Smart micro tissues for cardiac regeneration
M.H. van Marion, D.W.J. van der Schaft, C.V.C. Bouten and F.P.T. Baaijens

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Rationale
Annually, 1.2 million people suffer from myocardial infarction [1] (fig. 1). Injured heart tissue is not able to repair itself sufficiently, and therefore scar tissue will be formed, resulting in a reduced contractility and possibly heart failure. At present, stem cell therapy is seen as a promising treatment modality. However, homing, survival and differentiation of the cells is poor [2]. In view of this issue, the aim of this research is to develop autologous, sustainable and functional micro tissues for the regeneration of infarcted heart tissue into healthy myocardium.

Concept
We aim to develop small contractile cardiac micro tissues that are able to regenerate infarcted myocardial tissue (fig. 2). These micro tissues should preferably be autologous, smart (bioactive to enhance cell differentiation and tissue formation), injectable (non-invasive application in vivo), and detectable in vivo (e.g. MRI compatible).

Aim and Hypothesis
To develop functional myocardial tissue, contractile cells are needed. Differentiation of progenitor cells into contracting cardiac myocytes is a complicated process. Therefore, a new approach will be pursued (fig. 3), which is based on the hypothesis:

Differentiation of progenitor cells into contractile cardiac myocytes is promoted by the application of a combination of biological and physiological factors.

Experimental approach

I. Cell sources
- human cardiac myocyte progenitor cells (CMPCs, fig. 4)
- human mesenchymal stem cells

II. Biological factors
- multiple biochemical factors (e.g. growth factors)
- a 3D biomimetic environment (scaffold/polymer gel): adaptable stiffness (healthy tissue ~10 kPa, infarcted ~50 kPa [3])
- Peptide linkers (collagen type I, III)

III. Physiological factors
- electrical stimulation to promote contractility
- mechanical stretch to promote tissue formation and alignment

Analysis
- cell viability: PI-staining, BrdU labeling
- cell distribution and tissue formation: histological stainings
- cell differentiation: FACS, qPCR, immunological stainings
- functionality: contractility, Ca^{2+} flux

Objective
Results should lead to the development of a bioreactor for the production of smart, contractile micro tissues for cardiac regeneration. Regenerative capacity of those tissues will be tested in in vitro, ex vivo and in vivo model systems.

References: