SELECTED OPPORTUNITIES IN CARDIOMETABOLISM

METHODS AND PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF AGE-RELATED CARDIOMETABOLIC DISEASES (BIO15415)

BIO15415 – METHODS AND PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF AGE-RELATED CARDIOMETABOLIC DISEASES

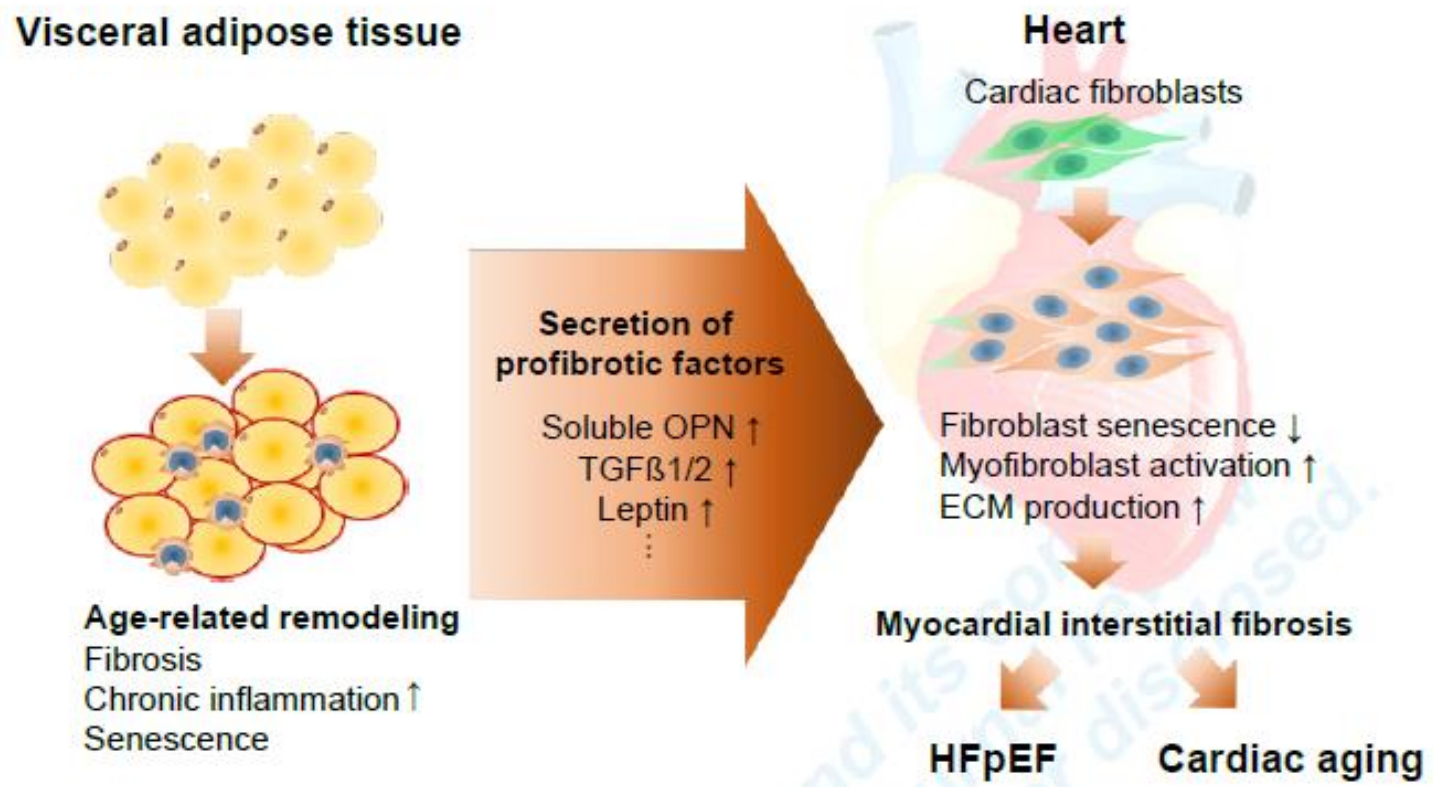
Product factsheet

Preclinical

- **Target:**
  - Osteopontin
- **Product:**
  - Small molecule, antibody
- **Application:**
  - Cardiac aging, age-related cardiometabolic diseases
- **Mechanism:**
  - Aging induces cardiac structural and functional changes linked to the increased deposition of extracellular matrix (ECM) proteins, including osteopontin, conducing to progressive interstitial fibrosis
  - Visceral adipose tissue (VAT) represents the main source of osteopontin during aging and alters heart structure and function via its profibrotic secretome
- **Rational / POC:**
  - Plasma osteopontin increased in mice during aging with VAT showing the strongest increase
  - VAT removal restores cardiac function in mice (decreases fibrosis, reduction of circulating osteopontin)
  - Oteopontin deficiency (KO mice) provided a comparable protection againt age-related cardiac fibrosis and dysfunction
  - Agelastatin A treatment of aged WT mice fully reversed age-related myocardial fibrosis and dysfunction.
- **Patent and publication:**
  - WO/2017/174681: METHODS AND PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF AGE-RELATED CARDIOMETABOLIC DISEASES
