Emerging roles of small and long non-coding RNAs in Cardiac Disease

Valorization

Socio-economic relevance

Heart failure (HF) is a global health problem, it affects 26 million people worldwide [1]. In total 27.7% of deaths were attributed to HF in 2015, which has increased over the years [2]. The diagnosis HF impacts the lives of patients and their relatives and friends. The quality of life of these patients is poor and the disease controls their daily activities [3]. Next to the physical boundaries they experience, the mental impact is also significant. At the moment, these patients are treated with drugs that only affect the symptoms, but will not cure the disease, such as angiotensin-converting enzyme inhibitors, beta blockers and diuretics [4]. Unfortunately, the fatality rate after hospitalization for HF is 42% in 5 years, which is still extremely high [2]. There are no other treatment options and therefore we have to invest money and time to find new therapies that can help these patients. Such new therapies may improve the quality of life, increase the life expectancy, and even prevent the development of HF.

Next to the impact on the patient's life, there is a huge economic burden that co-exists with HF. Due to an ageing population, the prevalence of HF will increase which will result in a tremendous cost for society [1,2]. Especially the costs for treating HF comorbidities and HF symptoms in youths are significant [2,5]. Therefore finding new therapies that will save lives, decrease care costs and help patients to improve quality of life will lower this burden.

To find new therapies, we have to understand the pathophysiology of heart failure and all its different symptoms and co-morbidities. In this thesis we aim to add small pieces to a big puzzle that represents cellular mechanisms involved in the development of HF. We investigated relatively new molecules, called non-coding RNAs (ncRNAs), that turn out to be important mediators of pathophysiology in different disease models of HF, and are also associated with human HF. Here we share these new findings and to show their potential, thereby we aim to open doors to find new ways to diagnose and treat HF.

Target groups

In this thesis we provide new insights in the mechanisms underlying HF, by investigating molecular mechanisms involved in several etiologies that can cause HF. Understanding which molecules are involved in cellular signaling pathways that underlie the heart's responses to pressure overload, viral myocarditis and metabolic-induced HF, improves basic knowledge of cell biology. The scientific community will benefit by improving awareness and by increased motivation to study these ncRNA molecules. In addition, the new functional roles of ncRNAs that we identified in this thesis might be applicable to cross scientific borders to other disciplines, such as cancer biology, neuroscience and liver metabolism. This has already been proven for *miR-200c*, *Neat1* and *Malat1* that all play a role in cancer biology [6–8].

Besides the scientific community, pharmaceutical companies are an important target group for this thesis; they invest in developing new drugs, including ncRNA-based therapies. Several attempts have been made to be able to deliver ncRNA therapy at the right place in the human body, such as antagomiRs. GapmeRs, siRNAs, and AAV9-based viruses [9]. Recently, the first clinical trial has been launched using siRNAs against a specific long ncRNA in patients with thymoma and autoimmune disease (NCT02948855; Clinical trial

database from US National Library of Medicine). In addition, we provide new insights in the role of ncRNAs that potentially can be used for future drug development.

In general, public institutes such as the NWO (Nederlandse Organisatie voor Wetenschappelijk Onderzoek) and the Netherlands Heart Foundation can profit from the data observed in this thesis. Based on the research results we share, one can actively discuss what the focus of cardiac research should be, and where investments need to be made.

Activities, products and innovations

This thesis presents basic research results that improve the knowledge of basic cell cardiology, as well as, deeper understanding of the pathophysiology of HF. Translating these results to clinical practice is the main goal, however still distant. This thesis is only a tip of the iceberg, many more efforts have to be made to explore this disease and to get a better understanding of the molecular and cellular processes involved in the development of HF. This thesis provides a piece of the big puzzle, and thereby may stimulate other researchers and other research areas to investigate ncRNAs. Moreover, we used several techniques to manipulate ncRNA levels *in vitro* and *in vivo*, using AAV9-based vectors, genetic knock-out models and synthetic oligos. These techniques need further development to assure limited side effects before they can be introduced into the clinic, but have great potential.

Cutting edge and innovative research is necessary to evolve and find new therapies. In this thesis we are the first to show that a small microRNA (*miR-200c*) is able to change the composition and activity status of a big protein such as titin (**Chapter 6**). In addition, we present long non-coding RNA *Neat1* as a new player in the development of cardiac disease. Genetically depleted *Neat1* mice are protected from cardiac hypertrophic remodeling and failure (**Chapter 4**). Finally, a synthetic oligo named s-mascRNA, shows the potential to inhibit viral replication in cardiac myocytes (**Chapter 5**). This proves the importance of ncRNA molecules for future drug development.

