Thomas Thum
Institute of Molecular and Translational Therapeutic Strategies (IMTTS), Hannover Medical School

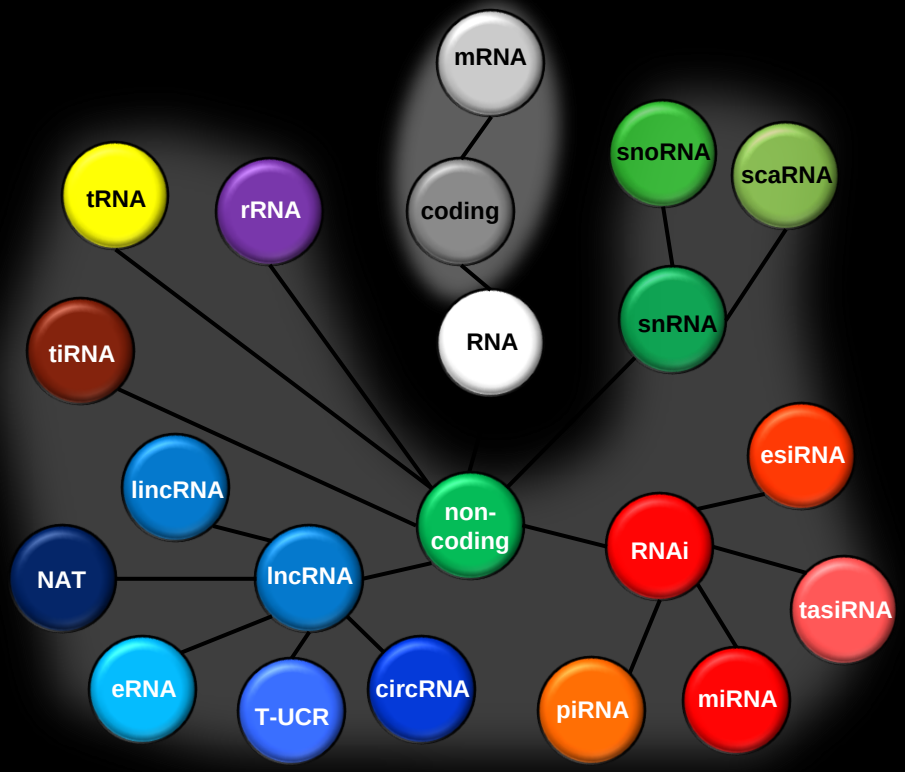
Cardior Pharmaceuticals, Founder & CSO/CMO

MicroRNAs as therapeutic tools

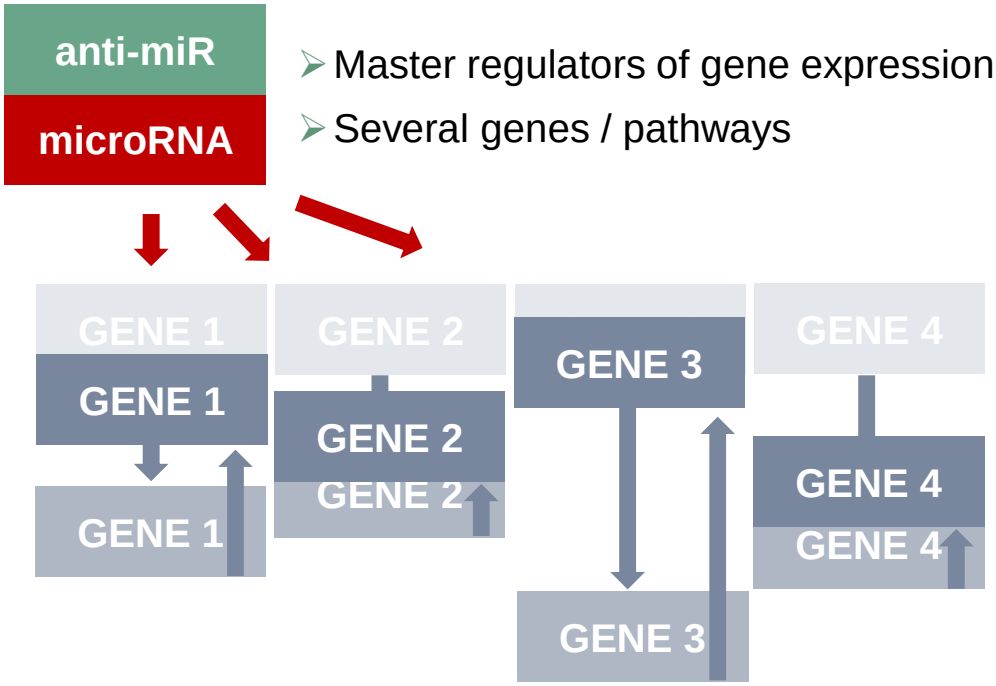
Disclosures: TT filed and licensed patents in the field of non-coding RNAs.
TT is founder and shareholder of Cardior Pharmaceuticals GmbH.

