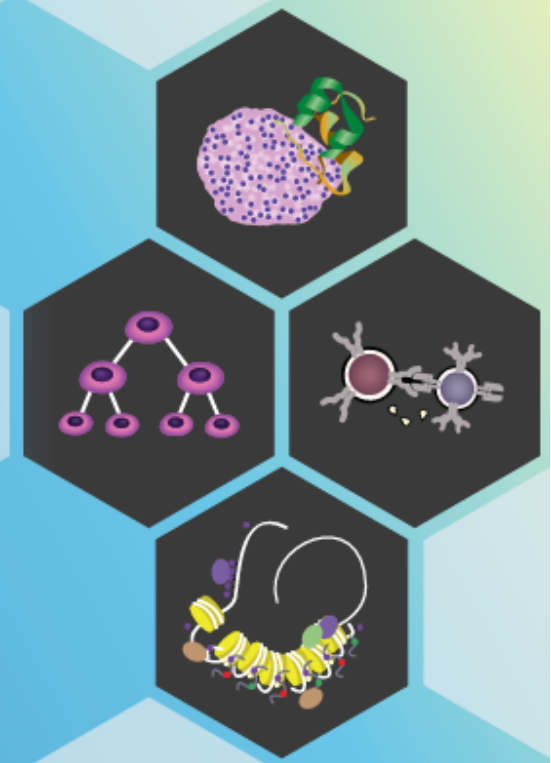
2024 RACHMIEL LEVINE-ARTHUR RIGGS

Diabetes Research Symposium

Exploring Mitochondrial Metabolism to Improve Cardiometabolic Health



Leigh Goedeke, PhD

Assistant Professor, Department of Medicine (Cardiology and Endocrinology)

The Cardiovascular Research Institute

The Diabetes, Obesity and Metabolism Institute

Icahn School of Medicine at Mount Sinai

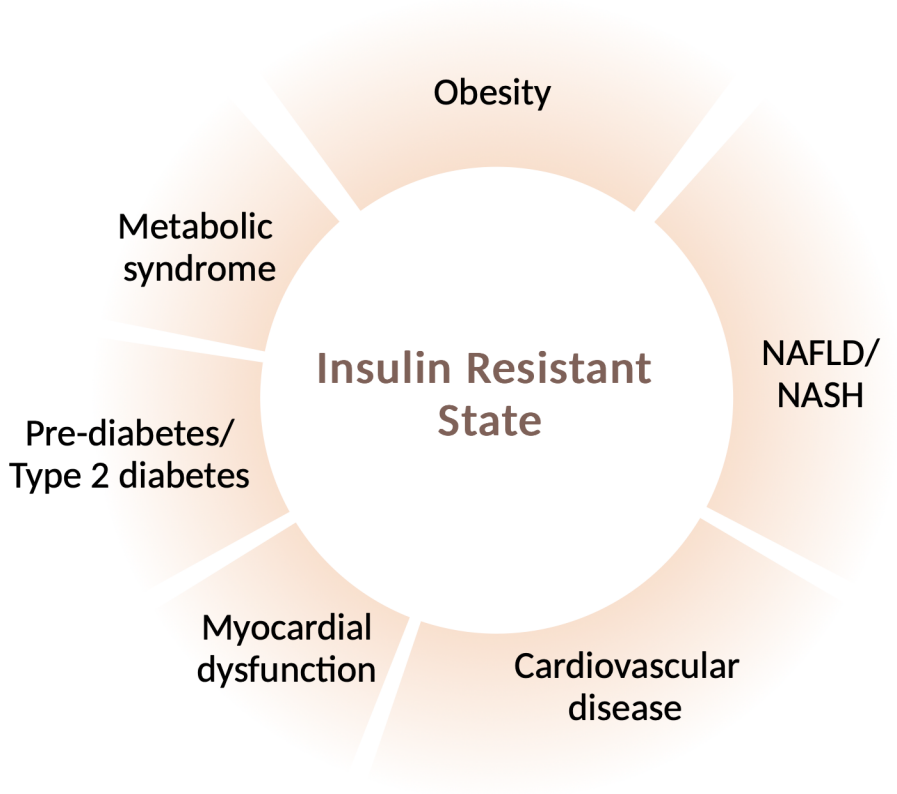
Disclaimer

This is a Non-CME Accredited Presentation.

Disclosures

Leigh Goedeke was an advisor for, and owns stock options in, OrsoBio.
OrsoBio owns the Yale intellectual property for CRMP.

The Insulin Resistant State is at the Core of Cardiometabolic Syndrome (CMS)



- Insulin resistant state
- Metabolic syndrome
- Prediabetes

→ Accelerated atherosclerosis and increased CVD risk

- Type 2 diabetes
- NASH
- Hypertension
- Chronic kidney disease

→ Amplification of vascular disease and risk of CVD events & myocardial dysfunction

Image modified from Garvey W & Mechanick JI, *Fuster and Hurst's The Heart* 2022 | Image created with BioRender.com

Current Management of CMS Focuses on Early Treatment Options that Encompass Vascular & Metabolic Outcomes

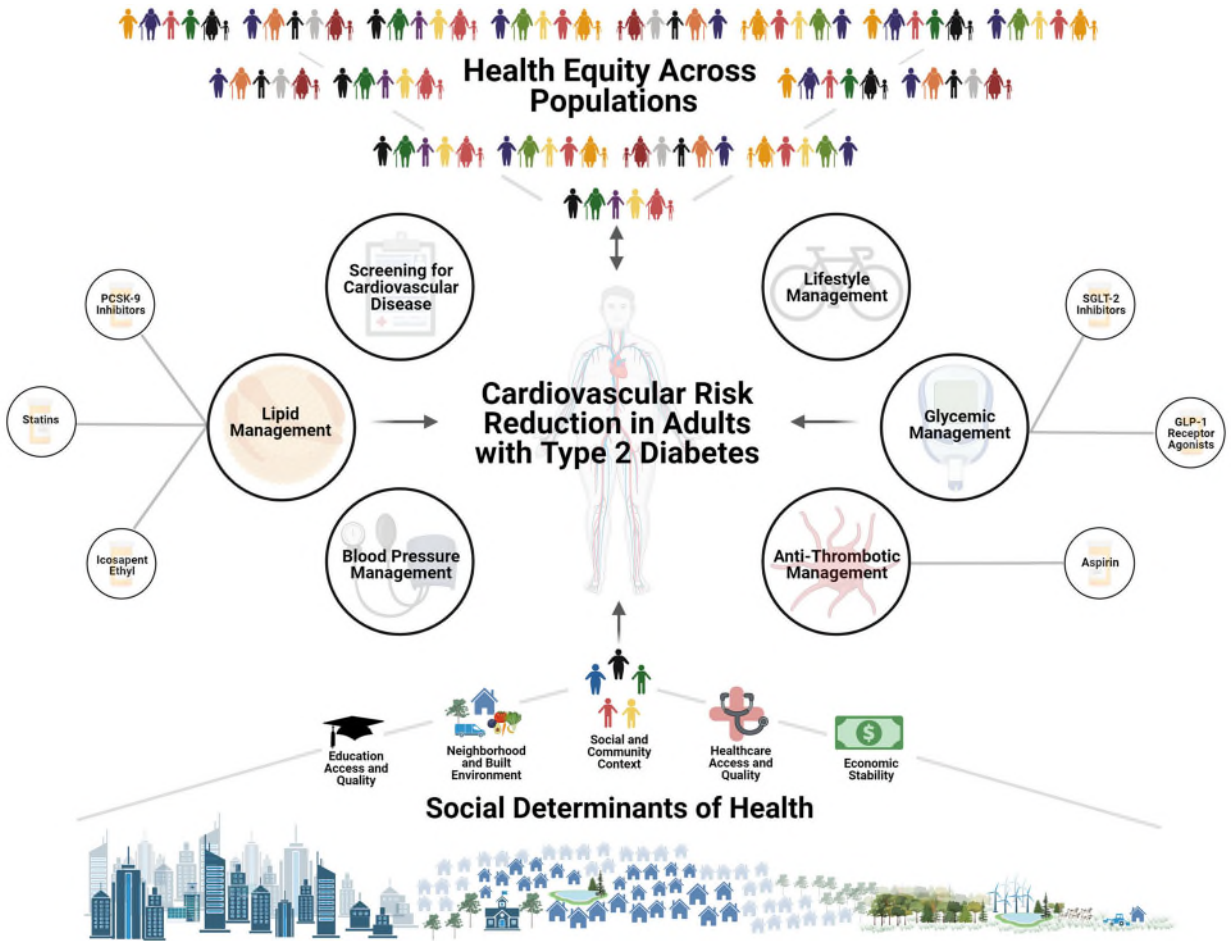
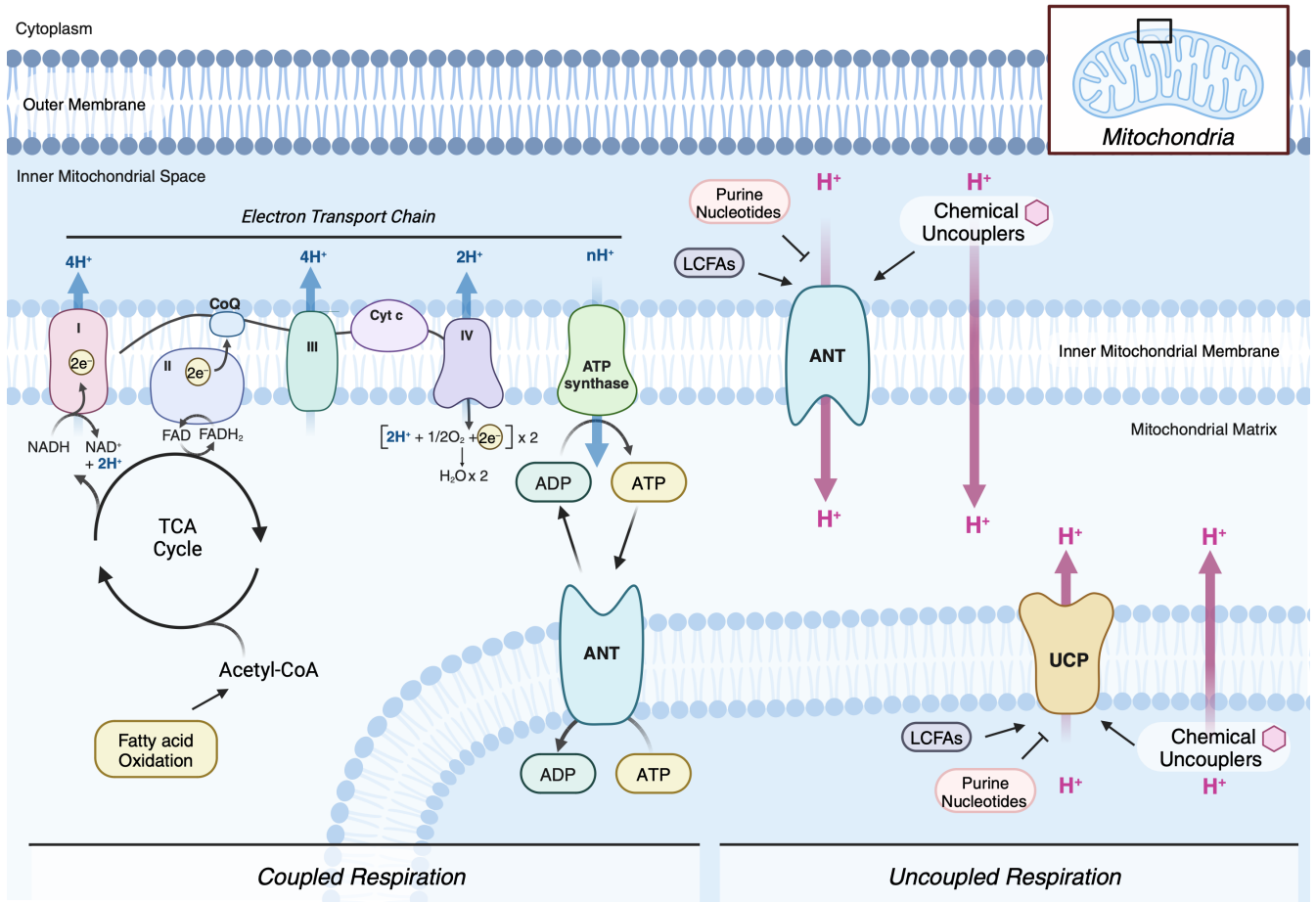


Image: AHA 2022

Mitochondrial Uncoupling



Improved Metabolic Health

1. ↓ ROS production → ↓ Oxidative Damage

2. ↑ ADP/ATP ratio → ↑ AMPK → ↑ FAO, ↓ DNL

3. ↑ Substrate oxidation → ↓ Acetyl-CoA → ↓ Glucose production; ↓ Ectopic Lipid → ↓ Insulin resistance

Image created with BioRender.com

History of 2,4 Dinitrophenol (DNP)

