Erfelijke hartziekten door onderzoek de wereld uit?

Rudolf A. de Boer, Cardioloog
Universitair Medisch Centrum Groningen

Hoofd Experimentele Cardiologie UMCG
Voorzitter Nederlandse Werkgroep Hartfalen
Lid Europese Hartfalen Board

Inleiding

- Waarom onderzoek?
- Elke hartziekte is erfelijk – monogenetisch versus multifactorieel
- Verbetering door organisatie – Durrer centrum
- Tools van modern onderzoek
- Patiënt participatie – gemeenschappelijke agenda

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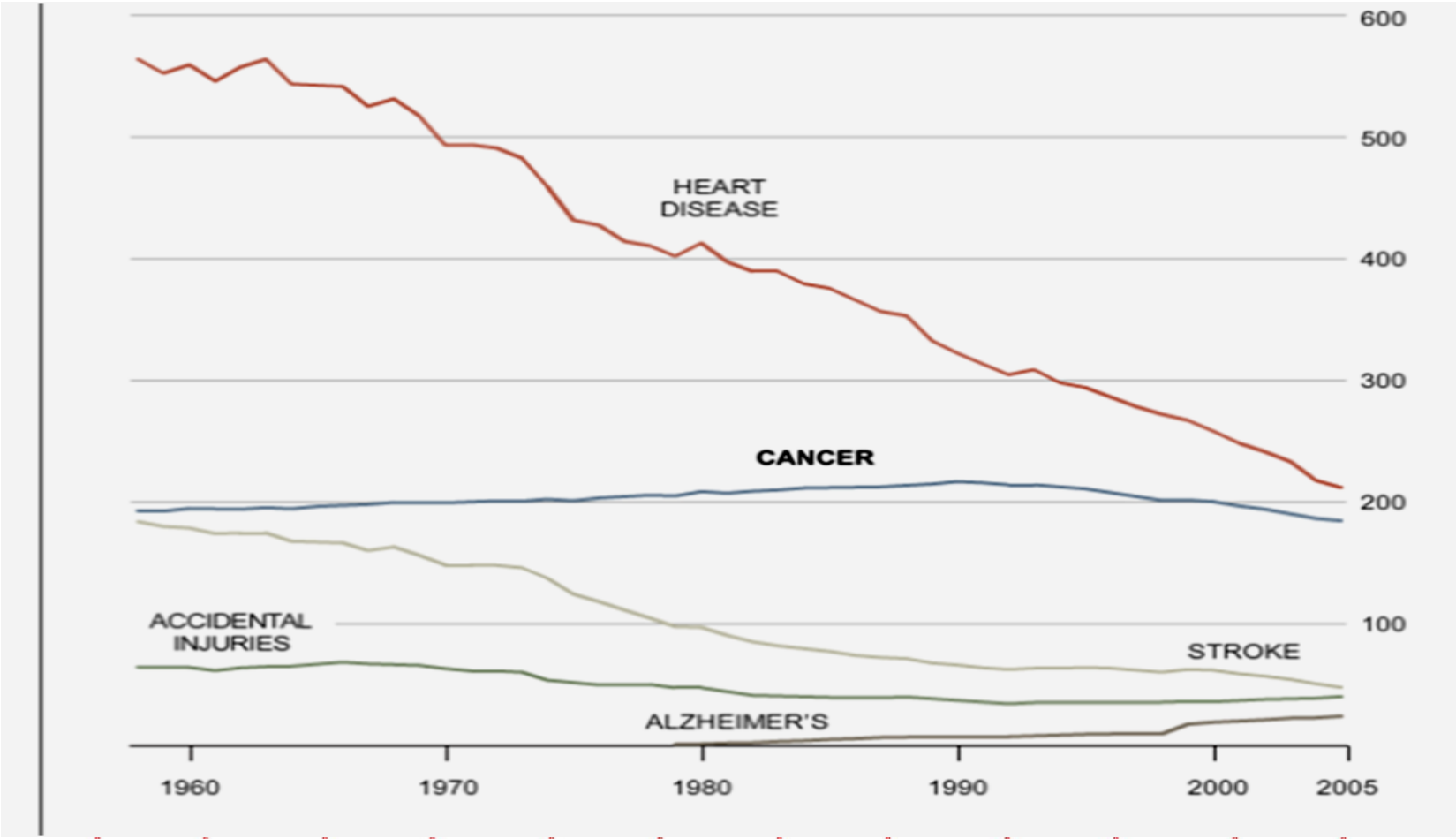
Waarom onderzoek?

Omdat het werkt



New York Times

- Waarom onderzoek?
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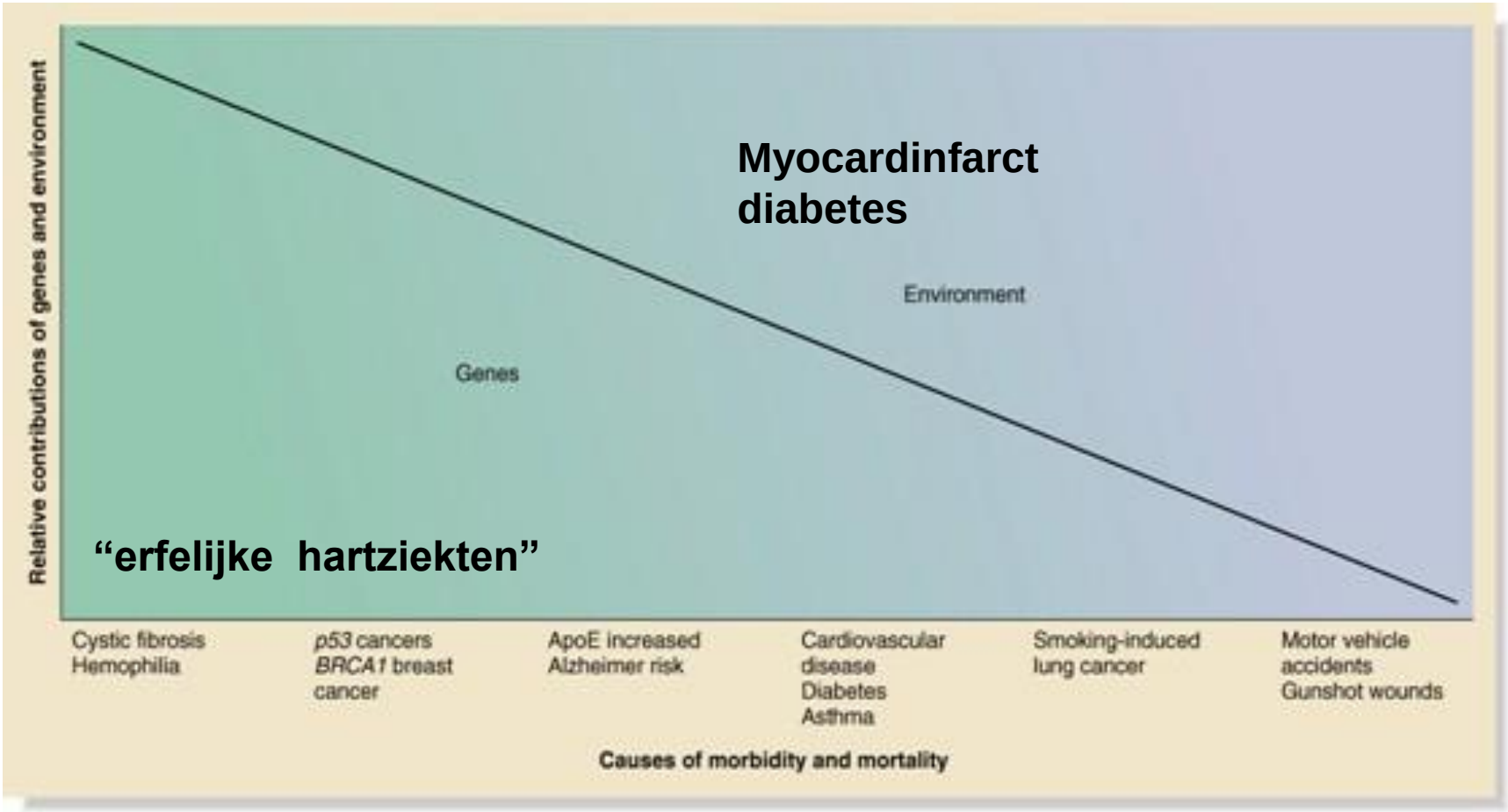
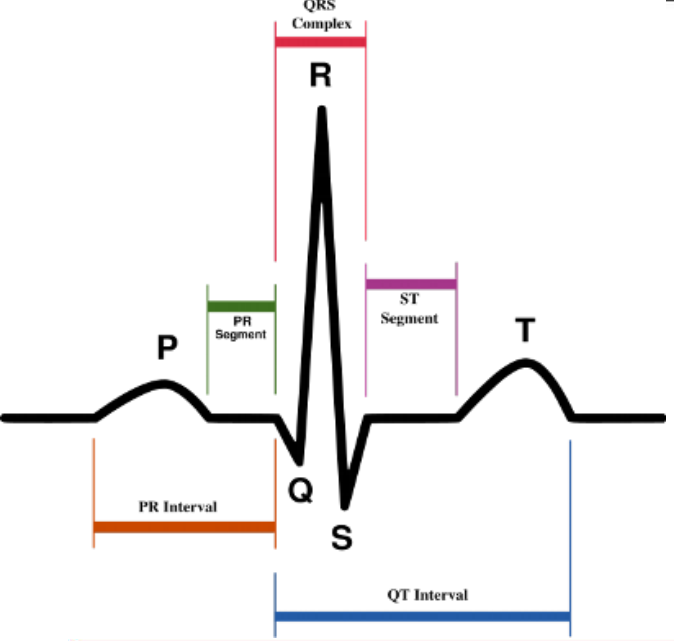
Monogenetisch versus multifactorieel




