Endogenous Leptin Induces Cardioprotection in Spontaneously Calorically Restricted Mice

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DISCLOSURE

NONE

Caloric restriction

- **life span**
  Extends longevity in numerous species including mammals
- Delays the onset of age-related pathologies including cardiovascular diseases
- Increases the resistance against ischemic injury in the heart of laboratory animals

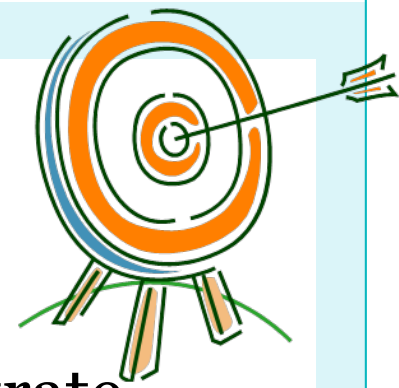
The αMUPA transgenic model

αMUPA mice spontaneously consume less food (~20%) compared to wild- type (WT)

A =18 month B

-Reduced body weight - Increased life span - Improved health

Objectives



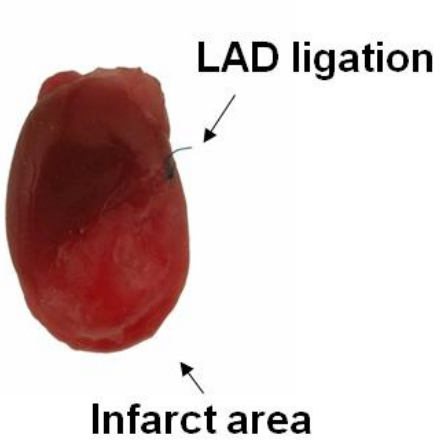
We aim to:

- Test whether αMUPA, as CR mice, demonstrate improved heart recovery following MI compared to WT.

- Investigate the possible factors in αMUPA hearts that lead to cardioprotection against ischemic damage.

Methods

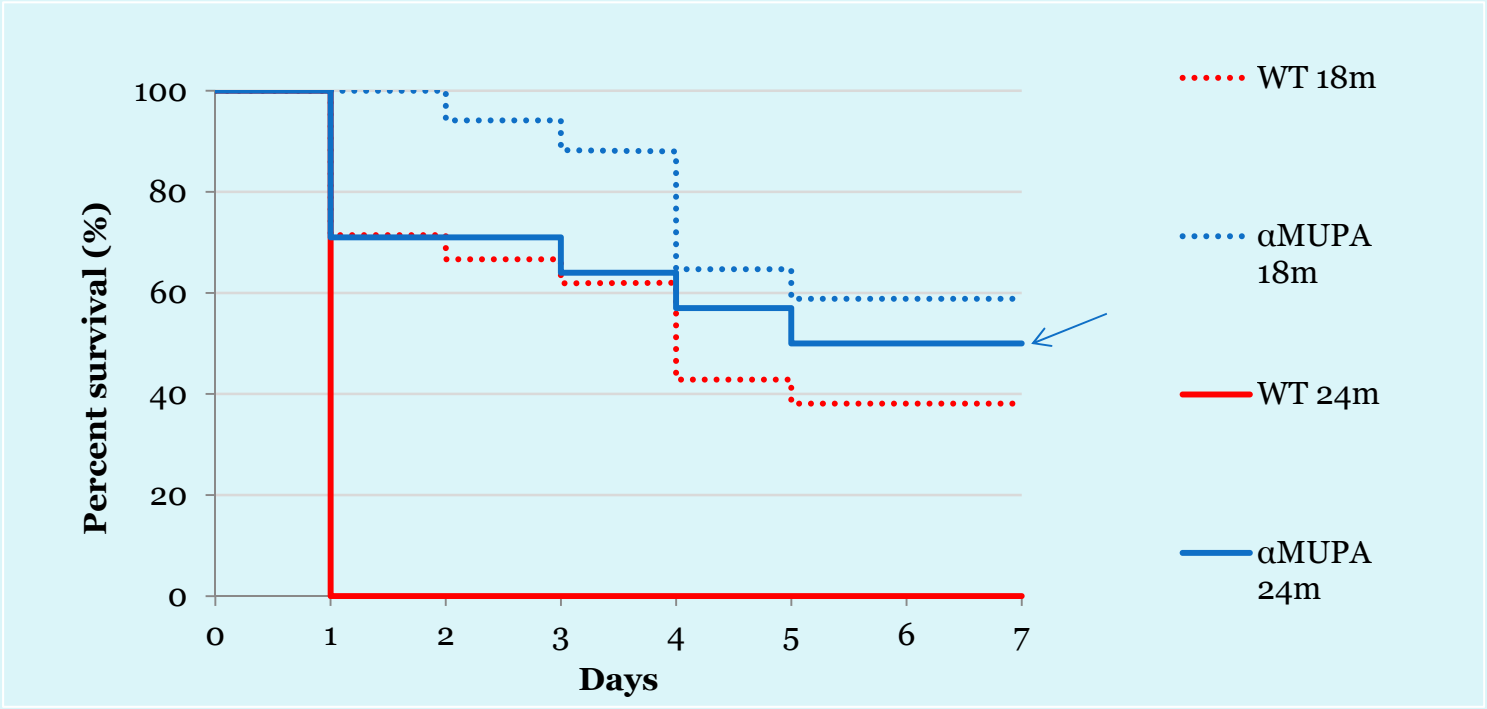
- Group
  young and old αMUPA and WT mice
- Surgery
  Ligation of left anterior descending (LAD) coronary artery of



