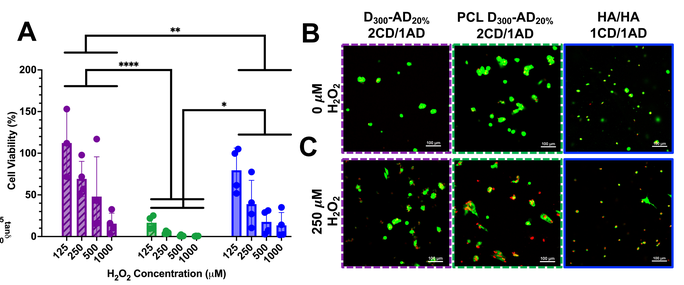


Figure 5. (**A-C**) Viability of encapsulated mMSCs indicates that NP/HA hydrogels containing PPS provide enhanced viability compared to similar non ROS-responsive shear-thinning hydrogels when subjected to increasing doses of H_2O_2.

NP/HA Hydrogel Degradation Profile is Mediated by Cellular Infiltration

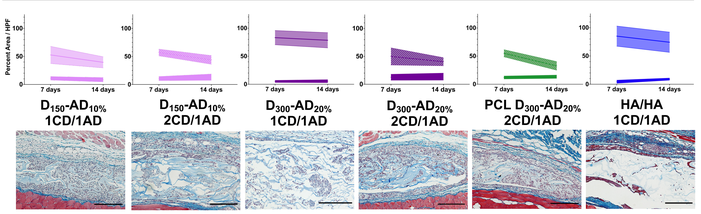


Figure 6. Histological evaluation of excised gel/tissue sections illustrates rate of cellular infiltration (bottom shaded curve) alongside hydrogel degradation (top patterned curve) and hydrogel biocompatibility with surrounding tissue. Scale bars represent 100 μm.

Conclusions

NP/HA SHEAR-THINNING HYDROGELS

Provide **dynamic range** of mechanical properties and shear-thinning behaviors

Allow for **modularity due to synergistic effects** of triblock composition and grafting of guest host complexes

Display **susceptibility to oxidative/enzymatic** degradation

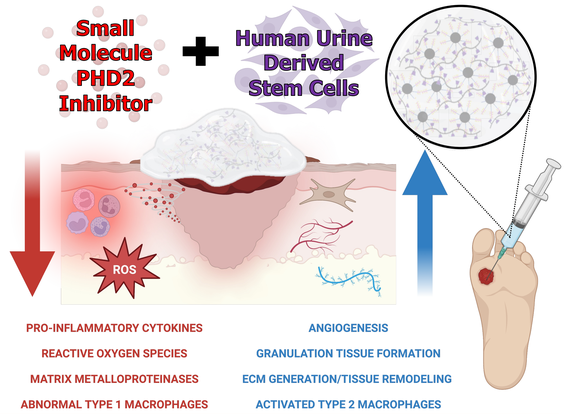
Possess injection forces below forces for **acceptable for clinical administration**

Capable of **protecting encapsulated cells** from cytotoxic ROS and mechanical shear stress

Demonstrate ***in vivo* degradation profile** mediated by surrounding tissue infiltration

Future Work

Improve synergistic therapeutic outcomes of small molecule PHD2 inhibitor and urine derived stem cells in chronic diabetic skin wounds by providing local delivery and retention in NP/HA hydrogels



References

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Acknowledgements

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