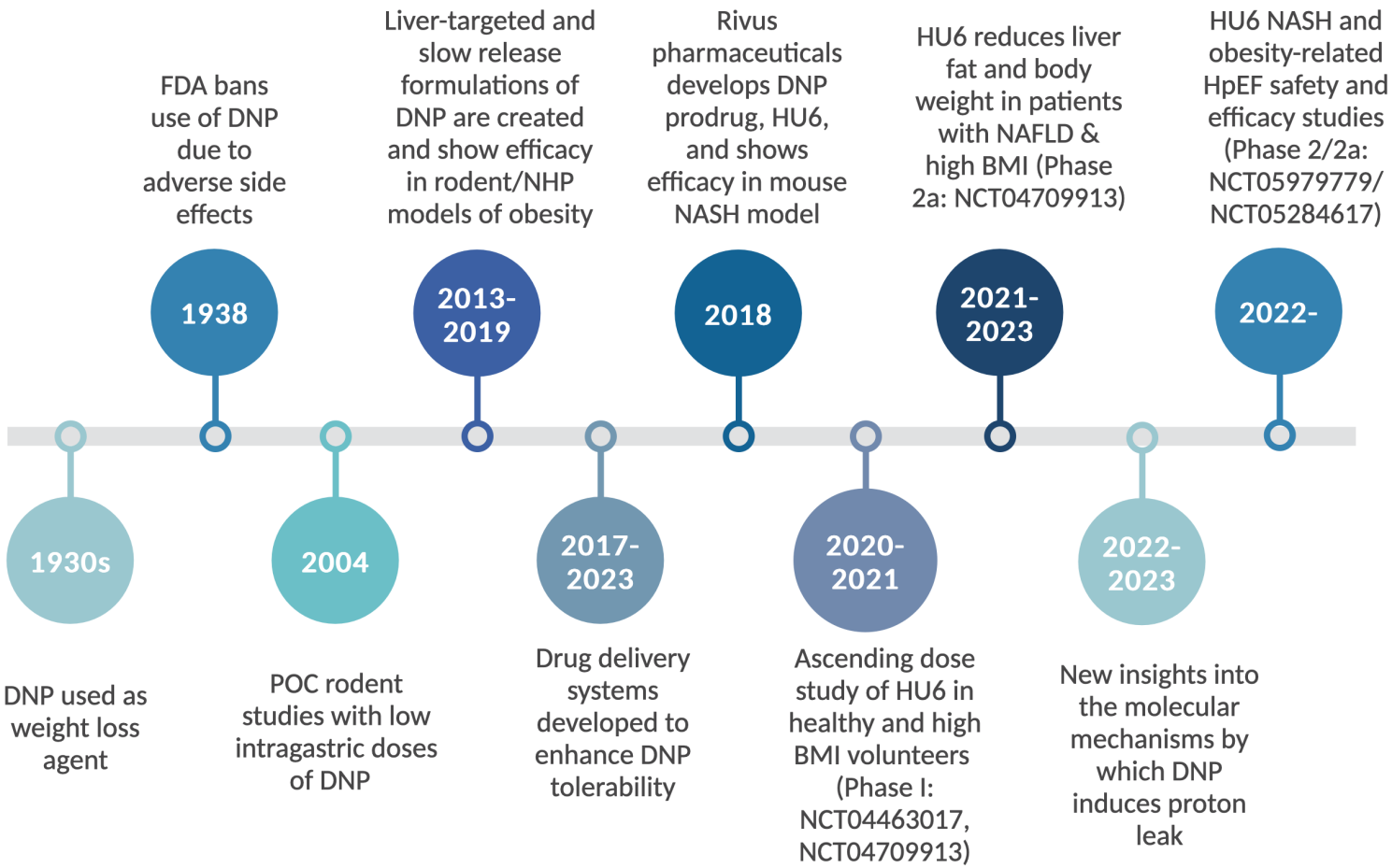


Image created with Biorender.com

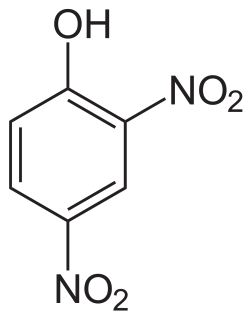
REPORT

Controlled-release mitochondrial protonophore reverses diabetes and steatohepatitis in rats

Rachel J. Perry[1,2,3], Dongyan Zhang[1], Xian-Man Zhang[2], James L. Boyer[2,4], Gerald I. Shulman[1,2,3,*]

+ See all authors and affiliations

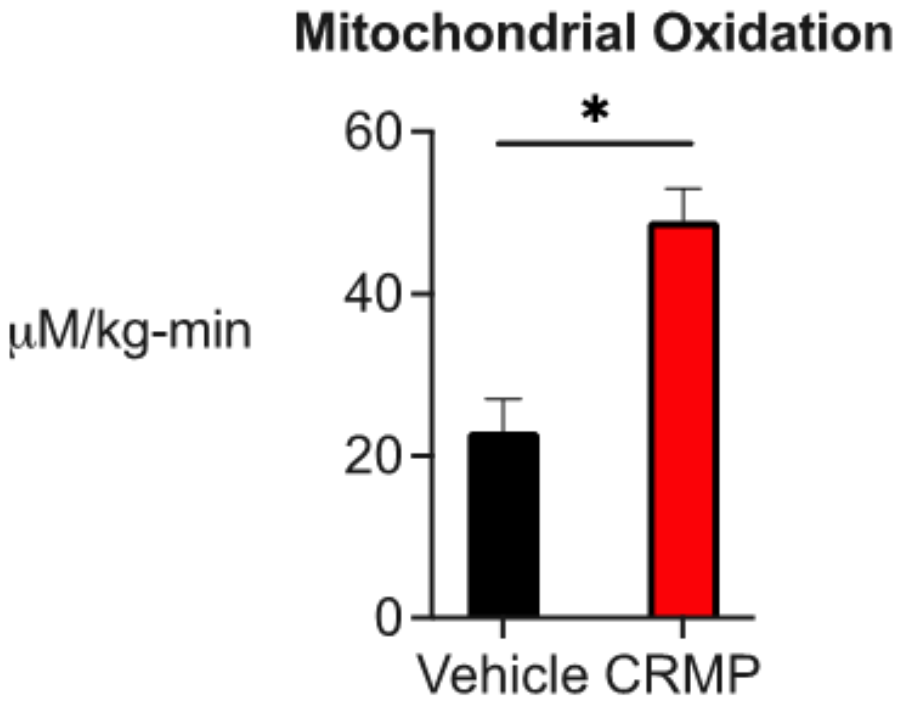
Science 13 Mar 2015:
Vol. 347, Issue 6227, pp. 1253-1256
DOI: 10.1126/science.aaa0672



- Controlled-release formulation of DNP
- Liver-directed by first-pass metabolism

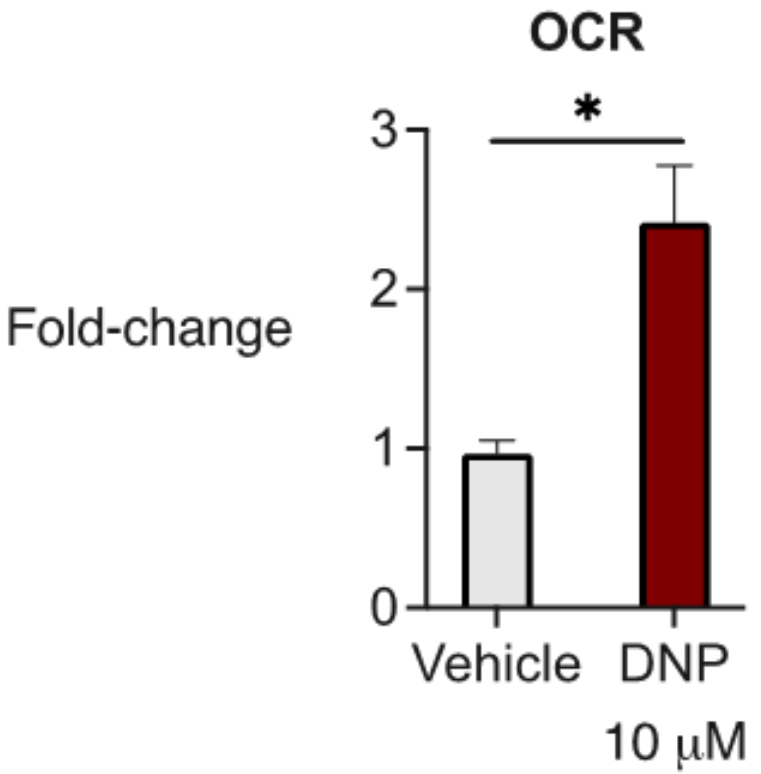
Acute CRMP Treatment Increases Hepatic Mitochondrial Oxidation

Male Sprague Dawley Rat

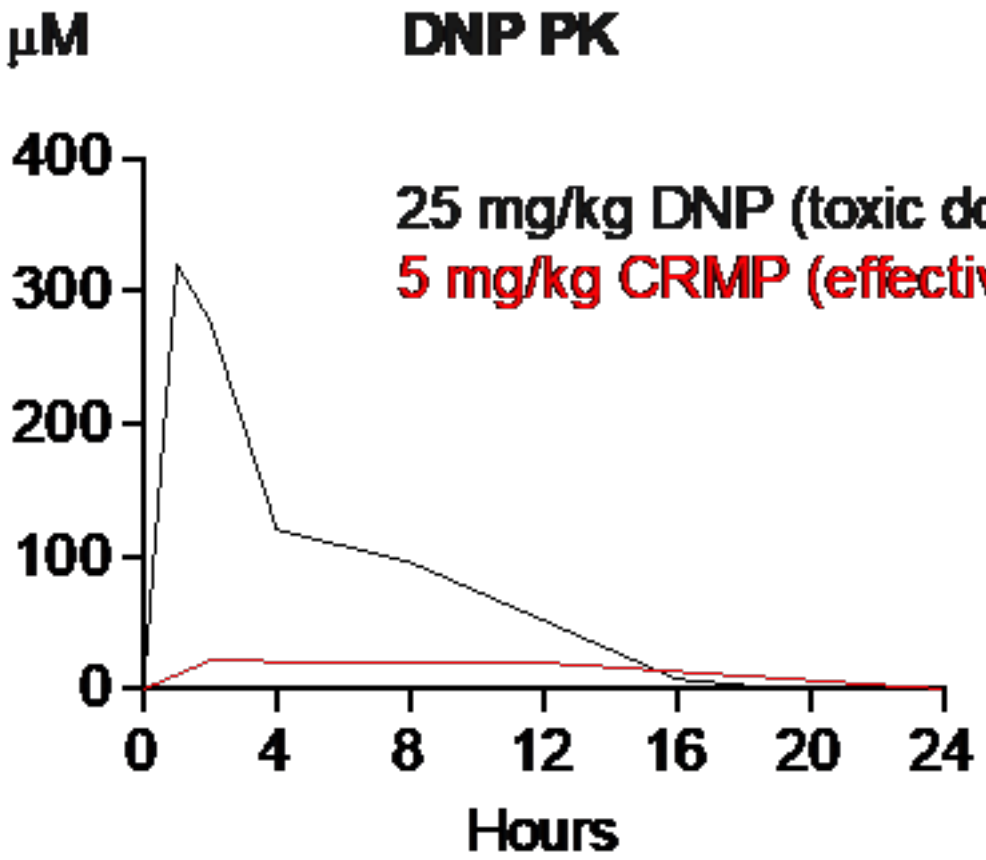


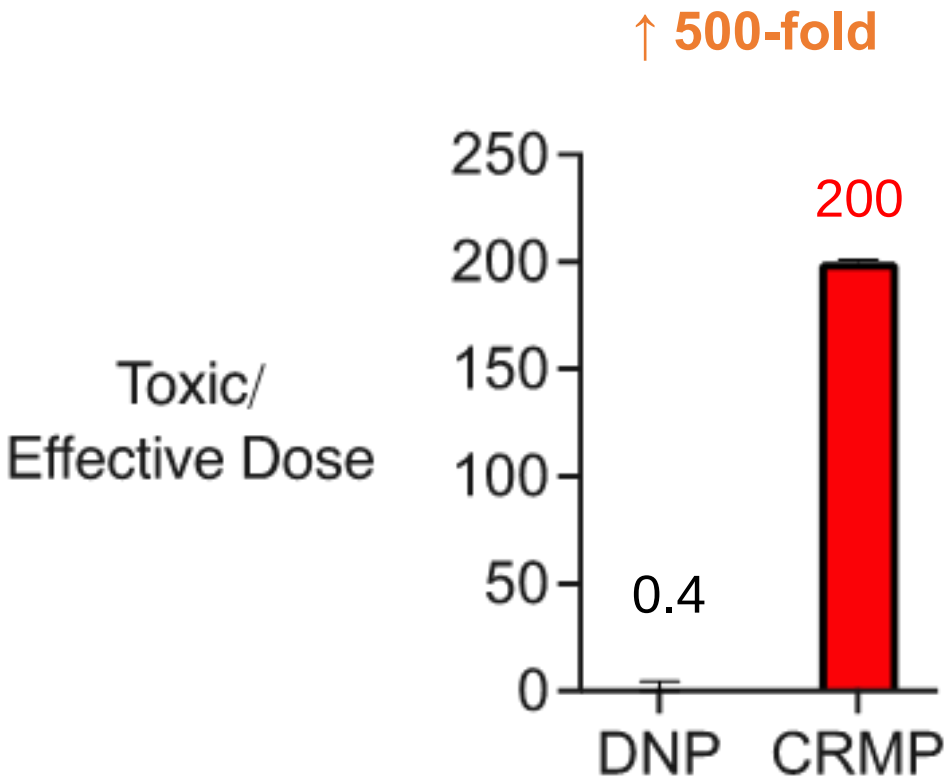
Liver DNP: 5-10 μM

Primary Rat Hepatocytes

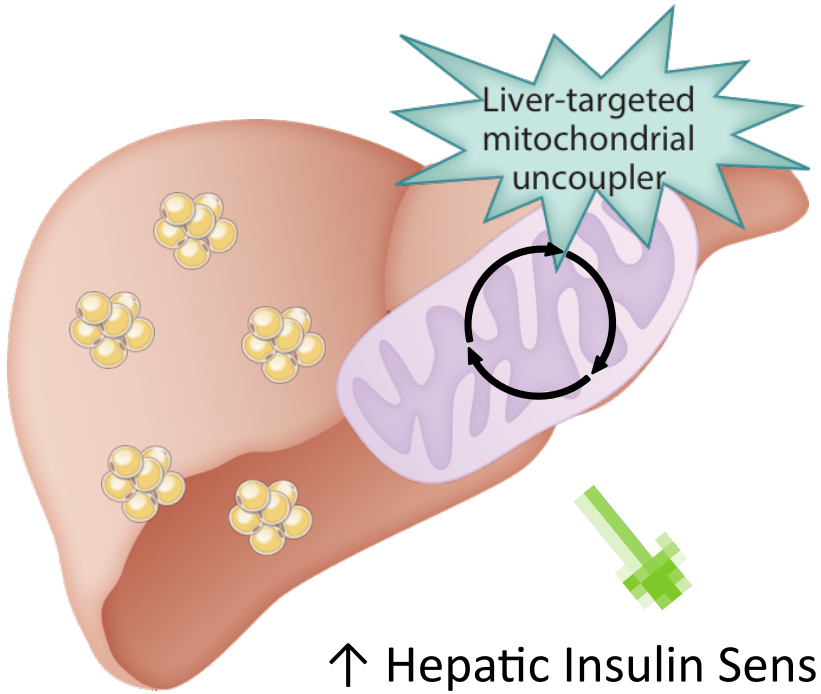


Controlled-Release Formulation of DNP Reduces Toxicity

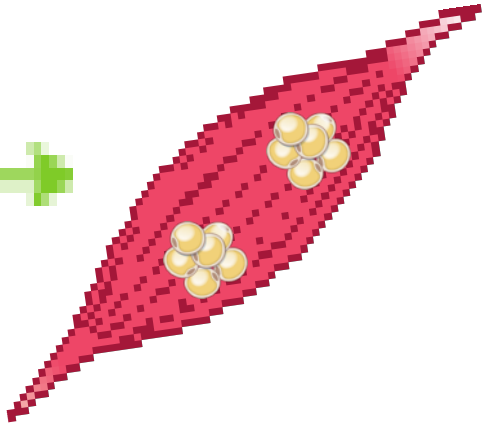




Mild Mitochondrial Uncoupling to Treat Steatotic Liver Disease and Insulin Resistance in Rodents



