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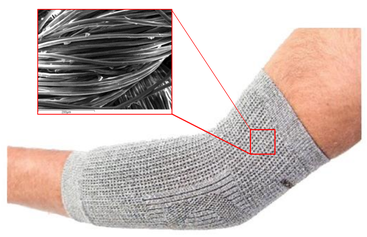
3D Pathological hTSPC Model for Evaluating Germanium-Based Anti-Inflammatory Intervention

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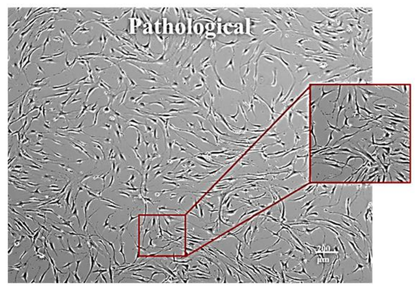
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1 INTRODUCTION

Tendon stem/progenitor cells (TSPCs) are essential for tendon homeostasis but become dysregulated in tendinopathy, showing increased inflammation markers, oxidative stress, and extracellular matrix (ECM) remodeling. **Germanium-embedded fabrics** (GEFs) are a class of medical devices that emit infrared radiation and negative air ions and may exert antioxidant and anti-inflammatory effects. Here, we investigate their impact on pathological TSPCs in a perfused 3D bioprinted model.

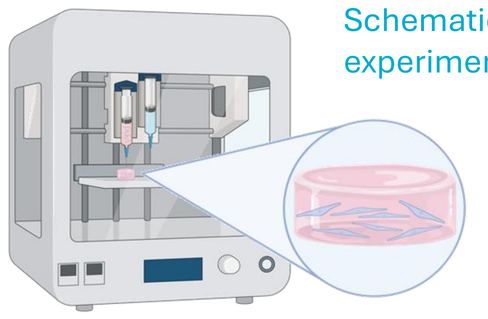


GEFs

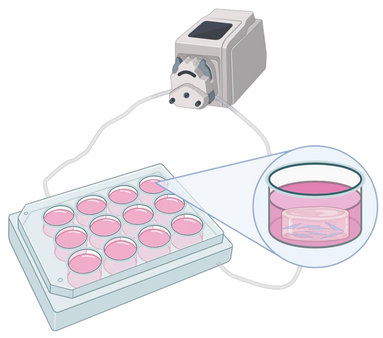


TSPCs

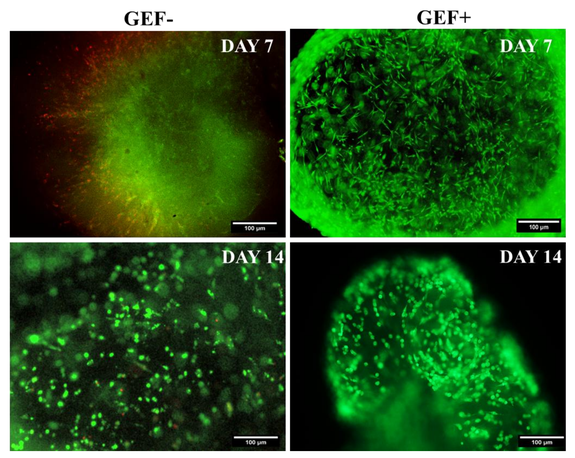
2 MATERIALS AND METHODS



Schematic overview of the experimental design.



3D bioplotted system under perfusion.

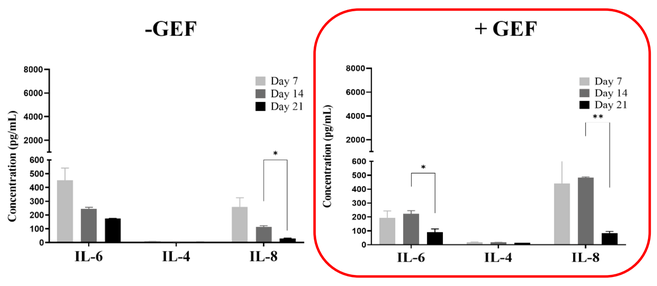


Live and Dead assay of 3D culture with and without GEF.

GEFs were characterized by **FE-SEM/EDX** and tested for NAI release within incubator conditions. Human TSPCs were isolated from tendinopathic Achilles tendon biopsies and cultured under tenogenic conditions (GDF-5, 100 ng/mL). Cells were grown in **3D bioprinted Methacrylated Collagen** (ColMA) scaffolds under **perfusion bioreactor conditions** for up to 21 days. Cell viability (Live/Dead), ROS production (DHE), gene expression (RT-qPCR), collagen I:III ratio (immunofluorescence), and cytokine release (Luminex assay) were evaluated.

