To:
European Society of Cardiology
The European Heart House
2035 Route des Colles - Les Templiers
06903 Sophia Antipolis
FRANCE

Utrecht, March 8th 2014

ESC First Contact Initiative Grant report

I want to start by extending my gratitude towards the European Society of Cardiology councils for providing me with the opportunity to visit and establish a connection with the Gladstone Institute of Cardiovascular Disease in San Francisco. The First Contact Initiative Grant allowed me to spend two weeks at lab of Prof. Deepak Srivastava in November of 2013.

The Gladstone Institute of Cardiovascular Disease is world renowned research center which investigates a wide spectrum of cardiovascular disorders with a special focus towards regenerative therapies. The staff includes Nobel Prize recipient Dr. Shinya Yamanaka, a pioneer in induced pluripotent stem cell (iPS) technology, which makes it a unique place to spend a period of time. I had the chance to sit through some exciting meetings about ongoing project inside institute from which I learned a great deal. The lab of Prof. Srivastava discovered direct cardiac reprogramming factors (*Ieda, et al Cell 2010*), with which they can transform fibroblast cells into fully functioning cardiomyocytes. This research has opened many new exciting opportunities within the cardiac field, by enabling the creation of patient specific cardiomyocytes from easily attainable biopsy and without the need of an intermediate iPS state.

The goal of this grant was to setup a collaboration between our two labs with a focus on trying to combine our lines of research. My PhD research has centered on strategies to improve cardiac cell therapy, especially with biocompatible materials. We have used various

techniques to encapsulate cells or place them on microcarriers. These approaches have improved the delivery of stem cells to the heart, however we noticed that there is a clear lack of cardiac differentiation independent of the cell type and delivery strategy used. In this respect, I thought that the reprogramming technology could play an important role by improving the formation of *de novo* heart muscle in the ischemic myocardium if used in combination with cell therapy approaches.

Although the initial aim was to explore the potential to use reprogrammed fibroblast as a cell source for tissue engineering application, discussion with lab members in San Francisco led me to refocus on the effect of the reprogramming factors in cardiomyocyte progenitor cells (CMPCs). Although CMPCs do not have to be reprogrammed, since they are already committed to the cardiac lineage, the reprogramming factors could be useful modulators of their therapeutic effects. We discussed the interest of studying the effects of the factors in cells with different epigenetic landscape. I had the opportunity to have individual meeting with the PhDs and post-docs researchers in the lab, which was a priceless experience to get a perspective on the techniques they use, the focus of their current research, and the hurdles and bottlenecks which are impeding the reprogramming process. I was also able to sit through reprogramming experiments and get a better feel for the implementation of the technology.

We have continued our collaboration after my visit to San Francisco. We have recently received the 7 human reprogramming factors from the Gladstone Institute discovered last year (*Fu et al, Stem Cell Reports 2013*) and we are going to send mesenchymal stem cells to San Francisco, as part of a newly setup material exchange program between our labs. We will soon start with experiments to test the optimal combination of factors to potentially increase the cardiogenic potential of the CMPCs, and how they affect the *in vivo* behavior and therapeutic effects of the stem cells. We will utilize some techniques that were shared and explained to me during my visit for testing the efficiency of cardiomyocyte formation.

To summarize, the grant was been extremely useful to set into motion a collaborative project between the University Medical Center Utrecht and the Gladstone Institute in San Francisco. I look forward to progressing with this research project together and also to other collaborative project that might arise from the findings. Furthermore, this visit has also

solidified my desire to apply for grants (such as EMBO long-term) this upcoming year to gain further international research experience, and hopefully be able to establish my own research line in the future. Finally I would like to thank Prof. Srivastava for allowing me to visit his lab and greatly appreciate his feedback on my own research. I also would like to thank Ji-Dong Fu for his help in explaining the lab's reprogramming research lines and serving as my contact person now that I am back in The Netherlands.

Yours sincerely,

Dries Feyen