QRS Complex
R
PR Segment
ST Segment
P
T
Q
S
PR Interval
QT Interval

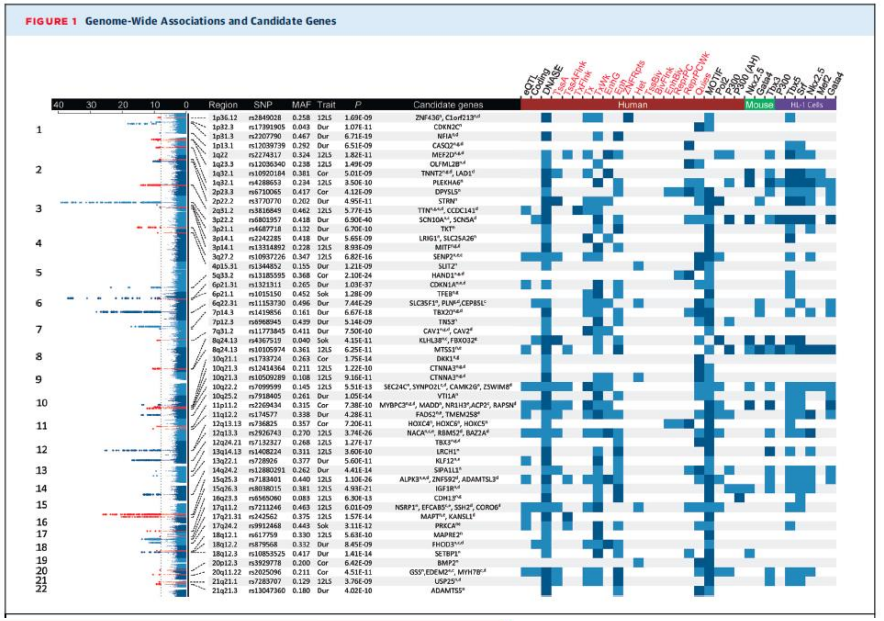
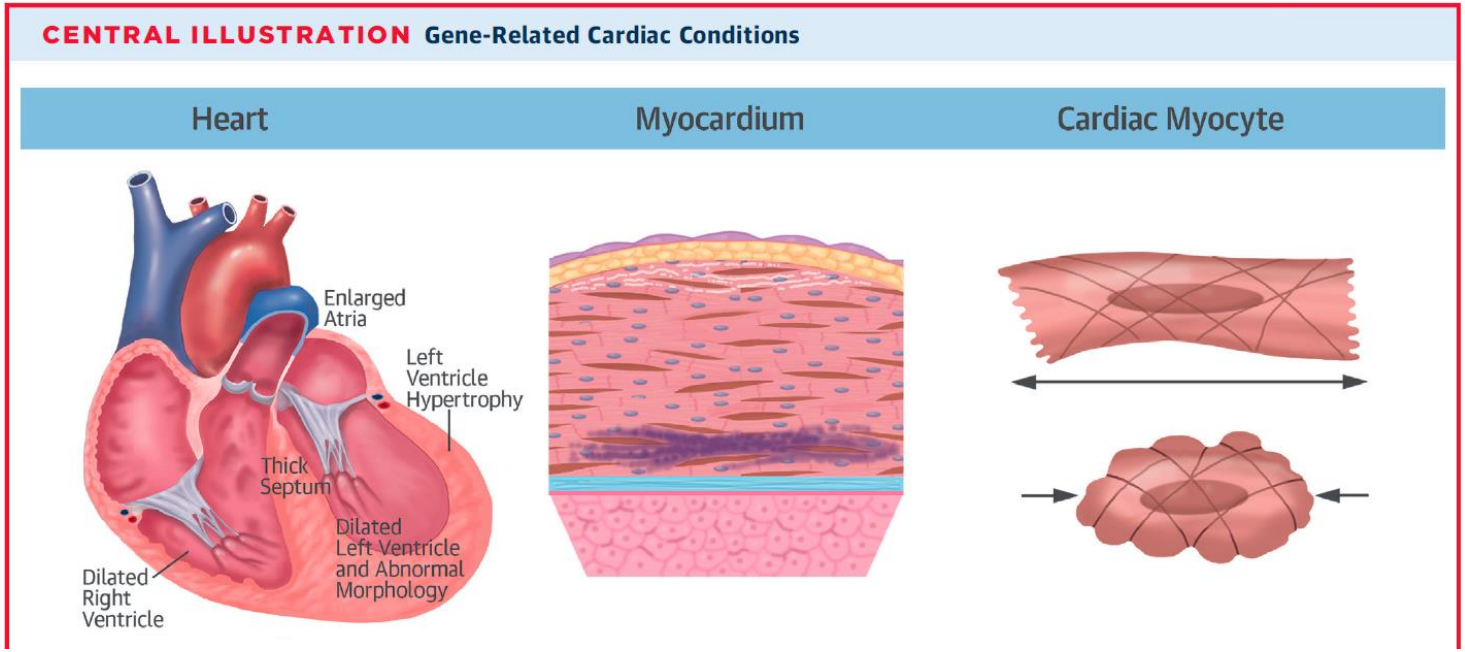
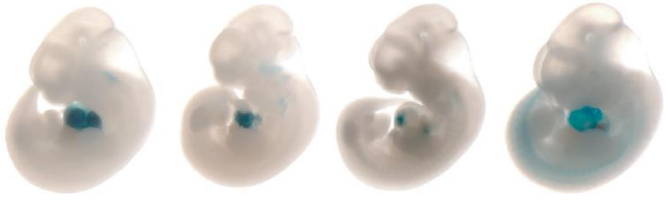


FIGURE 1 Genome-Wide Associations and Candidate Genes
Region
SNP
MAF
Trait
P
Candidate genes
Human
Mouse
Rt / Cells


CENTRAL ILLUSTRATION Gene-Related Cardiac Conditions
Heart
Myocardium
Cardiac Myocyte
Enlarged Atria
Left Ventricle Hypertrophy
Thick Septum
Dilated Left Ventricle and Abnormal Morphology
Dilated Right Ventricle

A

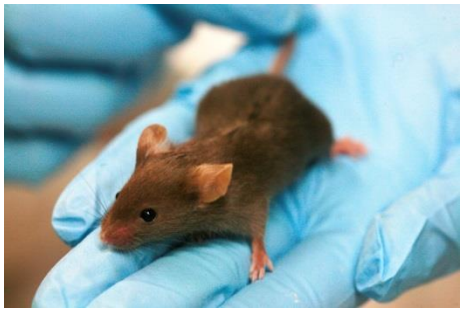


hs2177
chr3:38594857
-38597991
SCN5A

hs2188
chr6:118963898
-118966469
CEP85L, PLN

hs2266
chr3:38547891-
38551036
EXOG

hs2271
chr1:26292440-
26297330



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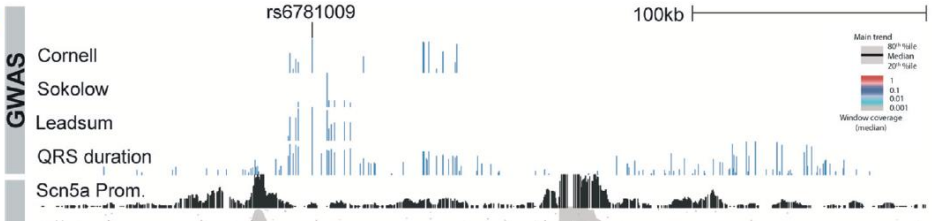
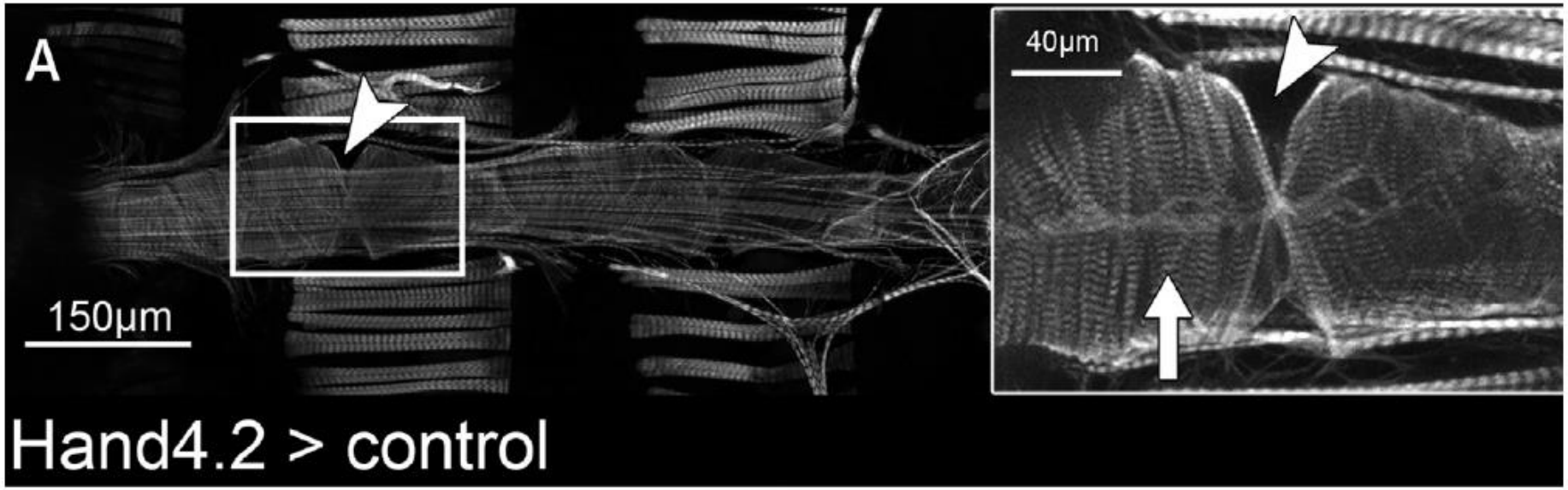
B





Van der Harst P, et al. *J Am Coll Cardiol.* 2016; **68**:1435-1448

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- Nederlands onderzoek toonaangevend in de wereld
  - DPP6 (VF gen)
  - Phospholamban
  - Lang QT syndroom / Brugada
  - Counseling
  - Organisatie
  - Informed consent van alle “cardiogenetische patiënten”

gesubsidieerd door Hartstichting
CVON Netherlands Cardiovascular Research Initiative

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ICIN Netherlands Heart Institute | Durrer Center

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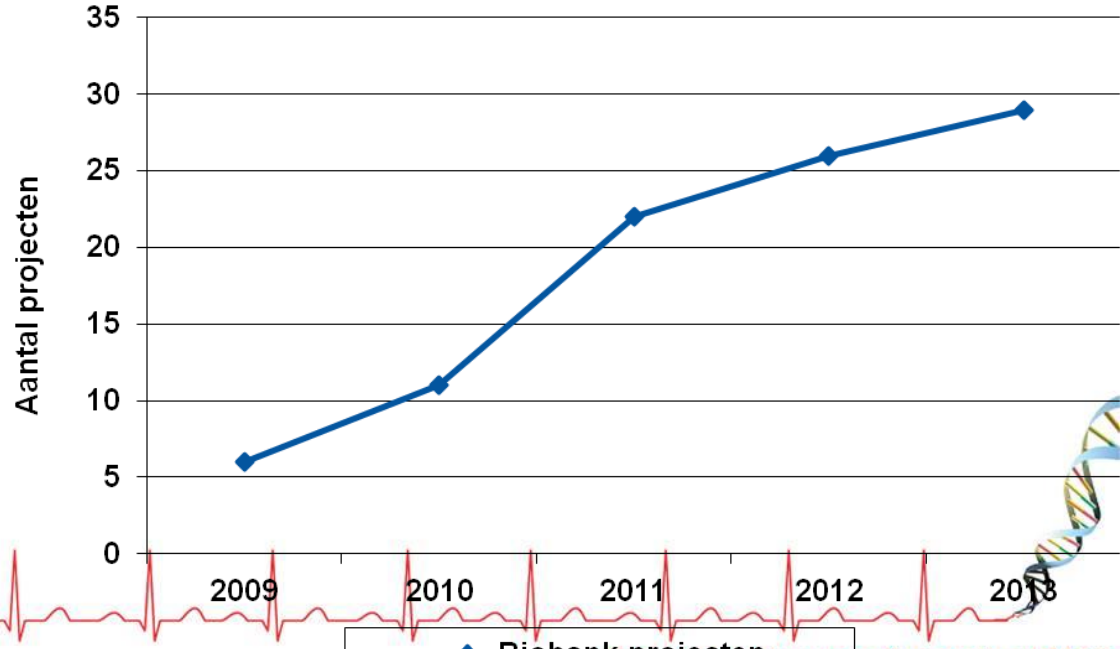
Durrer Center for Cardiogenetic Research



United we share, United we care

- Datamanagement: 8 projects
- eCRF building: 7 projects
- Biobank: 29 projects
- > 300.000 samples



De Hart & Vaatgroep

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STICHTING GENETISCHE HARTSPIERZIEKTE PLN

European Journal of Human Genetics (2015) 23, 1462–1467

www.nature.com/ejhg

EJHG Open

ARTICLE

A group approach to genetic counselling of cardiomyopathy patients: satisfaction and psychological outcomes sufficient for further implementation

Ellen Otten*,[1], Erwin Birnie[1], Adelita V Ranchor[2], J Peter van Tintelen[1] and Irene M van Lang

Journal of the American College of Cardiology
© 2010 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 55, No. 23, 2010
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2009.12.063

Heart Rhythm Disorders

Active Cascade Screening in Primary Inherited Arrhythmia Syndromes

Does It Lead to Prophylactic Treatment?