- Echocardiography
- Histological analysis
- ELISA
- Western blot

Results -
Increased survival

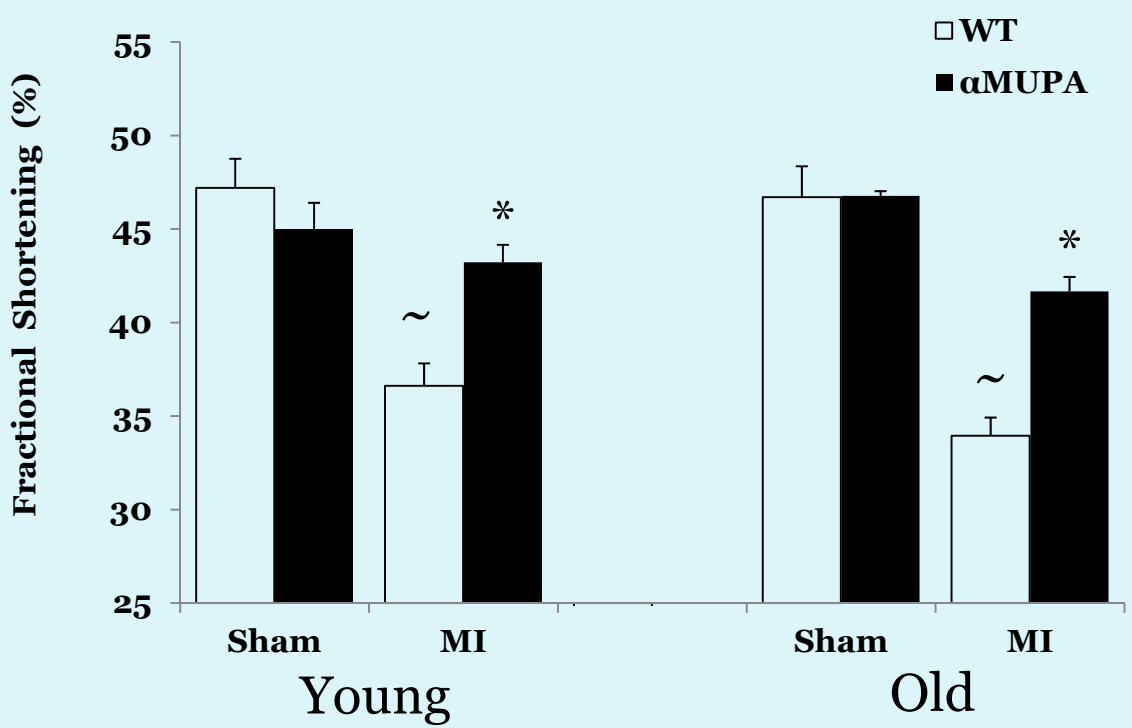
A Kaplan–Meier survival plot for αMUPA and WT mice after LAD ligation at different ages

