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Intervention in hepatic lipid metabolism : implications for atherosclerosis progression and regression

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LIST OF ABBREVIATIONS

ABCA1	ATP binding cassette transporter A1
ABCG1	ATP binding cassette transporter G1
ACAT	acyl-cholesterol acyl transferase
AD	atherogenic diet
ADPN	adiponutrin
ApoA-I	apolipoprotein A-I
ApoB	apolipoprotein B
ApoE ^{-/-}	apoE-deficient
ATGL	adipose triglyceride lipase
BMT	bone marrow transplantation
CCR	C-C chemokine receptor
CE	cholesteryl ester
CETP	cholesterol ester transfer protein
COUP-TF	chicken ovalbumin upstream promoter-transcription factor
CVD	cardiovascular disease
CYP7A1	cholesterol 7 alpha-hydroxylase
DGAT1	acyl-coenzyme A:diacylglycerol transferase 1
DMSO	dimethyl sulphoxide
EC	endothelial cell
FAS	fatty acid synthase
FC	free cholesterol
FCS	fetal calf serum
FFA	free fatty acids
FPLC	fast protein liquid chromatography
FXR	farnesoid X receptor
GAPDH	glyceraldehyde-3-phosphate dehydrogenase
GTC	guanidinium thiocyanate
HCA ₂	hydroxy-carboxylic acid receptor 2
HDL	high-density lipoprotein
HEK	human embryonic kidney
HFD	high-fat Diet
HPRT	hypoxanthine-guanine phosphoribosyltransferase
ICAM	intercellular adhesion molecule
IDL	intermediate-density lipoprotein
IL	interleukin
KC	Kupffer cell
KO	knockout
LCAT	lecithin-cholesterol acyltransferase
LDL	low-density lipoprotein
LDLr	LDL receptor
LDLr ^{-/-}	LDL receptor-deficient
LPL	lipoprotein lipase
LRP	LDLr-related protein
LXR	liver X receptor
MCP	monocyte chemoattractant protein
MTP	microsomal transfer protein

NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NR	nuclear receptor
Ox-LDL	oxidized LDL
PBS	phosphate buffered saline
PC	parenchymal cell
PCR	polymerase chain reaction
PGD ₂	prostaglandin D ₂
PGE ₂	prostaglandin E ₂
PL	phospholipids
PNPLA3	patatin-like phospholipase domain-containing protein 3
PPAR	peroxisomal proliferator activating receptor
RCT	reverse cholesterol transport
ROR	retinoid-related orphan receptor
RXR	retinoid X receptor
SMC	smooth muscle cell
SR-BI	scavenger receptor class B, type I
SREBP	sterol regulatory element binding protein
TC	total cholesterol
TG	triglycerides
Tg	transgenic
TNF	tumor necrosis factor
TRL	triglyceride-rich lipoproteins
VCAM	vascular cell adhesion molecule
VLDL	very-low-density lipoprotein
WT	wild-type
WTD	Western-type diet

LIST OF PUBLICATIONS

Full papers

Li Z, Calpe-Berdiel L, Saleh P, Van der Sluis RJ, Remmerswaal S, McKinnon HJ, Smit MJ, Van Eck M, Van Berkel TJC, Hoekstra M. Bone marrow reconstitution in ApoE^{-/-} mice: a novel model to induce atherosclerotic plaque regression. *Manuscript in preparation.*

Li Z, Van der Stoep M, Van der Sluis RJ, McKinnon HJ, Smit MJ, Van Eck M, Van Berkel TJC, Hoekstra M. LXR activation is essential to induce atherosclerotic plaque regression in C57BL/6 mice. *Submitted for publication.*

Li Z, Blad CC, Van der Sluis RJ, De Vries H, Van Berkel TJC, IJzerman AP, Hoekstra M. Effects of pyrazole partial agonists on HCA₂-mediated flushing and hepatic VLDL production in mice. *Submitted for publication.*

Li Z, Wang Y, Hildebrand RB, Van der Hoorn JWA, Princen HMG, Van Eck M, Van Berkel TJC, Rensen PCN, Hoekstra M. Niacin reduces plasma CETP levels by diminishing liver macrophage content in CETP transgenic mice. *Submitted for publication.*

Li Z, Kruijt JK, Van Berkel TJC, Hoekstra M. Gene Expression Profiling of Nuclear Receptors in Mouse Liver Parenchymal, Endothelial, and Kupffer Cells. *Submitted for publication.*

Hoekstra M, Van der Sluis RJ, **Li Z**, Van Berkel TJC. Profiling of the adrenal stress signature reveals candidate steroidogenic nuclear receptor targets. *Submitted for publication.*

Reuwer AQ, Van der Sluis RJ, **Li Z**, Goffin V, Twickler MTB, Kastelein J, Van Berkel TJC, Hoekstra M. Hyperprolactinemia in LDL receptor knockout mice is associated with a pro-atherogenic metabolic phenotype, but not with increased atherosclerosis. *Submitted for publication.*

Hoekstra M, Van der Sluis RJ, **Li Z**, Oosterveer MH, Groen AK, Van Berkel TJC. The farnesoid X receptor (FXR) stimulates adrenal steroidogenesis in mice. *Submitted for publication.*

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Hoekstra M, Lammers B, Out R, **Li Z**, Van Eck M, Van Berkel TJ. Activation of the nuclear receptor PXR decreases plasma LDL-cholesterol levels and induces hepatic steatosis in LDL receptor knockout mice. *Atherosclerosis suppl*. 2009;10:2.

CURRICULUM VITAE

Zhaosha Li was born on May 26th 1983 in Changsha, China. In 2001, she started her university education at Capital Normal University, Beijing, China, majoring in Biological Sciences. During her study, she did a 5-month internship at Chinese Academy of Agricultural Sciences (CAAS) titled 'Application of amplified ribosomal DNA restriction analysis in characterizing biodiversity of endophytic bacteria in rice'.

In 2005, she graduated with honors and came to The Netherlands to start her master study in Bio-Pharmaceutical Sciences, Faculty of Science, Leiden University, with Leiden University Excellence Scholarship. During this 2-year master program, she did a 9-month internship titled 'Role of macrophage scavenger-receptor BI and CD36 in atherosclerosis', under the supervision of Prof. Dr. Theo J.C. van Berkel and Dr. Ruud Out, at the Division of Biopharmaceutics, Leiden University, and a 6-month internship titled 'Effects of genetic variation in the human organic cation transporter hOCT1 on drug inhibition' with ULLA MSc Grant at Department of Pharmacy, Uppsala University, Sweden, under the supervision of Prof. Dr. Per Artursson and Dr. Gustav Ahlin.

From October 2007 to September 2011, she has been working as a PhD candidate (Assistent in Opleiding) at the Division of Biopharmaceutics, Leiden/Amsterdam Center for Drug Research (LACDR), Leiden University. Her PhD research was financially sponsored by Top Institute Pharma (TI Pharma) project T2-110-1 'Nuclear receptors as targets for anti-atherosclerotic therapies', under the supervision of promotor Prof. Dr. Theo J.C. van Berkel, co-promotor Dr. Menno Hoekstra, and TI Pharma principal investigator Dr. Martin-Jan Smit from MSD, Oss. Her research was mainly focused on the pathology and novel pharmaceutical interventions in hyperlipidemia, hepatic lipid metabolism, and atherosclerotic plaque regression. The results of this program are presented in this thesis.