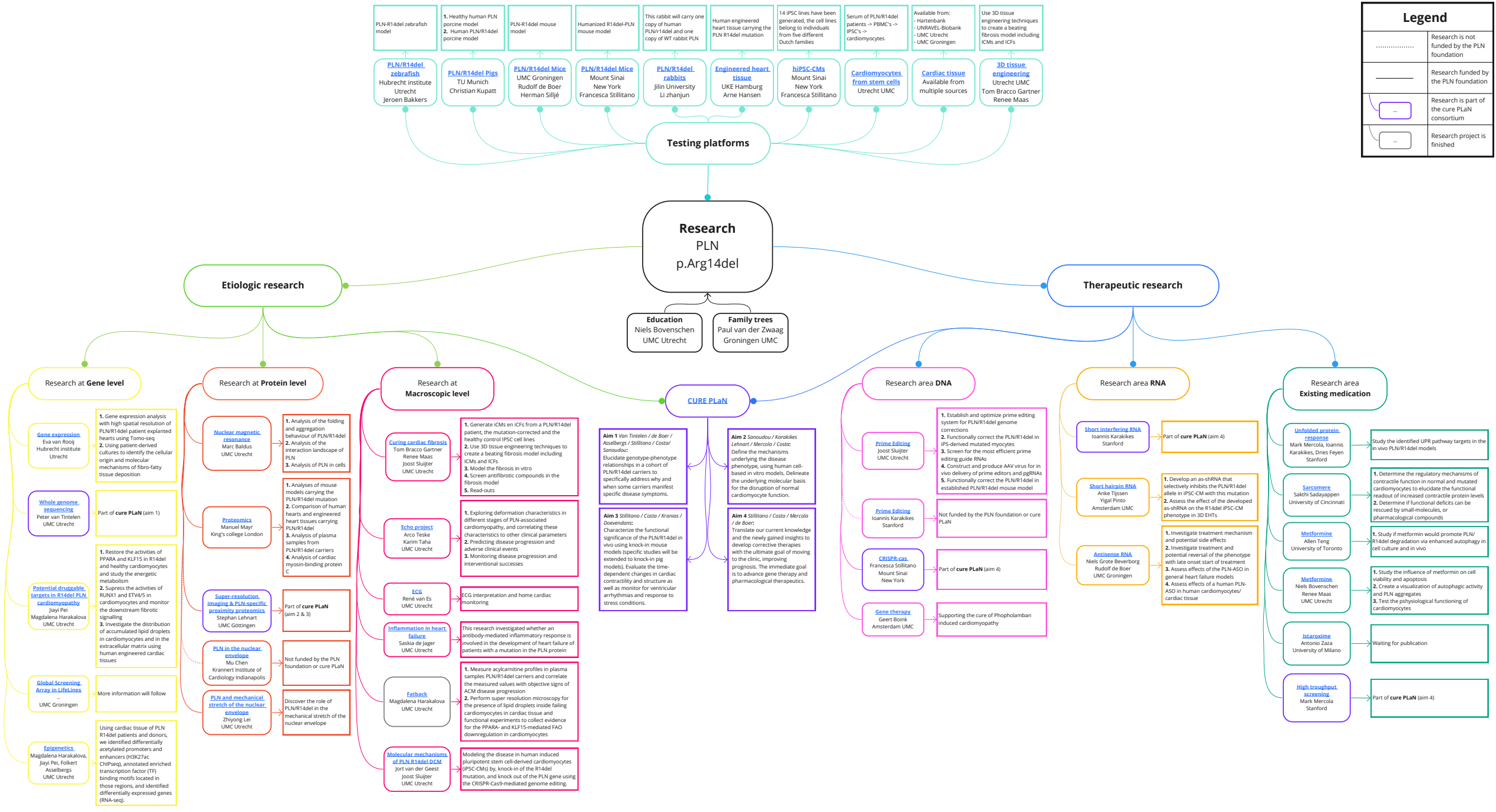
Legend
Research is not funded by the PLN foundation
Research funded by the PLN foundation
Research is part of the cure PLaN consortium
Research project is finished
PLN-R14del zebrafish model
1. Healthy human PLN porcine model
2. Human PLN/R14del porcine model
PLN-R14del mouse model
Humanized R14del-PLN mouse model
This rabbit will carry one copy of human PLN/r14del and one copy of WT rabbit PLN
Human engineered heart tissue carrying the PLN R14del mutation
14 iPSC lines have been generated, the cell lines belong to individuals from five different Dutch families
Serum of PLN/R14del patients -> PBMC's -> iPSC's -> cardiomyocytes
Available from:
- Hartenbank
- UNRAVEL-Biobank
- UMC Utrecht
- UMC Groningen
Use 3D tissue engineering techniques to create a beating fibrosis model including ICMs and ICFs
PLN/R14del zebrafish
Hubrecht institute Utrecht
Jeroen Bakkers
PLN/R14del Pigs
TU Munich
Christian Kupatt
PLN/R14del Mice
UMC Groningen
Rudolf de Boer
Herman Silljé
PLN/R14del Mice
Mount Sinai New York
Francesca Stillitano
PLN/R14del rabbits
Jilin University
Li zhanjun
Engineered heart tissue
UKE Hamburg
Arne Hansen
hiPSC-CMs
Mount Sinai New York
Francesca Stillitano
Cardiomyocytes from stem cells
Utrecht UMC
Cardiac tissue
Available from multiple sources
3D tissue engineering
Utrecht UMC
Tom Bracco Gartner
Renee Maas
Testing platforms
Research
PLN
p.Arg14del
Education
Niels Bovenschen
UMC Utrecht
Family trees
Paul van der Zwaag
Groningen UMC
Etiologic research
Therapeutic research
Research at Gene level
Research at Protein level
Research at Macroscopic level
CURE PLaN
Research area DNA
Research area RNA
Research area Existing medication
Gene expression
Eva van Rooij
Hubrecht institute
Utrecht
1. Gene expression analysis with high spatial resolution of PLN/R14del patient explanted hearts using Tomo-seq
2. Using patient-derived cultures to identify the cellular origin and molecular mechanisms of fibro-fatty tissue deposition
Whole genome sequencing
Peter van Tintelen
UMC Utrecht
Part of cure PLaN (aim 1)
Potential druggable targets in R14del PLN cardiomyopathy
Jiayi Pei
Magdalena Harakalova
UMC Utrecht
1. Restore the activities of PPARA and KLF15 in R14del and healthy cardiomyocytes and study the energetic metabolism
2. Supress the activities of RUNX1 and ETV4/5 in cardiomyocytes and monitor the downstream fibrotic signalling
3. Investigate the distribution of accumulated lipid droplets in cardiomyocytes and in the extracellular matrix using human engineered cardiac tissues
Global Screening Array in LifeLines
..
UMC Groningen
More information will follow
Epigenetics
Magdalena Harakalova,
Jiayi Pei, Folkert Asselbergs
UMC Utrecht