Hannover Medical School

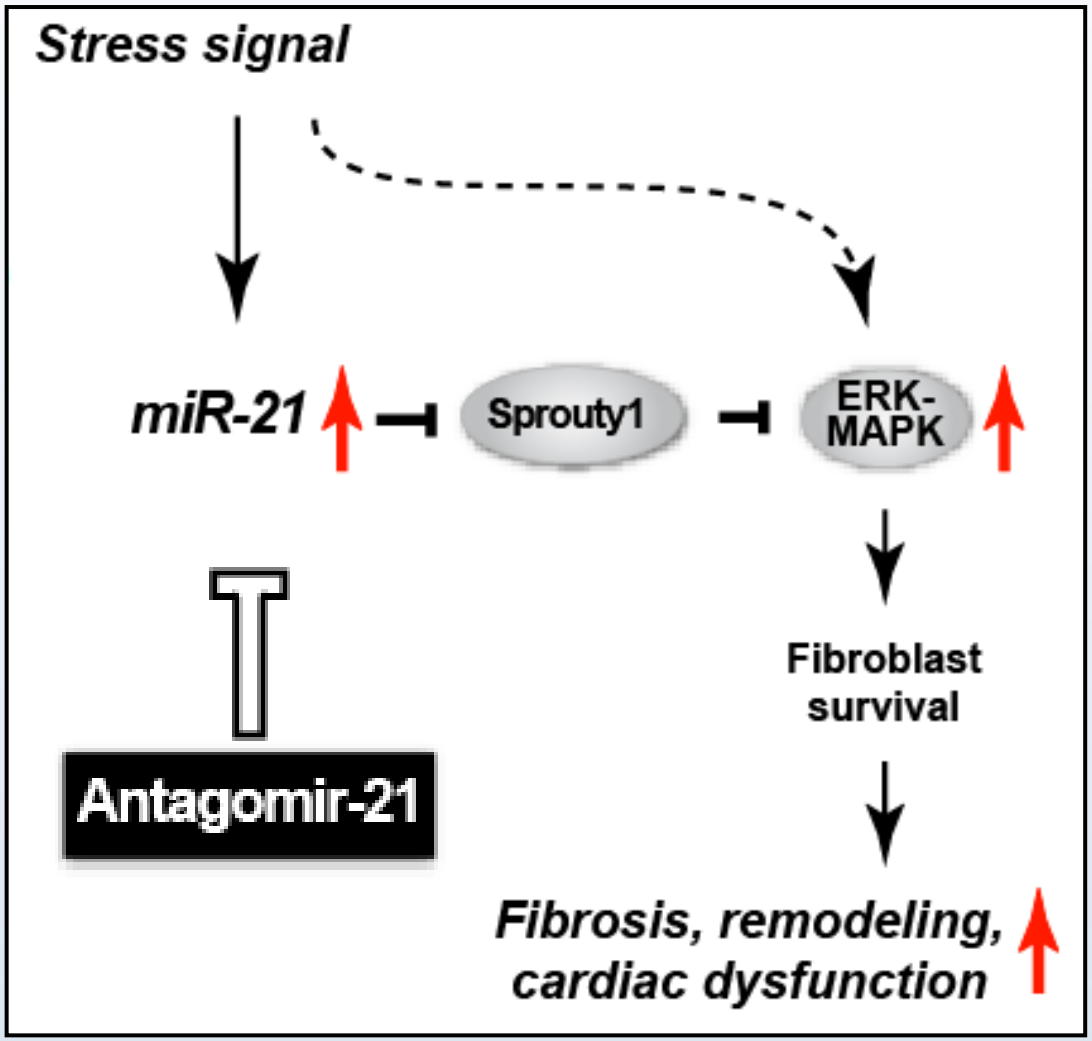
THE NON-CODING RNA WORLD



Why microRNAs ?

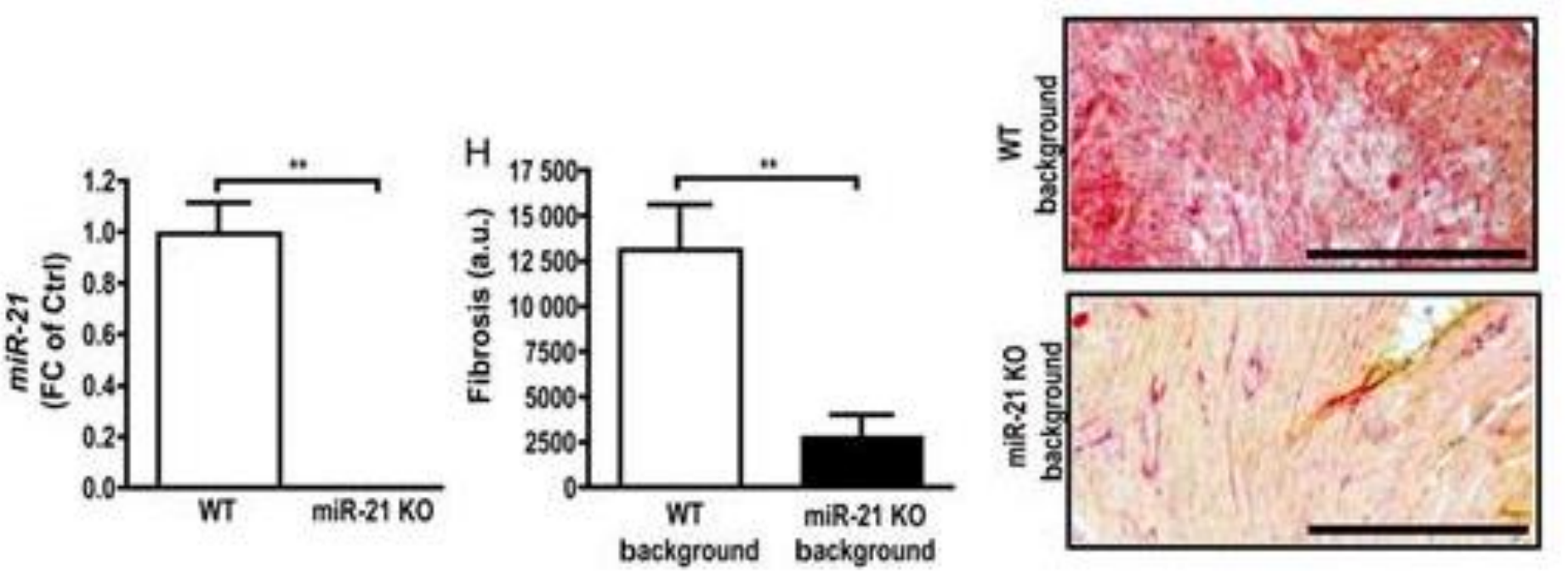


- Master regulators of gene expression
- Several genes / pathways



Nature, 2008:456:980-4

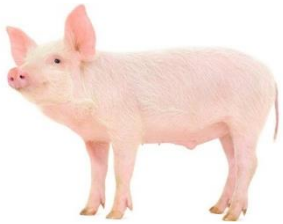
miR-21 knockout prevents fibrosis in transplanted hearts (in mice)



Cardiovascular Research, Volume 110, Issue 2, 15 May 2016

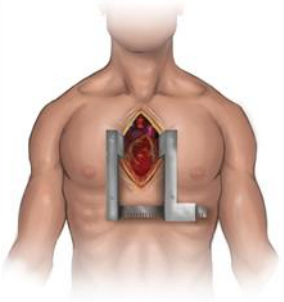
3R approaches – Living myocardium platform

adult
rat
(mouse)

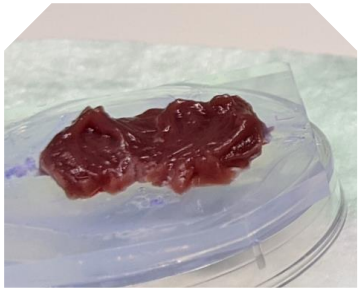


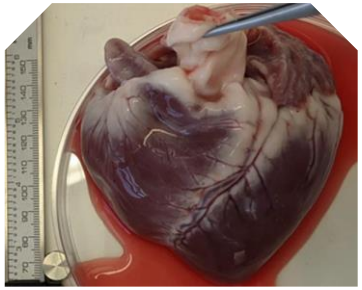
adult
pig

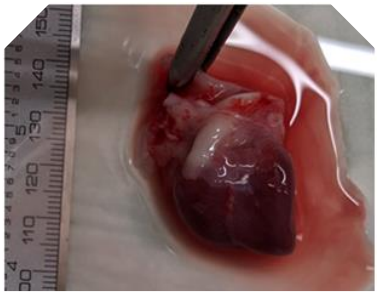
Neonatal pig

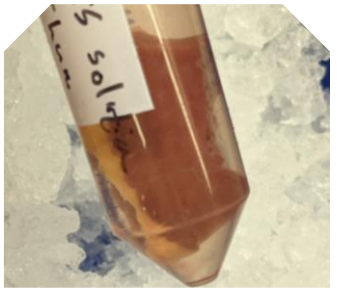


Human
(explant, LVAD, other)

