



Universiteit
Leiden
The Netherlands

Targeting glycolysis in endothelial cells to prevent intraplaque neovascularization and atherogenesis in mice

Perrotta, P.

Citation

Perrotta, P. (2021, March 24). *Targeting glycolysis in endothelial cells to prevent intraplaque neovascularization and atherogenesis in mice*. Retrieved from <https://hdl.handle.net/1887/3152433>

Version: Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/3152433>

Note: To cite this publication please use the final published version (if applicable).

Cover Page



Universiteit Leiden



The handle <https://hdl.handle.net/1887/3152433> holds various files of this Leiden University dissertation.

Author: Perrotta, P.

Title: Targeting glycolysis in endothelial cells to prevent intraplaque neovascularization and atherogenesis in mice

Issue Date: 2021-03-24



**Universiteit
Antwerpen**



**Universiteit
Leiden**

Targeting glycolysis in endothelial cells to prevent
intraplaque neovascularization and atherogenesis in mice

Paola Perrotta

Targeting glycolysis in endothelial cells to prevent
intraplaque neovascularization and atherogenesis in mice

PROEFSCHRIFT

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus Prof.dr.ir. H. Bijl,
volgens besluit van het College voor Promoties
te verdedigen op woensdag 24 Maart 2021
klokke 15:00 uur

door

Paola Perrotta

geboren op 11 September 1986

te Bari, Italië

Promotores

Prof. Dr. P.H.A. Quax

Leiden University Medical Center

Prof. Dr. W. Martinet

University of Antwerp

Co-promotor

Dr. M.R. de Vries

Leiden University Medical Center

Promotiecommissie

Prof. Dr. G.R.Y. De Meyer

University of Antwerp

Prof. Dr. W. Jukema

Leiden University Medical Centre

Prof. Dr. J. Hamming

Leiden University Medical Centre

Dr. I. Bot

University of Leiden

The research described in this thesis has been a collaborative effort of the Laboratory of Physiopharmacology from the University of Antwerp and the Department of Vascular Surgery in Leiden Medical University Centre from Leiden University. The research was financially supported by the Horizon 2020 program of the European Union – Marie Skłodowska Curie actions – ITN – MOGLYNET [grant number 675527] and the University of Antwerp (DOCPRO-BOF).

Financial support by the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged.

“Science knows no country, because knowledge belongs to humanity, and is the torch which illuminates the world”.

Louis Pasteur

Cover Image: Microscopic image of a vein graft with intraplaque neovessels

Cover design: Paola Perrotta

Printed by: Arte grafica, Lecce (Italy)

© Paola Perrotta 2021. All rights reserved. No part of this book may be reproduced, stored in a retrieval system or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without the prior permission of the holder of the copyright.

Table of Contents

Abbreviations		9
Chapter 1	General introduction and outline of the thesis	13
Chapter 2	Pharmacological strategies to inhibit intraplaque angiogenesis in atherosclerosis Perrotta P , Emini Veseli B, Van der Veken B, Roth L, Martinet W, De Meyer GRY. <i>Vascul Pharmacol.</i> 2019;112:72-78	39
Chapter 3	Animal models of atherosclerosis Emini Veseli B, Perrotta P , De Meyer GRA, Roth L, Van der Donckt C, Martinet W, De Meyer GRY. <i>Eur J Pharmacol.</i> 2017;816:3-13	61
Chapter 4	Partial inhibition of glycolysis reduces atherogenesis independent of intraplaque neovascularization in mice. Perrotta P , Van der Veken B, Van Der Veken P, Pintelon I, Roosens L, Adriaenssens E, Timmerman V, Guns PJ, De Meyer GRY, Martinet W. <i>Arterioscler Thromb Vasc Biol.</i> 2020;40:1168-1181	97
Chapter 5	Small molecule 3PO inhibits glycolysis but does not bind to 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase-3 (PFKFB3) Emini Veseli B, Perrotta P , Van Wielendaele P, Lambeir A, Abdali A, Bellosta S, Monaco G, Bultynck G, Martinet W, De Meyer GRY. <i>FEBS Letters.</i> 2020; 594(18):3067-3075	137
Chapter 6	PFKFB3 gene deletion in endothelial cells inhibits intraplaque angiogenesis and lesion formation in a murine model of venous bypass grafting Perrotta P , de Vries MR, De Meyer GRY, Quax P and Martinet W <i>Submitted for publication</i>	157