↓VLDL Production
↓ Plasma TG

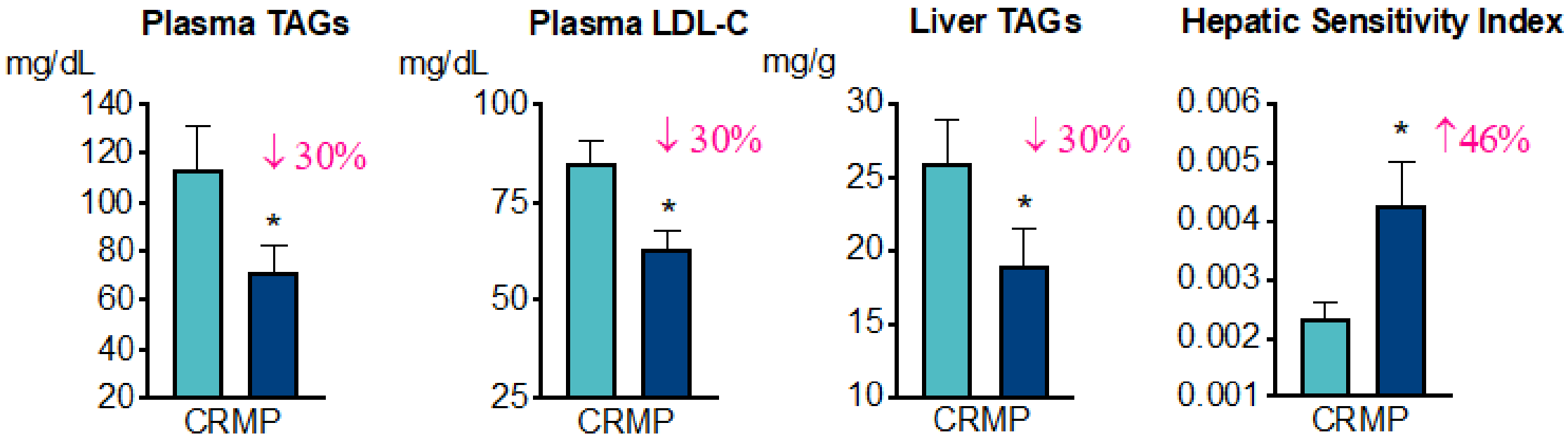


↑ Peripheral Insulin Sensitivity

↑ Hepatic Insulin Sensitivity

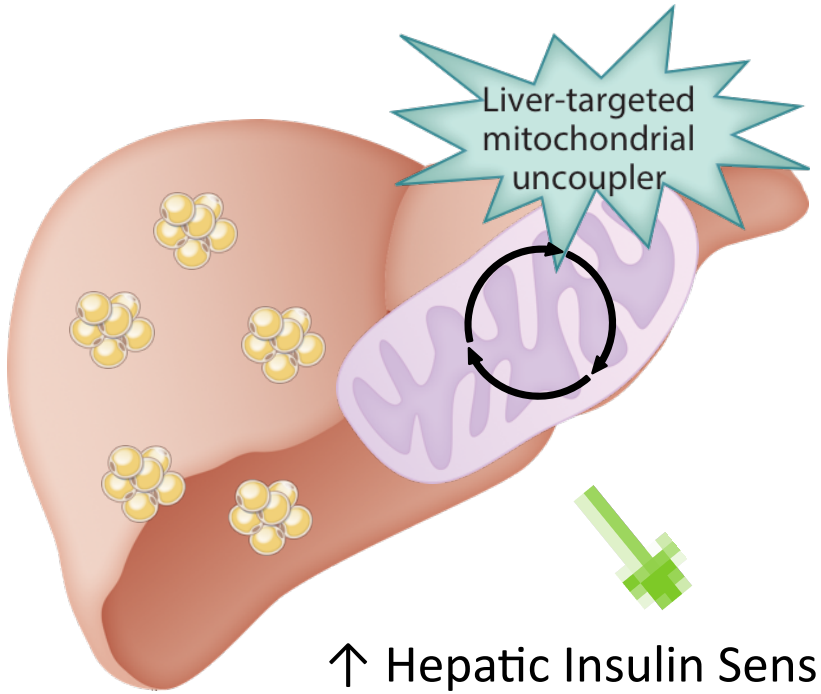
↓ Fasting Gluconeogenesis

CRMP Reduces Dyslipidemia, Hepatic Steatosis & Insulin Resistance in Dysmetabolic NHPs



Goedeke L et al *Sci Trans Med* 2019

Mild Mitochondrial Uncoupling to Treat CMS



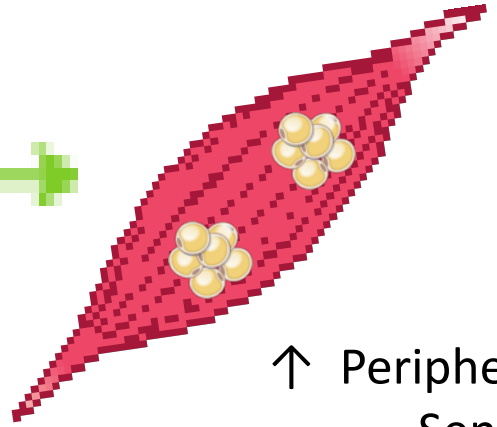
↑ Hepatic Insulin Sensitivity

↓ Fasting Gluconeogenesis

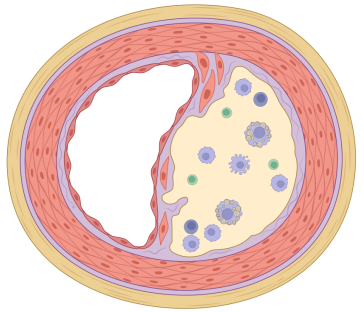
↓VLDL Production

↓ Plasma TG

↓ Plasma LDL-C

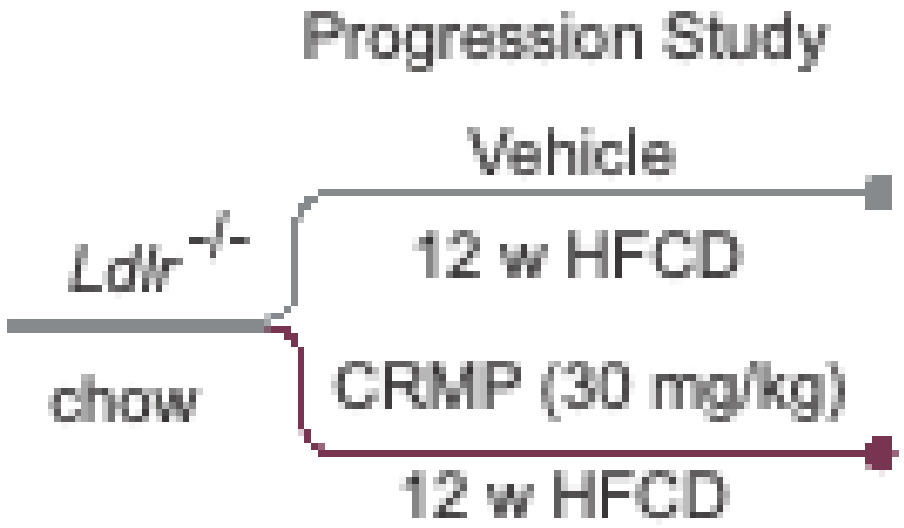


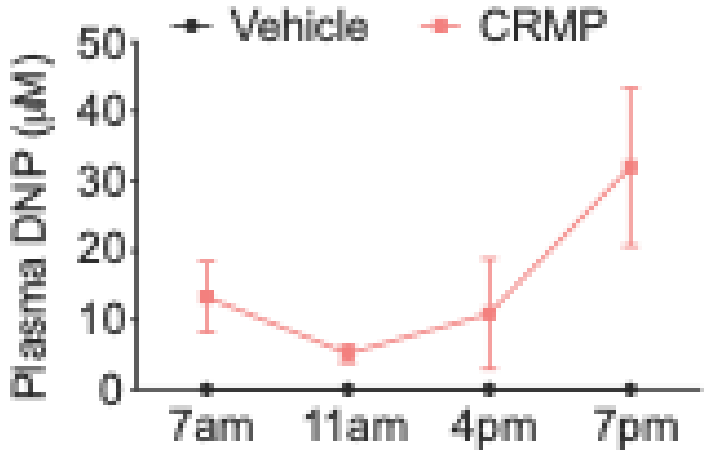
↑ Peripheral Insulin Sensitivity

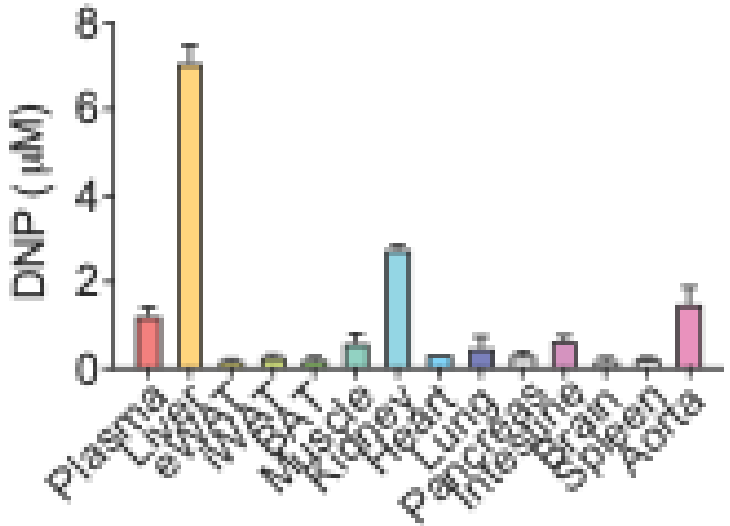


Atherosclerosis?

Atherosclerosis Progression Study

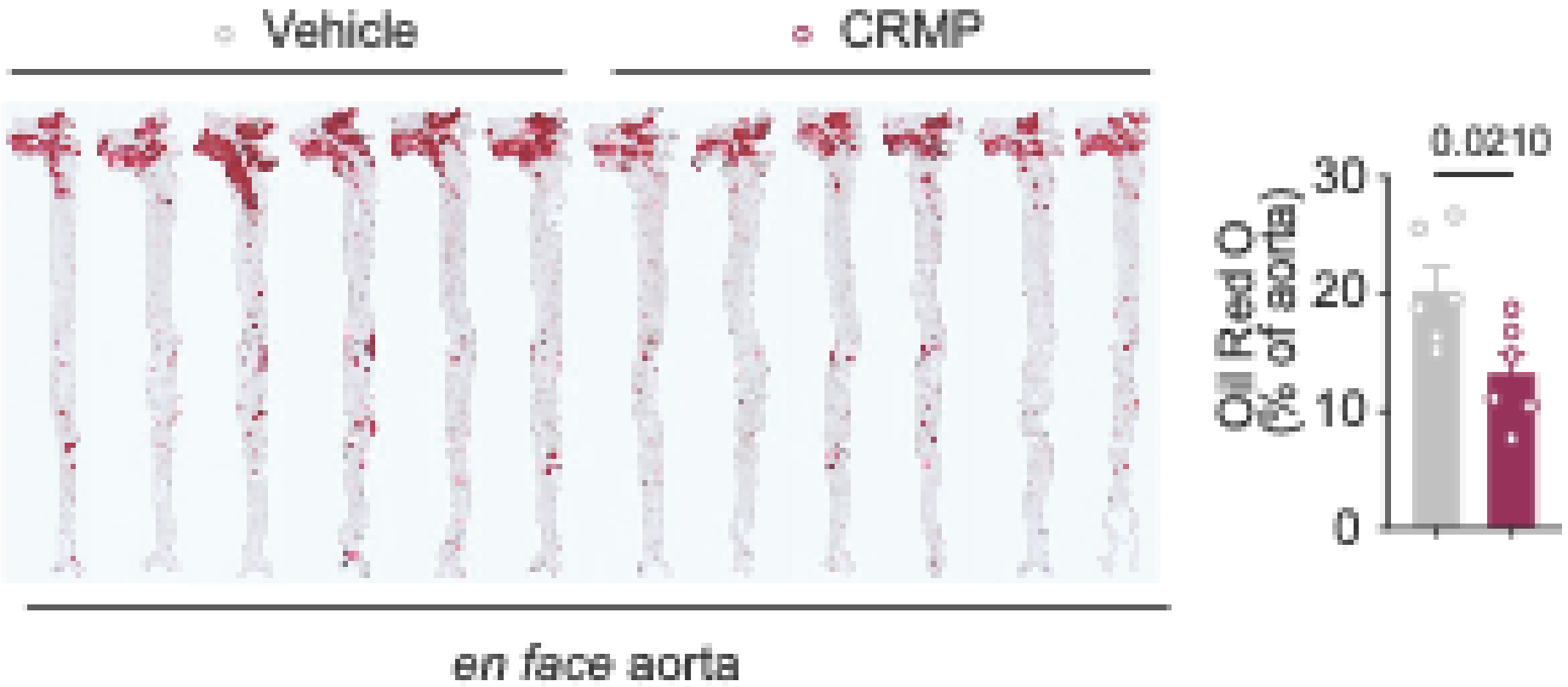






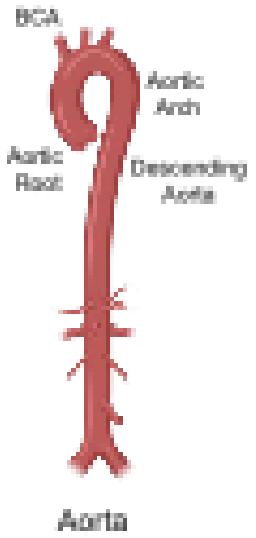
Gindri dos Santos, B. *et al Under preparation*