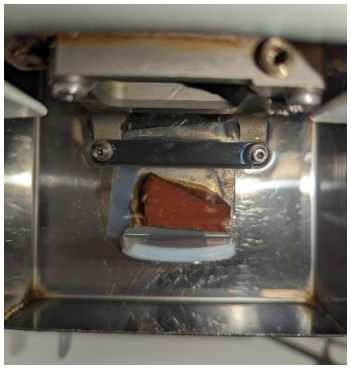


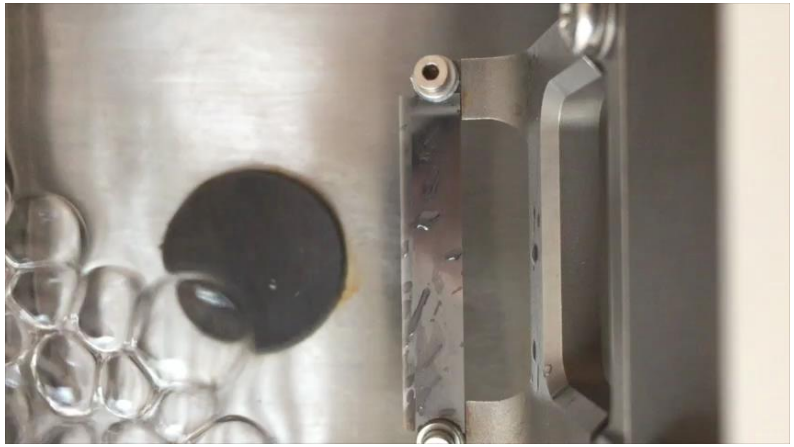




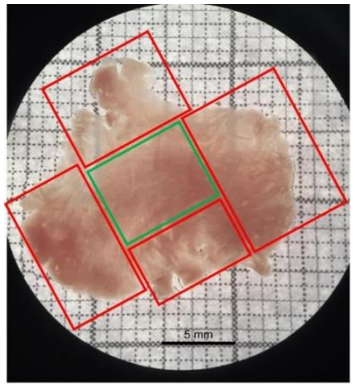


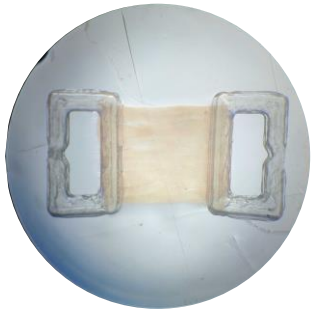
- **Production of living myocardial slices**



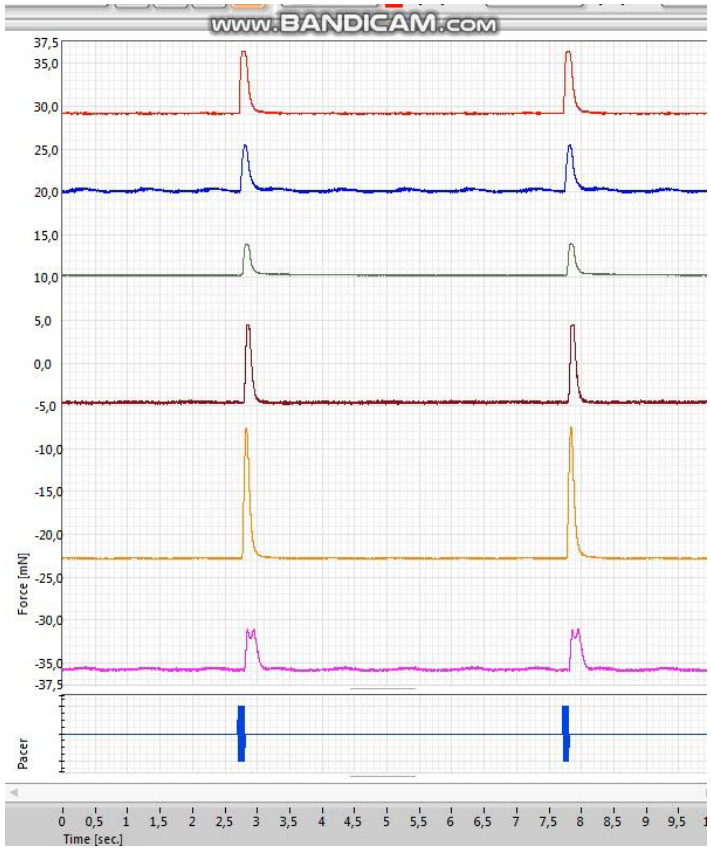


100-300µm thin LMS

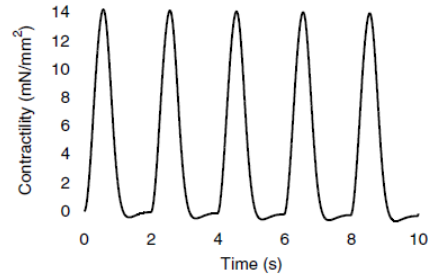


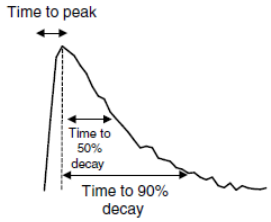


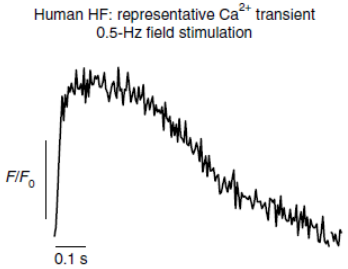
Ex-vivo cultivation

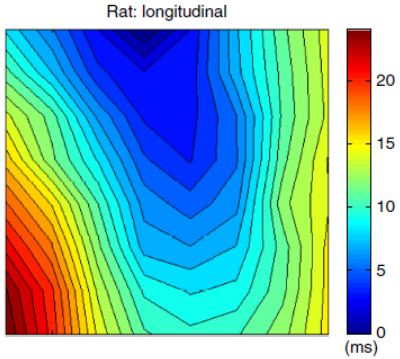


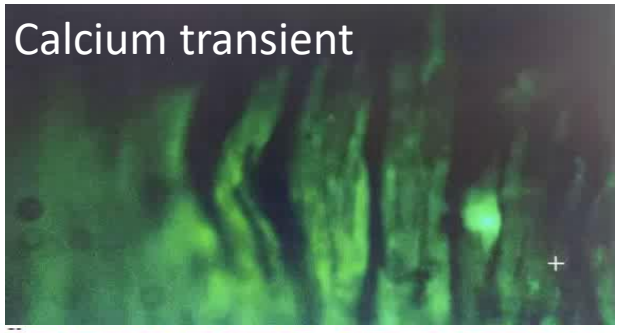
Functional, expressional & structural analysis