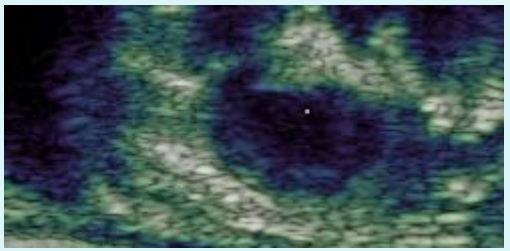


Survival was monitored for one week. (Kaplan-Meier, $P < 0.01$) n=10-20

Improved heart function

Fractional shortening, 24h following myocardial infarction

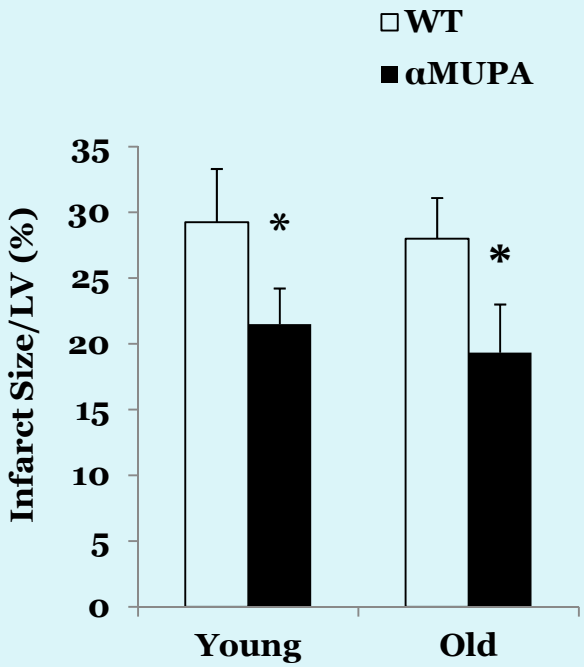


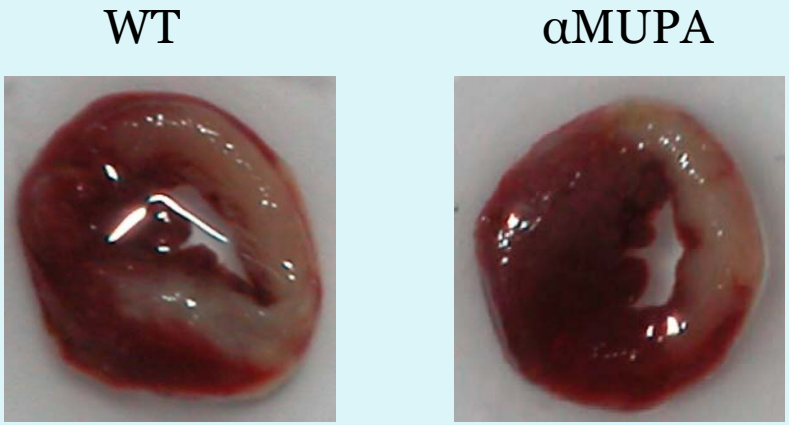


*p<0.05 αMUPA compared to WT mice, ~p<0.05 sham compared to MI, n=6-8/group.

