materials-driven regeneration

TU/e EINDHOVEN UNIVERSITY OF TECHNOLOGY

Modeling the foreign body response: a spheroid-based in vitro model



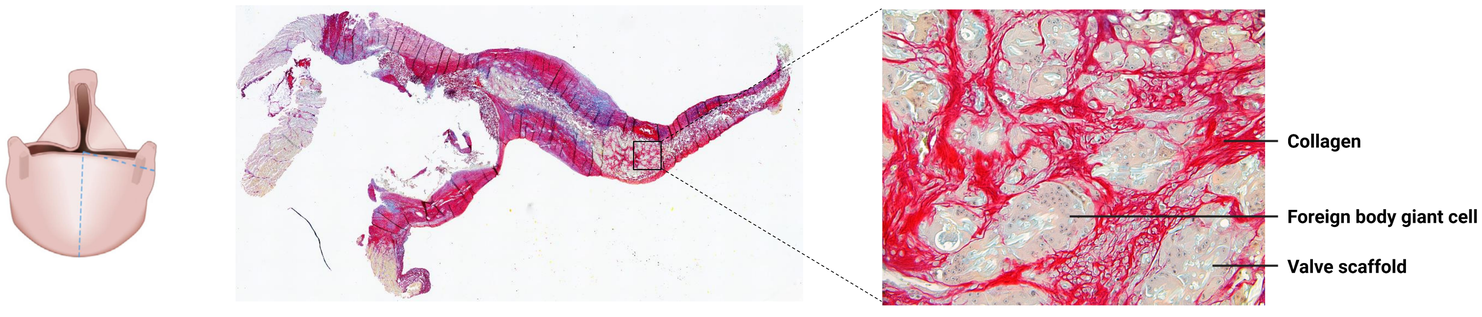
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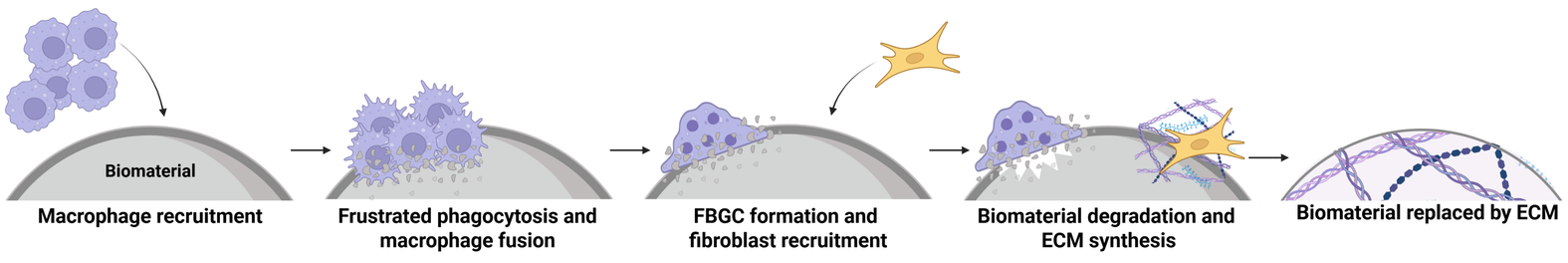
The role of FBGCs and fibroblasts in biomaterial remodeling

A key process in *in situ* tissue regeneration of biodegradable implants is the foreign body reaction (FBR). The FBR is characterized by the fusion of macrophages into foreign body giant cells (FBGCs), which can degrade the implant, while fibroblasts synthesize extracellular matrix (ECM) to replace the implant.[1]



Biomaterial-based valve leaflet (ureidopyrimidinone-polycarbonate) explanted 12 months post implantation in sheep[5]. Courtesy of Sylvia Dekker, stained with Picrosirius red, alcian blue, and Weigert's