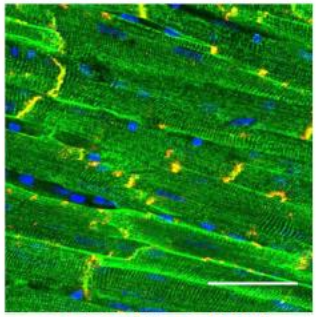


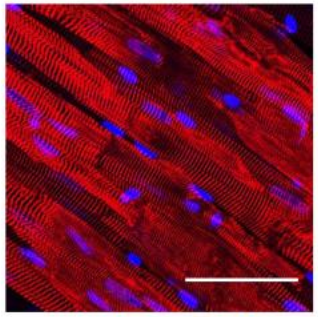






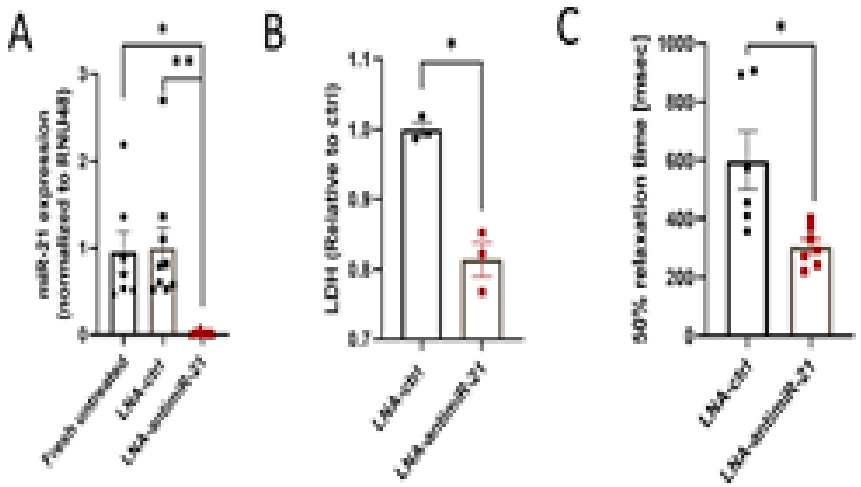






Watson et.al., Nat. Protocols 2017

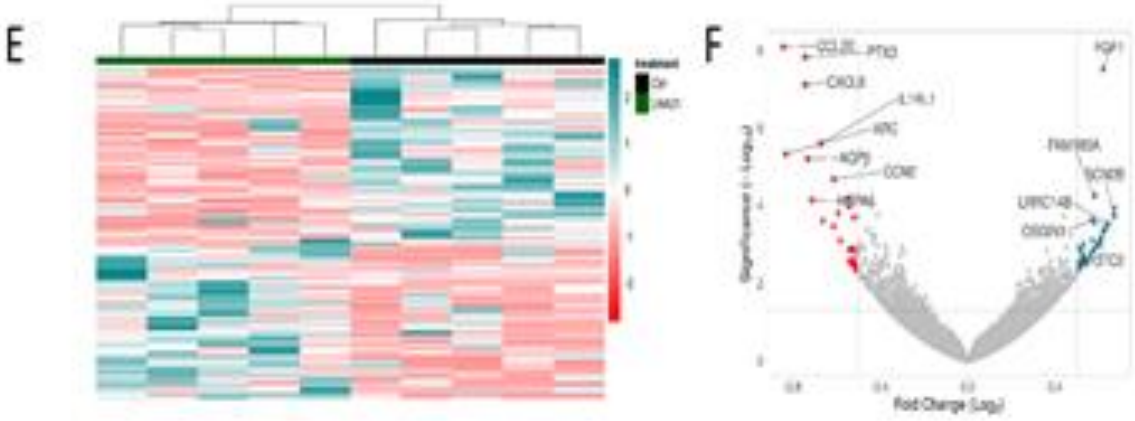
miR-21 silencing in living diseased human myocardium

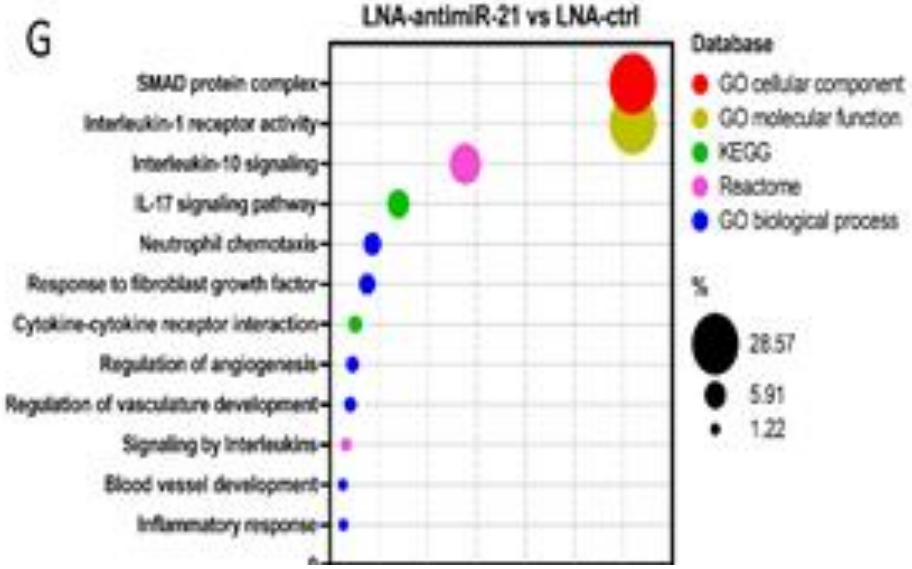


D

Patient	Age	Sex	Diagnosis	LV-EF (%)	Chronic medications
1	32	M	DCM	20	Empagliflozin, Eplerenone, Simvastatin, Allopurinol, Pantoprazole, Torsemide
2	61	M	DCM	15	Dobutamine, Indapamide, Torasemid, Allopurinol, Phenprocoumon
3	55	M	DCM	20	Empagliflozin, Eplerenone, Aspirin, Metformin, Sitagliptin, Simvastatin, Magnesium, Potassium, Zopiclone, Torsemide
4	41	F	DCM	10	Spironolactone, Carvedilol, Digitoxin, Clopidogrel, Amiodarone, Amlodipine, Sildenafil, Furosemide, Xipamide, Pantoprazole, Ursodiol, Potassium, Magnesium, L-Thyroxin
5	33	M	ICM	27	Enalapril, Metoprolol, Torasemid, Aspirin, Tacrolimus, Cotrim, Sildenafil

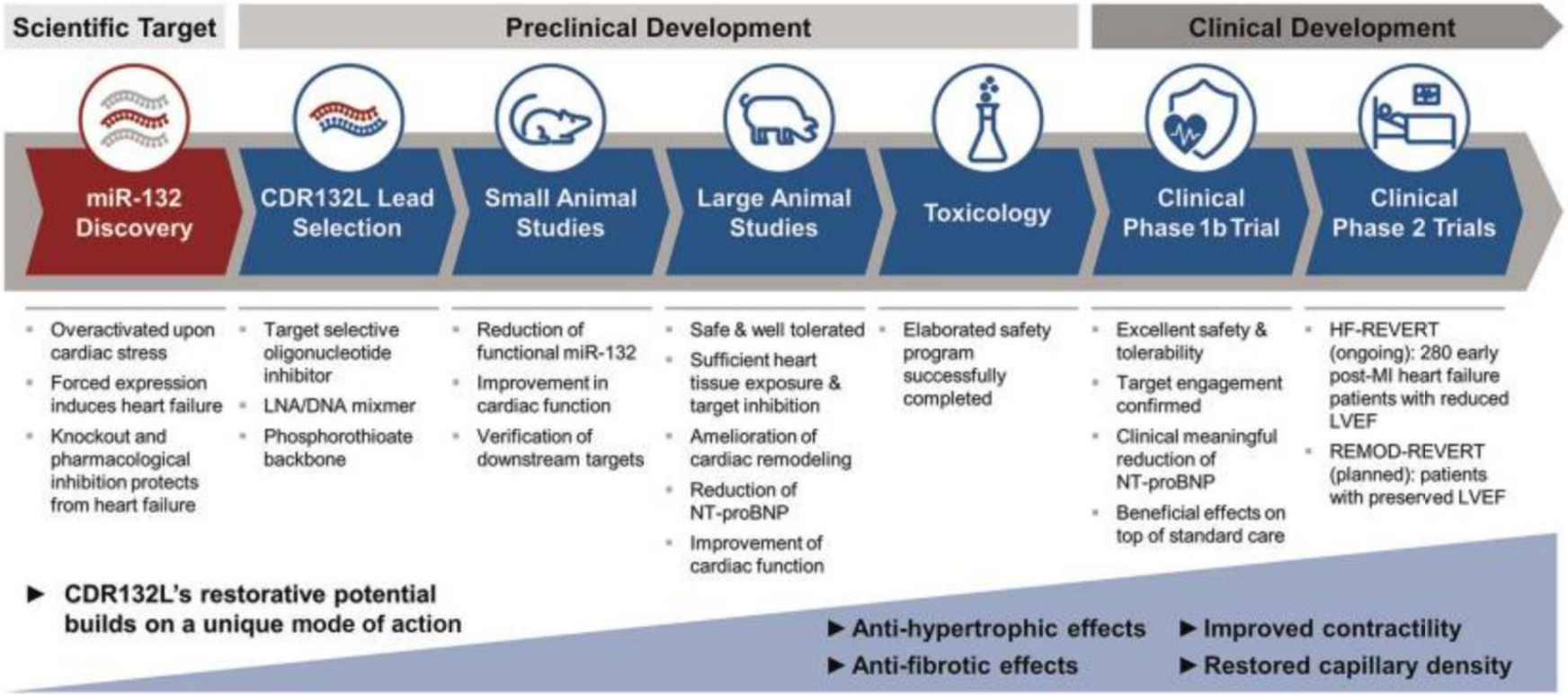
miR-21 silencing in living diseased human myocardium





