ESC First Contact Initiative Grant

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Dear ESC Council on Basic Cardiovascular Science,

I, Dr. Elise Kessler, would like to thank the ESC Council on Basic Cardiovascular Science for the opportunity to develop my project on *in vitro* models for heart failure (HF). With the support of the ESC First Contact Initiative Grant 2019, I was able to initiate a collaboration between the Department of Cardiology (Professor Dr. Ulf Landmesser) at the Charité in Berlin, Germany and the focus area Circulatory Health of the UMC Utrecht, The Netherlands, more precisely in the Laboratory of Experimental Cardiology of the UMC Utrecht and the Regenerative Medicine Center Utrecht (Professor Dr. Hester den Ruijter and Professor Dr. Joost Sluijter).

Background of the research

Heart failure with preserved ejection fraction (HFpEF) accounts for approximately 50% of all heart failure (HF) cases and compromises the quality of life for many women and men (Plitt GD 2018 Rev Cardiovasc Ther; Upadhya B 2017 J Am Ger Soc; Benjamin EJ 2019 Circulation). Several underlying co-morbidities are shown to be sex-specific, e.g. diabetes and obesity are associated with a higher risk of HF in women than men (Benjamin, EJ 2019 Circulation). These co-morbidities result in systemic and local cardiac inflammation, which is hypothesized to lead to endothelial dysfunction and in turn to myocardial damage (Shah SJ 2016 Circulation).
To mimic the human situation and reduce animal research, advanced *in vitro* approaches are required. As the syndrome of HFpEF is characterized by its heterogeneity, suitable *in vitro* models must incorporate several different cell types of the same donor to enable the evaluation of various pathophysiological pathways and reducing inter-donor reactivity. Such models are not yet available, thus an advanced system to screen for these co-morbidities and unravel the sex-specific molecular and cellular pathways involved is urgently needed.
As in patients with HFpEF, increased numbers of monocytes and macrophages have been reported, these inflammatory cell types seems of high importance in the pathophysiology of this syndrome (Glezeva N 2015 J Card Fail; Westerman D 2011 Circ

Heart Fail)and can be investigated *in vitro*. For this, the use of induced pluripotent stem cell (iPSC) derived monocytes in combination with iPSC derived cardiac cells from the same donor will mimic the human situation with high reproducibility as closely as possible. This model has the advantage that we can generate unlimited numbers of cells, exclude allogenic effects in future experiments and are able to focus on single comorbidities and unravel the role of sex differences herein. The use of iPSC derived cells will also enable us to reduce the use of laboratory animals and to mimic the human syndrome. To achieve this, I will collaborate with experts in the field in order to gain the necessary knowledge on iPSC derived cell differentiations and train myself to become an expert in the field of cardiac *in vitro* models.

Rationale and hypothesis of my research

This project aimed at creating a sex-specific iPSC *in vitro* model containing various cardiac cells of the same donor to investigate sex-differences in comorbidity-mediated HFpEF.

I hypothesized that comorbidities (such as diabetes and obesity) trigger systemic inflammation by sex-specific mechanisms and lead to sex-differences in HFpEF risk.

Use of the grant and personal development

I have been working in the cardiovascular field since the beginning of my PhD (defended January 2018). During my current postdoc at the UMC Utrecht, I want to establish an *in vitro* system mimicking the human cardiac (micro)environment of one donor to incorporate HF-associated comorbidities and investigate sex-differences *in vitro*.
Therefore, I aimed to create iPSC derived monocytes and macrophages of male and female donors. In order to learn how to generate iPSC derived monocytes and endothelial cells, I visited the group of Professor Dr. Landmesser at the Charité in Berlin, who is an expert in this field and his group is highly experienced in generating iPSC derived monocytes.
In the host institution, I received training on cell differentiations, in particular, I gained extensive experience in cell culture techniques and learned how to perform iPSC derived monocyte and endothelial cell differentiations. By the end of my stay I had prepared my own protocols for the differentiations and practiced the experiments on male and female healthy donor cells.
The data and experience based on this grant enabled me to receive additional funding for collaborations between these groups, as I received a Fellowship from the Netherlands Heart Institute to extend my research at the Charité, Berlin. Besides that, this First Initiative Grant strengthened not only the collaborations between these mentioned groups, but also my own research experience.

In the future, I will work at the Charité regularly and expand the collaboration, which was made possible by this ESC grant.

Yours sincerely,

Dr. E.L. Kessler