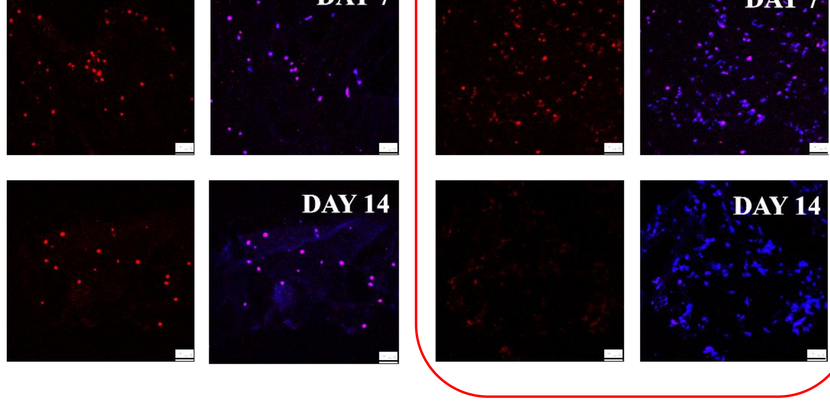
3 RESULTS

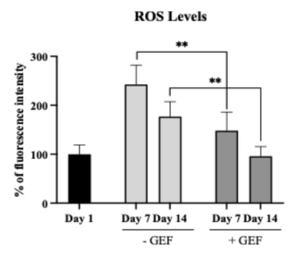
In 3D bioprinted and perfused cultures, pathological TPSCs retain and amplify their native pro-inflammatory phenotype, characterized by elevated ROS, increased IL-6 expression, and a predominance of collagen III, closely mimicking the diseased tendon microenvironment. Within this biomimetic system, exposure to GEF—associated with high levels of negative air ions—**reduces oxidative stress**, **enhances cell viability** and metabolic activity, and **promotes matrix remodeling**, as shown by an **increased COL1:COL3 ratio**.



Cytokine profile of hTSPCs cultured in 3D dynamic with and without GEF fabric

Moreover, GEF modulate the **cytokine profile**, significantly lowering **IL-6 levels** over time, indicating attenuation of inflammatory pathways. Overall, the 3D dynamic platform provides a physiologically relevant model to investigate tendon pathology and demonstrates the potential of GEF to restore tissue homeostasis and support regenerative processes.

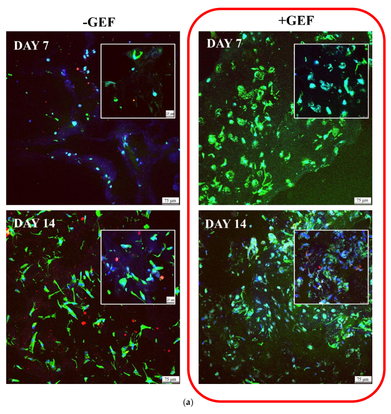


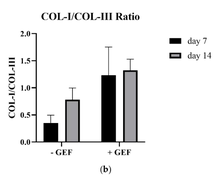


DHE assay for ROS detection in hTSPCs cultured in a 3D environment with or without GEF. Representative fluorescence images and quantitative analysis of ROS levels

4 DISCUSSION

GEF reduce ROS and restore cellular homeostasis, promoting tendon-specific matrix maturation with an increased COL1:COL3 ratio. The system exhibits a reduced inflammatory profile and a more physiological microenvironment, confirming the relevance of ColMA-based 3D models for studying tendon pathology. Overall, GEF show strong potential for tendon regeneration, warranting further in vivo validation.





Immunofluorescence analysis of type I (green) and type III (red) collagen deposition in ColMA 3D scaffolds

5 CONCLUSION

- ✓ 3D pathological TPSCs provide a robust, physiologically **relevant inflammatory model**.
- ✓ GEFs **effectively modulate inflammation**, representing a promising strategy for the treatment of chronic inflammatory conditions and tendon disorders.
- ✓ This platform enables targeted investigation **of cell–matrix interactions**, **cytokine signaling**, and tendon regeneration therapies.

ACKNOWLEDGEMENTS

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References:

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[2] Batti S, Lamparelli EP, Arianna M, Montella F, Myers G, Maffulli N, et al. Germanium-embedded fabrics attenuate oxidative stress and modulate cytokine activity in a progressive in vitro model of endothelial dysfunction. Front Bioeng Biotechnol. 2026; submitted.

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