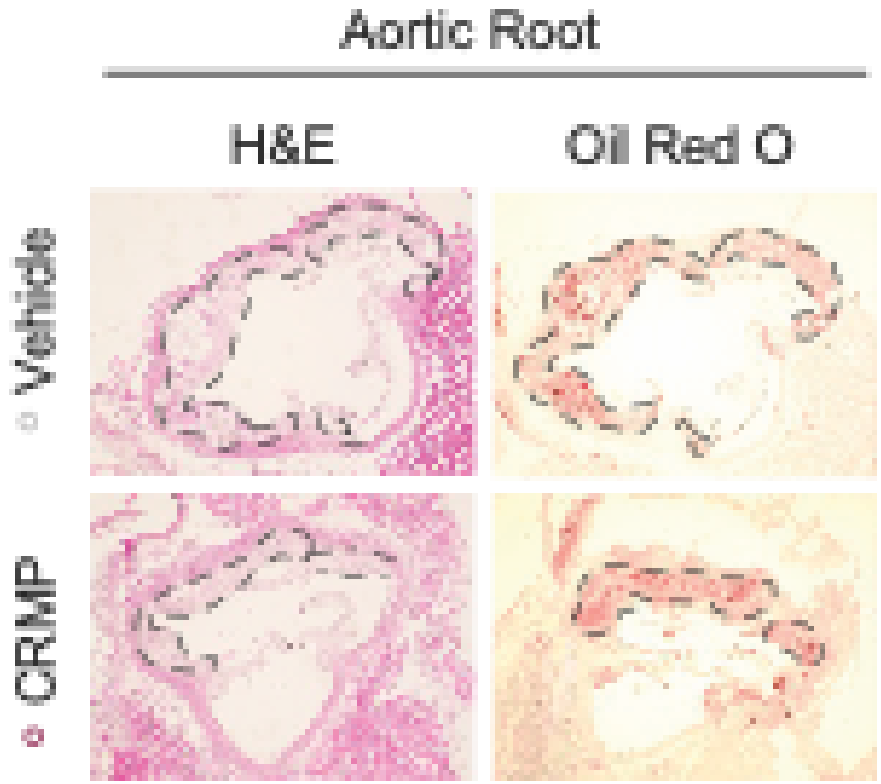
CRMP Reduces Atheroprogression in *Ldlr*$^{-/-}$ Mice

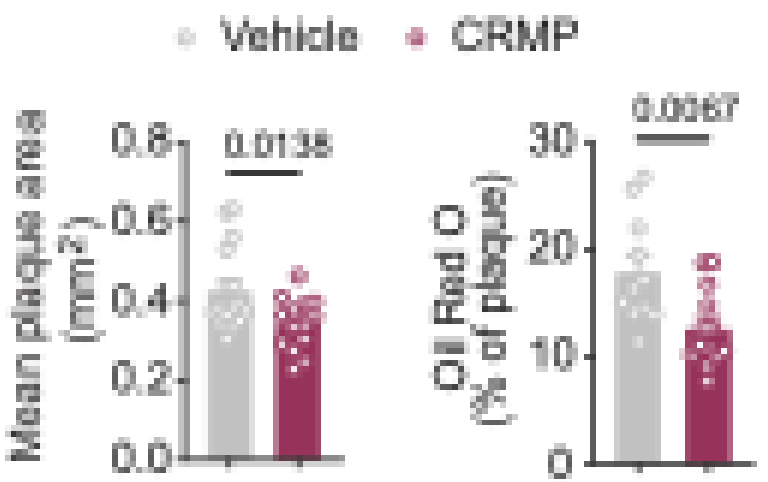


Gindri dos Santos, B. *et al Under preparation*

CRMP Reduces Plaque Area & Neutral Lipid Content in the Aortic Root

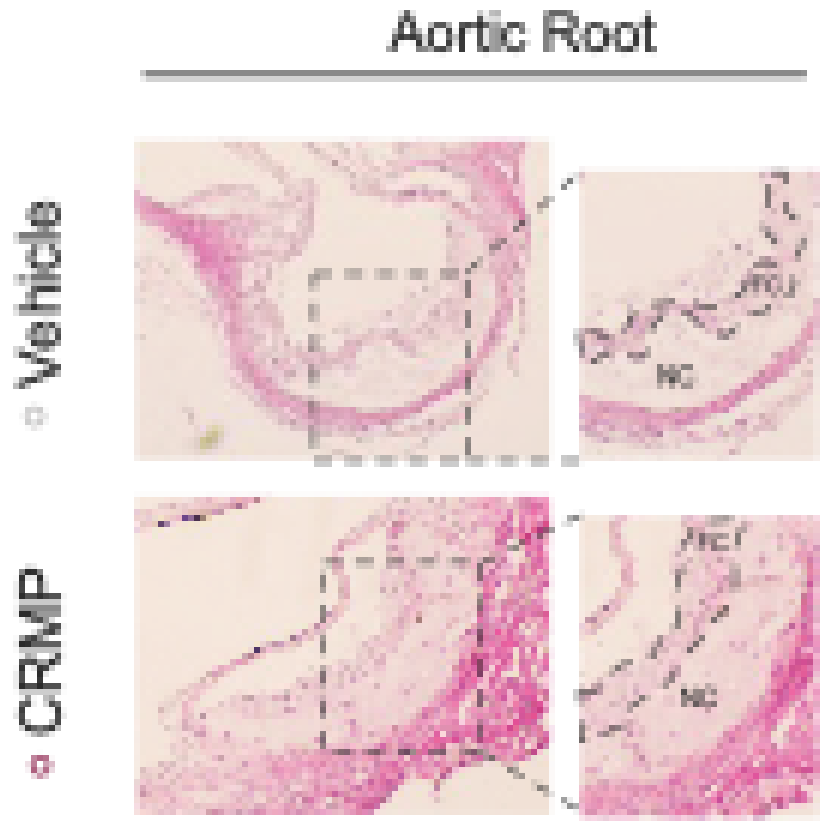


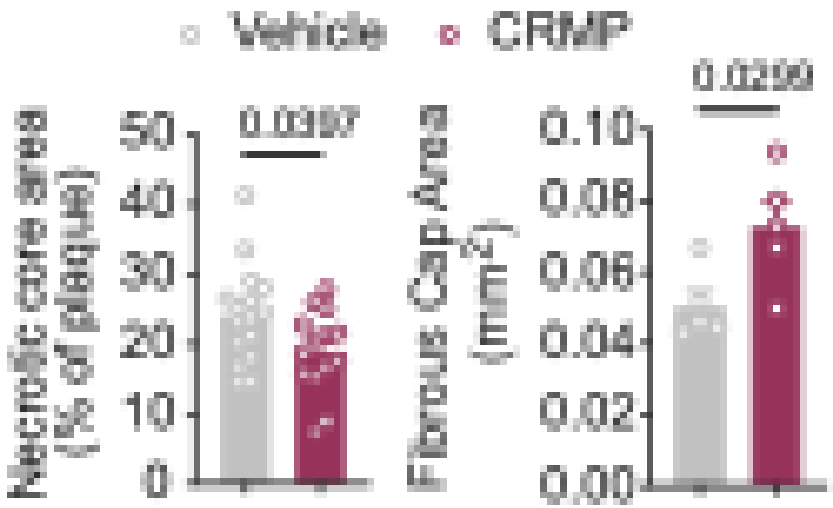




Gindri dos Santos, B. *et al Under preparation*

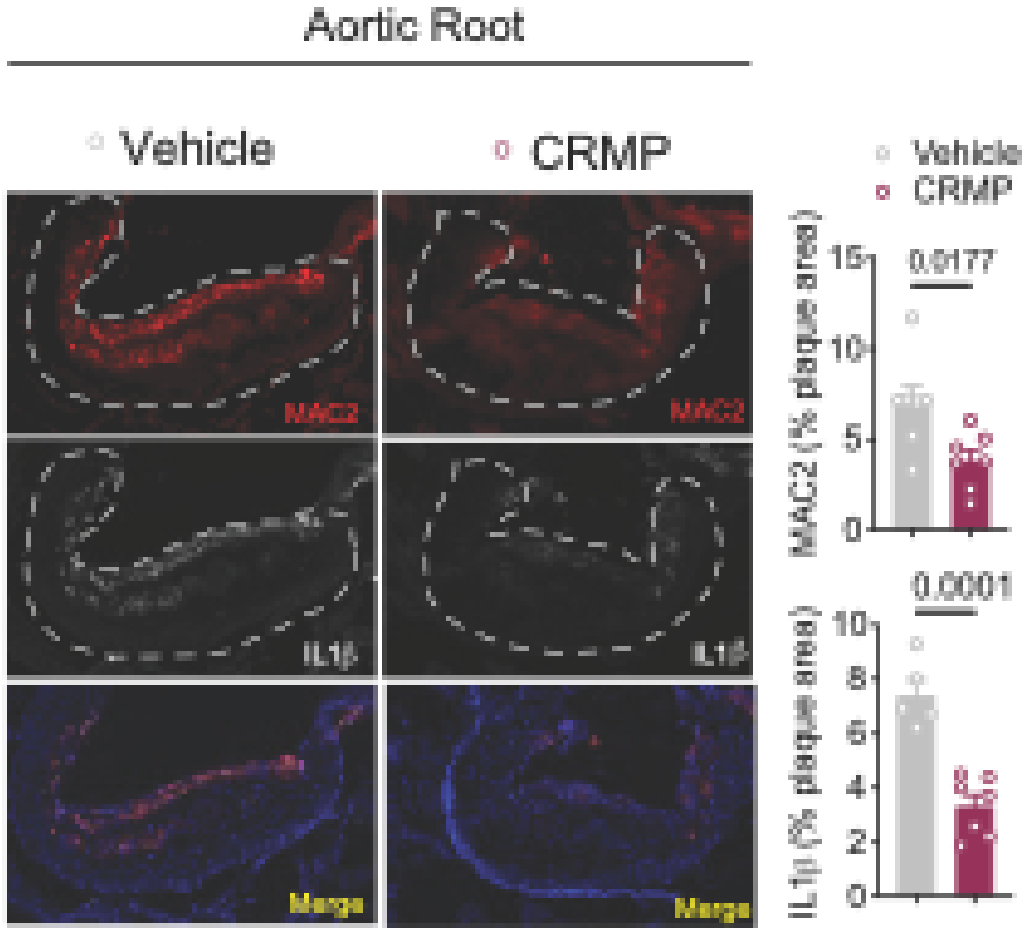
CRMP Treatment Increases Plaque Stability





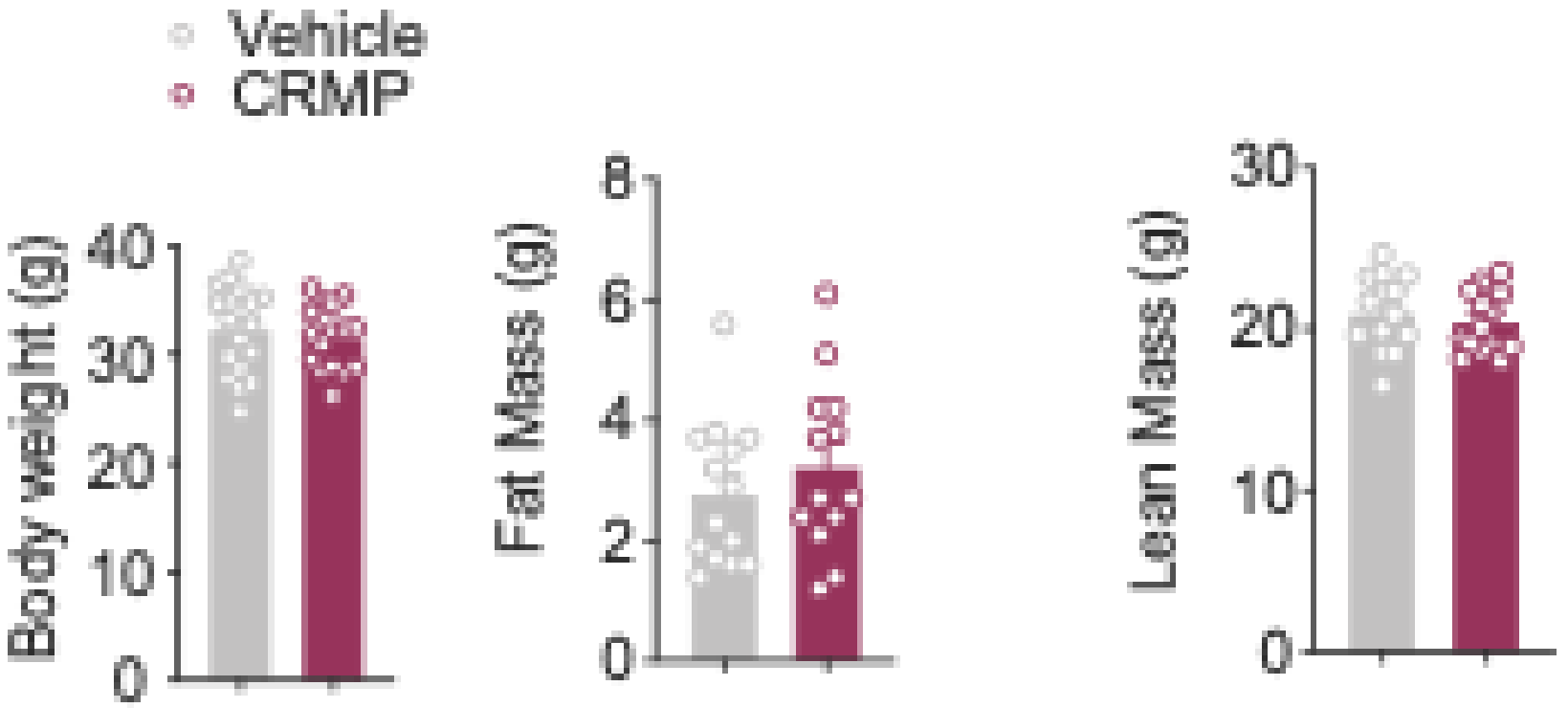
Gindri dos Santos, B. *et al Under preparation*