Heart pathology – reduced infarct size

TTC staining, *24h following myocardial infarction.*

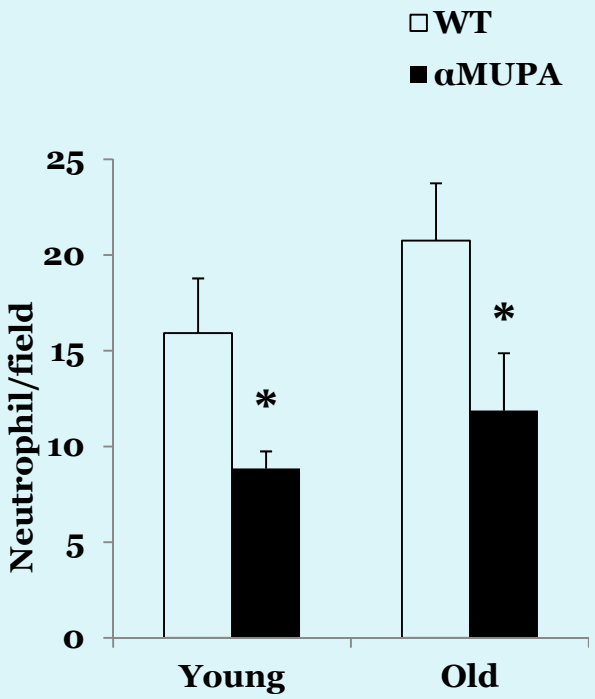


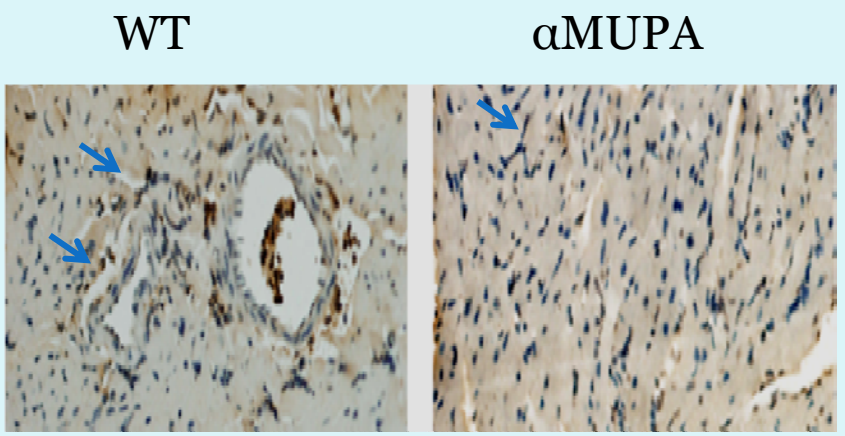


*p<0.05 αMUPA compared to WT mice , n=6-8/group.

Heart pathology – reduced inflammation

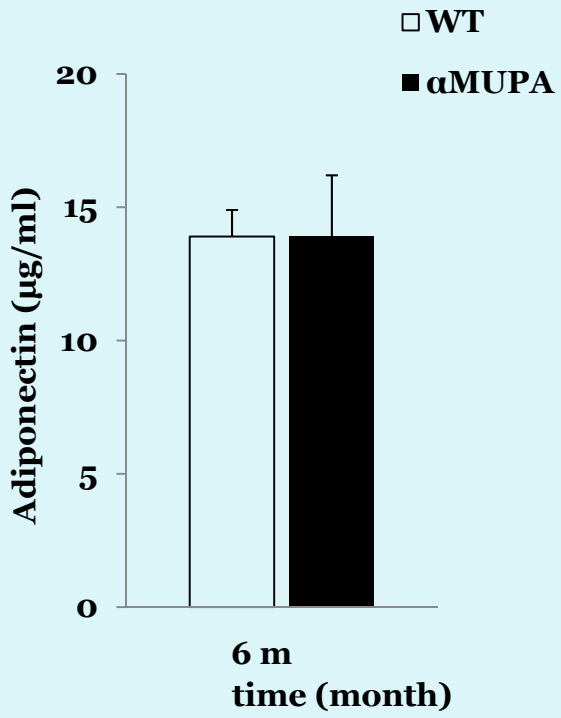
Neutrophil infiltration, *24h following myocardial infarction*

