Therapeutic targeting of protocadherin gamma A9 (Pcdhga9)

Martin Schwartz, PhD
Professor, Depts of Internal Medicine (Cardiovascular Medicine), Cell Biology and Biomedical Engineering

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Article

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Endothelial γ-protocadherins inhibit KLF2 and KLF4 to promote atherosclerosis

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Check for updates

Divyesh Joshi[1], Brian G. Coon[1], Raja Chakraborty[1], Hanqiang Deng[1], Ziyu Yang[2,3], Muhammad Usman Babar[2,3], Pablo Fernandez-Tussy[2], Emily Meredith[1], John Attanasio[4], Nikhil Joshi[4], James G. Traylor Jr.[5], Anthony Wayne Orr[5], Carlos Fernandez-Hernando[2], Stephania Libreros[2,3] & Martin A. Schwartz[1,6,7]

Vascular inflammation is the major cause of illness and death worldwide

Atherosclerosis

Heart attack

Stroke

Peripheral artery disease

Other indications:

- Diabetic retinopathy and kidney disease
- Hypertension (systemic and pulmonary)
- Acute lung injury
- Microvascular disease
- Dementia (directly in vascular, contributing to Alzheimers and Parkinsons)
- Covid-19 related vascular dysfunction
- Aging

Potential market: > billion patients?

Current treatments: lipid lowering (statins and lifestyle changes) and blood pressure control. 50% residual risk.

In development: anti-inflammatory treatments (e.g. anti-IL1β mAb)
Result: reduced deaths from cardiovascular events but increased deaths from infection. NOT APPROVED.


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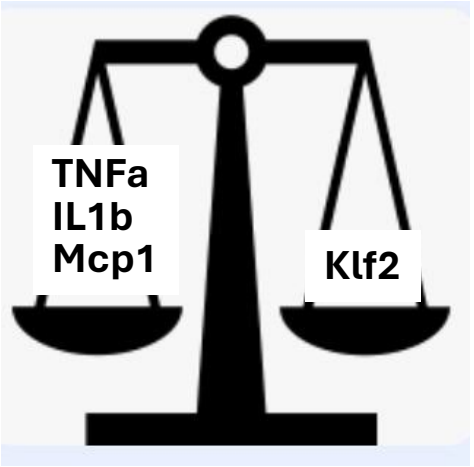
Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

P.M. Ridker, B.M. Everett, T. Thuren, J.G. MacFadyen, W.H. Chang, C. Ballantyne, F. Fonseca, J. Nicolau, W. Koenig, S.D. Anker, J.J.P. Kastelein, J.H. Cornel, P. Pais, D. Pella, J. Genest, R. Cifkova, A. Lorenzatti, T. Forster, Z. Kobalava, L. Vida-Simiti, M. Flather, H. Shimokawa, H. Ogawa, M. Dellborg, P.R.F. Rossi, R.P.T. Troquay, P. Libby, and R.J. Glynn, for the CANTOS Trial Group*

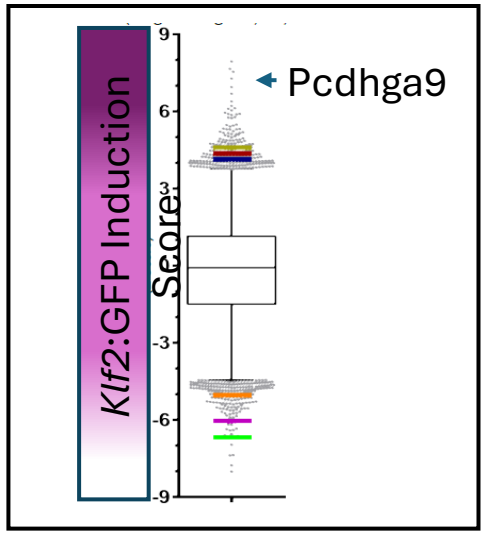
Critical balance between pro- and anti-inflammatory factors



