# In Vitro Study of G-CSF on Diabetic Cardiomyopathy Using Human Induced Pluripotent Stem Cells.

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Introduction: Diabetic cardiomyopathy (DCM) is a complication of type 2 diabetes, with known contributions of high fat diet and life style. Diabetes causes pathological remodeling of cardiac muscle, which impairs heart function. Recently, we demonstrated that granulocyte colony-stimulating factor (G-CSF), a cytokine known to promote tissue repair and regeneration, has accelerated recovery and improved cardiomyocyte (CM) functions in DCM.

Objectives: Investigate the mechanisms underlying cardiomyocyte recovery induced by G-CSF in DCM, which are still unknown.

Materials and Methods: Cell structure and imaging will be performed by electron microscopy, confocal microscopy and PerkinElmer Operetta system. Gene expression analysis will be performed following manufacturer's instruction.

Discussion and Results: First we will develop an in vitro DCM model for iPS-derived cardiomyocytes differentiation. This human-specific DCM model has been used in studies of cardiac hypertrophy, arrhytmia and metabolism. Because DCM is a disease of adult CMs, human iPSC-CMs will be exposed to maturation medium (containing insulin and fatty acids, but no glucose). The structural and molecular

impact of this manipulation will be investigated with a-actinin immunofluorescece (IF), gene expression (myosin light chain, sarcoplasmic reticulum markers, G-CSFR expression) and whole-cell calcium current. Next, we will expose human-iPSC-derived CMs to a control- or diabetogenic-like culture medium and characterize CM and phenotypic surrogates of DCM-induced condition. Finally, G-CSF will be administered to DCM model of human-iPSC-derived CMs. CM proliferation, function and G-CSF signaling pathway JAK/STAT will be analyzed.

Conclusion: With this project, we propose that G-CSF is critically involved in cardiomyocyte recovery during development DCM, and may be used to boost the yield of cardiomyocytes from iPS for their potential application to regenerative medicine.

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Keywords: G-CSF; Diabetic Cardiomyopathy; Diabetes type 2; Human IPS.