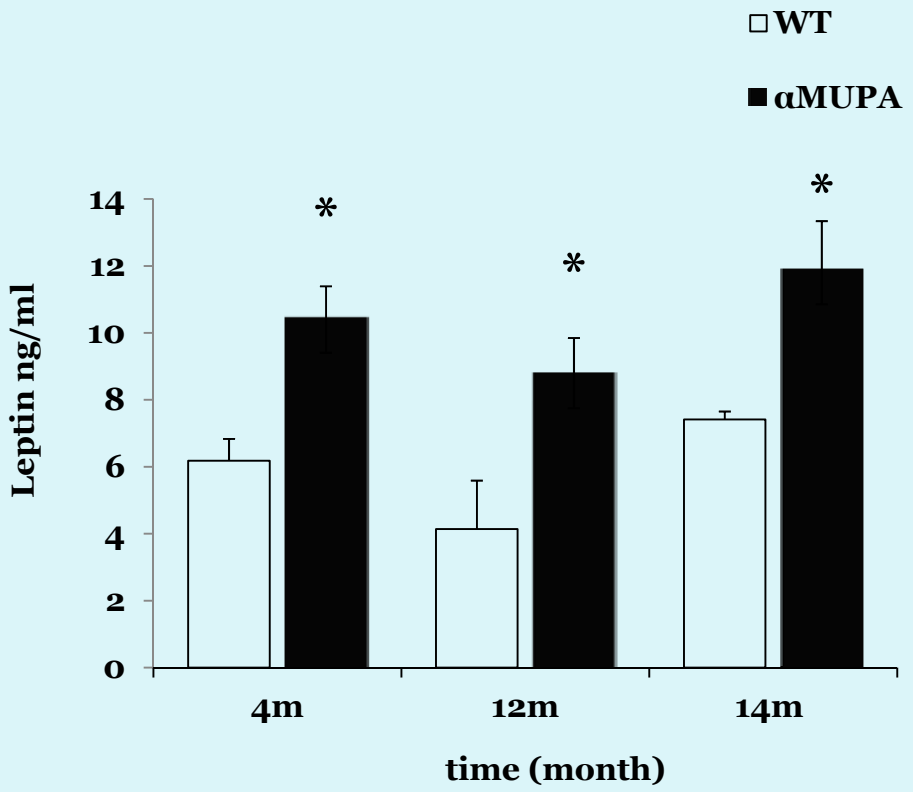




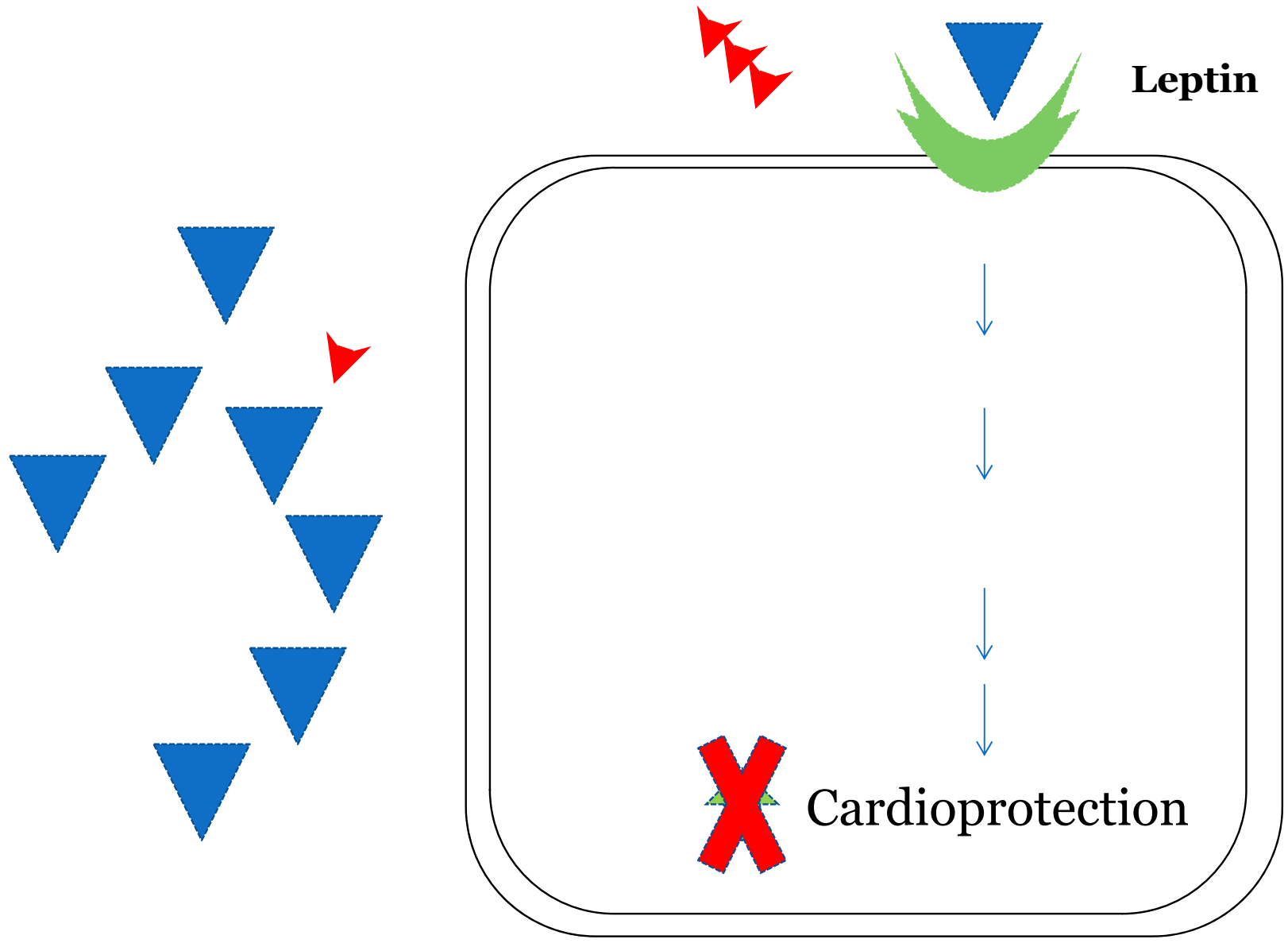
*p<0.05 αMUPA compared to WT mice , n=4/group.