Nynke Hofman, MSc,* Hanno L. Tan, MD, PhD,† Marielle Alders, PhD,*
Irene M. van Langen, MD, PhD,* Arthur A. M. Wilde, MD, PhD†
Amsterdam, the Netherlands

RESEARCH ARTICLE

AMERICAN medica

Family Letters Are an Effective Way to Inform Relatives About Inherited Cardiac Disease

Wilma P. van der Roest,[1]* José M. Pennings,[2] Marian Bakker,[1] Maarten P. van den and J. Peter van Tintelen[1]

[1]Clinical Genetics Section, Department of Genetics, University Medical Center Groningen, University of Groningen, Gr The Netherlands

[2]Department of Health Sciences/Metamedica, University Medical Center Groningen, University of Groningen, Groning

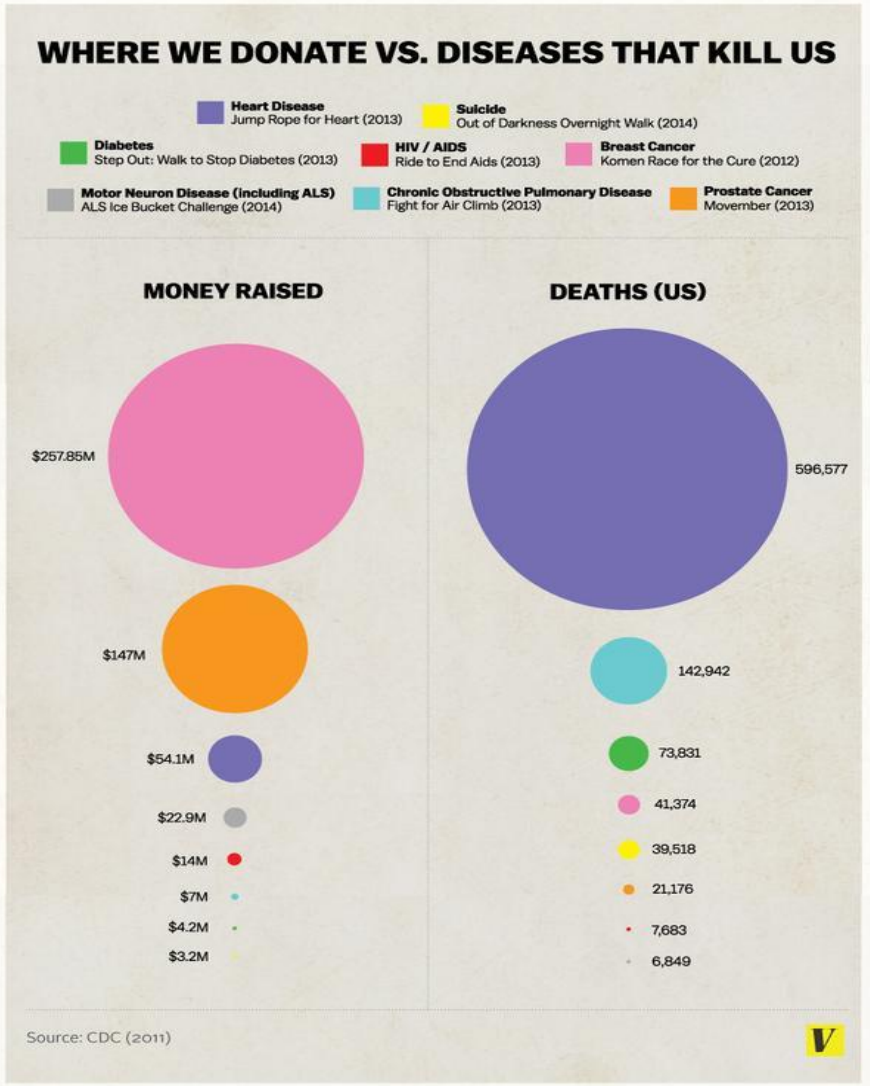
[3]Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlanc

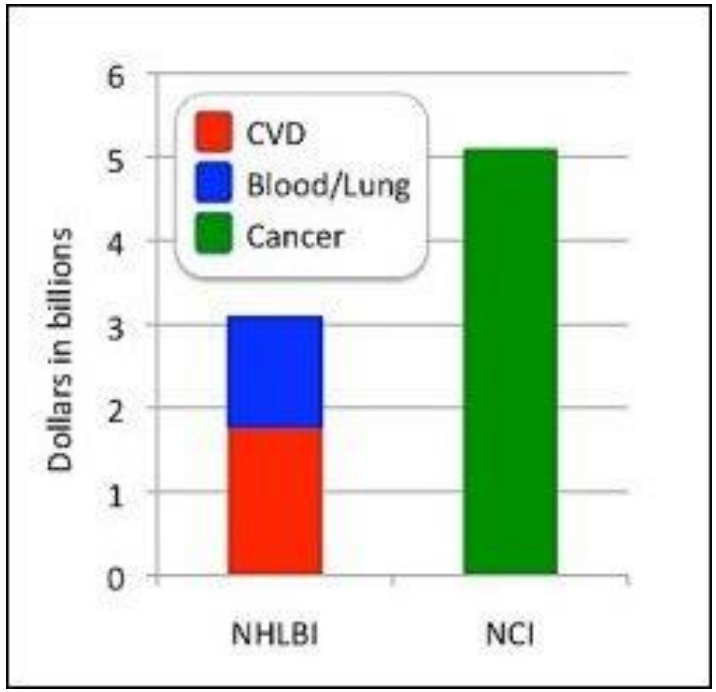
STUDY DESIGN ARTICLE

Rationale and design of the CAREFUL study

The yield of CARdiogenetic scrEening in First degree relatives of sudden cardiac and UnexpLained death victims <45 years

A. Hendrix, C. van der Werf, M.L. Bots, E. Birnie, J.J. van der Smagt, C.J. W. Borleffs, A. Vink, H.C. van Weert, P.A.F.M. Doevendans, A.A.M. Wilde, A. Mosterd, I.M. van Langen





- Hart- en vaatziekten
- Borstkanker
- Prostaatkanker
- COPD

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WE ARE THE ESC

WORKSTREAM 1: RESEARCH

SHAPE POLICY TO ADVANCE CVD RESEARCH

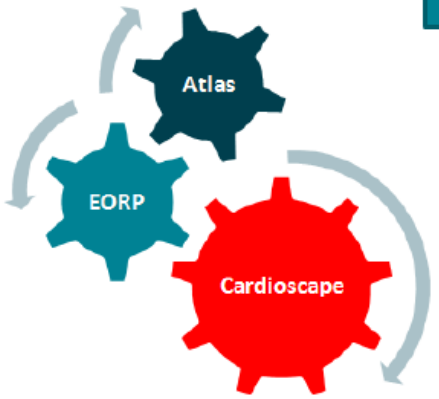
Objective 1
Long-term strategic planning of CVD research in Europe

Objective 2
Identification and promotion of CVD research funding

Objective 3
Optimising Policy and Regulatory environment

Objective 4
Promoting Academic careers, embed research in Training

Objective 5
Position ESC as best source of comprehensive information on CVD research



www.escardio.org

- Campaign for European Council for Health Research
- Advise EC DG Research, DG Santé, Scientific Panel for Health
- Advocating on legislation:
  - Clinical Trials
  - Data Protection
  - Animal Research
- Comparative research funding intelligence
- Improve training in research: Liaison with EHA, Universities, Education Committee

EUROPEAN SOCIETY OF CARDIOLOGY®

- Waarom onderzoek?
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Cardiology, from bed to bench and vice versa

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Klinische data
- Geneticas
- GWAS
- Biomarkers

Extern
Results from collaborations

Hartfalen
Cardiale functie
Gezondheid

Cardiac function

Organ
- Langendorff

Animal models
- Chirurgical models
- Genetic models
- (Neuro)hormonal models
- Exercise models

Cellen
- Primary mouse and rat cardiomyocytes and fibroblasts
- Stem cell derived human cardiomyocytes

Cardiac function & Remodeling

Fibrosis & Hypertrophy

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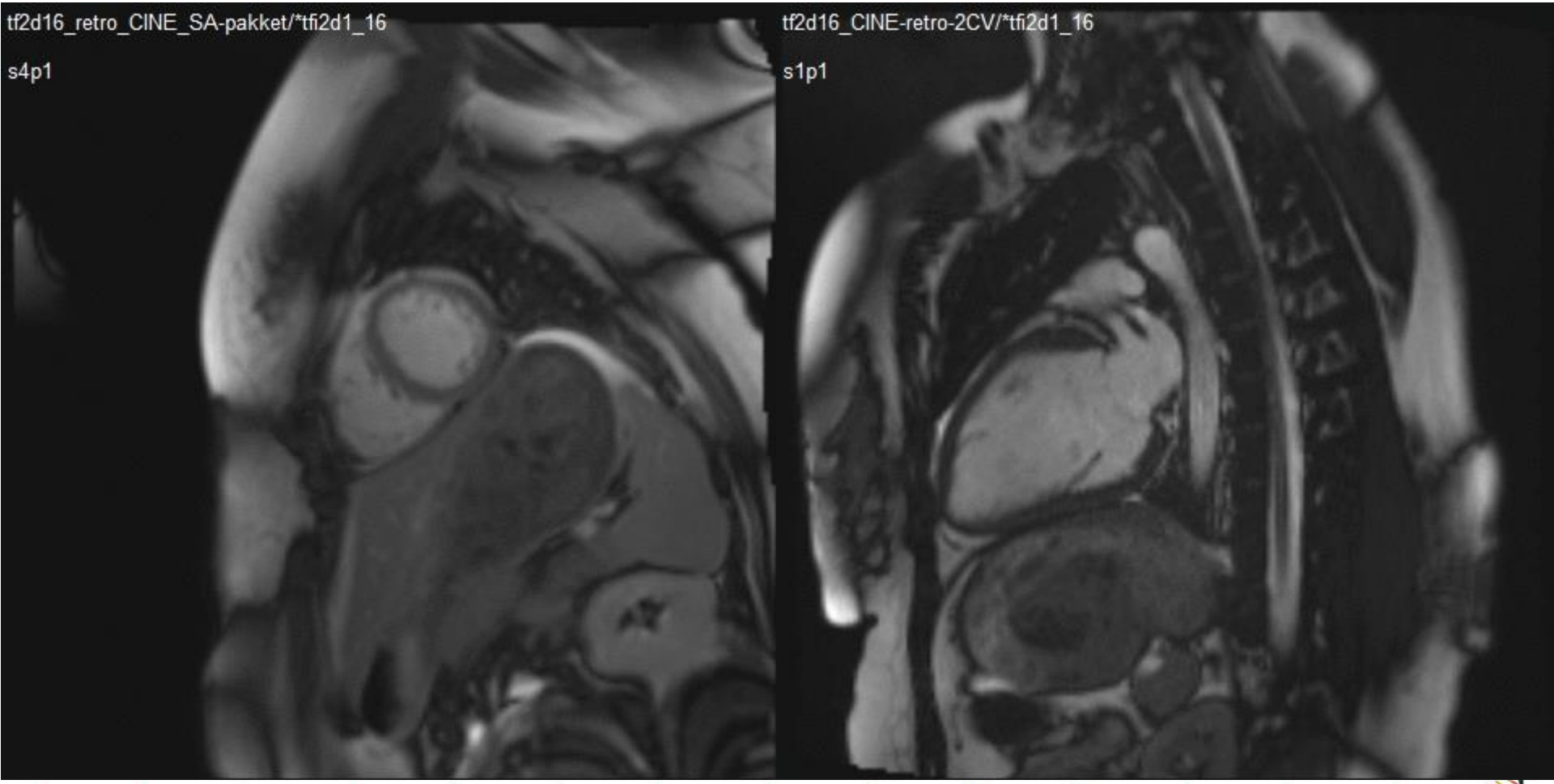
MRI: normale hartfunctie (mens)