submitted, IP protected

CENTRAL ILLUSTRATION: Development Path of miR-132 Antisense Inhibitor, Designed to Halt and Reverse the Development of Detrimental Cardiac Remodeling



Viereck J, et al. J Am Coll Cardiol Basic Trans Science. 2023;8(12):1595-1598.

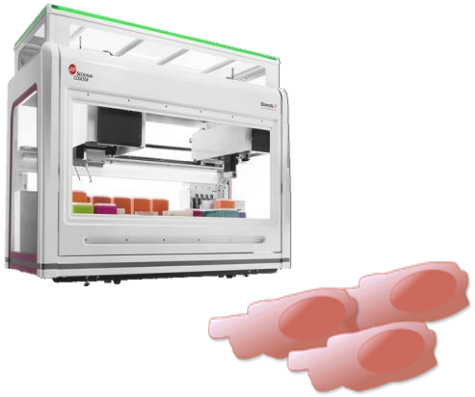
miR-132 is a Highly Relevant Target in Heart Failure

Identification of the therapeutic target and concept

MicroRNA Library Screen

Nature Communications, 2012

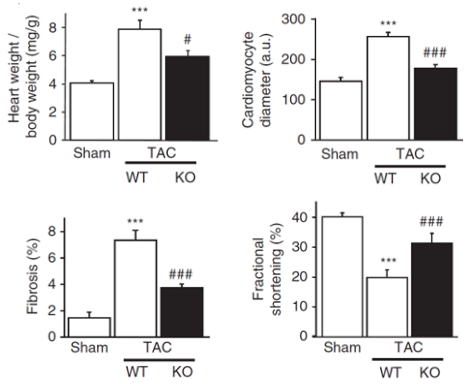
…for hypertrophic growth and BNP secretion identified pathological effects of miR-132 in cardiomyocytes



miR-132 Knockout Mice

Nature Communications, 2012

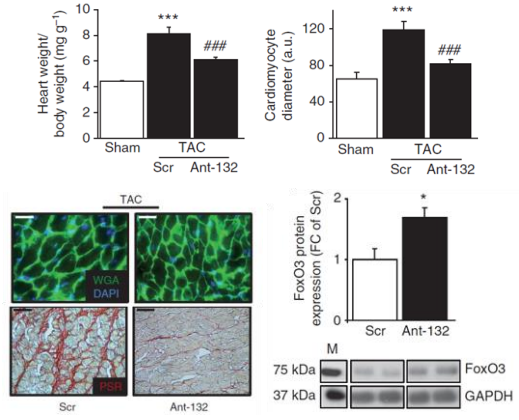
…are basically normal but are protected from pathological adverse remodeling including cardiac hypertrophy and fibrosis



Pharmacological inhibition

Nature Communications, 2012

…with an antagomir prevents pressure-overload-induced heart failure in mice by de-repressing the miR-132 target FOXO3a



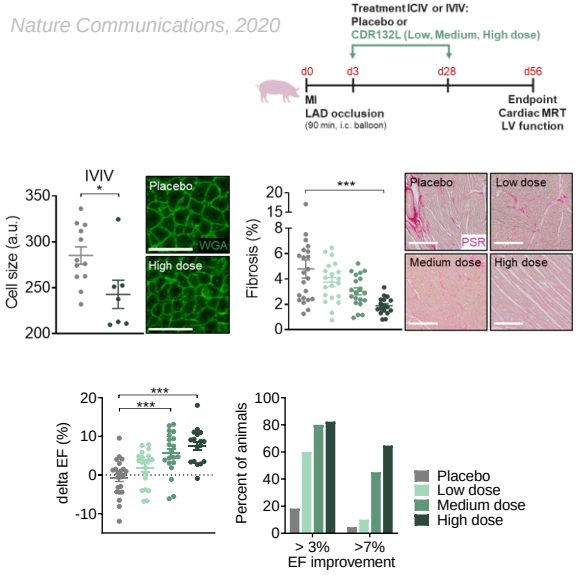
► **Induction of cardiac miR-132 levels mechanistically leads to cardiac remodeling and heart failure.**

CDR132L Reverses Ischemic and Non-ischemic HF

Clinically relevant data confirmed in (world-largest) GLP-like studies of HF large animal models (n>200)

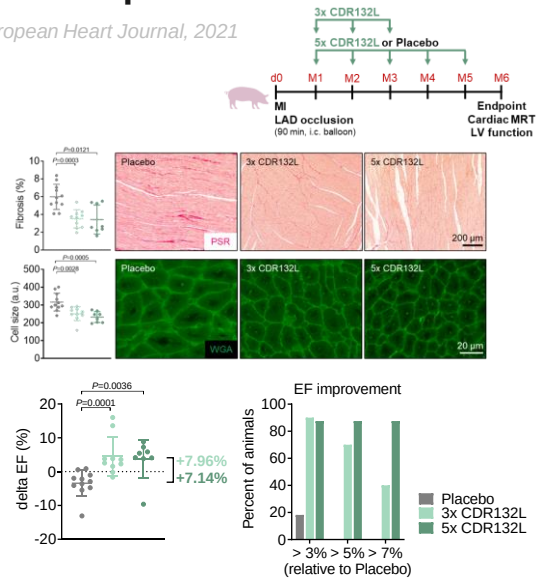
Early post-MI HF (subacute)