Using cardiac tissue of PLN R14del patients and donors, we identified differentially acetylated promoters and enhancers (H3K27ac ChIPseq), annotated enriched transcription factor (TF) binding motifs located in those regions, and identified differentially expressed genes (RNA-seq).
Nuclear magnetic resonance
Marc Baldus
UMC Utrecht
1. Analysis of the folding and aggregation behaviour of PLN/R14del
2. Analysis of the interaction landscape of PLN
3. Analysis of PLN in cells
Proteomics
Manuel Mayr
King's college London
1. Analyses of mouse models carrying the PLN/R14del mutation
2. Comparison of human hearts and engineered heart tissues carrying PLN/R14del
3. Analysis of plasma samples from PLN/R14del carriers
4. Analysis of cardiac myosin-binding protein c
Super-resolution imaging & PLN-specific proximity proteomics
Stephan Lehnart
UMC Göttingen
Part of cure PLaN (aim 2 & 3)
PLN in the nuclear envelope
Mu Chen
Krannert Institute of Cardiology Indianapolis
Not funded by the PLN foundation or cure PLaN
PLN and mechanical stretch of the nuclear envelope
Zhiyong Lei
UMC Utrecht
Discover the role of PLN/R14del in the mechanical stretch of the nuclear envelope
Curing cardiac fibrosis
Tom Bracco Gartner
Renee Maas
Joost Sluijter
UMC Utrecht
1. Generate iCMs en iCFs from a PLN/R14del patient, the mutation-corrected and the healthy control IPSC cell lines
2. Use 3D tissue engineering techniques to create a beating fibrosis model including ICMs and ICFs
3. Model the fibrosis in vitro
4. Screen antifibrotic compounds in the fibrosis model
5. Read-outs
Echo project
Arco Teske
Karim Taha
UMC Utrecht
1. Exploring deformation characteristics in different stages of PLN-associated cardiomyopathy, and correlating these characteristics to other clinical parameters
2. Predicting disease progression and adverse clinical events
3. Monitoring disease progression and interventional successes
ECG
René van Es
UMC Utrecht
ECG interpretation and home cardiac monitoring
Inflammation in heart failure
Saskia de Jager
UMC Utrecht
This research investigated whether an antibody-mediated inflammatory response is involved in the development of heart failure of patients with a mutation in the PLN protein
Fatback
Magdalena Harakalova
UMC Utrecht
1. Measure acylcarnitine profiles in plasma samples PLN/R14del carriers and correlate the measured values with objective signs of ACM disease progression
2. Perform super resolution microscopy for the presence of lipid droplets inside failing cardiomyocytes in cardiac tissue and functional experiments to collect evidence for the PPARA- and KLF15-mediated FAO downregulation in cardiomyocytes
Molecular mechanisms of PLN R14del DCM
Jort van der Geest
Joost Sluijter
UMC Utrecht
Modeling the disease in human induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) by, knock-in of the R14del mutation, and knock out of the PLN gene using the CRISPR-Cas9-mediated genome editing.