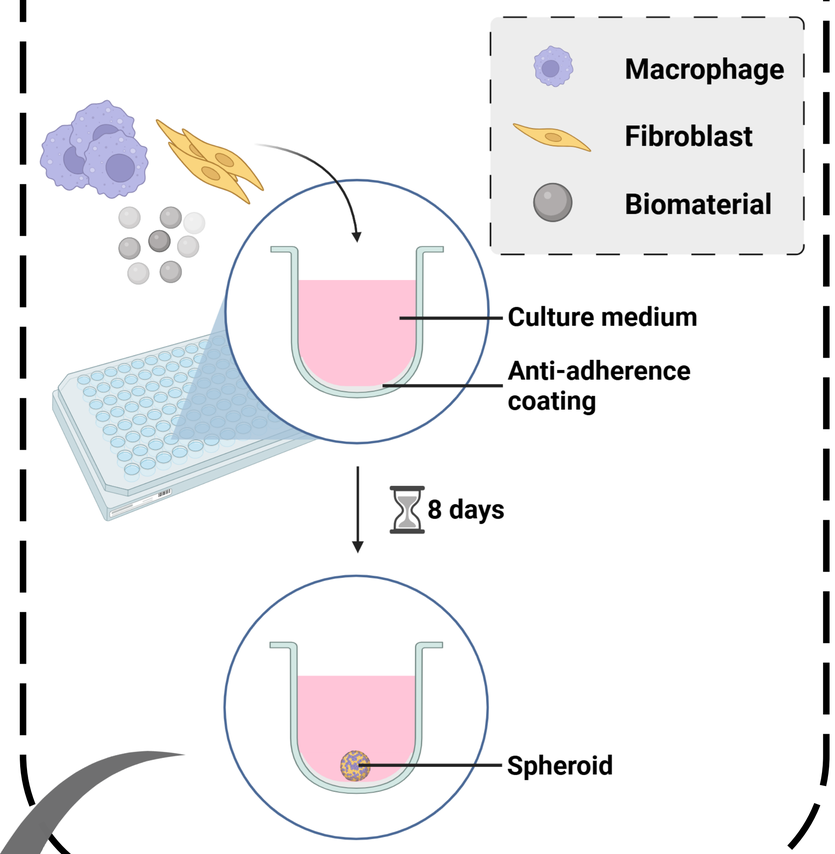
Successful tissue regeneration requires a balance between degradation and regeneration, which may be governed by crosstalk between macrophages, FBGCs and fibroblasts. Previous research shows that crosstalk between macrophages and fibroblasts affects fibrotic activity, macrophage polarization, and FBGC formation.[2,3] However, the effect of their crosstalk on implant remodeling, as well as the influence of FBGCs, remains largely unexplored.



The effect of macrophage-fibroblast crosstalk on balancing implant remodeling

Workflow for spheroid-based model of biomaterial-driven tissue regeneration[4]

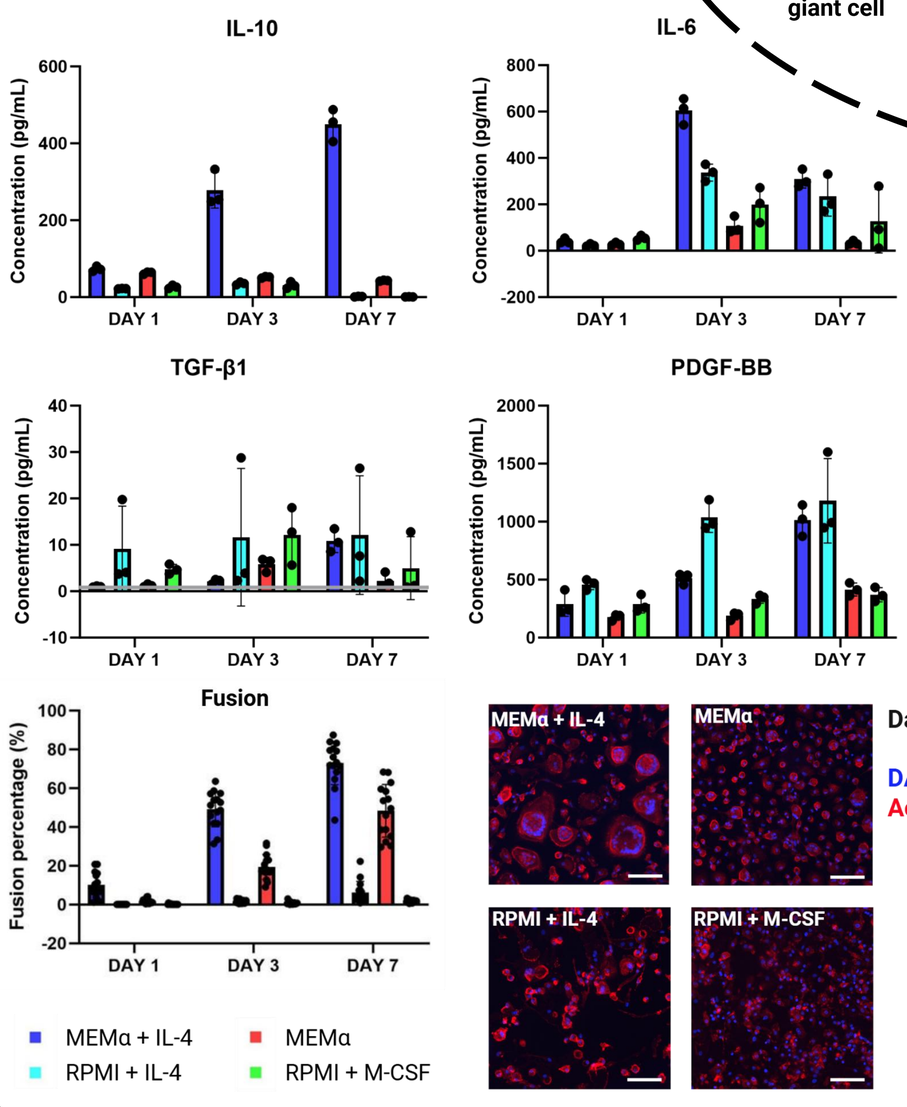
Macrophages were derived either from PMA-primed THP-1 cells or from peripheral blood mononuclear cells (PBMCs) differentiated with M-CSF.