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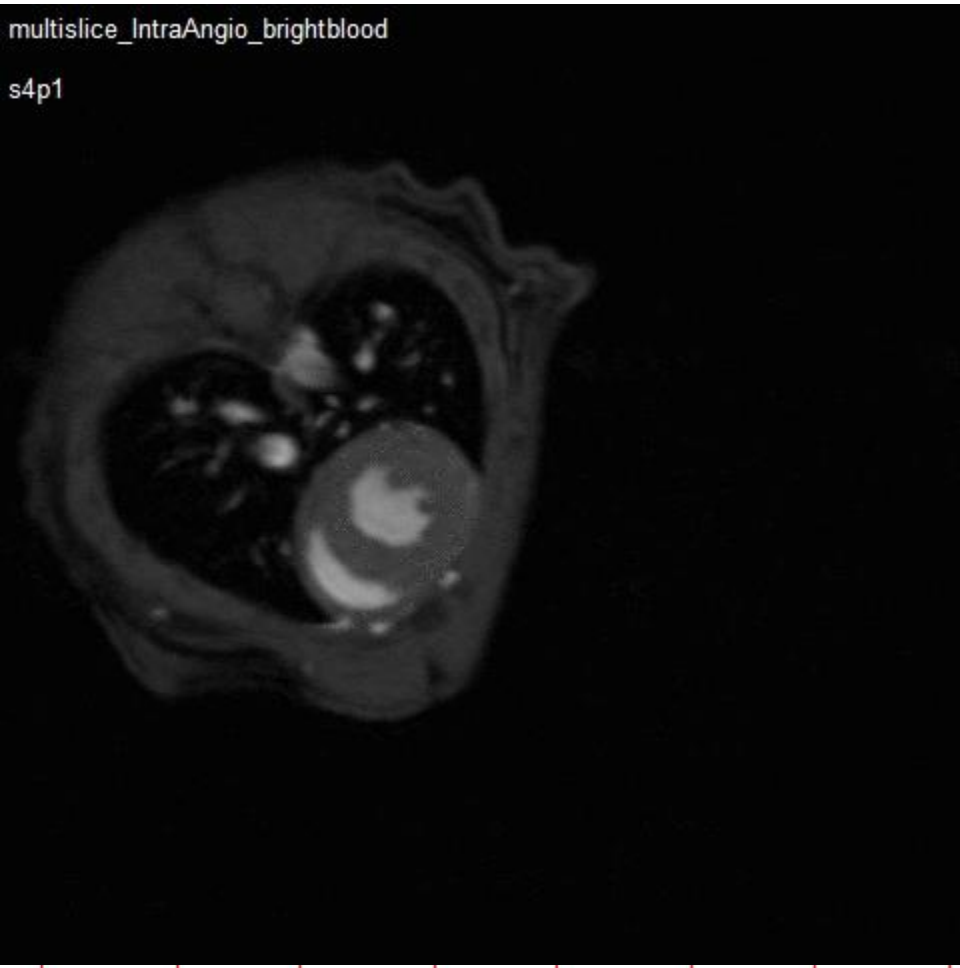
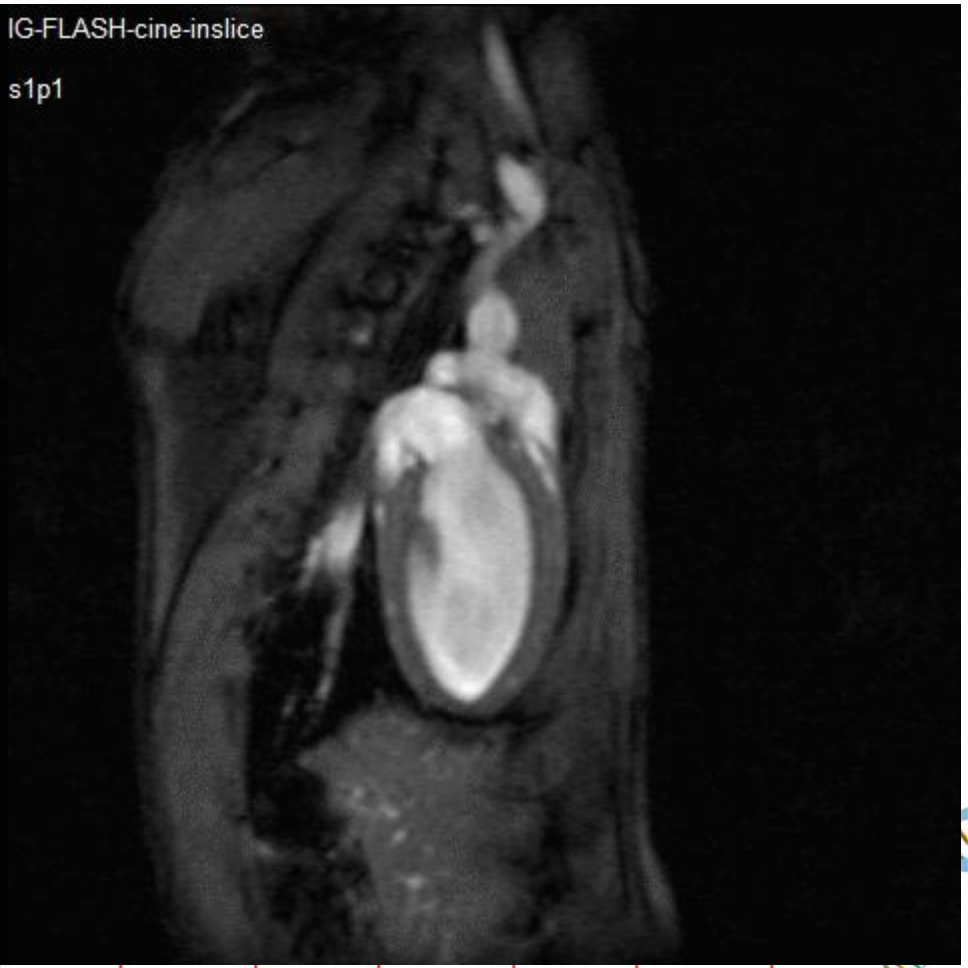
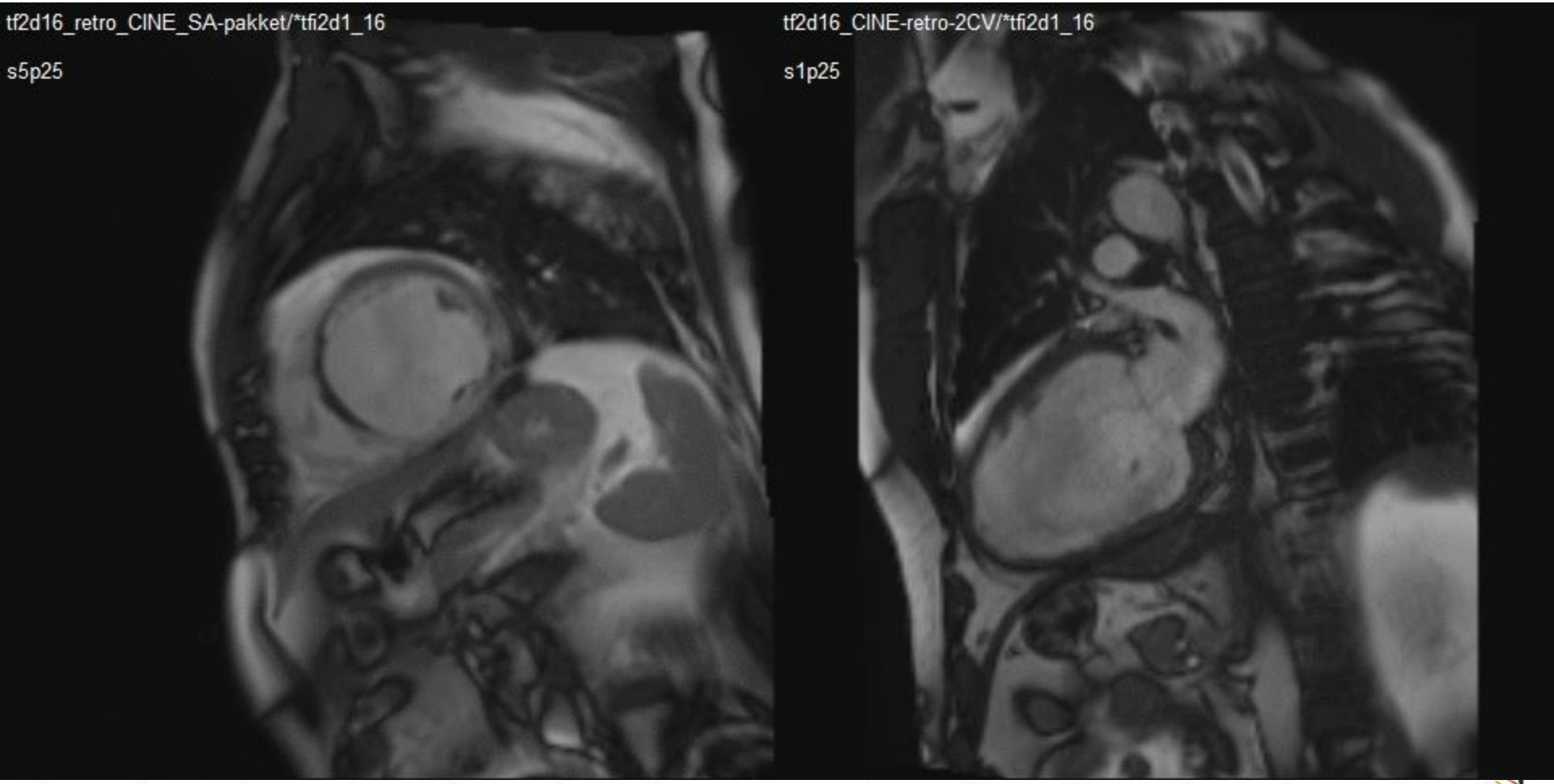
MRI: normale hartfunctie (muis)





MRI: hartfunctie na infarct (mens)



