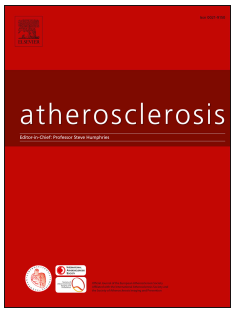
# Accepted Manuscript




Escaping the atherogenic trap: Preventing LDL fusion and binding in the intima

Martin Houde, Miranda Van Eck

PII: S0021-9150(18)30275-2

DOI: 10.1016/j.atherosclerosis.2018.05.032

Reference: ATH 15527

To appear in: *Atherosclerosis*

Received Date: 8 May 2018

Accepted Date: 16 May 2018

Please cite this article as: Houde M, Van Eck M, Escaping the atherogenic trap: Preventing LDL fusion and binding in the intima, *Atherosclerosis* (2018), doi: 10.1016/j.atherosclerosis.2018.05.032.

# Escaping the atherogenic trap: Preventing LDL fusion and binding in the intima

Martin Houde[1], Miranda Van Eck

BioTherapeutics Division, Leiden Academic Centre for Drug Research, Universiteit Leiden, Einsteinweg 55, 2333CC, Leiden, Zuid-Holland, Netherlands

[1]Author for Correspondence
m.houde@lacdr.leidenuniv.nl

**Key words**: Apolipoprotein B; Cathepsin G; Chymase; Low-density lipoprotein; Mast cells; Proteoglycan

Low-density lipoprotein (LDL) cholesterol plasma concentrations have served as the target of clinical treatment of atherosclerosis-related diseases since the development of simvastatin three decades ago. Targeting endogenous cholesterol synthesis by the inhibition of β-hydroxy-β-methylglutaryl co-enzyme A (HMG-CoA) reductase, statins have since become a mainstay in the lowering of plasma cholesterol and LDL levels and the improvement of cardiovascular outcomes such as myocardial infarction and stroke. Augmented LDL-lowering with the Nieman-Pick C1-like-1 (NPC1L1) inhibitor ezetimibe or with proprotein convertase subtilisin/kexin-9 (PSCK9) inhibitors, respectively blocking exogenous cholesterol absorption or improving plasma LDL clearance, further ameliorates treatment outcomes. However, a large population of patients still experience cardiovascular events even with extremely low LDL-C concentrations [1]. Therefore, new therapeutic strategies are needed to help these patients. Studies aimed at increasing high-density lipoprotein cholesterol (HDL-C) plasma levels with niacin (vitamin B3), peroxisome proliferator-activated protein-α (PPAR-α) agonists (fibrates) and cholesterol ester transfer protein (CETP) inhibitors, and even the full length recombinant ApoA1 mimetic CER-001 provide little to no improvement of cardiovascular outcomes when added to statins [2, 3]. The failure of plasma HDL-C enhancing treatments highlighted a critical part of atherosclerotic cholesterol metabolism: lipoprotein functionality. For instance, apolipoprotein A1 (ApoA1), the main HDL apolipoprotein, can be oxidized by myeloperoxidase and proteolyzed to detrimental