CRMP Treatment Reduces Macrophage and IL-1β Content in the Aortic Root



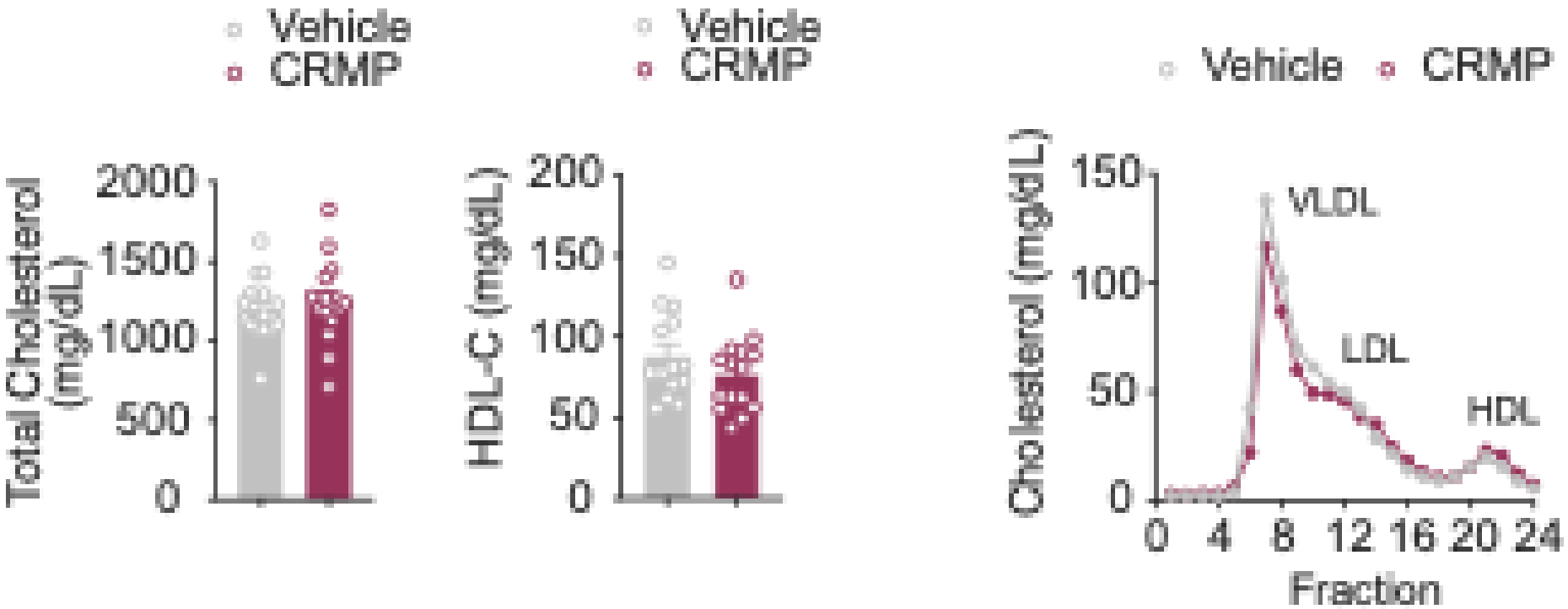
Gindri dos Santos, B. *et al Under preparation*

CRMP Does Not Alter Body Composition



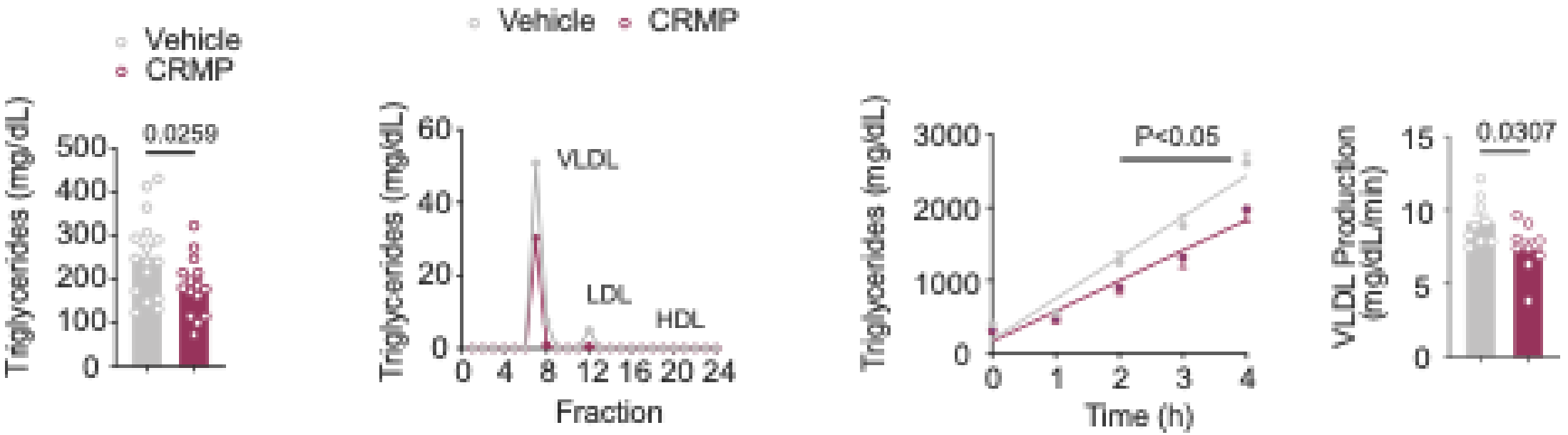
Gindri dos Santos, B. *et al Under preparation*

CRMP Does Not Alter Plasma Cholesterol Levels

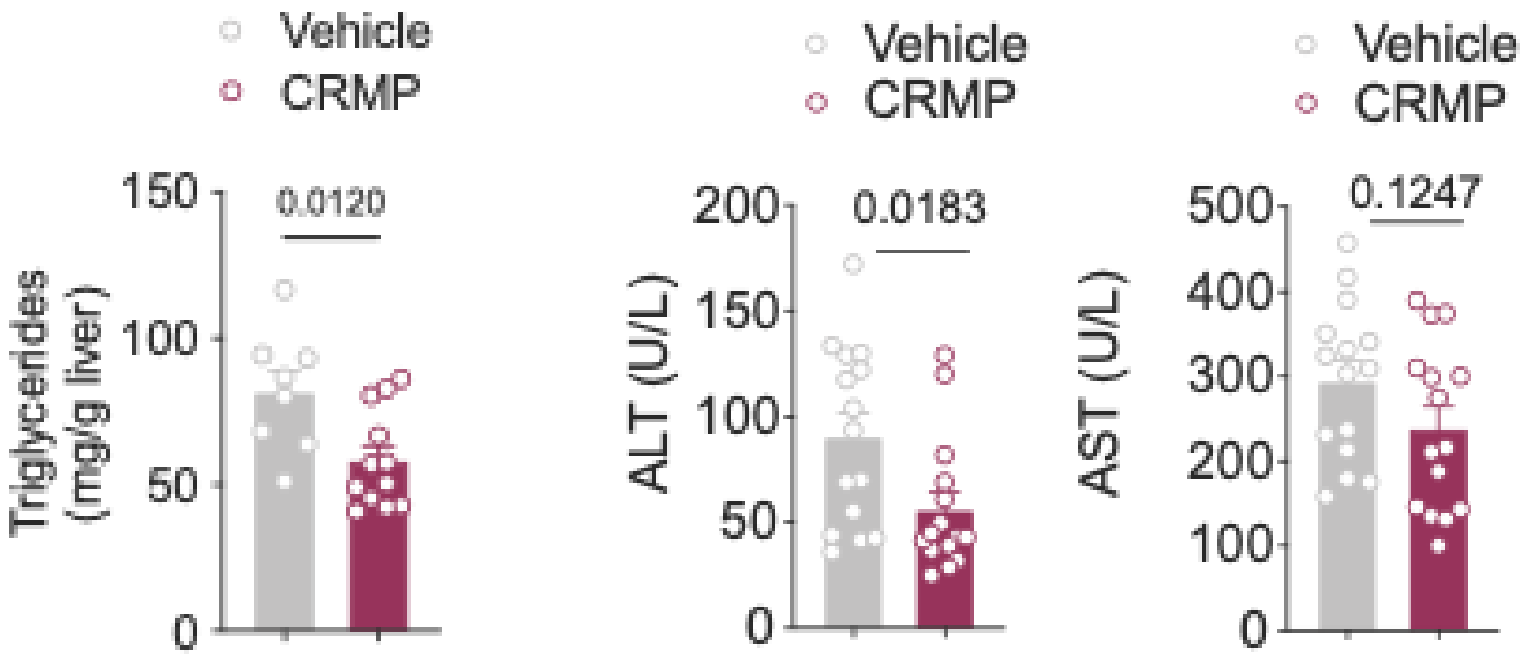


Gindri dos Santos, B. *et al Under preparation*

CRMP Reduces Plasma VLDL- and LDL-Triglyceride Levels

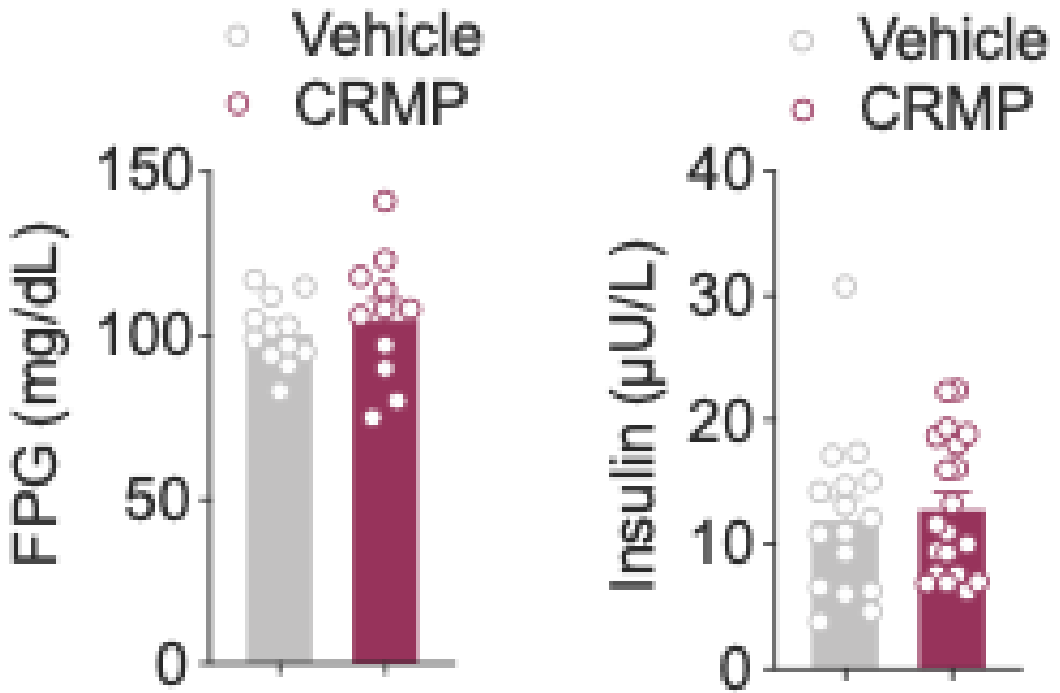


CRMP Reduces Hepatic Steatosis



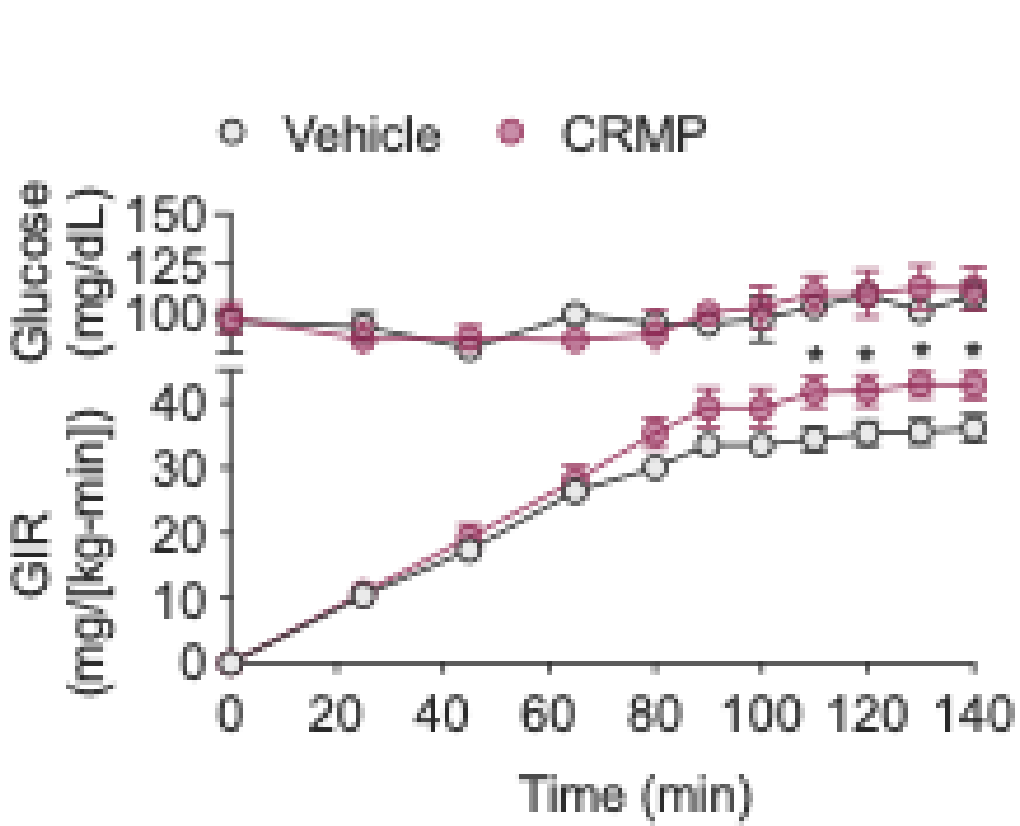
Gindri dos Santos, B. *et al Under preparation*

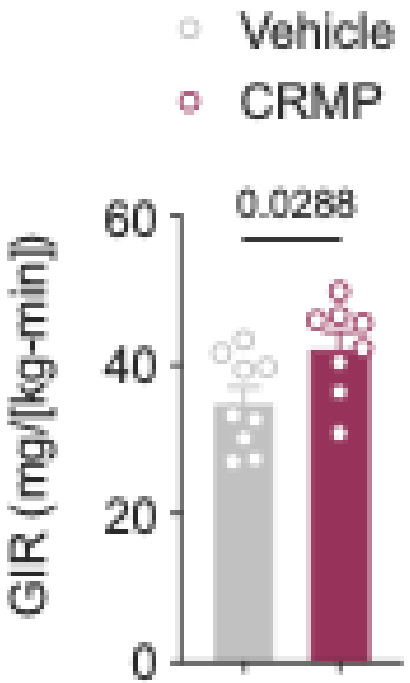
CRMP Treatment Does Not Alter Fasting Plasma Glucose or Insulin Levels