Adiponectin & Leptin



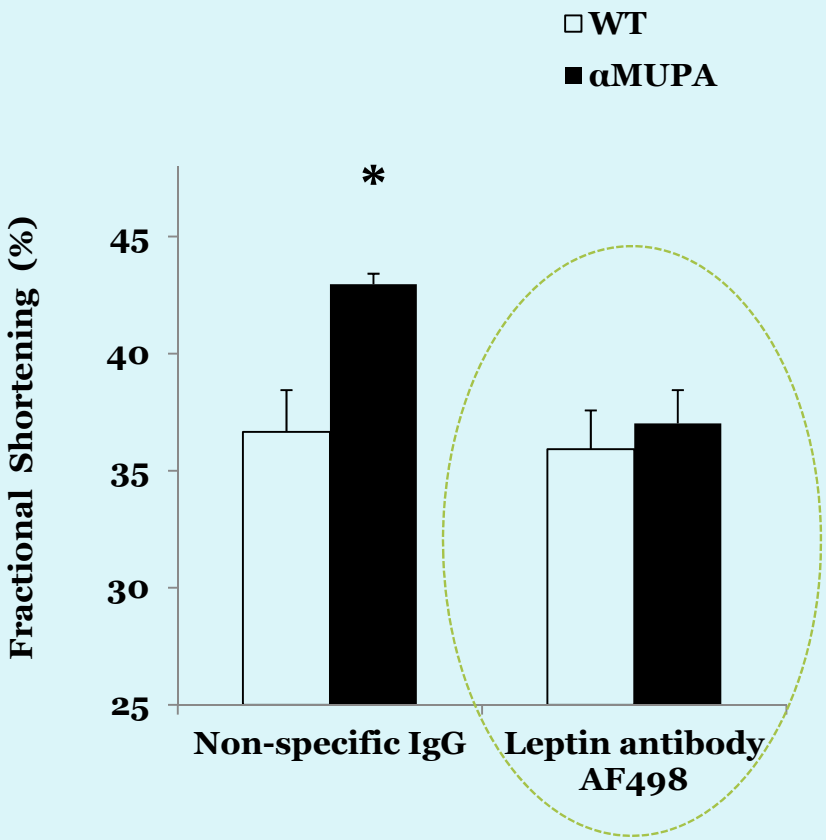


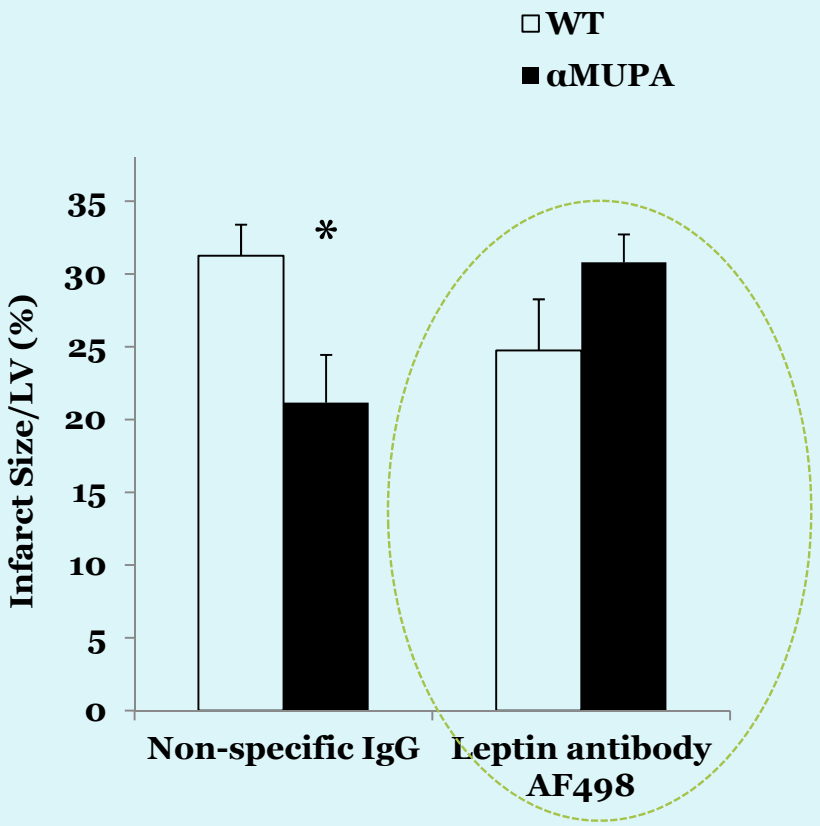
*p<0.05 αMUPA compared to WT mice , n=6/group.



IV injection of antibodies against leptin (AF498)