Nature Communications, 2020



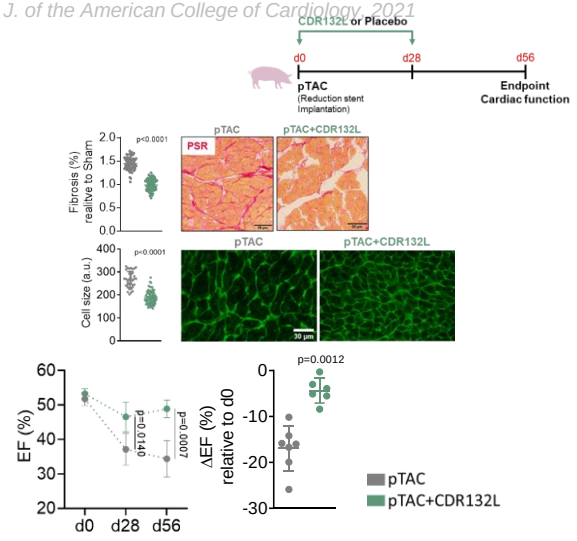
Chronic post-MI HF

European Heart Journal, 2021



Pressure-overload induced HF

J. of the American College of Cardiology, 2021

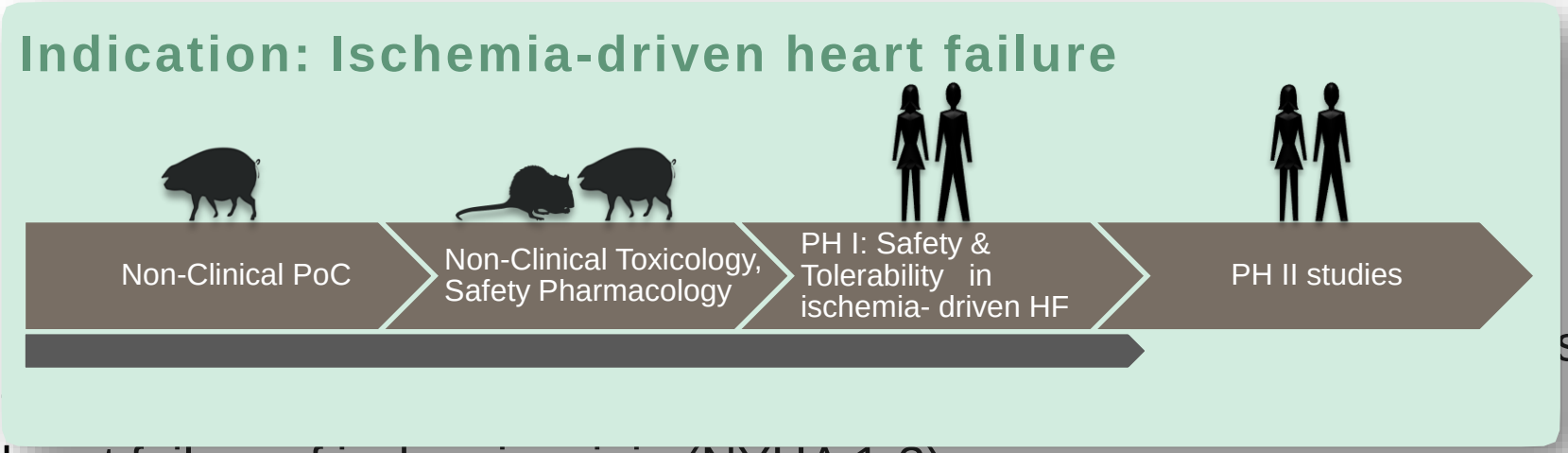


► **Broad safety margin and good tolerability with dose dependent improvement of cardiac function, including inhibition and reversal of fibrosis and pathological heart growth.**

CDR132L has a Unique Mode of Action

Ucar et al. 2012, *Nat Commun.;* Foinquinos et al. 2020, *Nat Commun.;* Batkai et al. 2021, *Eur Heart J.;* Täubel et al. 2021, *Eur Heart J.;* Hinkel et al. 2021, *J Am Coll Cardiol.*; Schimmel et al. 2021, *J Mol Cell Cardiol.*

Path to the clinics

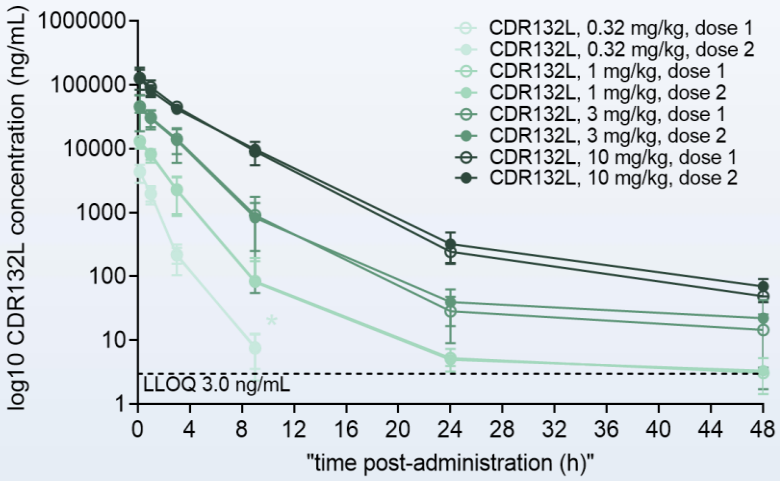


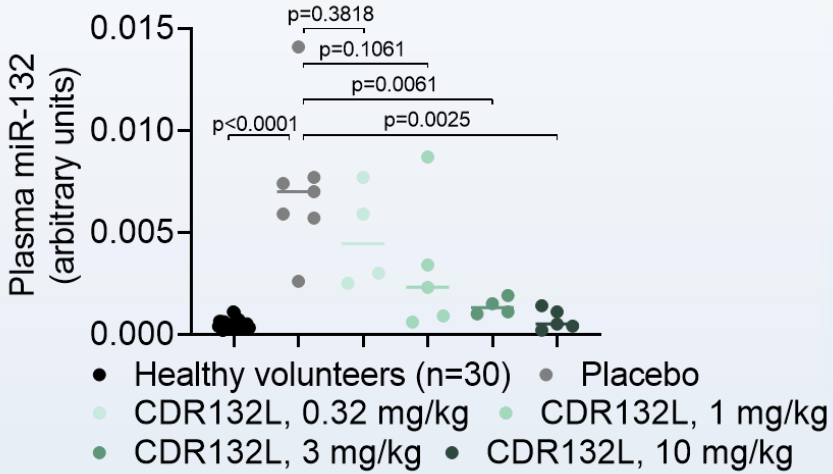
- S
heart failure of ischemic origin (NYHA 1-3).
- CDR132L was administered to 28 patients at dose-escalating single and matching repeat doses (5:2 randomized; at 4 weeks intervals).
- Primary endpoint: safety
- Secondary endpoint: pharmacokinetic (PK) profile of CDR132L

Täubel et al., **Eur Heart J**, *2021*

Cardior

World-wide first study of an oligonucleotide therapeutics in heart failure patients (phase 1b study; *NCT04045405*)

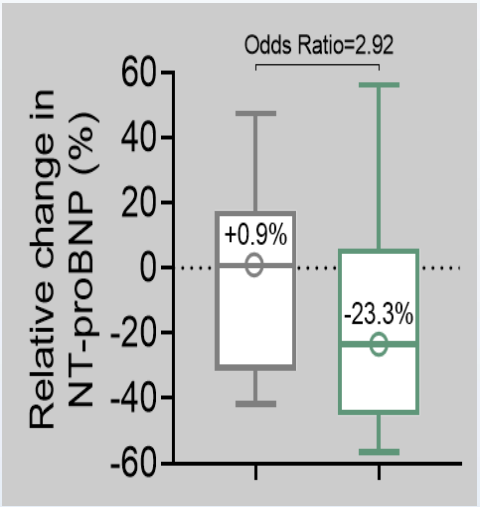




- ✓ **Dose-linear pharmakokinetic profile**
- ✓ **Succesfull target engagement in HF patients**

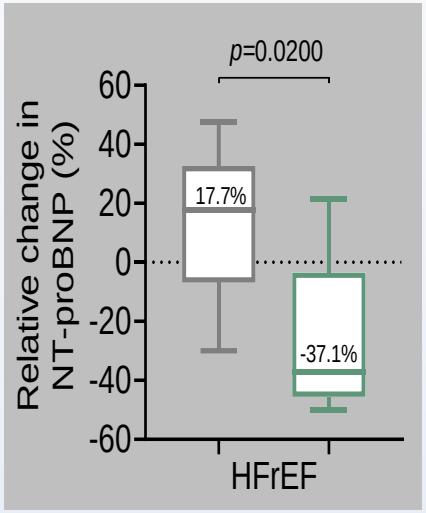
Täubel et al., **Eur Heart J**, *2021*

World-wide first study of an oligonucleotide therapeutics in heart failure patients (phase 1b study; *NCT04045405*)



NT-proBNP relative change per group

Median (circles) and 25%/75% interquartile ranges (bars) for relative changes of NT-proBNP from baseline to day 112.