Biomaterial degradation and ECM synthesis

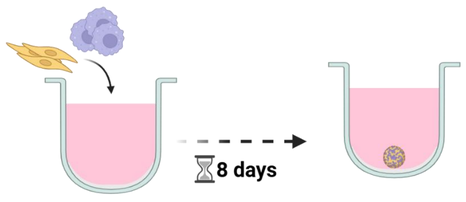
Macrophage fusion alters the fibrosis-associated cytokine secretome

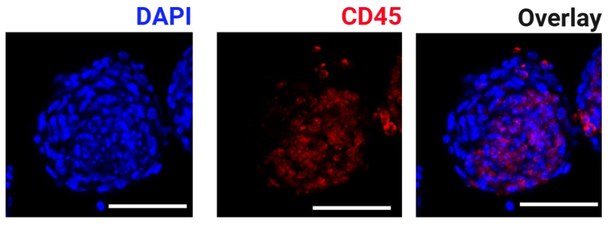
Cytokine secretion measured using LegendPlex (BioLegend) and fusion percentage determined using microscopic imaging assessed under varying culture conditions.



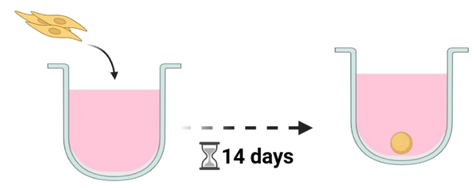
THP-1 monocytes are successfully integrated in dermal spheroids

CD45 staining was used to identify THP-1 cells within the spheroids.

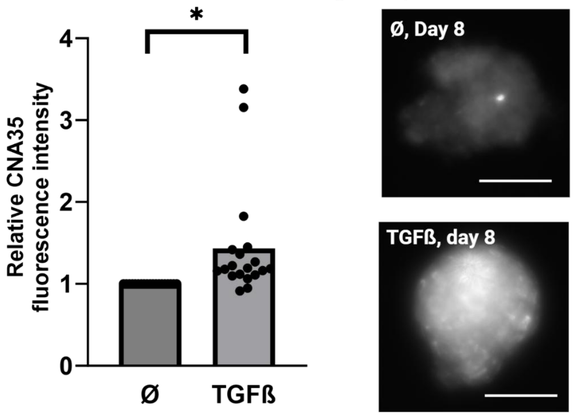




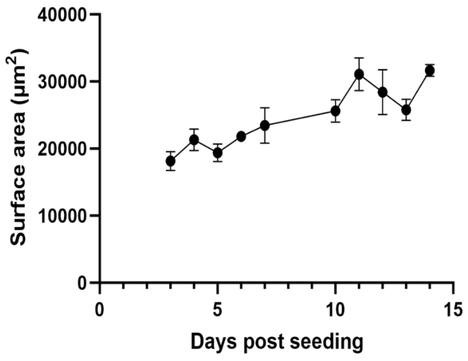
Dermal spheroids grow over time and increase collagen synthesis in response to TGFß

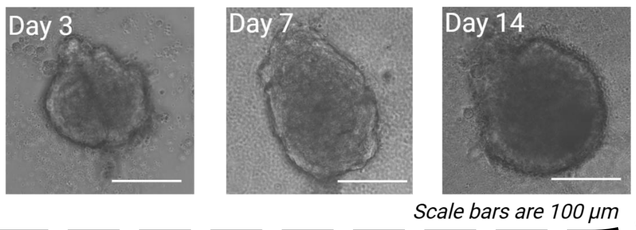


TGFß increases collagen synthesis



Dermal spheroid growth over time





Scale bars are 100 µm

Conclusions

Our results indicate that macrophage fusion alters the secretion of fibrosis-associated cytokines, with IL-10 showing a positive correlation with macrophage fusion. Meanwhile, the dermal spheroid data demonstrate the model's potential for studying fibrosis. By incorporating biomaterials and an immune-component in the FBR spheroid model we aim to study the crosstalk between FBGCs and fibroblasts and their functional balance between biomaterial degradation and tissue regeneration.

1). De Kort BJ et al. Acta Biomater. 2021;135:243–259; 2) Froom ZSCS et al. J Biol Chem 2025;301(6):110203; 3) Stewart CL et al. Front Immunol. 2024;15:1411872. 4) Tan Y et al. Biomater Sci. 2020;8(7):1951–1960. 5) Uiterwijk M et al. JACC Basic Transl Sci. 2020;5(12):1187–1206. Images created with BioRender