  - Visceral Adipose Tissue Drives Cardiac Aging Through Modulation of Fibroblast Senescence by Osteopontin Production. Sawaki D et al., Circulation, 2018

Graphical Abstract

Visceral adipose tissue mediates age-related cardiac fibrosis through secretion of profibrotic factors stimulating myocardial fibroblasts and impairing fibroblast senescence.



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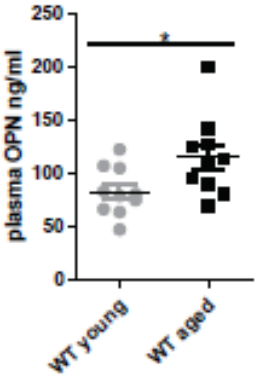
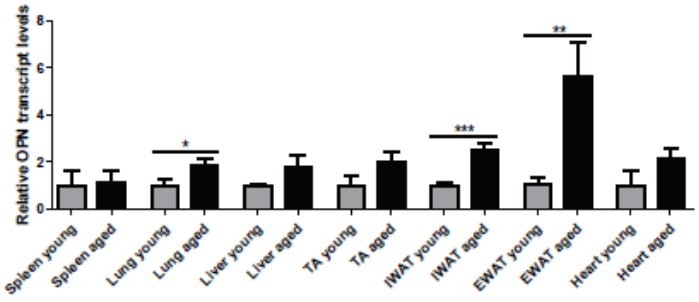
Proof of concept

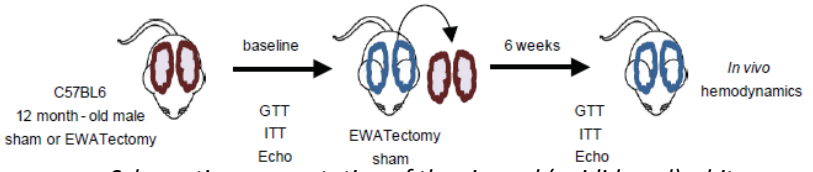
Visceral adipose tissue is a major source of osteopontin during aging and plays a key role in inducing myocardial fibrosis and cardiac dysfunction during aging.



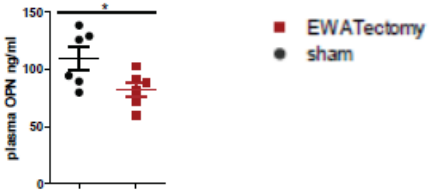
Plasma OPN levels in aged vs. young WT mice



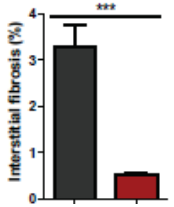
Relative OPN gene expression in organs of young and aged WT mice (TA: anterior tibial muscle; IWAT and EWAT, inguinal and epididymal white adipose tissue, respectively)



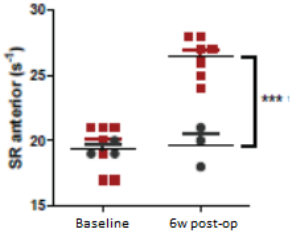
Schematic representation of the visceral (epididymal) white adipose tissue removal (EWATectomy) protocol in aged WT mice.



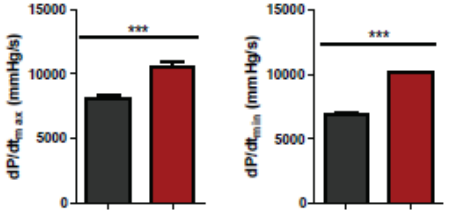
Plasma levels of OPN after sham surgery or EWATectomy



Sirius Red staining and quantification of myocardial interstitial fibrosis



Echocardiographic strain rate (SR) assessment before/after sham surgery (grey dots) and EWATectomy (red dots)