The leptin neutralizing antibody abrogates cardioprotection

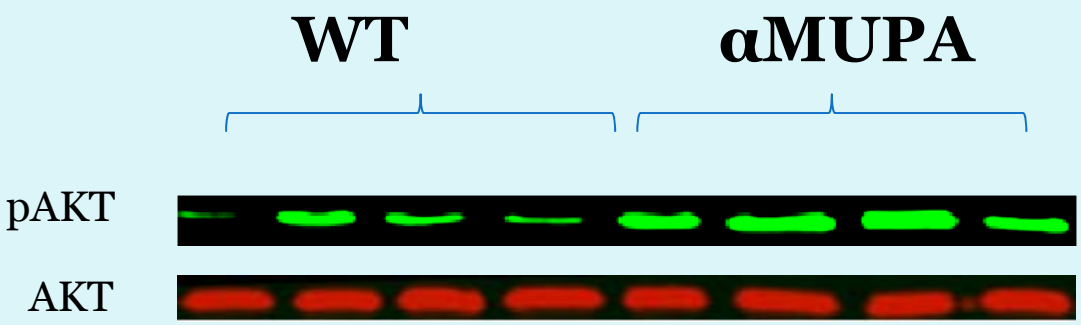


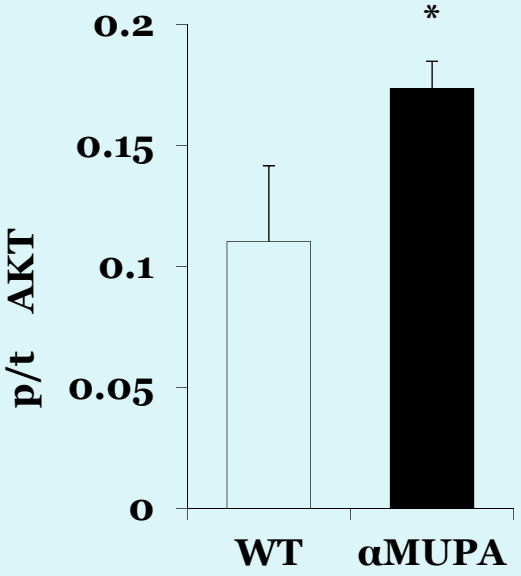


*p<0.05 αMUPA compared to WT mice, n=5-8/group.