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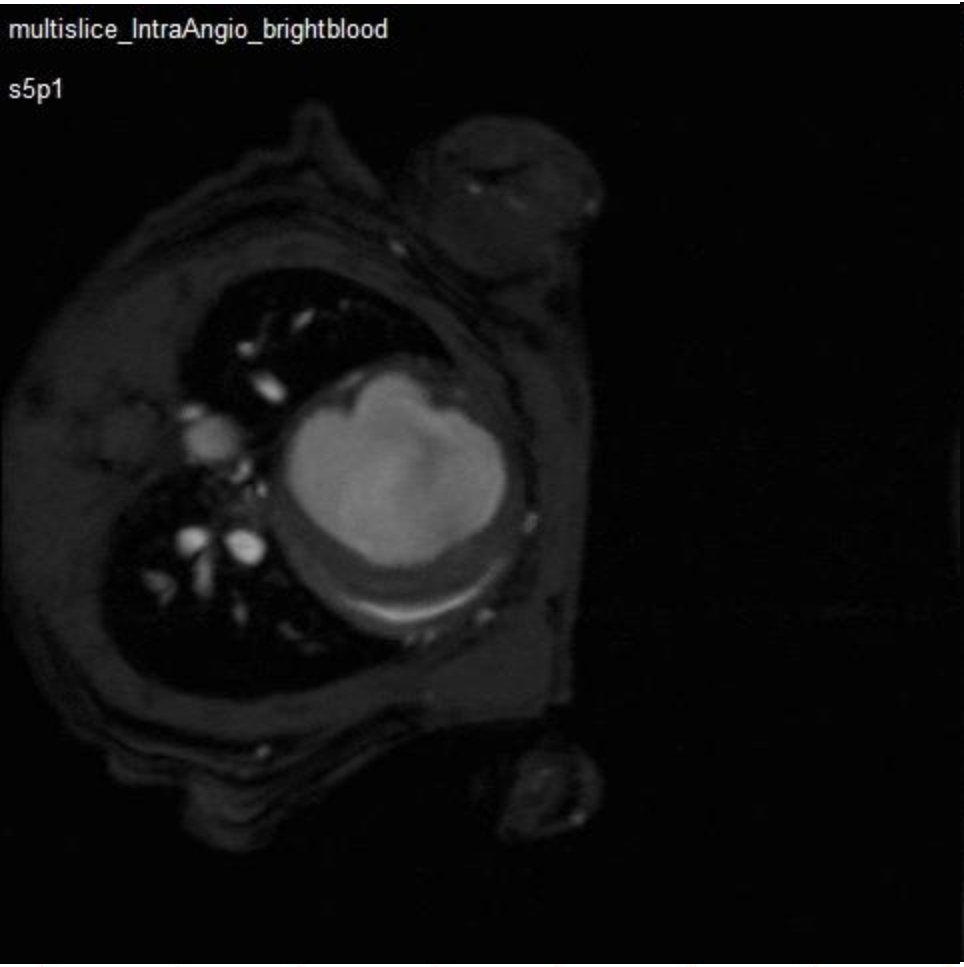
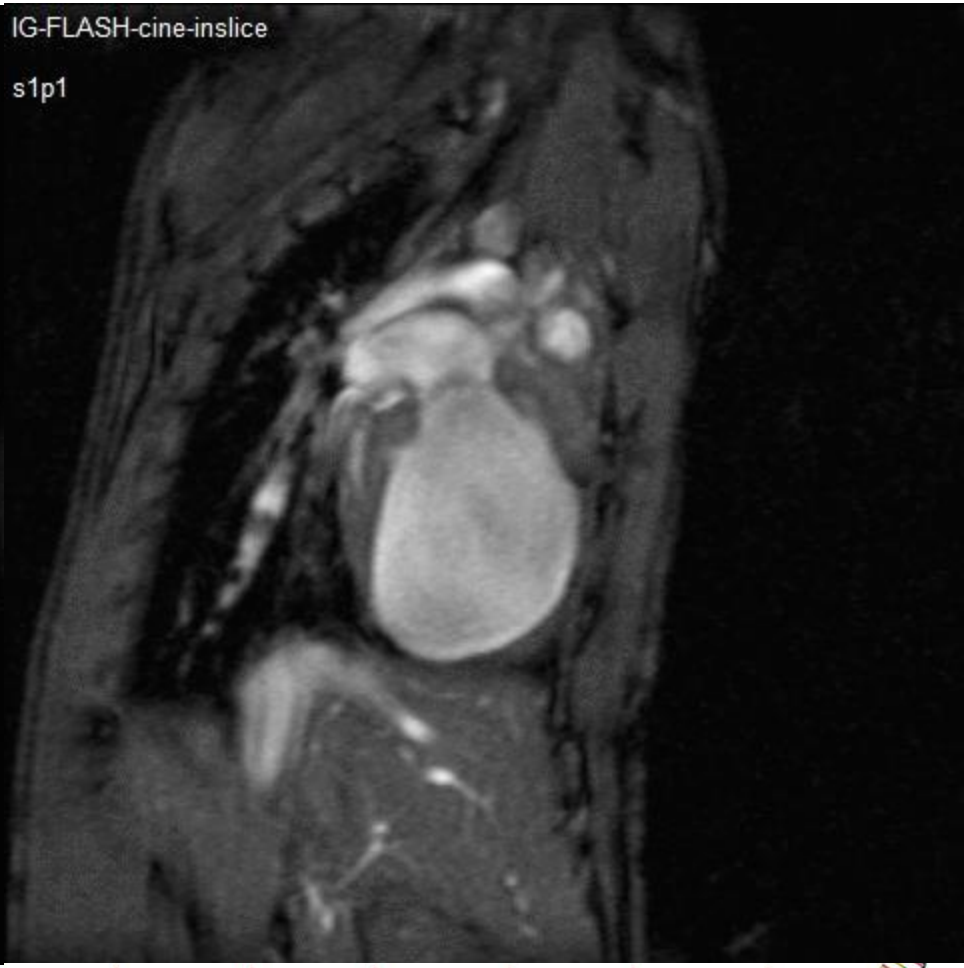
MRI: hartfunctie na infarct (muis)





construction of a conditional PLN R14 del mouse

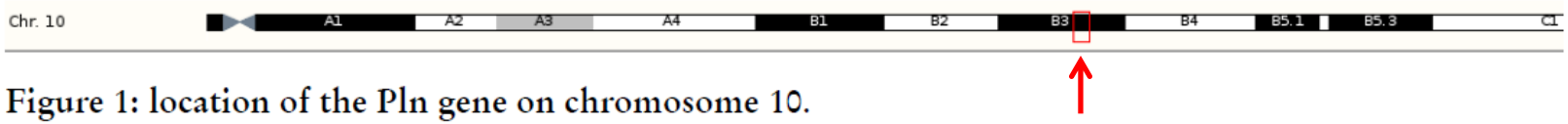
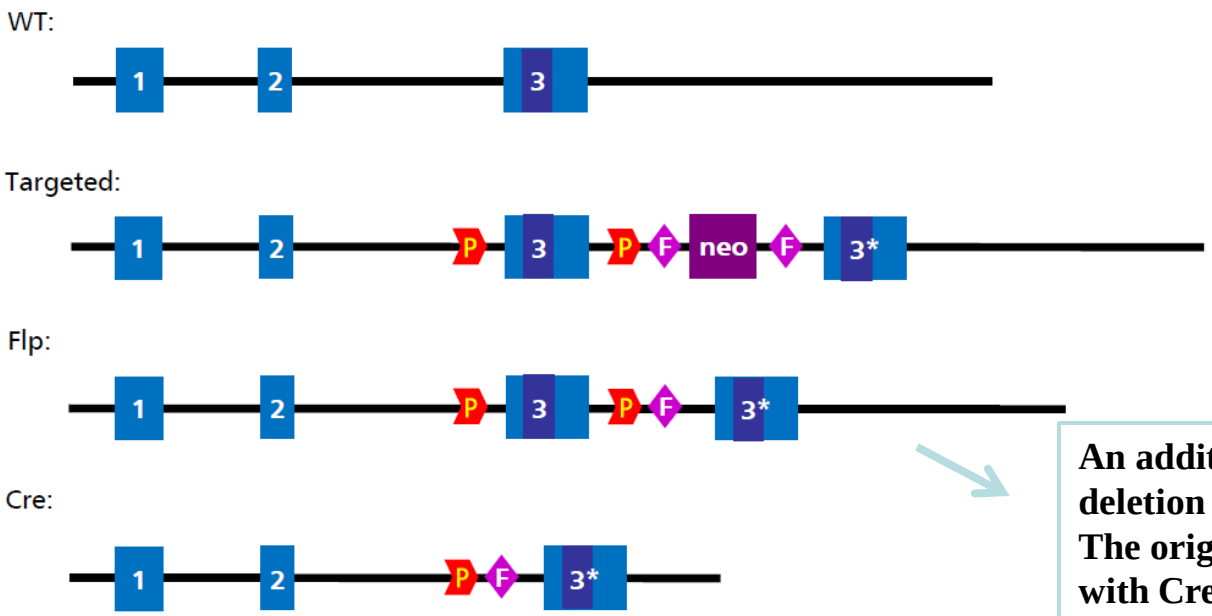


Figure 1: location of the Pln gene on chromosome 10.



An additional exon with the R14 deletion has been introduced in mice. The original exon can be removed with Cre recombinase.

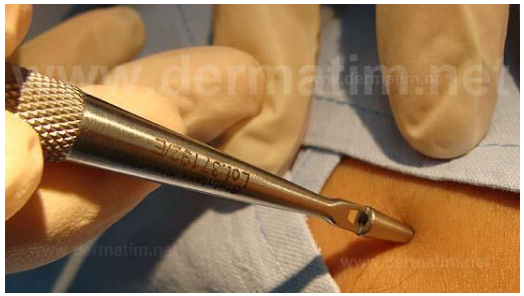
F = Flp recombination site (FRT)