In vivo hemodynamic assessment (dP/dtmax & dP/dtmin) at the end of the protocol

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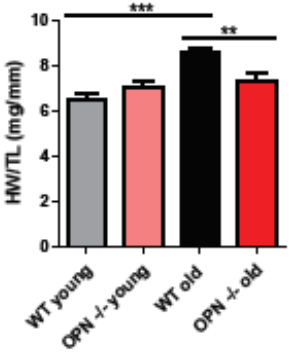
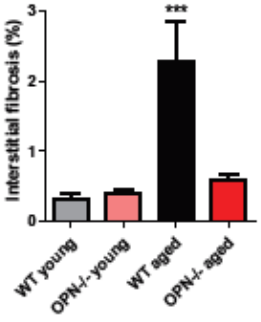
Proof of concept

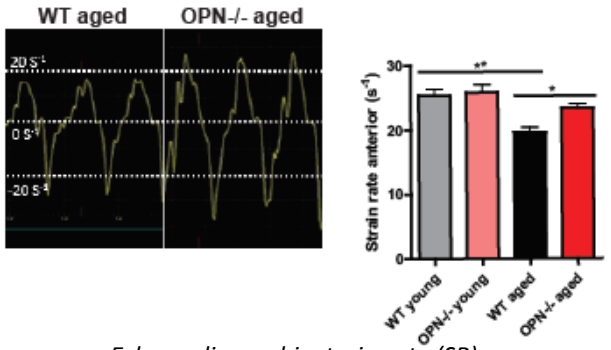
Osteopontin-deficient mice are protected against age-related myocardial fibrosis and cardiac dysfunction



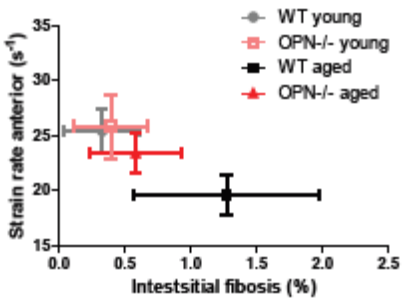
Heart weight to tibia length (HW/TL) in young and aged WT and OPN KO mice



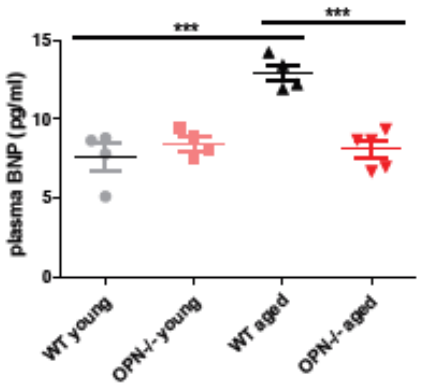
Sirius Red staining of the ventricular myocardium



Echocardiographic strain-rate (SR) curves and quantification by peak values in aged WT and OPN-/- myocardium



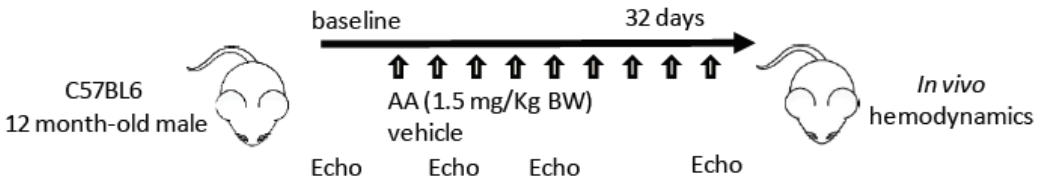
Bi-plot of mean ± SD comparing interstitial myocardial fibrosis versus SR (systolic function)



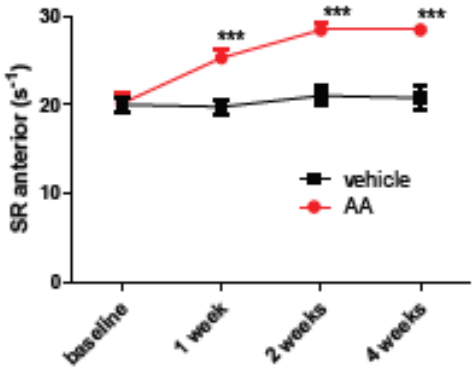
Plasma BNP levels

Proof of concept

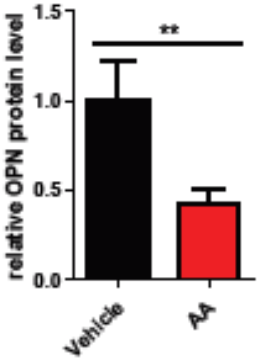
The osteopontin inhibitor Agelastatin A restores juvenile cardiac structure and function in aged WT mice.



