

MicroRNA-199b in the heart

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Chapter 7

Impact paragraph



Cardiovascular diseases have been the leading cause of death worldwide for over 40 years¹, with the World Health Organization nowadays estimating almost 18 million deaths every year². Besides the societal impact of cardiac disease in patients and caregivers' quality of life, it also leads to productivity losses, contributing to an exacerbated economic burden³. The annual healthcare costs currently exceed the \$320 billion, a number expected to rise to \$818 billion by 2030⁴ in the United States.

Aortic Stenosis (AS) is the most prevalent valvular disease in the so-called developed world. As there is a positive correlation between age and AS prevalence, an increase in prevalence is expected with an aging population⁵. Patients suffering from AS can remain asymptomatic for long periods while the disease progresses, contributing to its poor diagnosis and prognosis⁶⁻⁸. These are further delayed and worsened by the incomplete understanding of disease's pathophysiological mechanisms, intrinsically heterogeneous and complex⁹. Thus, new models and platforms are needed to investigate the pathology and fill the current knowledge gaps.

In this thesis we describe a large animal model of AS, whose resemblance with a clinical scenario makes it a suitable platform to study the disease. Our model is versatile enough to mimic both early and later stages of cardiac hypertrophy, which can allow the investigation of the pathophysiological mechanisms involved in its onset and progression. The socioeconomic impact of our work goes even further by constituting a suitable platform to study new therapeutic approaches.

Despite the growing burden throughout the past decades, efficient therapeutic approaches targeting AS are challenging to develop. So far, the only successful strategy consists of aortic valve replacement (AVR)⁵. However, the strict inclusion/exclusion criteria leave several patients without effective therapeutic options to tackle a progressively dysfunctional heart¹⁰. Developing new solutions to serve these patients and help others delaying disease progression is urgent. Great scientific efforts have been in place, with numerous preclinical findings reported in the recent years. However, disappointing translation to clinics has been responsible for considerable economic losses paired with slow advances in drug development^{11,12}. Although the cost of bringing a drug from discovery to market is highly variable, several estimations have indicated a value above \$2 billion¹¹. Thus, despite the already significant investment in the preclinical phase, only about 25.5% of the cardiovascular therapies succeed from Phase 1 to approval¹², contributing to a drastic negative financial impact. Among the causes for the disappointing translation to clinics is the use of unsuitable animal models that do not resemble a human disease, compromising the clinical relevance of

the findings⁹. Thus, our work presents valuable contribution, not only for basic, but also translational research, a scientific field of crucial importance for clinical success.

As the molecular pathophysiological mechanisms are unveiled, a growing interest in targeting the root cause rather than the symptoms has led to a paradigm change in drug development. The first non-coding RNA (ncRNA)-based drug entering clinical trials for the treatment of heart disease was CDR132L (Cardior Pharmaceuticals GmbH), currently in Phase 2 (NCT05350969)¹³. Results from Phase 1 showed CDR132L to be safe and effective, bringing an optimistic perspective to cardiac research and pharmacology¹³. While it paves its way to the market to address ischemic heart disease, our work suggests a new ncRNA-based therapy (Ant-199b-5') targeting pressure overload-induced cardiac hypertrophy. Our preliminary findings in porcine and 3D humanized models are relevant for the scientific community, as they constitute the basis for a translational research work eventually leading to successful clinical outcomes.

The contribution of our research for the cardiovascular field is not limited to left ventricle-related failure, but it also brings new insights about right ventricle hypertrophy. Despite its associated morbidity and mortality, research in right ventricle hypertrophy and failure has been behind the one concerning the left ventricle. So far, no drugs have been approved to specifically target right ventricle failure¹⁴, which can partially be explained by the limited awareness of the differences between left and right ventricle, often addressed with the same strategies¹⁴. As these strategies fail to succeed and show even opposite effects in the different ventricles^{15,16}, the need for specific, targeted approaches becomes obvious. Here we demonstrate that pressure overload can trigger different molecular mechanisms in each ventricle, highlighting the importance of treating each as a unique substrate. Our findings can help further understand these differences while potentially helping to disclose a new therapeutic target in right ventricle disease.

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