Press Release

Independent Peer-Reviewed Study Validates Therapeutic Mode of Action of Cardior's First-in-Class Heart Failure Program

- *Publication of international research group in* Frontiers in Cardiovascular Medicine *confirms key role of miR-132 in cardiovascular diseases*

Hanover, Germany, March 29, 2021 - Cardior Pharmaceuticals GmbH, a clinical-stage biotech company focused on the development of non-coding RNA (ncRNA) based therapeutics for patients with cardiovascular diseases, announced today that a recent peer-reviewed study confirms the therapeutic mode of action of Cardior´s lead program CDR132L. CDR132L blocks the naturally occurring microRNA miR-132 which, if overexpressed, is a key driver of heart failure.

The study was published in *Frontiers in Cardiovascular Medicine* (doi:10.3389/fcvm.2021.592362) by an international group of scientists from Stanford University School of Medicine (USA), the University Medical Center Utrecht (The Netherlands) and Shanghai University (China).[1]

In their publication, Lei et al. investigate the molecular mechanisms of two microRNAs, miR-132 and miR-212, in modulating cardiomyocyte contractility, which is impaired in the pathological progression of heart failure. Using both hypertrophic heart failure mice models and human cardiac tissue, the researchers could show that an up-regulation of miR-132 in heart failure impairs cardiac contractile function by targeting SERCA2a. This important protein is involved in the regulation of calcium handling in the heart and in maintaining the regular heart contractionrelaxation cycles. Dysregulated calcium handling is assumed to play a central role in limited cardiac function. The results suggest that inhibition of miR-132 can be a promising therapeutic approach to improve cardiac function in heart failure patients.

The findings are supported by a previous publication of a team of scientists from the Cardiovascular Research Institute, National University of Singapore (Singapore), in *Molecular Therapy* in 2020 (doi:10.1016/j.ymthe.2020.04.006).[2] In this publication, the authors show that upregulation of both miR-132 and miR-212 in an in vivo transverse aortic constriction (TAC) mouse model leads to pathological hypertrophy - an effect that can be reversed by therapeutic miRNA antagonists.

"We are delighted about the growing body of evidence that miR-132 plays a crucial role in the development of heart failure," said Prof. Thomas Thum, CSO of Cardior Pharmaceuticals. "Our approach of blocking miR-132 and thereby halting the process of cardiac disease has now been validated by a number of independent research groups worldwide. In our own studies, we have shown that our lead compound CDR132L not only regulates SERCA2a, but a number of key targets in cardiac remodelling. Based on the recently reported promising Phase Ib data of CDR132L, we are committed to provide heart failure patients with a first-ever causal treatment approach in the next years."

Cardior expects to initiate a clinical Phase II trial with CDR132L later this year.

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About CDR132L

CDR132L is an antisense oligonucleotide developed by Cardior Pharmaceuticals inhibiting themicroRNA-132 (miR-132), a non-coding microRNA that regulates cardiac hypertrophy andremodeling in cardiomyocytes by targeting well-defined pathways. miR-132 is a regulatory master switch to control cardiac function and a promising, causal therapeutic target in heart failure therapy. Expression of miR-132 is increased in various pathological cardiac conditions in both animals and humans, and previous preclinical studies have shown that miR-132 is essential for driving the pathological growth of cardiomyocytes. In a randomized, double-blind, placebo-controlled, dose-escalating Phase Ib study CDR132L showed excellent safety and tolerability, linear dose-dependent pharmacokinetic (PK) and promising pharmacodynamic (PD) properties in heart failure (HF) patients on guideline directed medication. The study design combined dose escalation with repeat dosing (day 1 and 28) at 4 dose levels. 28 patients received CDR132L or placebo (5:2 randomized in 4 cohorts) via shortterm (15 min.) intravenous infusions.

About Cardior Pharmaceuticals

Cardior Pharmaceuticals is a clinical-stage, privately held German biopharmaceutical company pioneering the development of curative and preventive heart failure therapeutics based on noncodingRNAs (ncRNAs). Cardior's therapeutic approach is using distinctive ncRNA signatures driving the molecular reprogramming that causes maladaptive remodeling and heart failure. Drug candidates developed by Cardior represent first-in-class ncRNA therapeutics and diagnostics for patients with myocardial infarction and various forms of heart failure. Founded in 2016 based on the work of cardiologist Prof. Dr. Dr. Thomas Thum of Hannover Medical School, the Company is funded by a consortium of leading investors: LSP, BioMedPartners, Boehringer Ingelheim Venture Fund (BIVF), Bristol-Myers Squibb (BMS) and High-Tech Gründerfonds (HTGF).

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[1] Lei Z, Wahlquist C, el Azzouzi H, Deddens JC, Kuster D, van Mil A, Rojas-Munoz A, Huibers MM, Mercola M, de Weger R, Van der Velden J, Xiao J, Doevendans PA and Sluijter JPG (2021). miR-132/212 Impairs Cardiomyocytes Contractility in the Failing Heart by Suppressing SERCA2a. Front. Cardiovasc. Med. 8:592362. doi: 10.3389/fcvm.2021.592362

[2] Lavenniah A, Luu TDA, Li YP, Lim TB, Jiang J, Ackers-Johnson M, Foo RS (2020). Engineered Circular RNA Sponges Act as miRNA Inhibitors to Attenuate Pressure Overload-Induced Cardiac Hypertrophy. Mol Ther. Jun 3;28(6):1506-1517. doi: 10.1016/j.ymthe.2020.04.006.