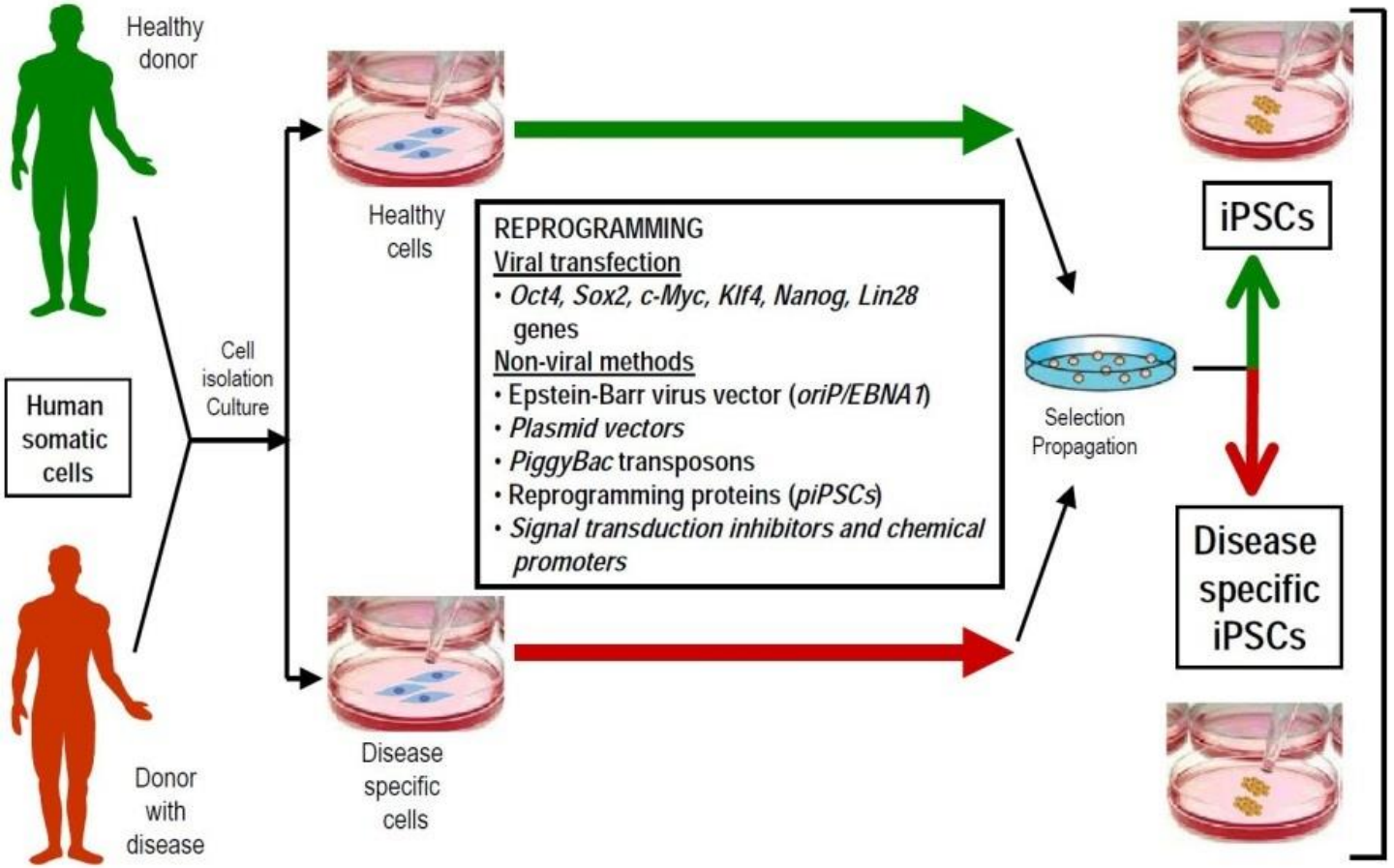
= exon, non-coding

= coding region

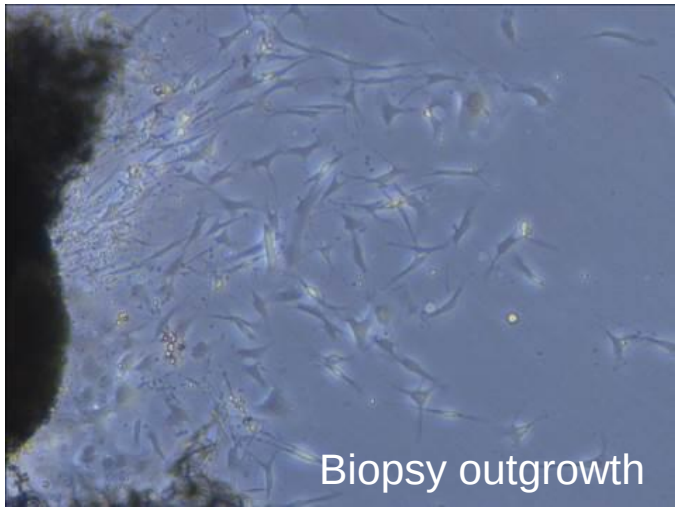
P = Cre recombination site (loxP)

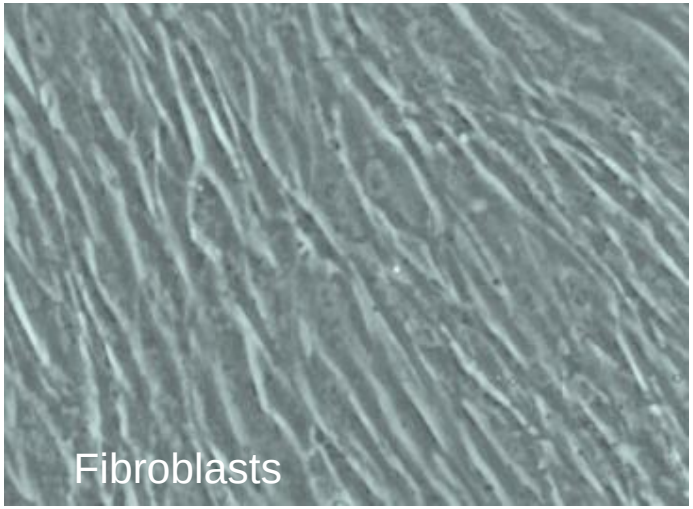
neo = neomycin resistance



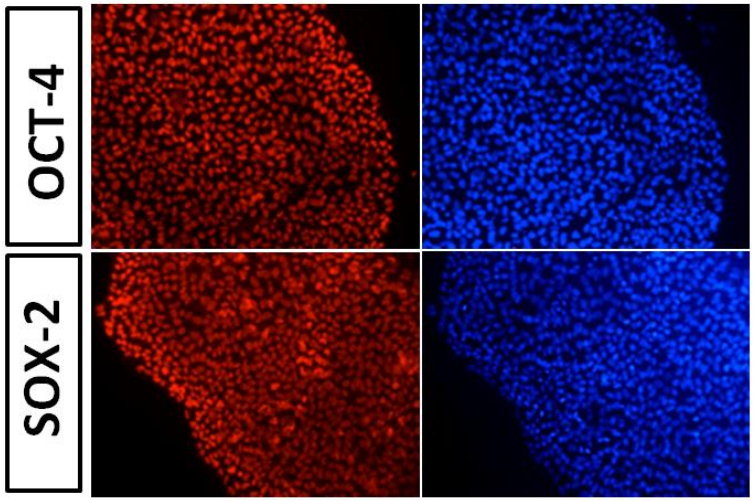

Healthy donor
Human somatic cells
Donor with disease
Cell isolation Culture
Healthy cells
Disease specific cells
REPROGRAMMING
Viral transfection
• Oct4, Sox2, c-Myc, Klf4, Nanog, Lin28 genes
Non-viral methods
• Epstein-Barr virus vector (oriP/EBNA1)
• Plasmid vectors
• PiggyBac transposons
• Reprogramming proteins (piPSCs)
• Signal transduction inhibitors and chemical promoters
Selection Propagation
iPSCs
Disease specific iPSCs

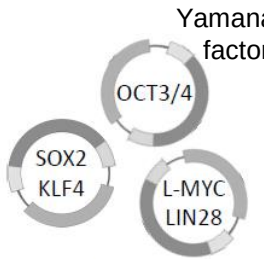
van huid fibroblast naar induced Pluripotent Stamcel (iPS)





hiPSC colony





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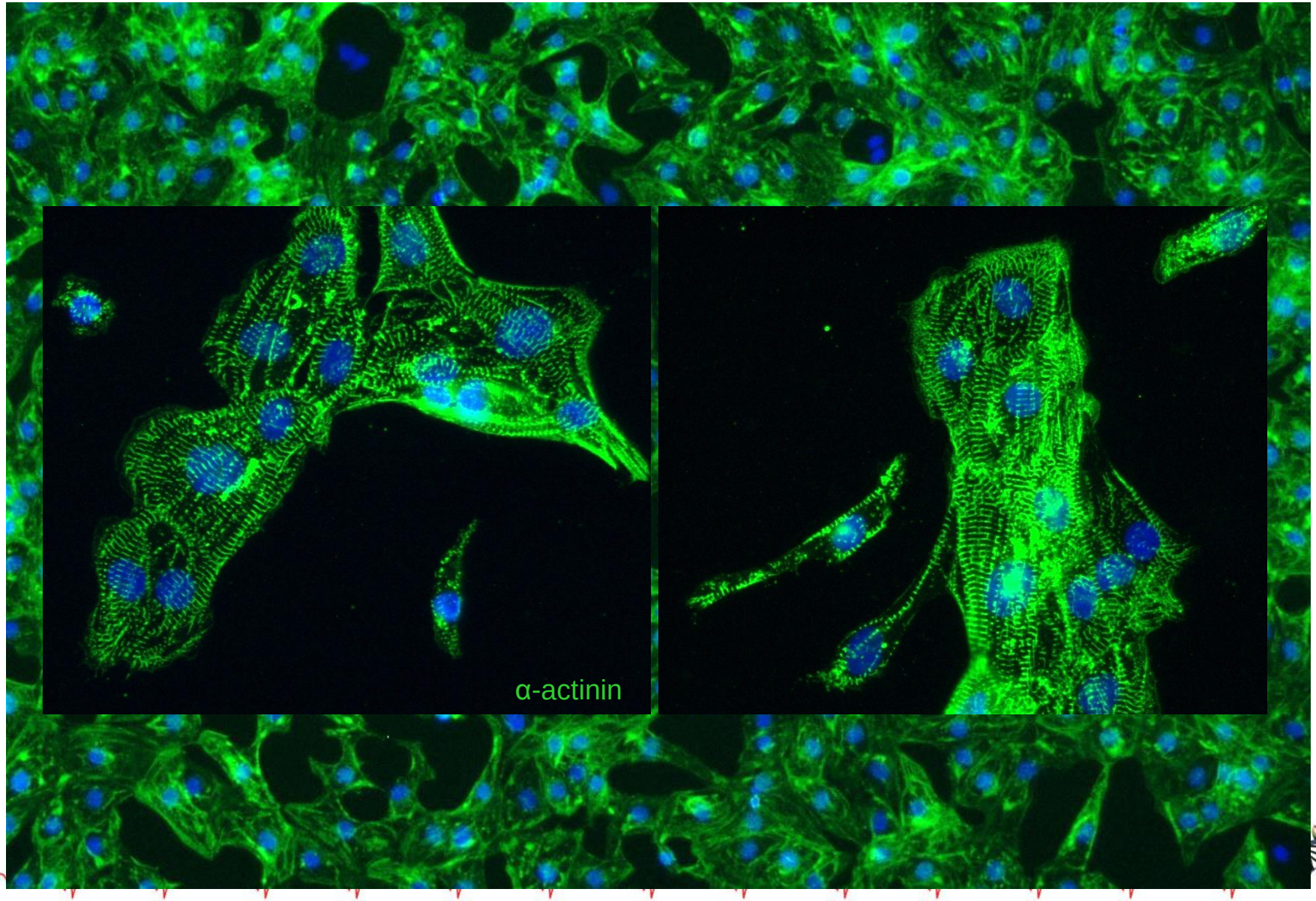
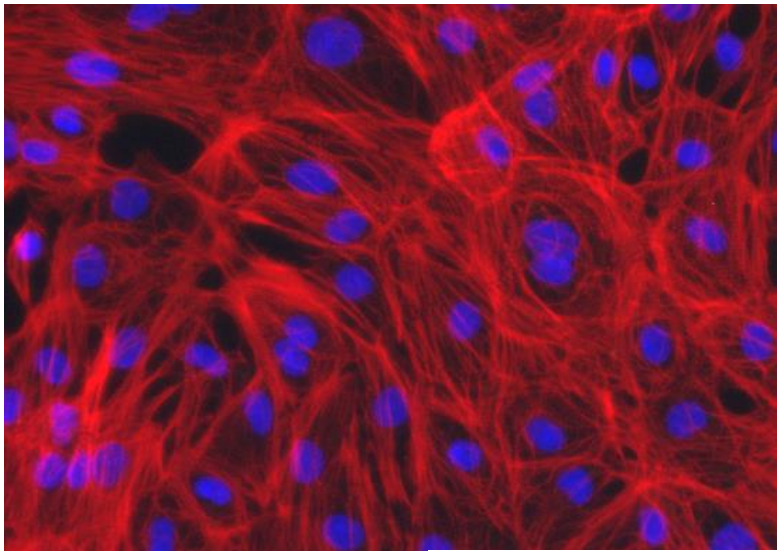
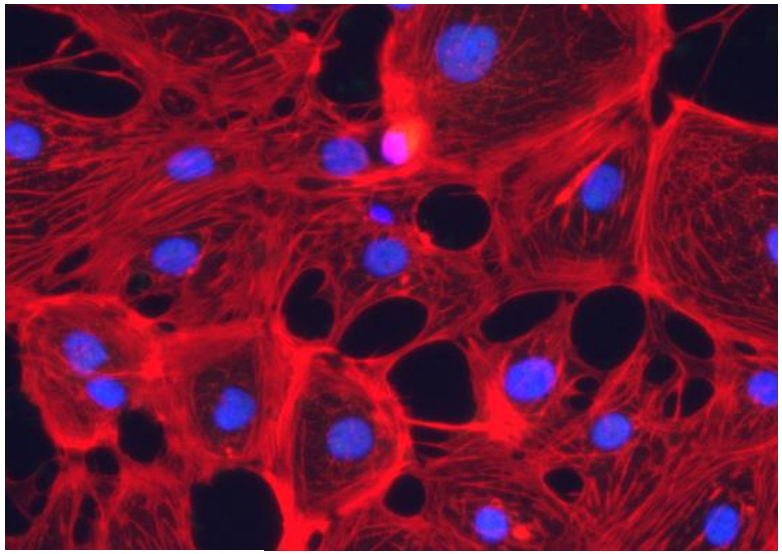
iPS kunnen “hartspiercellen” worden

