Small molecule Wnt inhibitor: First-in-class therapy for atherosclerosis

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- Expertise in vascular inflammation, steroid microenvironments, endothelial cells, Wnt signaling

Cardiovascular disease prevalence continues to *increase*

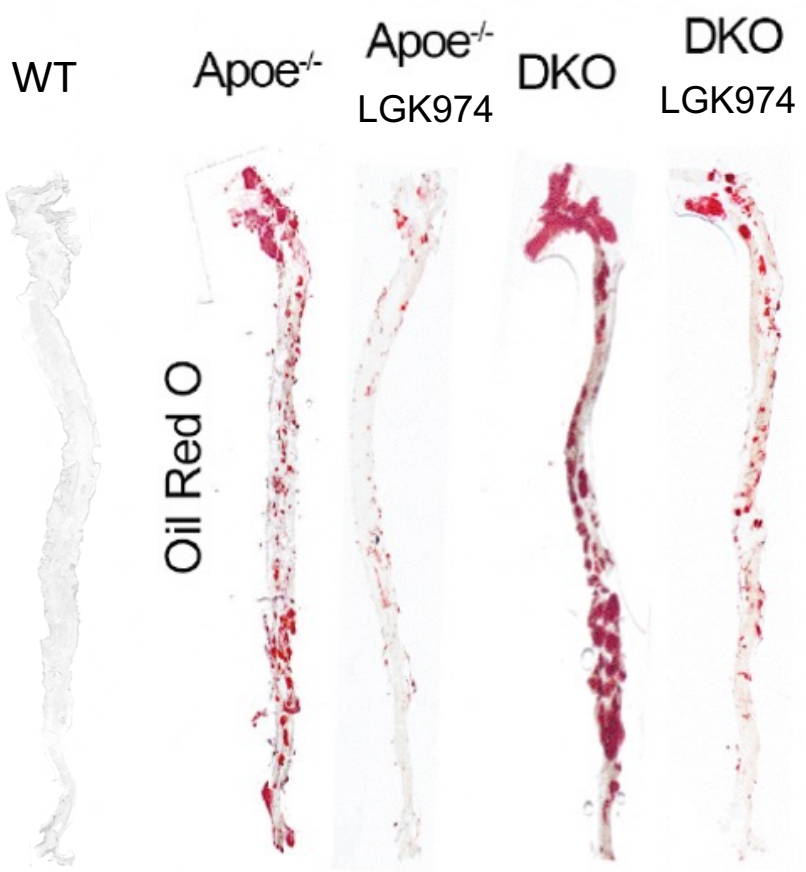
2030	Mortality will exceed 23 million deaths
2021	Global cardiovascular drug market totaled $79 billion
2015	17.3 million deaths, totaling more than $316B in healthcare costs and lost productivity
2010	FDA approved nearly 30 new drugs

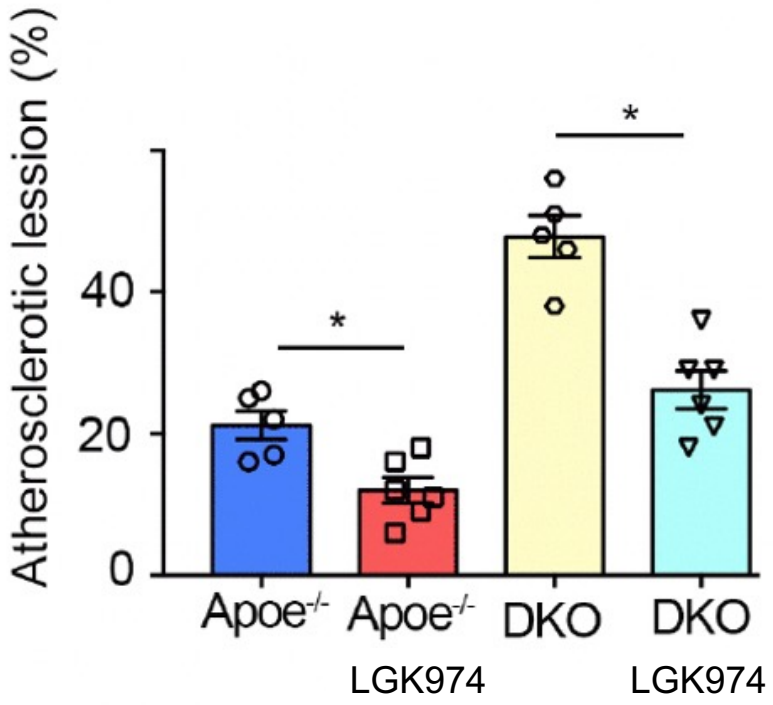
Current therapeutic landscape

Besides modifiable lifestyle factors, mainstay of therapy for CVD is use of lipid-lowering agents