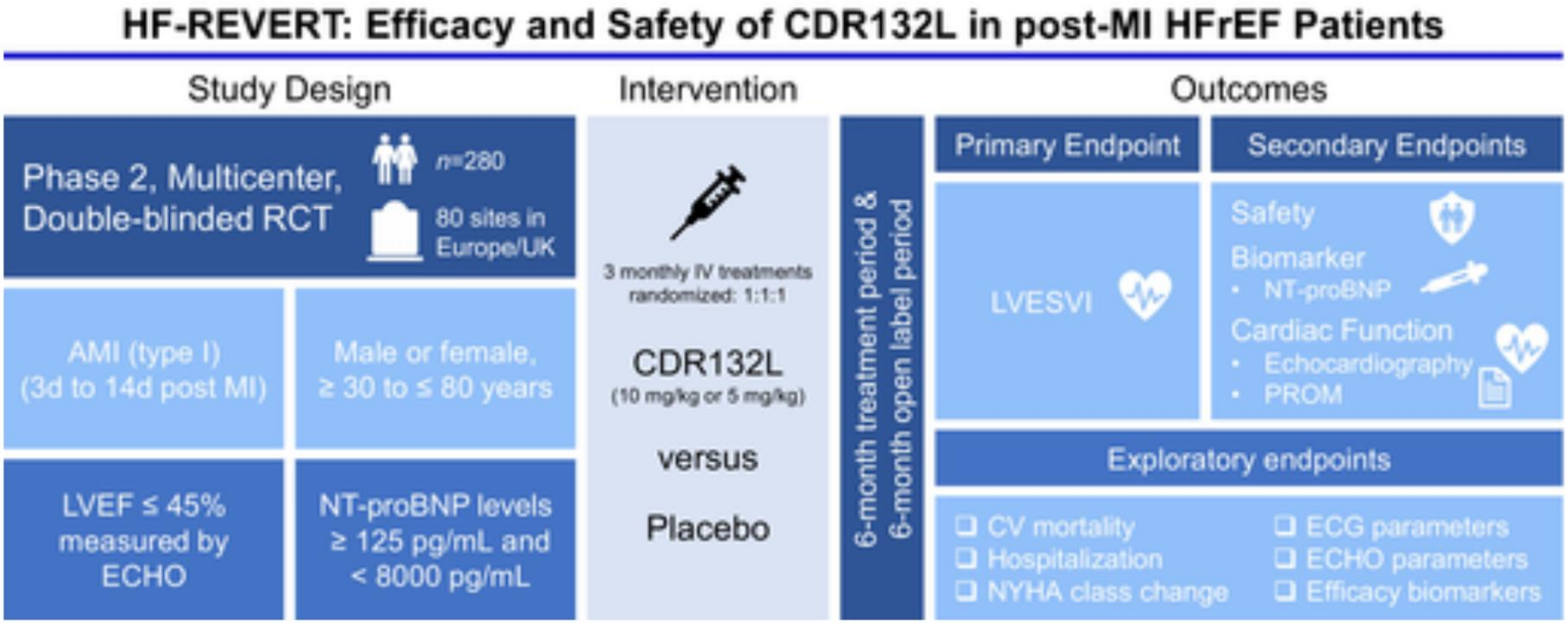


HFrEF subpopulation

- ✓ **Very good safety and tolerability**
- ✓ **Clinically meaningful** median **reduction** of 23.3 % for **NT-proBNP**
- ✓ **Indicative cardiac functional improvements**