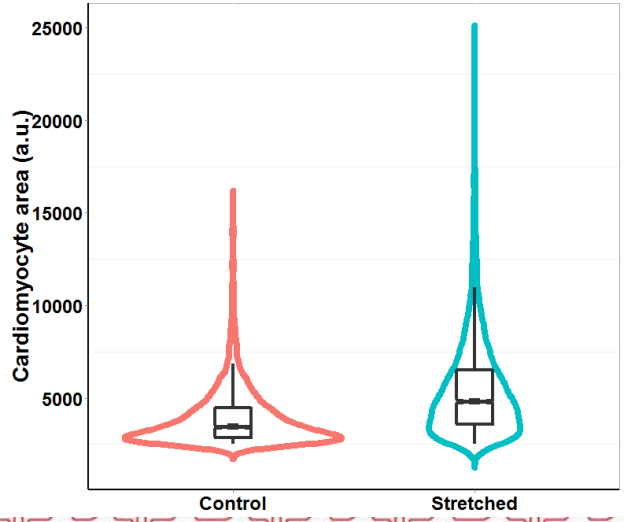


Hoes M & Van der Meer P, unpublished

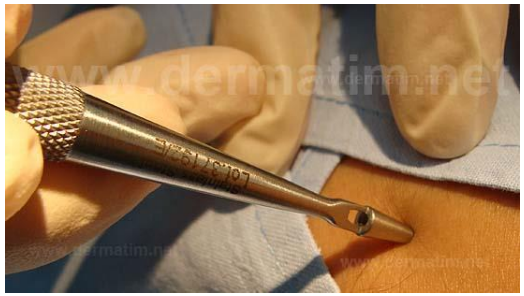
Rek op deze “hartspiercellen” leidt tot verdikking







Hoes M & Van der Meer P, unpublished



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Donor with disease

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- *Signal transduction inhibitors and chemical promoters*

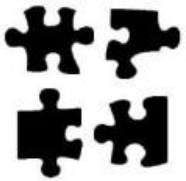
Selection Propagation

iPSCs

Disease specific iPSCs

CELL THERAPY

HUMAN PATHOLOGY MODELLING



DRUG DISCOVERY

www.elsevier.nl/kennis/article/2015/05/nog-nooit-was-het-zo-makkelijk-om-dna-te-veranderen-1763754W/

Zoeken

ELSEVIER

Actueel | #VS2016 | Opinie | Weekblad | Partners | Abonneren

KENNIS

Nog nooit was het zo makkelijk om DNA te veranderen.

Een nieuwe techniek maakt furore binnen de moleculaire biologie: CRISPR-cas. Over gaatjes prikken in DNA.

Stan Brouns (37), microbioloog aan de Wageningen Universiteit, is een echte wetenschapper. Puur uit nieuwsgierigheid werkt hij aan het immuunsysteem van bacteriën. Ook zij hebben last van infecties door virussen die de bacteriecel binnendringen en doen dood en verderf zaaien.

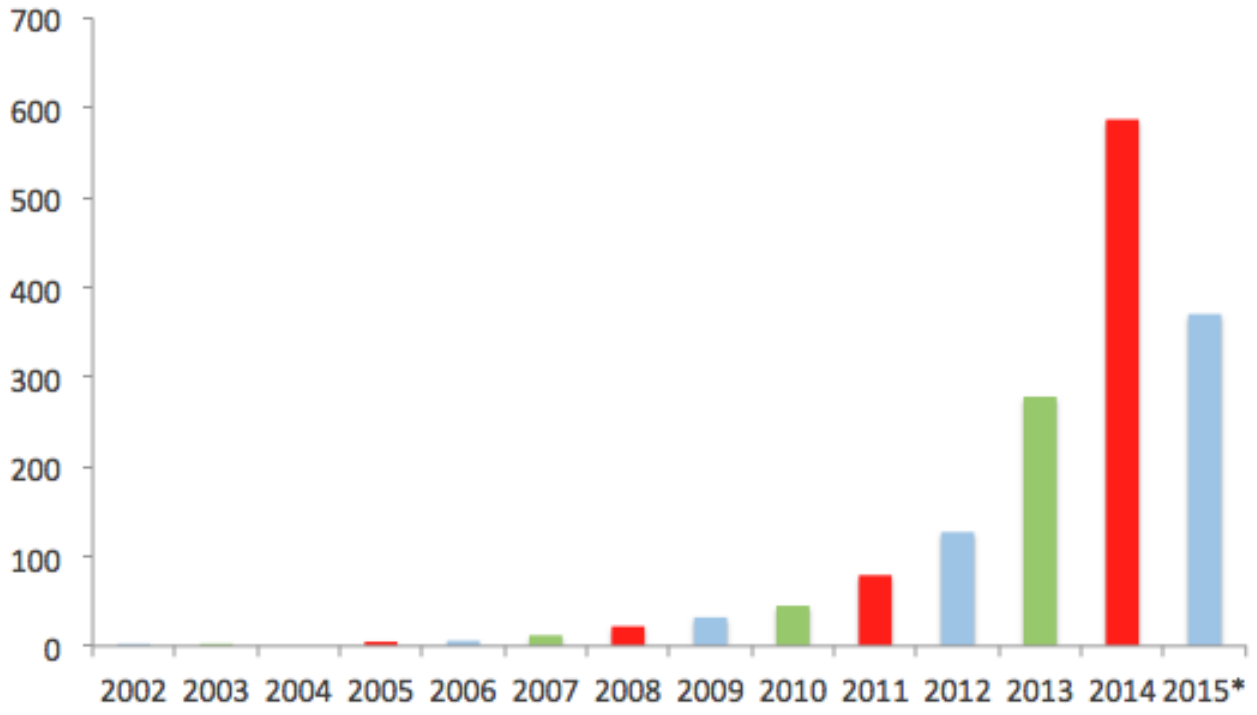
Door Hidde Boersma - - 19 mei 2015 -

Deel dit artikel:

MEER KENNIS

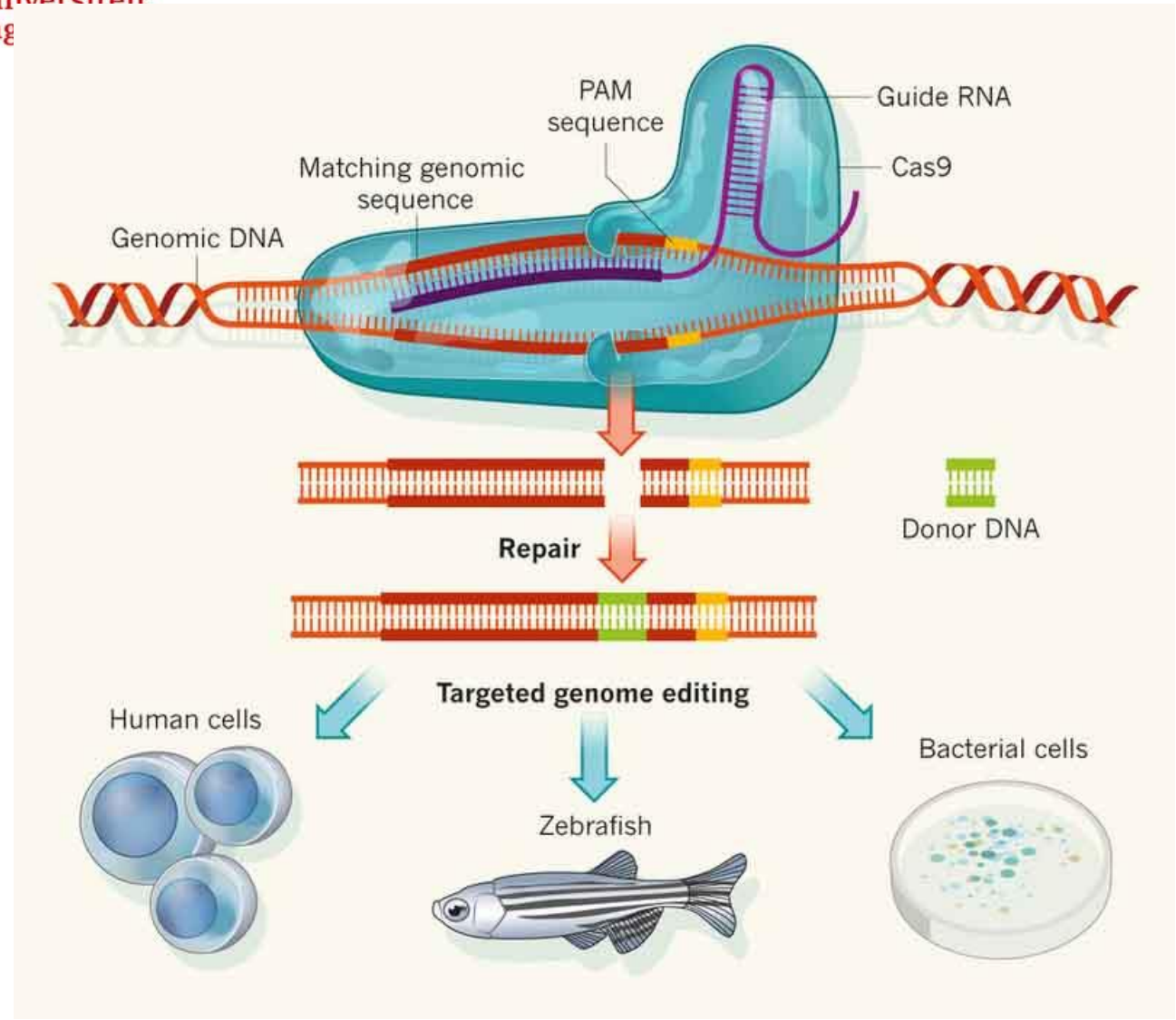
15:54
28-10-2016

CRISPR Mentions in Scientific Publications Since 2002



Source: PubMed

*As of April 2015.