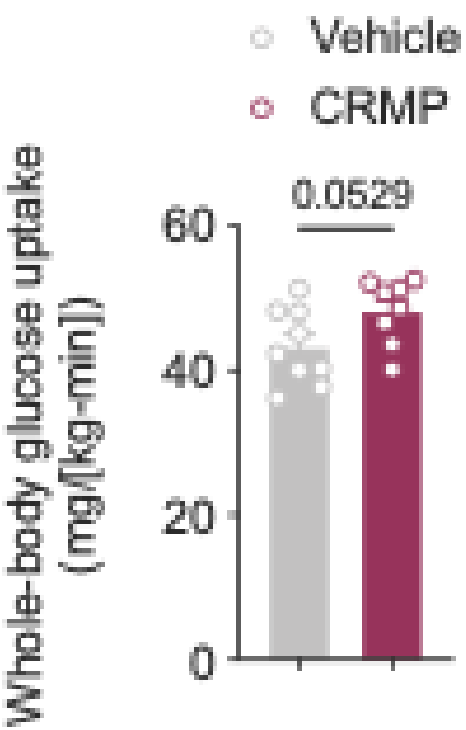


Gindri dos Santos, B. *et al Under preparation*

CRMP Treatment Increases Whole Body Insulin Sensitivity

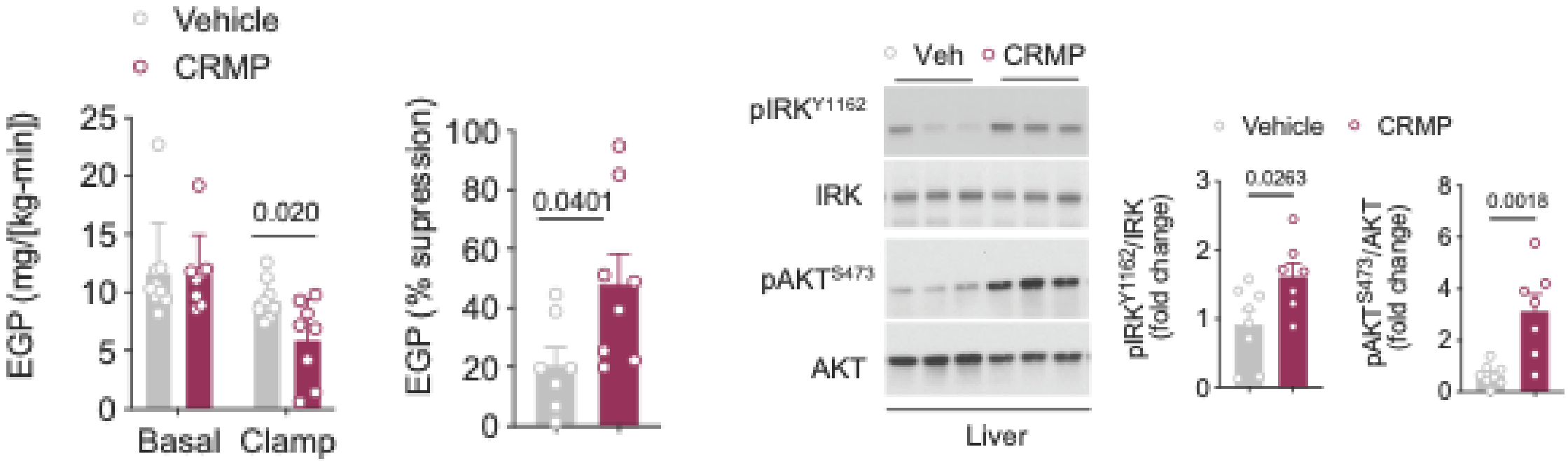






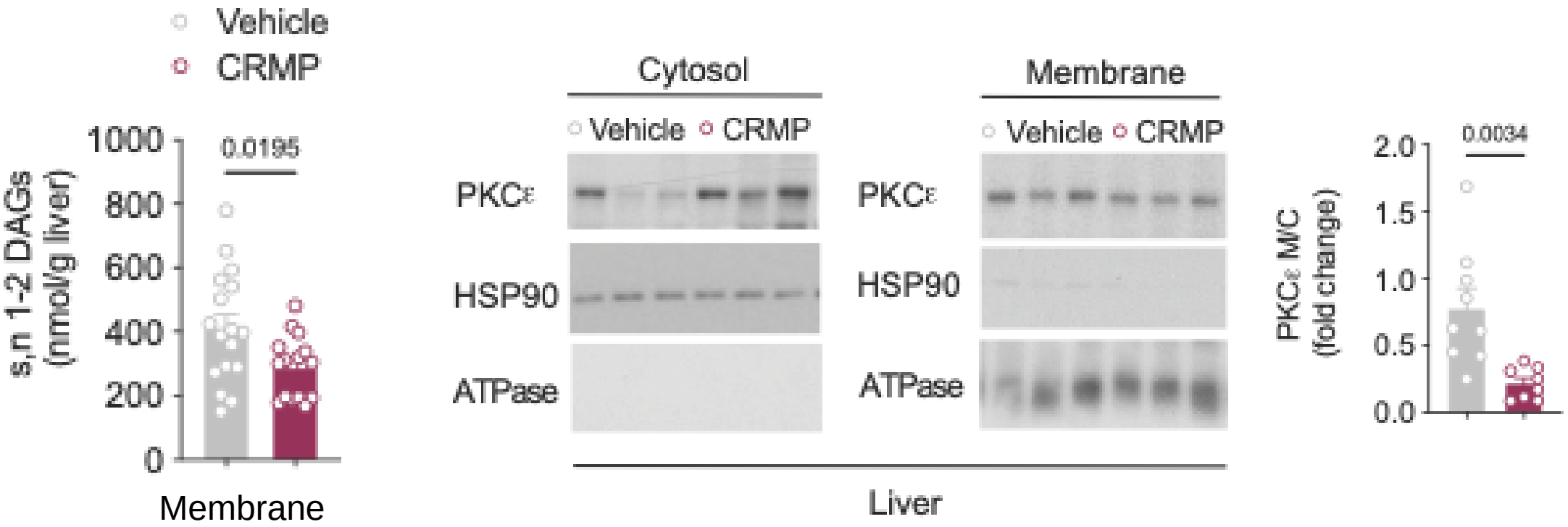
Gindri dos Santos, B. *et al Under preparation*

CRMP Treatment Increases Hepatic Insulin Sensitivity

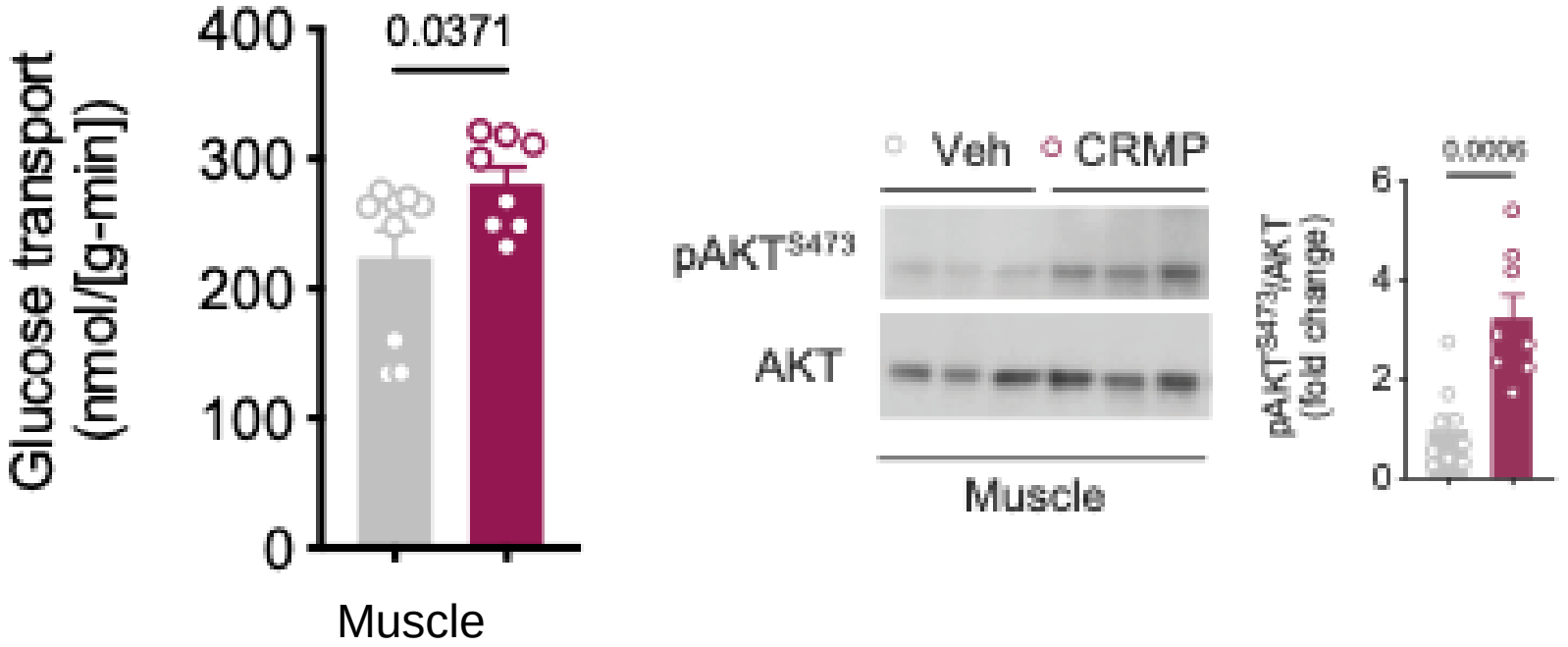


Gindri dos Santos, B. *et al Under preparation*

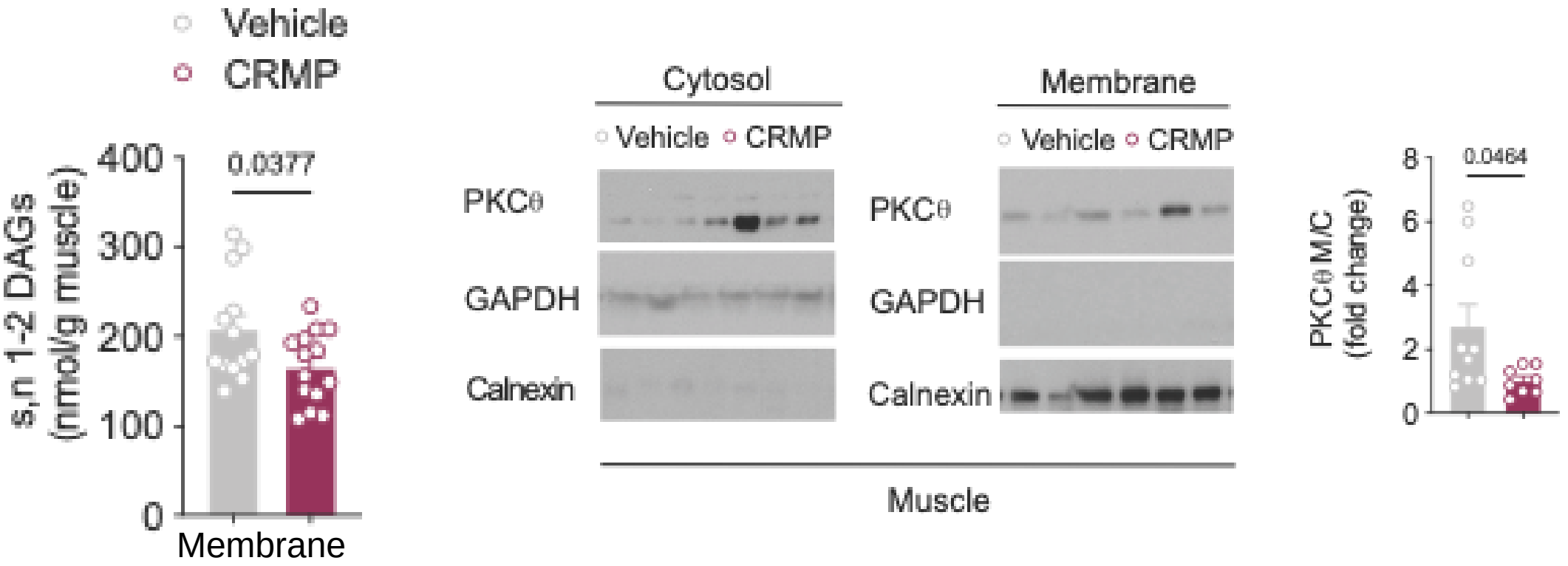
CRMP Treatment Reduces Hepatic DAG Content & PKCε M/C Translocation



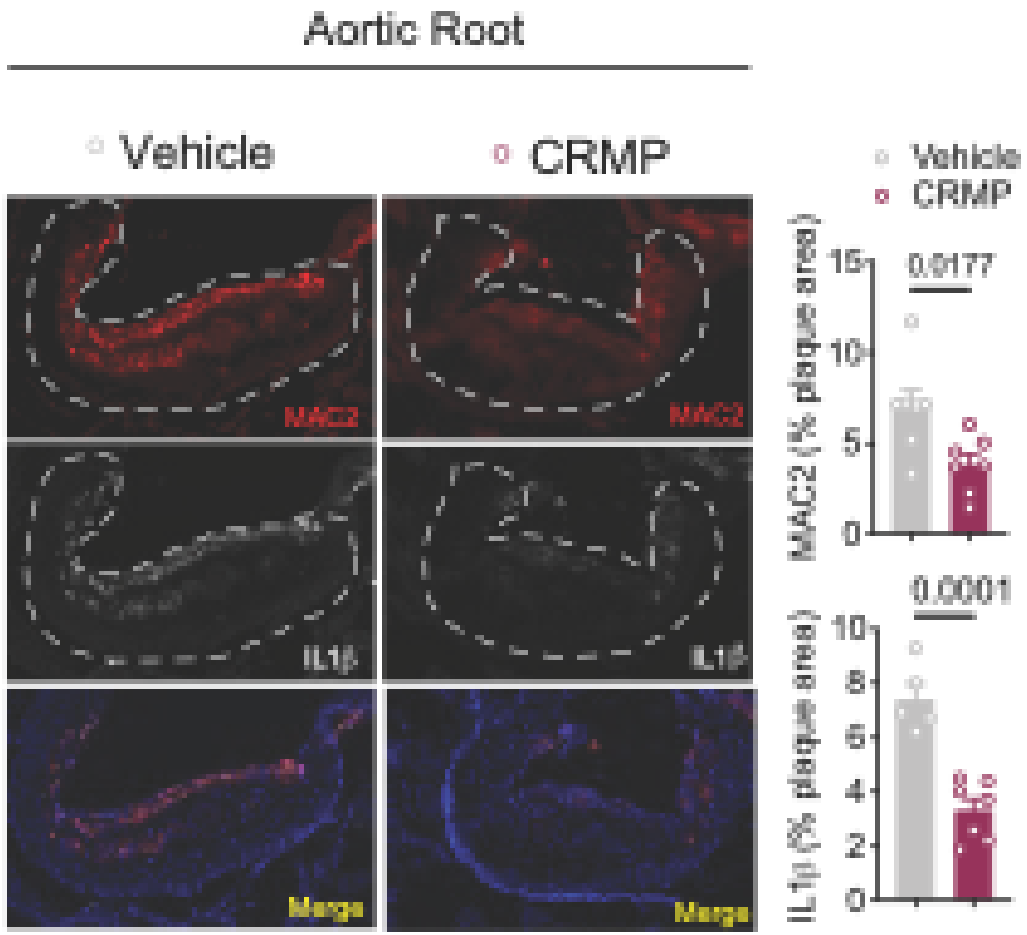
CRMP Treatment Increases Muscle Insulin Sensitivity

