

# PCSK9 inhibition could ameliorate atherosclerosis and cardiovascular disease by immune mechanisms.

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Disclosures: None

# Declaration of interest

- Consulting/Royalties/Owner/ Stockholder of a healthcare company (Minor ownership in Athera Biotechnologies and Annexin Pharmaceuticals, unrelated to PCSK9)

# Declaration of Interest

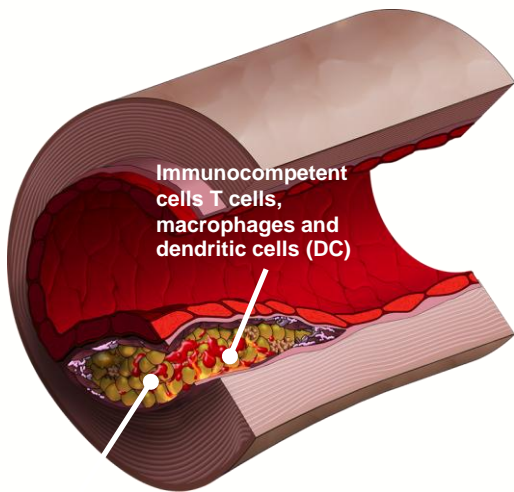
- No conflict of interest



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# Background



*Foam cells, dead cells,  
calcifications, debris,  
oxidized LDL*

- Atherosclerosis is the major cause of cardiovascular disease (CVD)
- Atherosclerosis is a vascular inflammation, where immune mechanisms are likely to play a key role.
- Lipids such as OxLDL are implicated as triggering pro inflammatory factors
- Despite available lipid lowering drugs, there is a huge need for novel types of therapies, modulating immune system and acting anti-inflammatory
- Treatments are emerging! IL-1 inhibition is a promising candidate
- **But are we already treating the inflammation?**
- Yes, most likely: Statins!
- We here investigate immune modulatory effects of PCSK9 and inhibition of it.

# Purpose and key points about methods



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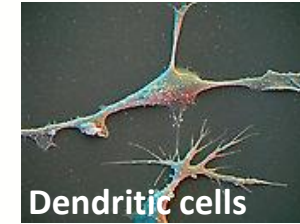
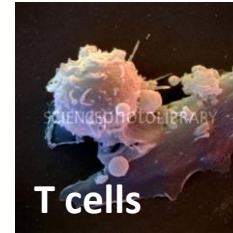
- Immunocompetent cells T cells, macrophages and dendritic cells (DC) are major components of human atherosclerotic plaques
- DC and T cell activation could play major role in promoting MI and stroke
- We study how human T cells from plaque interact with DC from the same individual
- Immune effects of PCSK9 and inhibition by silencing of the gene are studied in our ex vivo models

# Should we ask the mouse about immunity and PCSK9 in atherosclerosis and CVD?



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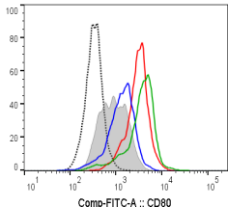
- CVD in animal models is not = CVD in humans.
- Lipids and immune reactions in human atherosclerosis are different from animal models!
- Ex vivo model of immune interactions
- Co-culture of human DC and T cells
- Source: Human plaques /peripheral blood

# PCSK9 played an essential role in DC maturation, proinflammatory cytokine production and the subsequent T cell proliferation induced by oxLDL .

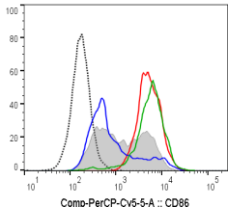


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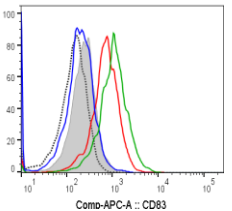
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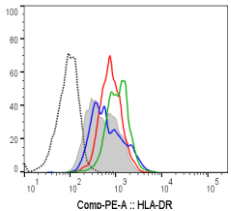
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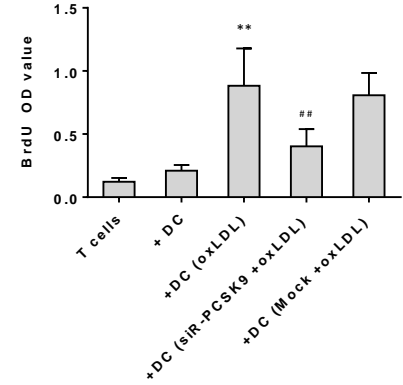
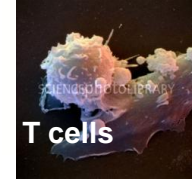
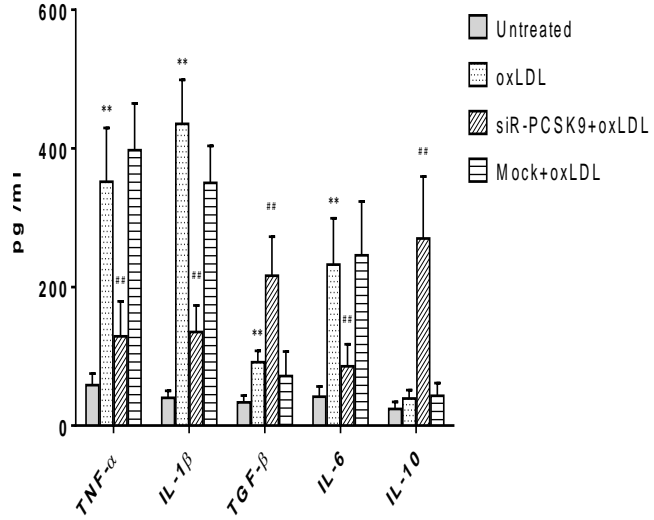
CD86



CD83



HLA-DR



# Results

- OxLDL but not LDL induced DC-mediated T cell activation and induced PCSK9 in DCs
- OxLDL promoted DC maturation into a pro-inflammatory phenotype
- T cells exposed to OxLDL-treated DCs proliferated and activated pro-inflammatory T cells
- Silencing of PCSK9 reversed the OxLDL effects and *T regulatory cells*
- OxLDL induced miRNA let-7c, miR-27a, miR-27b, miR-185. Silencing PCSK9 repressed miR-27a and to a lesser extent let-7c



# Conclusions



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- Inhibition of PCSK9 is anti-inflammatory and immune modulatory, *induction T regulatory cells upon OxLDL-activation.*
- PCSK9-inhibition may protect against atherosclerosis and CVD through immune mechanisms, independent of LDL-lowering.