Eur Heart J, *2021*

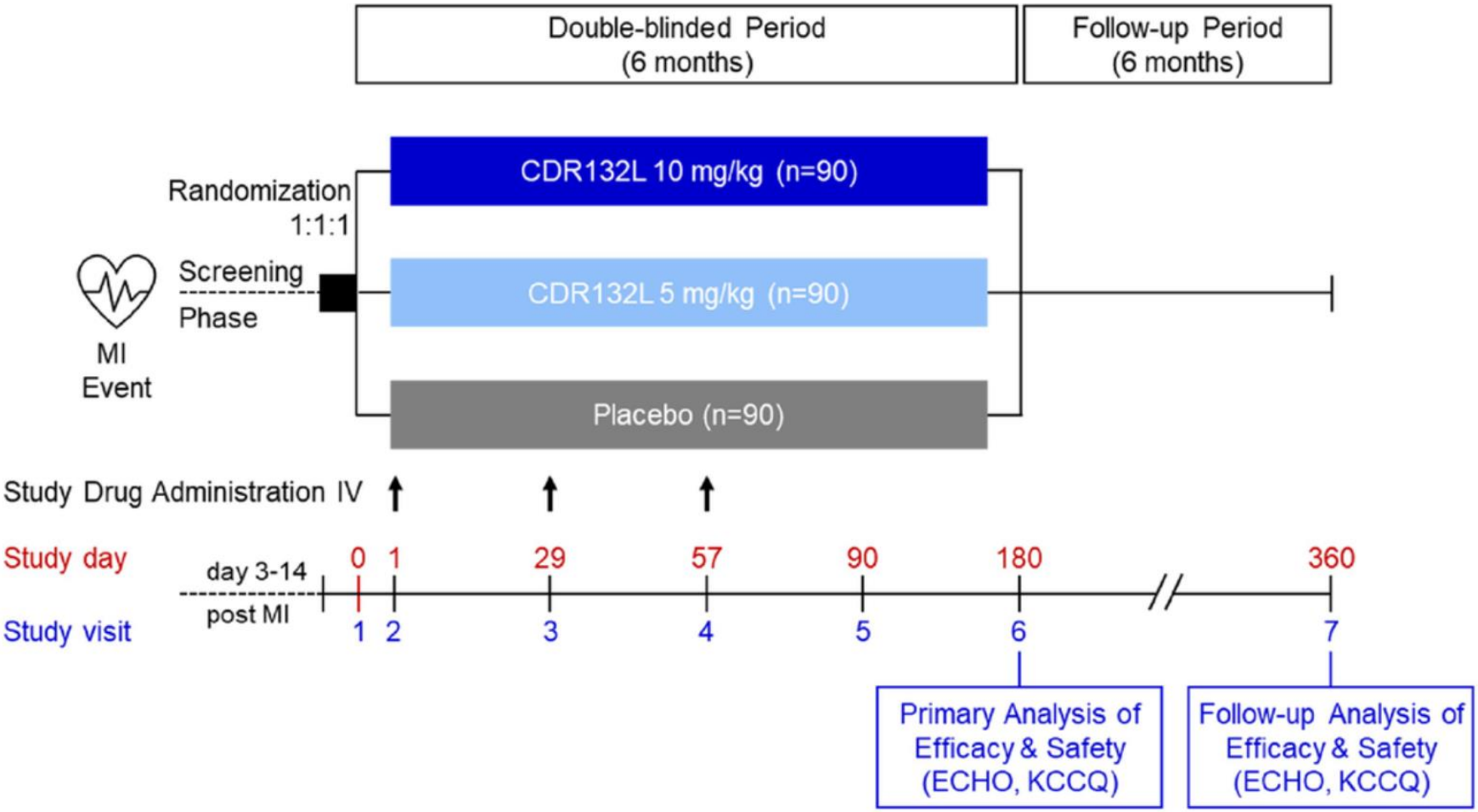
HF-REVERT: Multicenter Phase 2 study



Eur J Heart Fail, *in press*

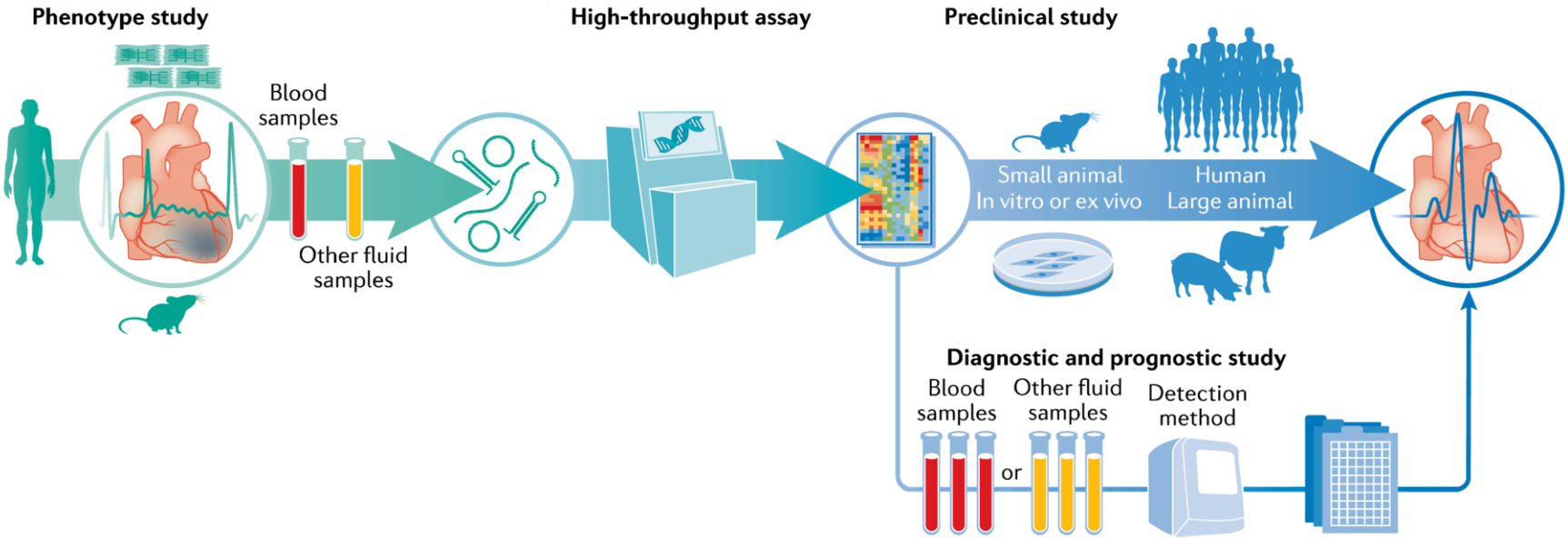
HF-REVERT: Study Design

(PIs Johann Bauersachs & Scott Solomon)



Eur J Heart Fail, *in press*

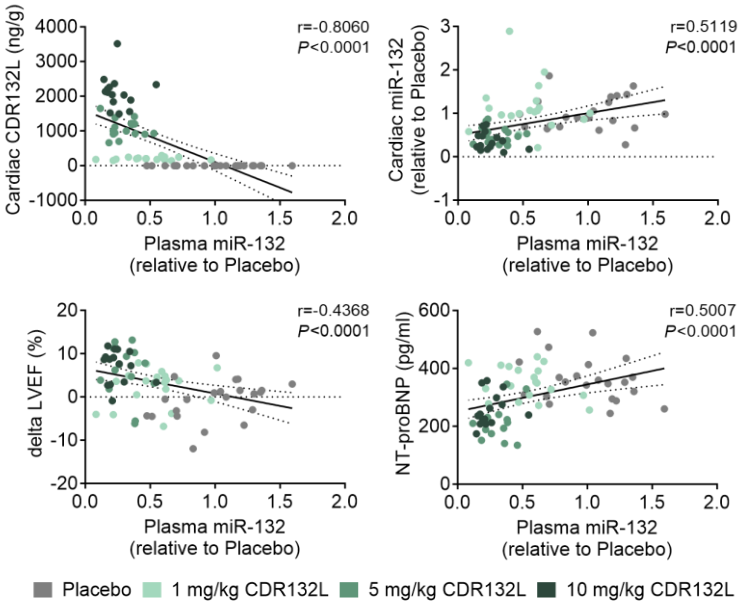
MicroRNA are Emerging Next-generation Tools in Molecular Diagnostics



Lu & Thum et al. 2019, *Nature Reviews Cardiology*

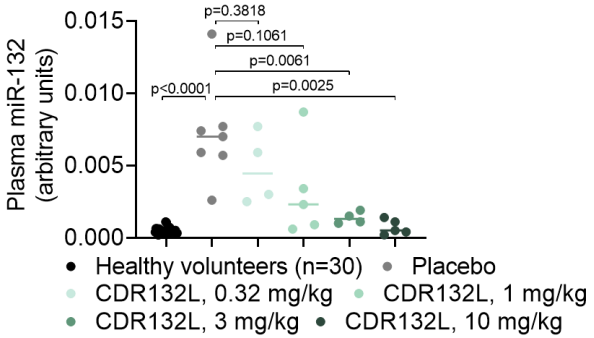
Plasma Levels of miR-132 Correspond with Compound Levels and Molecular Activity of CDR132L in the Heart

Pig model of Subacute Post-MI HF
Dose-dependent correlations established



Translation

Clinical Phase 1b Study in Humans
Sustained low levels of plasma miR-132



Täubel et al. 2021a, *Eur Heart J.*

Cardior

miR-132 Biomarker Development Successfully Completed with CE Mark

CardiorHealth miR-132 Plasma PCR Kit (IVD)

- ✓ Technical development completed with Biotype GmbH
- ✓ Verified in Clinical Phase 1b samples
- ✓ CE Mark successfully registered at BfArM

Federal Institute for Drugs and Medical Devices

CE

Cardior

Thank you!

Acknowledgement

Fondation Leducq

Bundesministerium für Bildung und Forschung

Deutsche Forschungsgemeinschaft DFG

HOMAGE

rebirth Cluster of Excellence

Deutsche Herzstiftung

FIBRO TARGETS

Cardior

LONGHEART erc

SEVENTH FRAMEWORK PROGRAMME