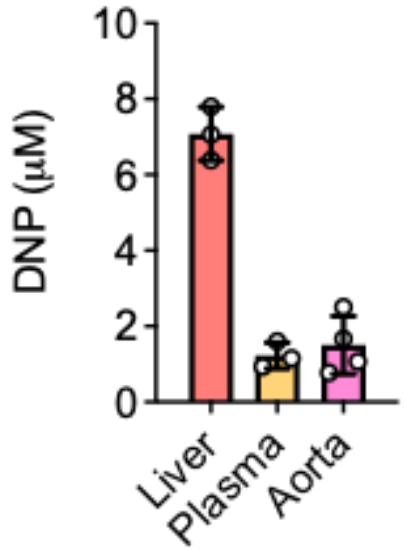


CRMP Treatment Reduces Muscle DAG Content & PKCθ M/C Translocation



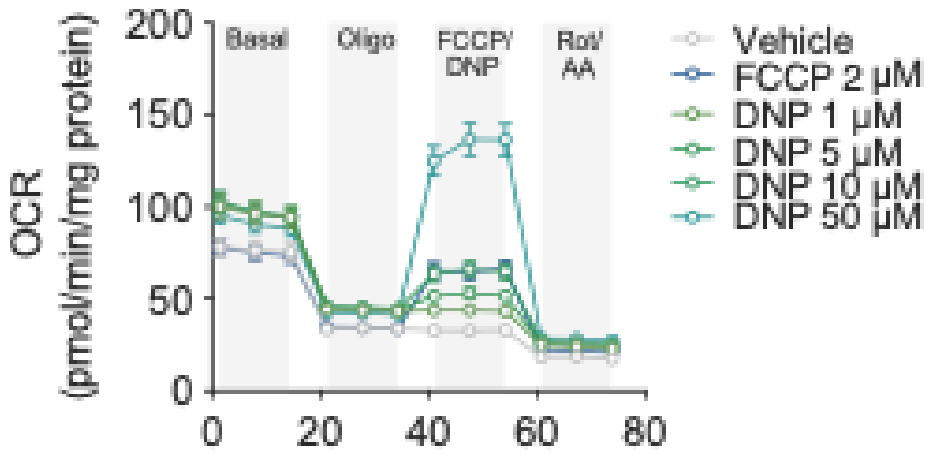
CRMP Reduces Plaque IL-1β: Localized vs Systemic Effect?

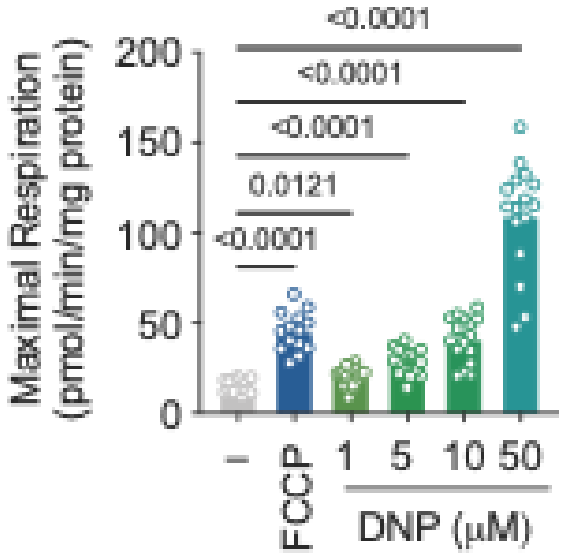




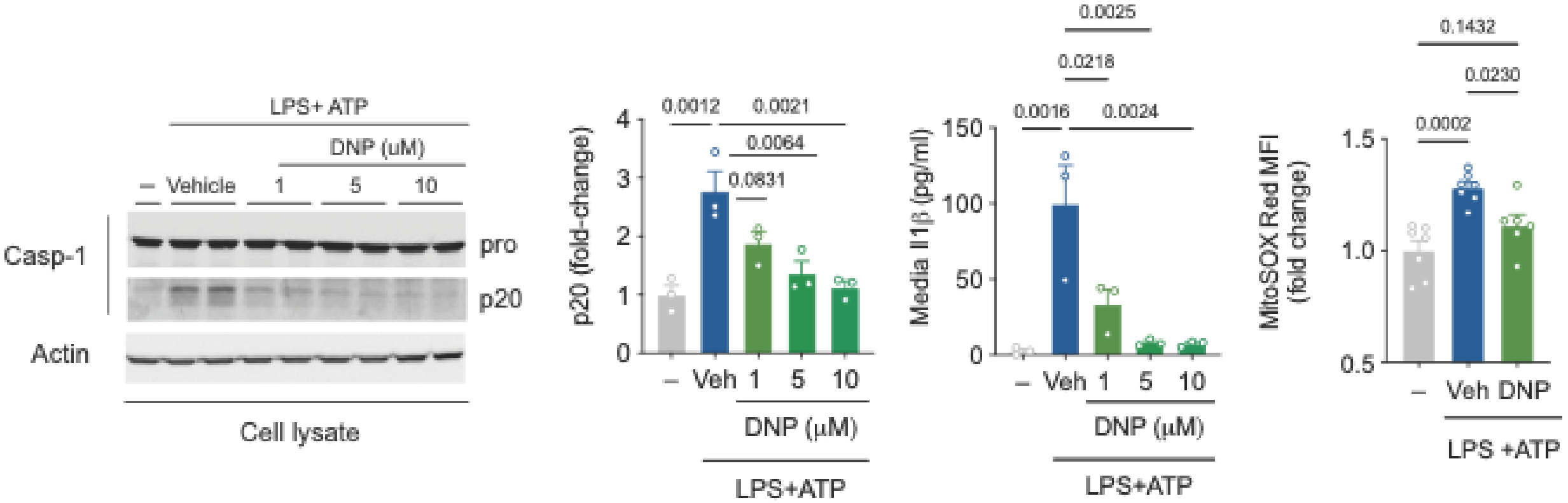
Gindri dos Santos, B. *et al Under preparation*

DNP Increases Mitochondrial Respiration in BMDMs





DNP Dose-Dependently Decreases Inflammasome Activation in BMDMs



Mitochondrial Uncoupling for the Treatment of CMS

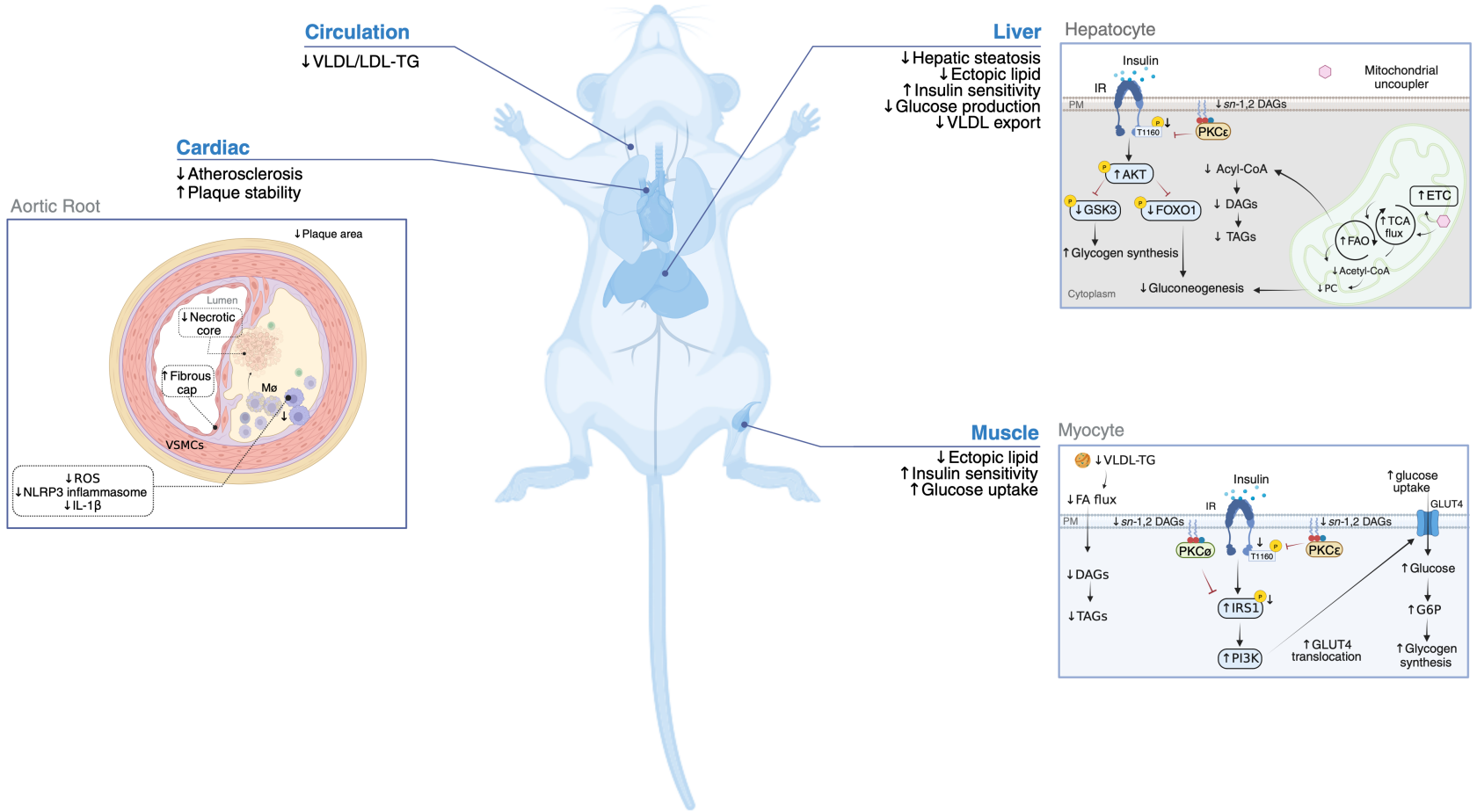


Image created with BioRender.com

Conclusions

- Mild mitochondrial uncoupling with CRMP is a safe and effective therapeutic strategy to improve dyslipidemia, hepatic steatosis and insulin resistance in dysmetabolic mice and non-human primates

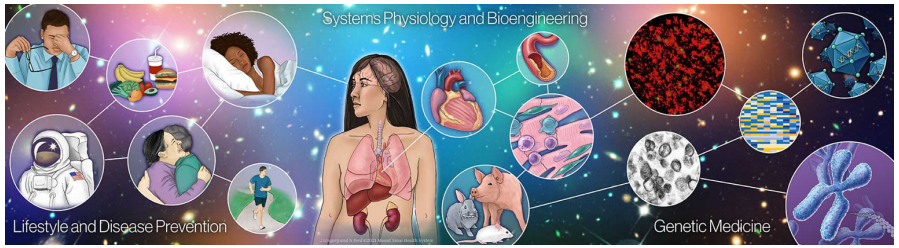
- CRMP reduces atheroprogression and increases plaque stability in high-fat cholesterol diet-fed *Ldlr*$^{-/-}$ mice through increases in hepatic and macrophage mitochondrial inefficiency

- Supports clinical validation studies of CRMP for CMS-associated co-morbidities

- Expands the field beyond current CMS treatment options:
  - Life-style modifications, GLP-1 analogs/GLP-1RAs etc.