PAM sequence
Guide RNA
Cas9
Matching genomic sequence
Genomic DNA
Donor DNA
Repair
Targeted genome editing
Human cells
Zebrafish
Bacterial cells

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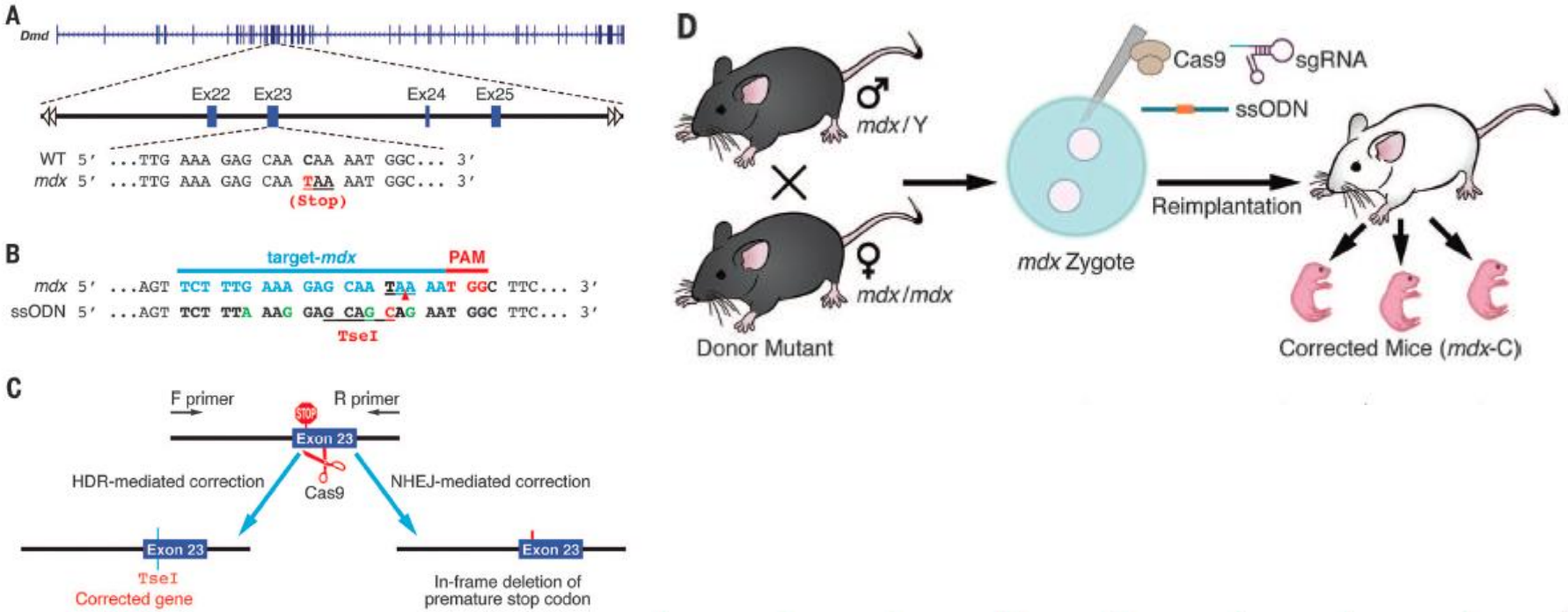
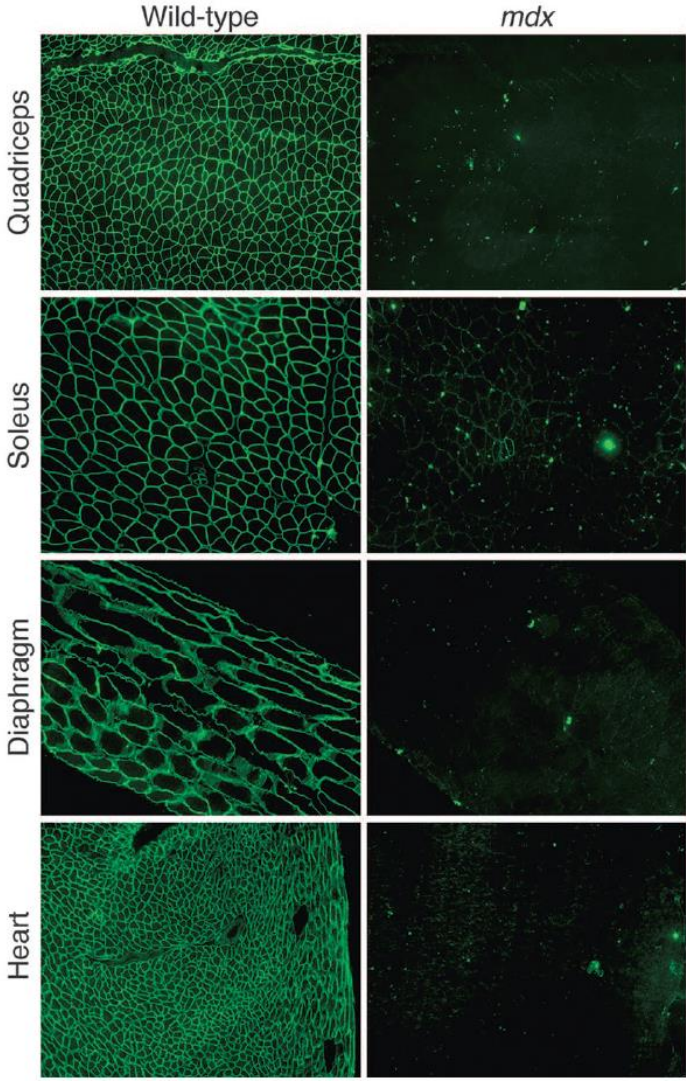
Prevention of muscular dystrophy in mice by CRISPR/Cas9–mediated editing of germline DNA

Chengzu Long,[1*] John R. McAnally,[1*] John M. Shelton,[2] Alex A. Mireault,[1] Rhonda Bassel-Duby,[1] Eric N. Olson[1†]



Long C, et al. *Science.* 2014; **345**:1184-1188



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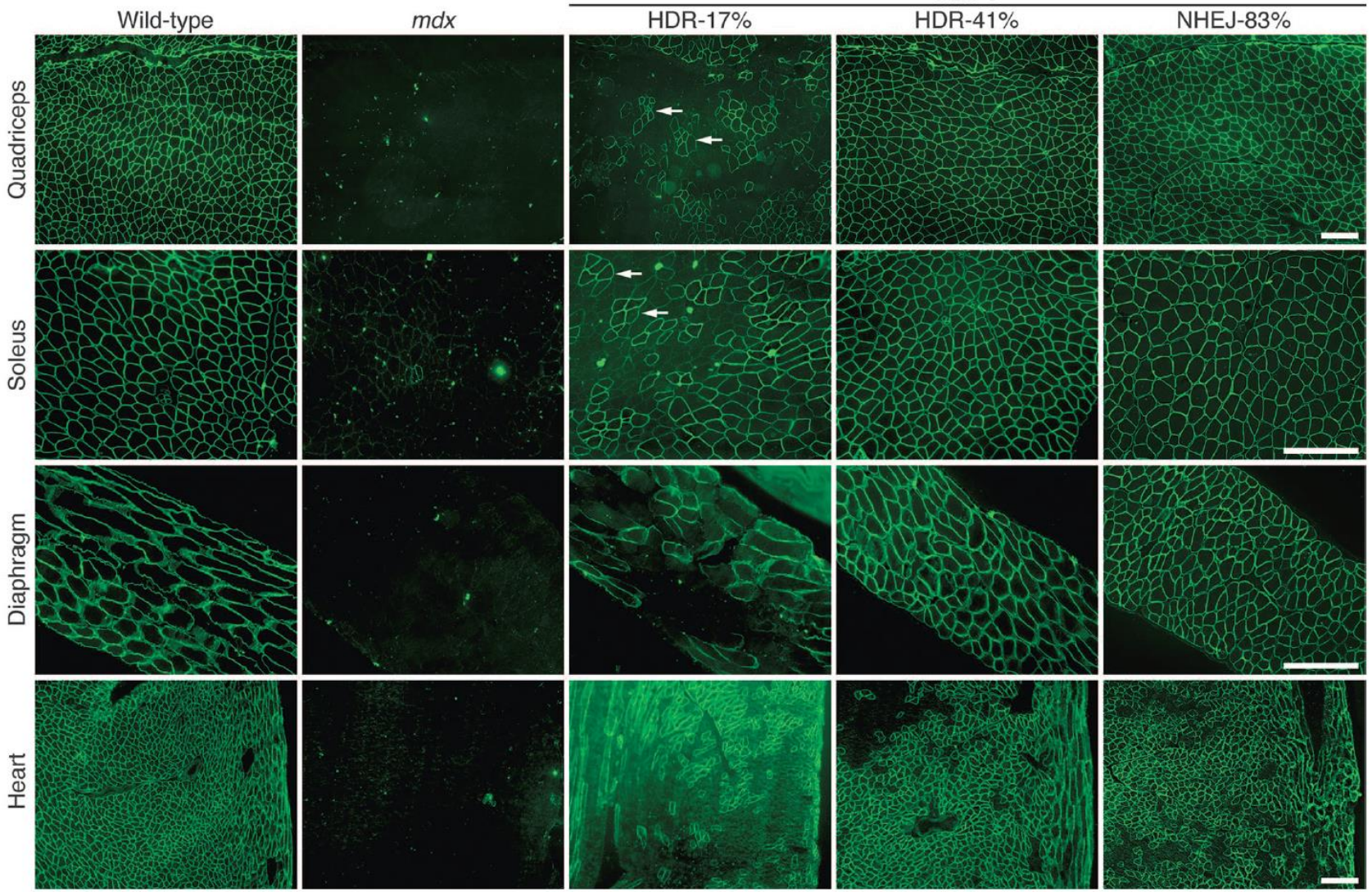

Long C, et al. *Science.* 2014; **345**:1184-1188

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BIOMEDICINE

First trial of CRISPR in people

Chinese team approved to test gene-edited cells in people with lung cancer.

Nature. 2016; **535**:476-477

- Waarom onderzoek?
- Elke hartziekte is erfelijk – monogenetisch versus multifactorieel
- Verbetering door organisatie – Durrer centrum
- Tools van modern onderzoek
- Patiënt participatie – gemeenschappelijke agenda

Gemeenschappelijke agenda

- We doen ons onderzoek niet op u, maar met u!

- Graag komen wij in contact met u
  - Opstellen agenda
  - In kaart brengen behoefte(s)
  - Aanscherpen protocollen
  - Genereren van ideeën en een agenda

Conclusie

- We kunnen hartziekten steeds beter behandelen maar er is nog veel te doen!
- Moderne technieken zijn aanwezig en zullen de ontwikkelingen versnellen
- Het Nederlandse CV onderzoek werkt met u aan een toekomst met minder (erfelijke) hartziekten