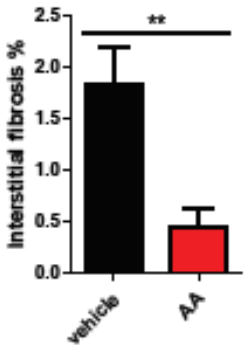
Schematic representation of the Agelastatin A (AA) treatment protocol in aged WT mice.



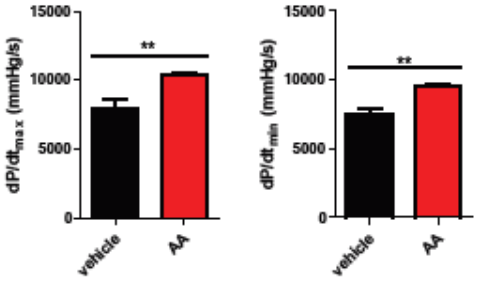
Echocardiographic strain-rate (SR) from baseline to 4 weeks of treatment with vehicle or AA



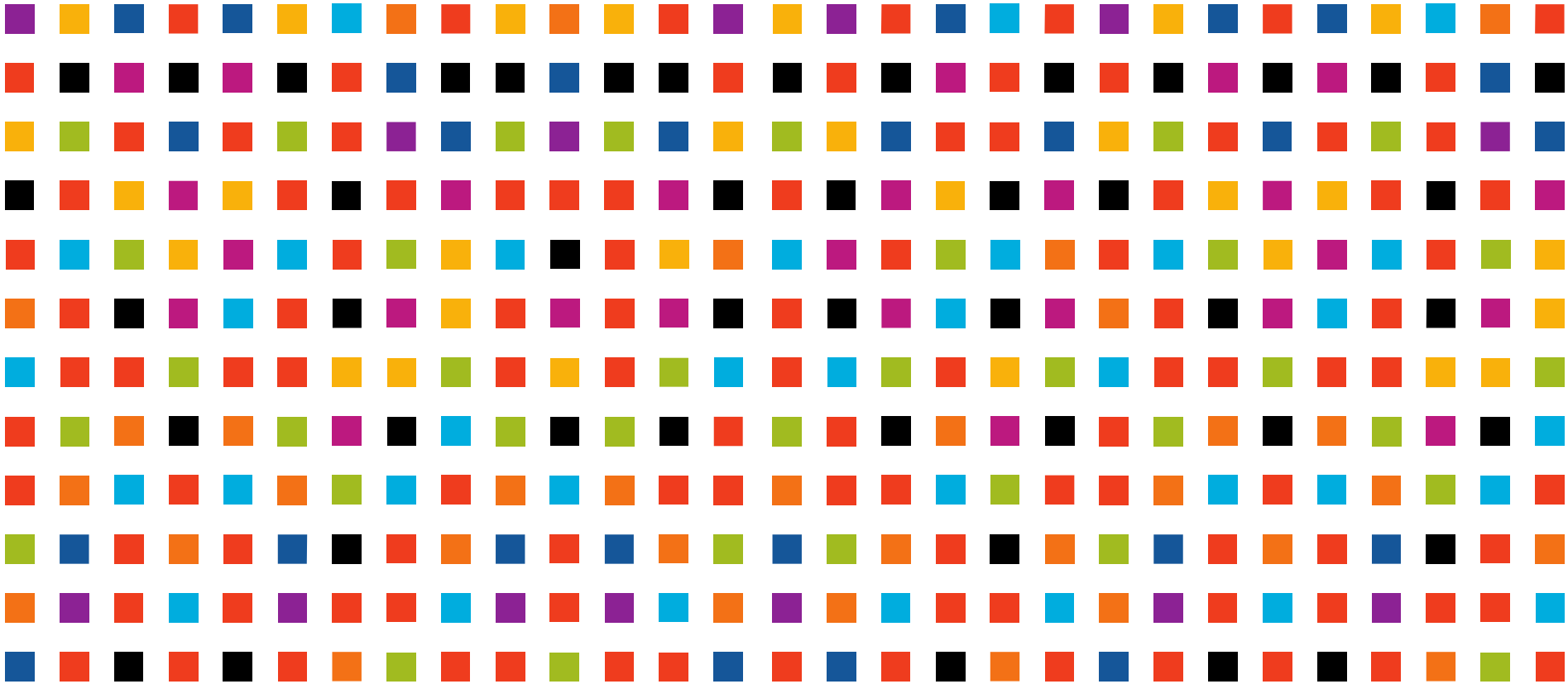
OPN protein levels relative to β-actin



Sirius Red staining and quantification of myocardial interstitial fibrosis



In vivo hemodynamic assessment (dP/dtmax, dP/dtmin) 4 weeks after vehicle or AA treatment



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