Wnt signaling was identified as a key mechanistic pathway for CVD through an unbiased genomic screen in our laboratory, yet NO THERAPY targeting this pathway currently exists

Effect of Wnt inhibition





Reversal of aortic lipid deposition by 50%

Novel mechanism

Lipid-lowering

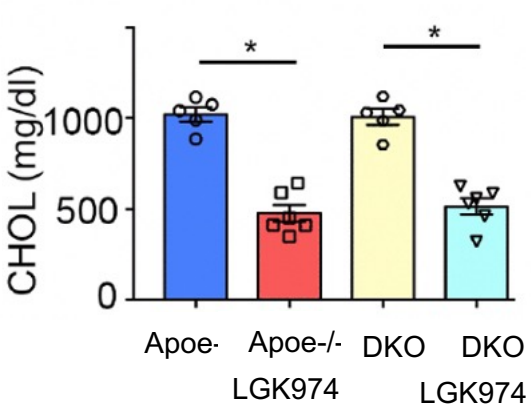
AND

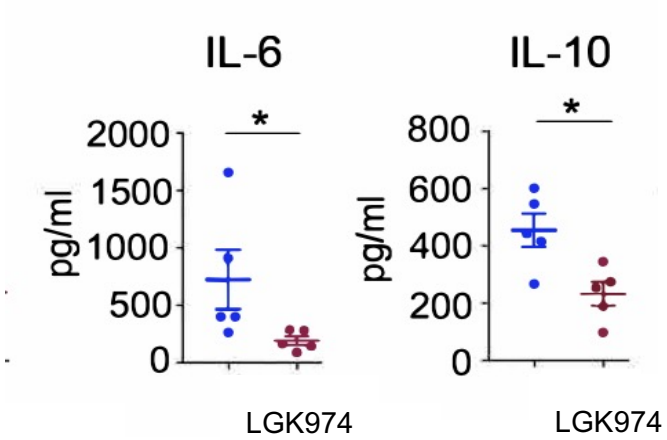
Reversal of lipid deposition

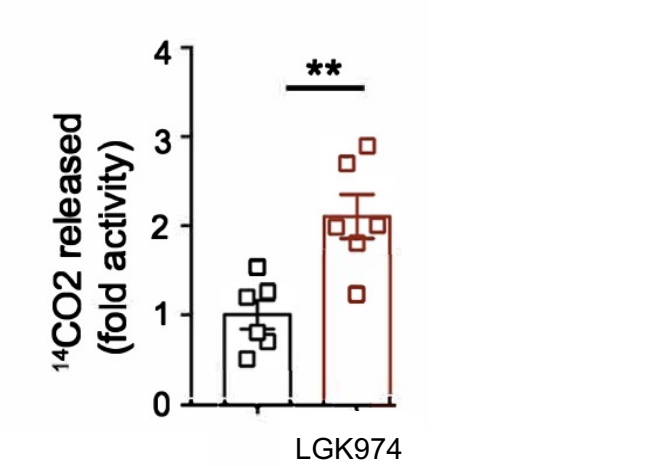
PCSK9i + statin → 35%-40 decrease in total chol

Mitigation of inflammatory cytokines

Restoration of fuel preference defects







Progress-to-date

Awarded $3.1 million in NIH funds to study this mechanism

IP: Patent has been issued as of June 2022; claim set allows for use of Wnt inhibitors as therapy for cardiovascular disease

Represents a first-in-class novel therapeutic

Proposed Use of Funds

	Experimental design	Timeline and Milestones	Where	$$
Phase 1: Find novel lead compounds	IN Cell Analyzer 2200 to assess Wnt signaling in endothelial cells treated with curated libraries of small molecules: • Bioactive lipids • Nuclear receptor ligands • Maybridge diversity	0-6 months Assessment of endpoints: 1. Quantification of nuclear translocation of beta-catenin in endothelial cells 2. Wnt-dependent gene expression via optimized luciferase reporter assay (in-hand)	Yale Center for Molecular Discovery, home lab	$30K
Phase 2: Dose-finding range and preliminary tox study	In vivo studies (rodent) • Escalating dosing • Repeated daily dosing • Maximum tolerated dose	6-18 months 1. Morbidity and mortality observations 2. Body weight 3. Toxicokinetic sample collection 4. Hematology and clinical chemistry 5. Macroscopic tissue examination and histology	Charles River	$165k