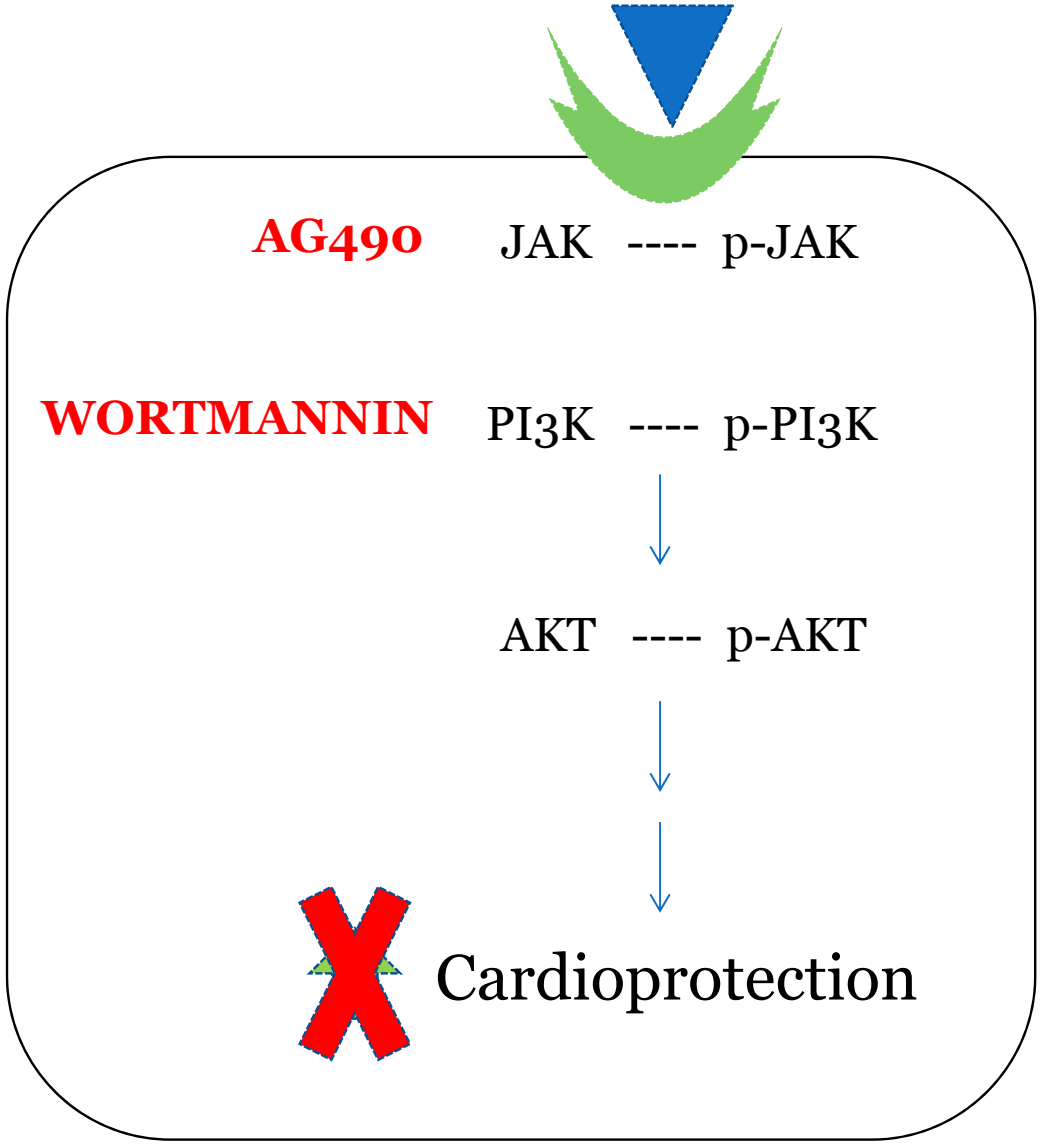
AKT activation

- Metabolism
- Cell survival





*p<0.05 pAKT levels αMUPA compared to WT mice , n=6/group



IP injection of JAK or PI3K inhibitor (AG490 OR Wortmannin)

Summary

- αMUPA resemble CR mice and show increased cardioprotection and attenuated heart ageing.
- Leptin is involved in αMUPA cardioprotection by activating AKT.

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