Tissue-engineered models of human pathological cardiac tissue through bioartificial scaffolds

# Free Session

*Tissue and organ models*

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**TISSUE-ENGINEERED MODELS OF HUMAN PATHOLOGICAL CARDIAC TISSUE THROUGH BIOARTIFICIAL SCAFFOLDS**

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**Please select your preferred method of presentation:** Special Symposium - Oral ONLY
**Symposium:** Engineered Microenvironments in Disease
**Introduction:** Myocardial infarction (MI) causes the loss of billions of cardiomyocytes, followed by a pathological process, which leads to myocardial fibrosis and stiffening, and possible cardiac function impairment [1]. Although fully recovery of human heart functionality is currently not possible, many strategies are under investigation with the aim to regenerate myocardial tissue [2].
*In vitro* models of human pathological cardiac tissue able to reproduce post-infarct microenvironment are highly demanded, as predictive tools to screen new regenerative therapies [3]. However, human cardiac fibrotic tissue is characterised by a high variability of composition and mechanical properties, depending on infarct size, its location in the ventricle, time from heart attack and specific zone in the same infarcted area.
In this work, 2D and 3D "bioartificial" scaffolds were produced based on polycaprolactone (PCL), a well-known biocompatible synthetic polymer, surface grafted with gelatin (G), a cell-adhesive protein. The effect of scaffold architecture on the composition and structure of the engineered human cardiac fibrotic tissues was evaluated.
**Experimental methods:** 2D and 3D polycaprolactone (PCL) scaffolds were prepared by electrospinning (Linari Engineering) and melt-extruded additive manufacturing (Rokit Invivo), respectively. Gelatin (G) was grafted on the scaffold surface by a two-step method based on: (i) 3,4-Dihydroxy-D,L-phenylalanine (DOPA) polymerisation (PCL-polyDOPA) and (ii) incubation in G solution (PCL-polyDOPA-G). Control PCL-G scaffolds were also prepared. After each functionalization step, physicochemical (ATR-FTIR, XPS, QCM-D), morphological (SEM and profilometry) and mechanical (tensile stress-strain tests, nanoindentation) characterizations were performed. Cardiac fibroblasts isolated from human ventricle (HCFs, PromoCell) were cultured on the scaffolds for up to 3 weeks at a density of $7x10^4$ cells/$cm^2$: their adhesion, proliferation and cardiac protein expression were analysed by immunofluorescence and Western Blot analysis, compared to 2D cultures.
**Image:**

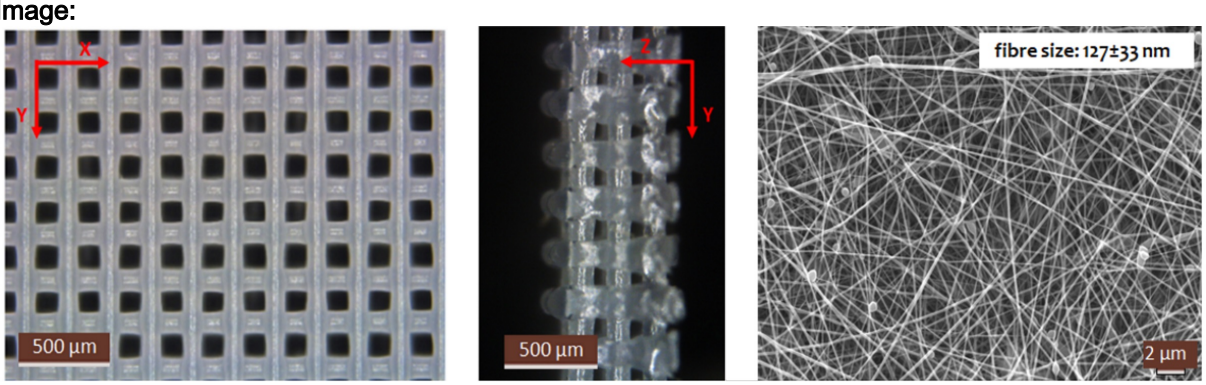


*Figure 1. Optical microscopy images of a 3D scaffold (left images) and a 2D scaffold (right image)*

**Results and discussions:** Electrospun 2D PCL scaffolds were obtained with both a random and an aligned fibre morphology. Square- or rectangular-meshed 3D scaffolds with interconnected pores were produced by melt-extrusion additive manufacturing (Figure 1).

Successful surface modification of PCL-polyDOPA-G scaffolds was demonstrated. Morphology of PCL-polyDOPA-G scaffolds did not significantly change compared to PCL scaffolds, while their surface roughness was slightly increased. HCFs cultured on PCL-polyDOPA-G scaffolds showed improved attachment and proliferation compared to non-functionalized PCL scaffolds. The expression of fibrotic markers (α-SMA) and the secretion of typical cardiac extracellular matrix proteins (Fibronectin, Laminin, Tenascin and Collagen IV) were confirmed. Scaffold geometry affected the type of deposited proteins and their distribution and orientation.

**Conclusions:** In this work, 2D and 3D bioartificial PCL-polyDOPA-G scaffolds supported long-term HCF culture, while their structure affected HCF adhesion, fibrotic marker expression and cardiac protein deposition. A comparison of the composition and mechanical properties of the engineered constructs with human infarcted samples will allow to define a platform of PCL-polyDOPA-G scaffolds for the modelling of different degrees of cardiac fibrosis. Results of this study could be beneficial for the treatment of cardiac fibrosis associated with other pathologies than ischaemic cardiomyopathy, including inherited cardiomyopathy mutations, metabolic syndrome, diabetes, and ageing.

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**Disclosure of Interest**: None Declared

**Keywords**: 3D scaffolds for TE applications, Artificial extracellular matrix, In vitro tissue models