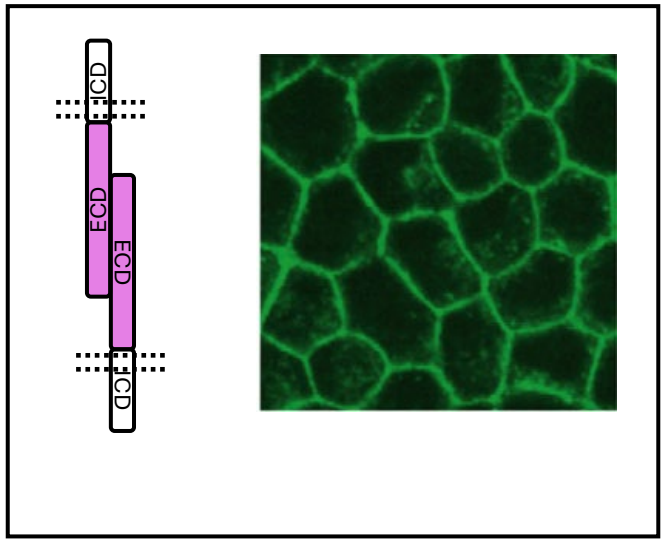
The critical protective transcription factor in endothelial cells is Klf2

Whole genome CRISPR screen to identify regulators of Klf2 expression

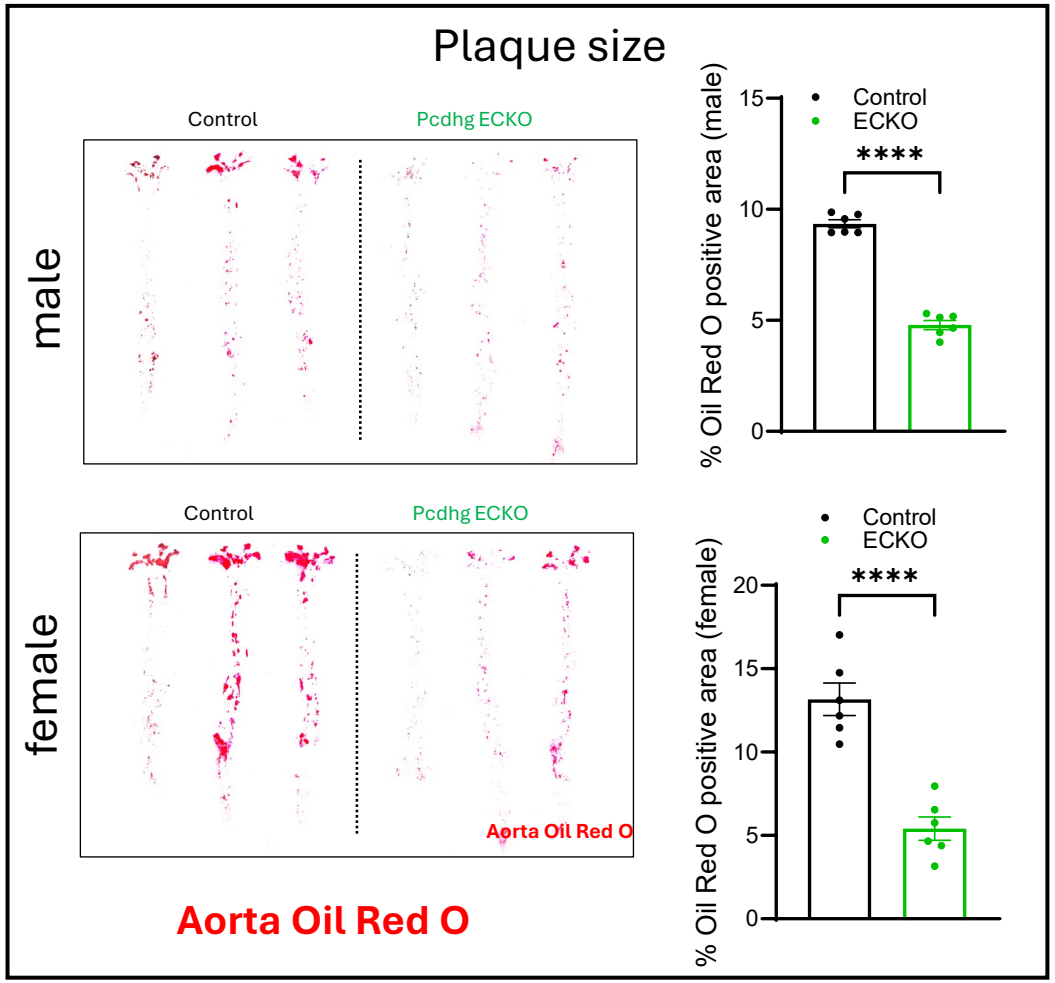
Klf2 CRISPR screen hits



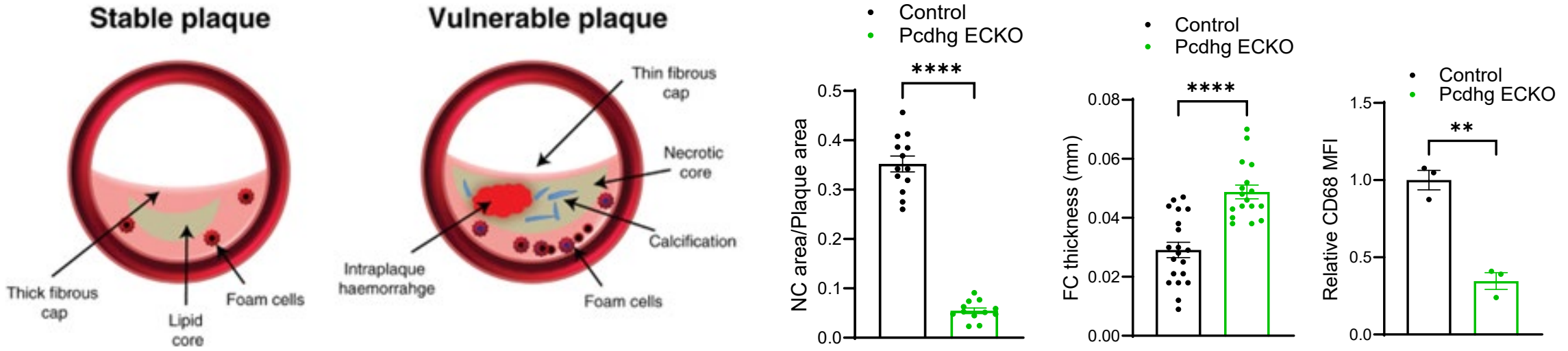
Protocadherins mediate cell-cell adhesion



Deleting endothelial Pcdhγ in mice reduces atherosclerosis

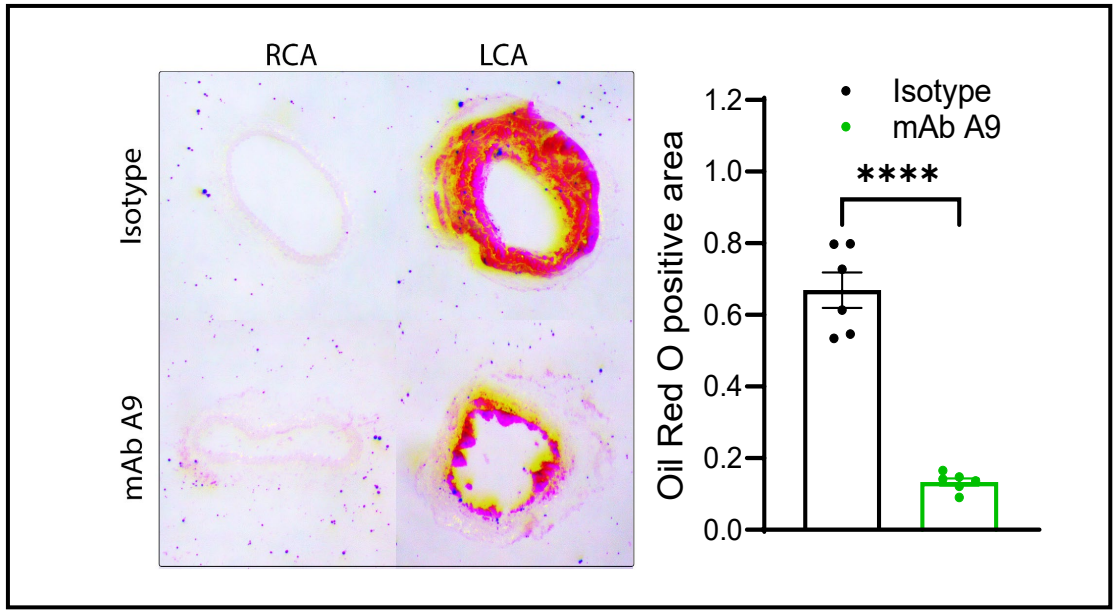


...and drastically improves plaque phenotype



Without any increase in susceptibility to viral or bacterial infections!

An antibody that blocks homophilic adhesion of Pcdhga9 also reduces atherosclerosis in a mouse model



Proposal:

1. Make cross reactive humanized therapeutic antibody to human Pcdhga9. (Inflection point!)

2. Make a mouse with humanized Pcdhga9 for testing the antibody in safety and disease models.