# ImmunoTools *special* Award 2014

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## The role of myeloid bone marrow-derived cells in the pathogenesis of cardiomyopathy in systemic sclerosis

### Aim

The main aim of our project is to comprehensively investigate the pathogenesis of cardiac fibrosis in patients with systemic sclerosis with particular focus on the role of myeloid bone marrow-derived cell compartment in these processes.

### Background

Systemic sclerosis (SSc) is an autoimmune disease with chronic vasculopathy and inflammation, leading to fibrosis in the skin and multiple internal organs. Throughout last years, there was a shift over SSc-related death causes, indicating inflammatory dilated cardiomyopathy (iDCM) as a major cause of death [1]. iDCM is caused by myocarditis (e. g. viral or autoimmune), which progressively leads to ventricular dilation, fibrosis and ultimately, heart failure[2]. Myofibroblasts, the main cell type responsible for the pathogenic deposition of excess extracellular matrix (i. e. fibrosis) can either originate from resident cardiac fibroblasts or migrate from the bone marrow. In an animal model for experimental autoimmune myocarditis (EAM) that closely resembles the iDCM phenotype, it was demonstrated that more than 60 % of cardiac myofibroblasts originated from bone marrow[3].

### Project Description

Firstly, we plan to characterize inflammatory cells and fibroblasts/myofibroblasts within endomyocardial biopsies from patients with active or inactive SSc with documented cardiac involvement. For this purpose we will use antibodies against the myofibroblast marker α-SMA, markers for myeloid cells (CD45) and special macrophage markers (CD11b, CD80, CD86, CD105).

Secondly, we will isolate myeloid cell populations from SSc patients and healthy controls as they are recognized as potent producers of inflammatory cytokines and/or representing the cellular sources of myocardial myofibroblasts in different heart injuries. The myeloid cell compartment will be analyzed by flow cytommetry with ImmunoTools antibodies for the presence and proportion of different subsets, such as monocytes ($CD14^+$), phagocytes ($CD16^+$), endothelial cells ($CD44^+$) and progenitor cells ($CD133^+$).

Myeloid cells will be further cultivated and differentiation to myofibroblasts will be induced with various ImmunoTools cytokines such as TGF-β, GM-CSF and M-CSF. The effect of these cytokines on differentiation will be assessed using qRT-PCR and IHC for myofibroblast

markers and differences between cells from SSc patients and healthy controls will be evaluated. A cytokine expression profile of these differentiated cells will be created using qRT-PCR and ELISA technology.

In a parallel assay, we will analyze serum from SSc patients and control subjects in respect to the content in proinflammatory cytokines (e. g. IL-1β, IL-6). The impact of these proinflammatory mediators on the induction of myofibroblast differentiation will be tested in human cardiac fibroblasts, which represent another potential cell source for myofibroblasts. Further, we will assess the effect of myeloid cell populations derived from SSc patients on the differentiation potentials and functions of human cardiac fibroblasts using direct co-culture system.

Lastly, we will trace fate and functions of mouse myeloid cell populations in two SSc mouse models: a) Fra-2 transgenic mice developing the phenotype of iDCM, and b) human myeloid cell populations administrated into NOD/SCID mice, which will be treated with angiotensin II to develop myocardial inflammation and fibrosis.

**Significance of the project**

The experiments described above are expected to identify key cellular sources and molecular mechanisms of myocardial fibrogenesis. If we are able to successfully target these pathways in SSc animal models or even humanized SSc models, this will be the basis for the development of novel and effective therapies targeting the often fatal cardiac involvement in SSc patients. The ImmunoTools *special* Award would greatly facilitate the continuation of this project.

**References:**


[1] Boueiz A et al. Cardiac complications of systemic sclerosis: recent progress in diagnosis. *Curr Opin Rheumatol*. 2010;**22**:696-703

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[3] Kania G et al. Heart-infiltrating prominin-1/CD133+ progenitor cells represent the cellular source of transforming growth factor beta-mediated cardiac fibrosis in experimental autoimmune myocarditis. *Circ Res*. 20009;**105**:462-470