Aim 1 Van Tintelen / de Boer / Asselbergs / Stillitano / Costa/ Sanoudou:
Elucidate genotype-phenotype relationships in a cohort of PLN/R14del carriers to specifically address why and when some carriers manifest specific disease symptoms.
Aim 2 Sanoudou / Karakikes Lehnart / Mercola / Costa:
Define the mechanisms underlying the disease phenotype, using human cell-based in vitro models. Delineate the underlying molecular basis for the disruption of normal cardiomyocyte function.
Aim 3 Stillitano / Costa / Kranias / Doevendans:
Characterize the functional significance of the PLN/R14del in vivo using knock-in mouse models (specific studies will be extended to knock-in pig models). Evaluate the time-dependent changes in cardiac contractility and structure as well as monitor for ventricular arrhythmias and response to stress conditions.
Aim 4 Stillitano / Costa / Mercola / de Boer:
Translate our current knowledge and the newly gained insights to develop corrective therapies with the ultimate goal of moving to the clinic, improving prognosis. The immediate goal is to advance gene therapy and pharmacological therapeutics.
Prime Editing
Joost Sluijter
UMC Utrecht
1. Establish and optimize prime editing system for PLN/R14del genome corrections
2. Functionally correct the PLN/R14del in iPS-derived mutated myocytes
3. Screen for the most efficient prime editing guide RNAs
4. Construct and produce AAV virus for in vivo delivery of prime editors and pgRNAs
5. Functionally correct the PLN/R14del in established PLN/R14del mouse model
Prime Editing
Ioannis Karakikes
Stanford
Not funded by the PLN foundation or cure PLaN
CRISPR-cas
Francesca Stillitano
Mount Sinai New York
Part of cure PLaN (aim 4)
Gene therapy
Geert Boink
Amsterdam UMC
Supporting the cure of Phopholamban induced cardiomyopathy
Short interfering RNA
Ioannis Karakikes
Stanford
Part of cure PLaN (aim 4)
Short hairpin RNA
Anke Tijssen
Yigal Pinto
Amsterdam UMC
1. Develop an as-shRNA that selectively inhibits the PLN/R14del allele in iPSC-CM with this mutation
2. Assess the effect of the developed as-shRNA on the R14del iPSC-CM phenotype in 3D EHTs
Antisense RNA
Niels Grote Beverborg
Rudolf de Boer
UMC Groningen
1. Investigate treatment mechanism and potential side effects
2. Investigate treatment and potential reversal of the phenotype with late onset start of treatment
3. Assess effects of the PLN-ASO in general heart failure models
4. Assess effects of a human PLN-ASO in human cardiomyocytes/ cardiac tissue
Unfolded protein response
Mark Mercola, Ioannis Karakikes, Dries Feyen
Stanford
Study the identified UPR pathway targets in the in vivo PLN/R14del models
Sarcomere
Sakthi Sadayappen
University of Cincinnati
1. Determine the regulatory mechanisms of contractile function in normal and mutated cardiomyocytes to elucidate the functional readout of increased contractile protein levels
2. Determine if functional deficits can be rescued by small-molecules, or pharmacological compounds
Metformine
Allen Teng
University of Toronto
1. Study if metformin would promote PLN/R14del degradation via enhanced autophagy in cell culture and in vivo
Metformine
Niels Bovenschen
Renee Maas
UMC Utrecht
1. Study the influence of metformin on cell viability and apoptosis
2. Create a visualization of autophagic activity and PLN aggregates
3. Test the pshysiological functioning of cardiomyocytes
Istaroxime
Antonio Zaza
University of Milano
Waiting for publication
High troughput screening
Mark Mercola
Stanford
Part of cure PLaN (aim 4)