Acknowledgements

Icahn School of Medicine at Mount Sinai



Goedeke Lab
Bernardo Gindri dos Santos
Niki Brisnovali
Myles Coven
Connor Haney
Seonghun Yoon

McAlpine Lab
Teresa Gerhardt

Fernández-Hernando Lab
Carlos Fernández -Hernando
Noemi Rotllan
Jonathan Sun
Xinbo Zhang

Suárez Lab
Yajaira Suárez
Alberto Canfrán-Duque

Gary W. Cline
Rachel J. Perry

Shulman Lab
Gerald Shulman
Kitt Falk Petersen
Ali Nasiri
Mario Kahn
Irina Smolgovsky
John Stack
Xian-Man Zhang
Xiaoxian Ma
Wanling Zhu

OrsoBio, Inc
G. Mani Subramanian
Rob Myers

Funding

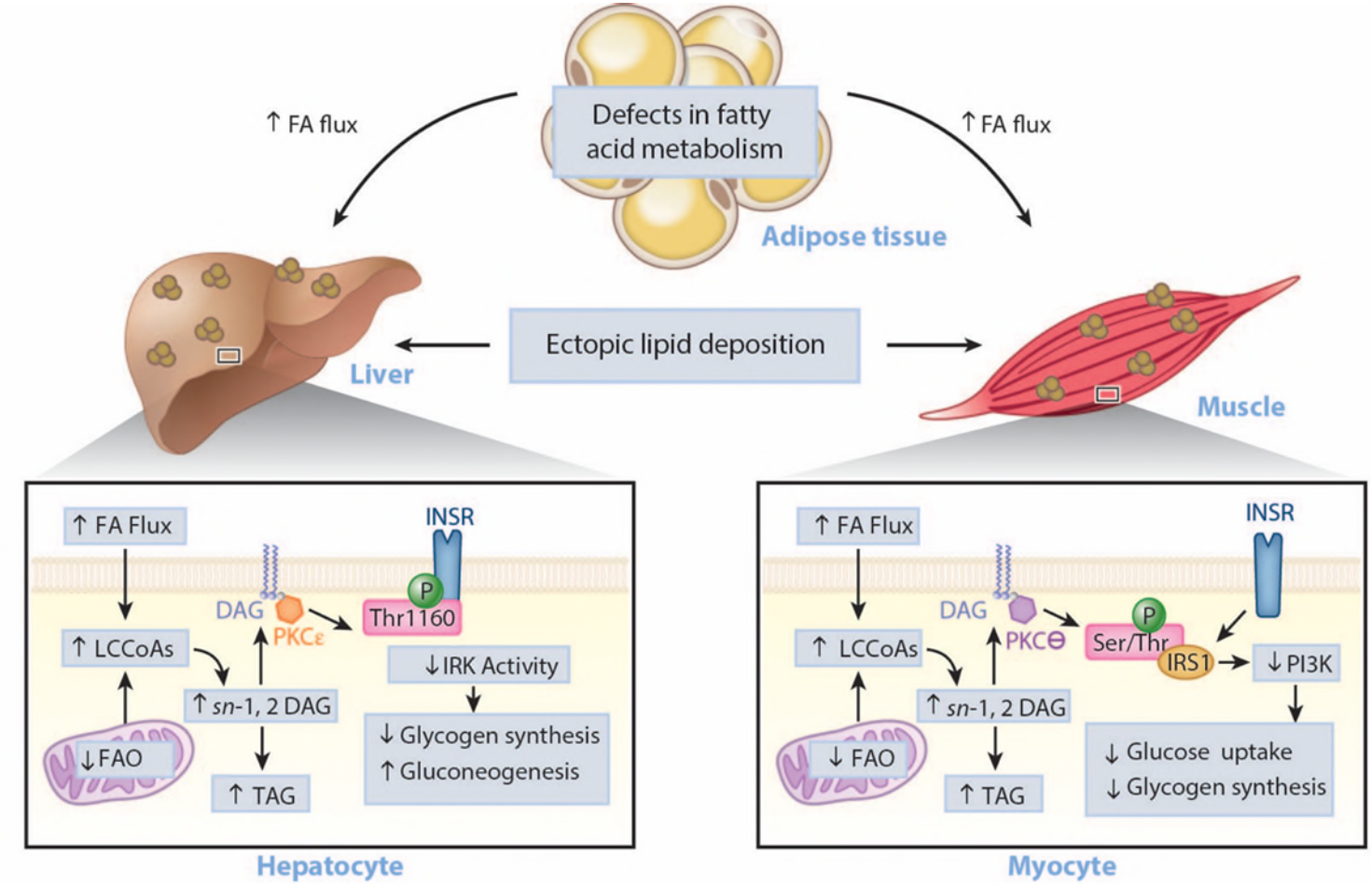
R00 HL150234 (NIH)
Schneider-Lesser Foundation
ES-DRC Pilot & Feasibility Award

VBT Vascular Biology & Therapeutics

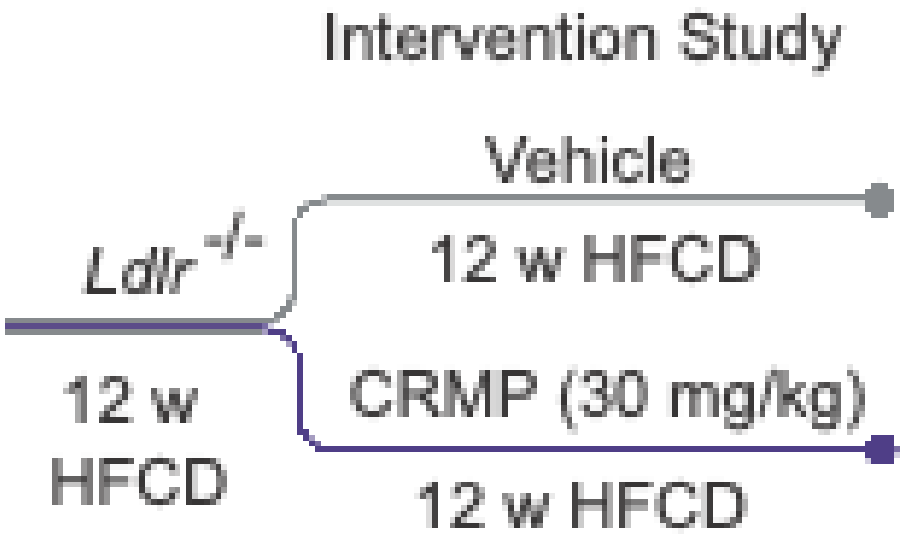
orsobio

Backup Slides

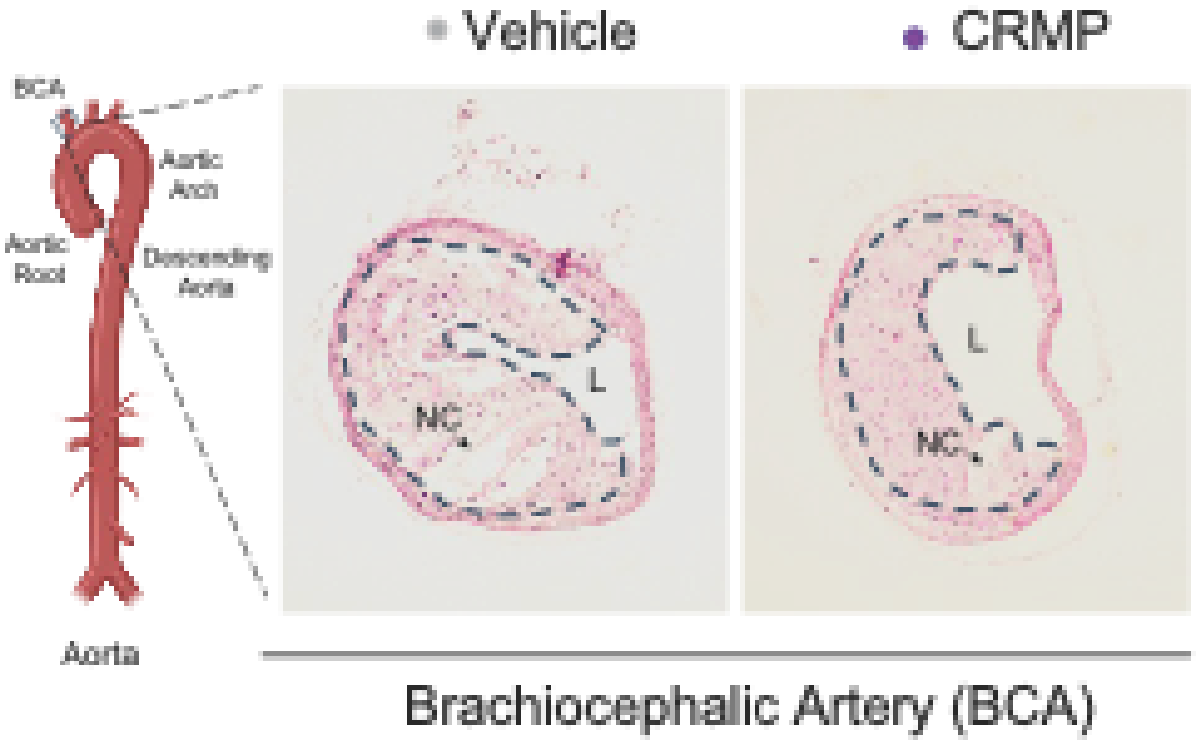
Ectopic Lipid Accumulation is a Driver of Liver & Muscle Insulin Resistance

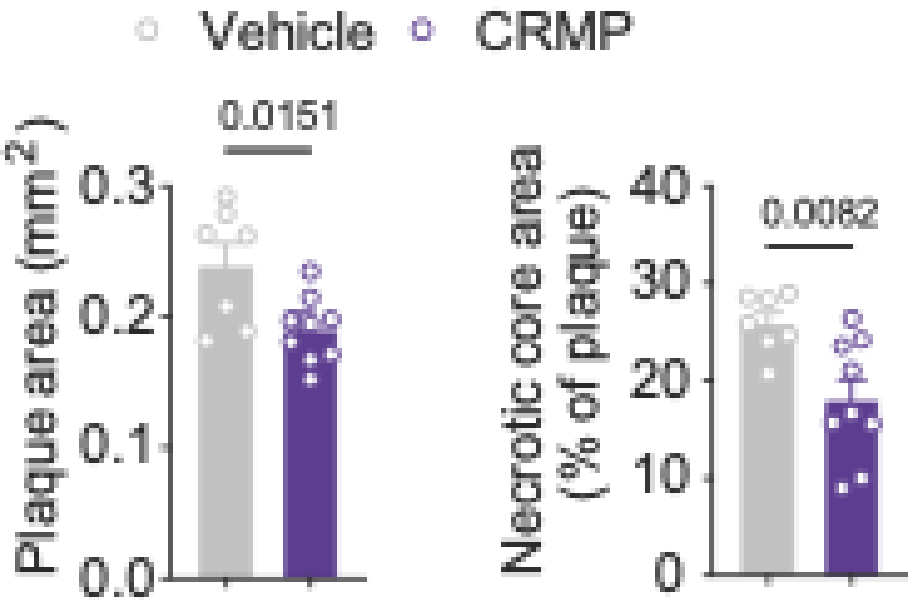


Atherosclerosis Intervention Study

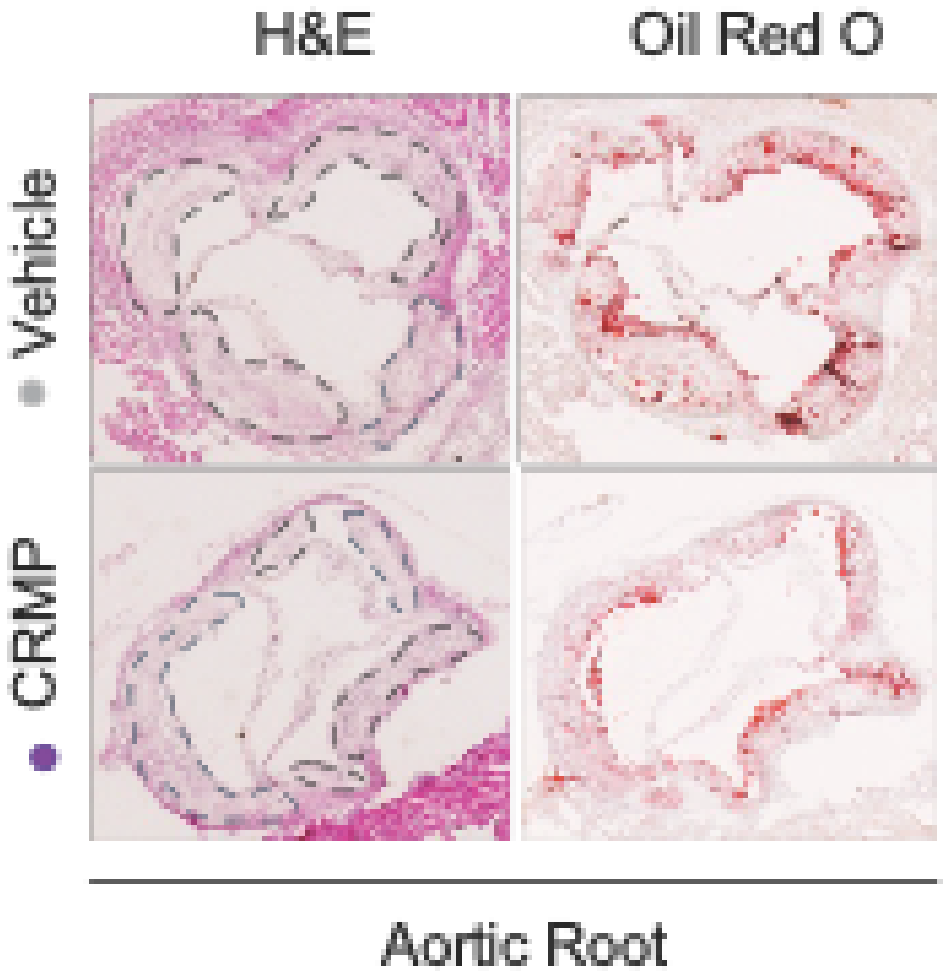


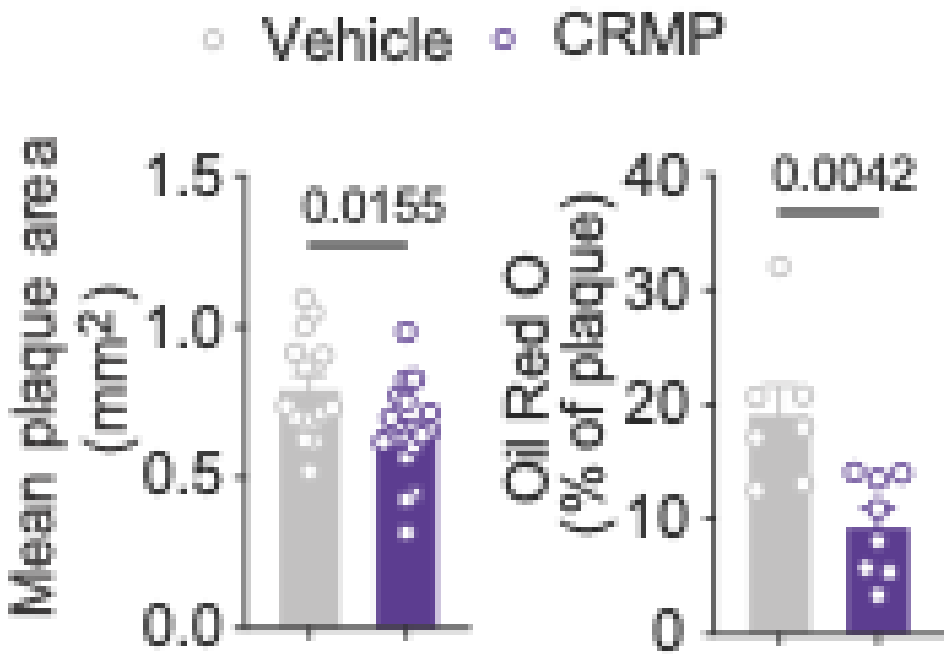
CRMP Reduces Late-Stage Atherogenesis in *Ldlr*$^{-/-}$ Mice





CRMP Reduces Late-Stage Atherogenesis in *Ldlr*$^{-/-}$ Mice





CRMP Treatment Increases Plaque Stability in *Ldlr*$^{-/-}$ Mice