Planning and realization

To be able to translate the findings in this thesis to the clinic will be the main goal and challenge of the future. Upcoming studies have to prove the possibility and applicability of using oligo-based tools to change the levels of ncRNAs and alter outcome. In addition, investigating the mode of actions of these molecules in the heart is crucial to be able to understand exactly what is happening in a pathophysiological condition such as HF.

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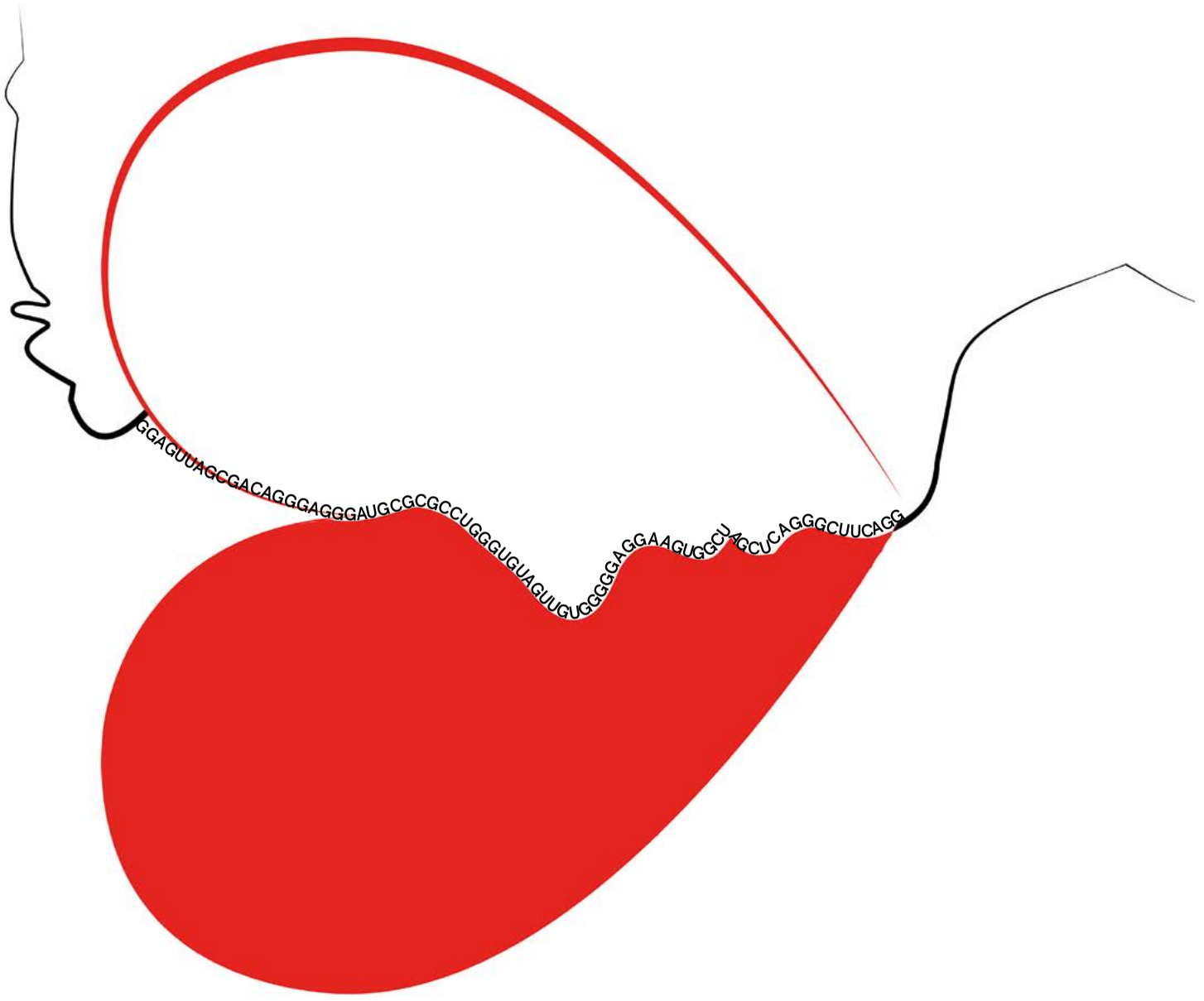
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