Chapter 7	[18F]ZCDD083: A PFKFB3-Targeted PET tracer for atherosclerotic plaque imaging	189
	De Dominicis C, Perrotta P , Dall'angelo S, Wyffels L, Staelens S, De Meyer G. R. Y, Zanda M. <i>ACS Medicinal Chemistry Letters</i> .2020;11:933-939	
Chapter 8	Three-dimensional imaging of intraplaque neovascularization in a mouse model of advanced atherosclerosis	209
	Perrotta P , Pintelon P, de Vries MR, Quax PHA, Timmermans JP, De Meyer GRY, Martinet W. <i>Journal of Vascular Research</i> .2020; 57(6):348-354.	
Chapter 9	Summary and future perspectives	227
Nederlandse samenvatting		241
Curriculum Vitae		251
List of Publications		253
Acknowledgments		255

Abbreviations:

AA: aortic arch

ApoE: apolipoprotein E

ATP: adenosine triphosphate

CA: carotid artery

CD31: cluster of differentiation 31

CPT1: carnitine palmitoyltransferase 1A

CHD: coronary heart disease

DCM : dichloromethane

DMSO: dimethylsulfoxide

EC: endothelial cell

EF: ejection fraction

ECM : extracellular matrix

FAO: fatty acid oxidation

FAS : fatty acid synthesis

Fbn: fibrillin

FDG: fluorodeoxyglucose

FGF: fibroblast growth factor receptor

FS: fractional shortening

F-1,6-P₂ : fructose -2,6-bisphosphate

F-6-P: fructose-6-phosphate

GAPDH: Glyceraldehyde-3-Phosphate Dehydrogenase

GLUT: Glucose transporter

HAEC: human aortic endothelial cell

HDL: high-density lipoprotein

HE: haematoxylin-eosin

HIF: hypoxian inducible factor

HK: Hexokinase

HMG-CoA: 3-hydroxy-3-methylglutaryl-coenzyme A

HUVEC: Human umbilical vein endothelial cell

ICAM-1: intercellular cell adhesion molecule

iDISCO: immunolabeling-enabled 3D Imaging of Solvent Cleared Organs

IL: interleukin
iNOS: inducible nitric oxide synthase
IP/PI: intra-plaque
IVRT: isovolumic relaxation time
i.p.: intraperitoneal
i.v.: intravenous
KLF2: Kruppel Like Factor 2
 α -KG: α -ketoglutaric acid
LDH: lactate dehydrogenase
LDL: low-density lipoprotein
LDLR: LDL receptor
LV: left ventricular
LVID: left ventricular internal diameter
MI: myocardial infarction
MMP: matrix metalloproteinase
NADH: nicotinamide adenine dinucleotide
OOA: oxalacetate
Ox: oxidized
PAD: peripheral arterial disease
PDGF: platelet-derived growth factor
PET: positron emission tomography
PFK-1: 6-phosphofructo-1 -kinase
PFKFB3: 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3
PF: platelet factor
PFPE: paraformaldehyde fixed paraffin embedded
PGI: phosphoglucose isomerase
Plgf: placenta growth factor
PCSK9: Proprotein convertase subtilisin/kexin type 9
PGK: phosphoglycerate kinase
SMC: smooth muscle cell
TCFA : thin cap fibroatheroma
TGF- β : transforming growth factor- β
TIA: transient ischaemic attack

TNF- α : Tumor necrosis factor alfa

VCAM-1 : vascular cell adhesion molecule-1

VEGF: vascular endothelial growth factor

VEGFR : VEGF receptor

vWF: von Willebrand factor

WD : western-type diet

WT: wild type

3PO: 3-(3-pyridinyl)-1-(4-pyridinyl)-2-propen-1-one

3D: three dimensional

