

Notch Signaling Inhibitor ADPO-002 Promotes Browning in Human Adipose Tissue Explants

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Disclosures

Muhammad Raisul Abedin is an employee and senior scientist at Adipo Therapeutics, LLC in Indianapolis, Indiana, USA

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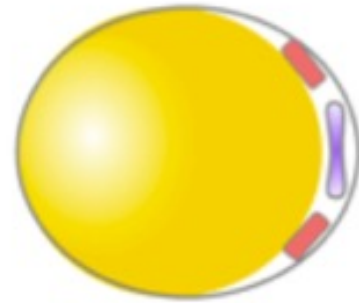
The presentation includes evidence-based contents only

The presentation is not offering any clinical recommendations

Background

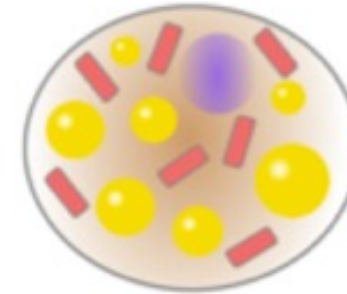
Adipocyte Browning

● - Lipid droplets ■ - Mitochondria ● - Cell Nucleus



White adipocyte

Browning
→



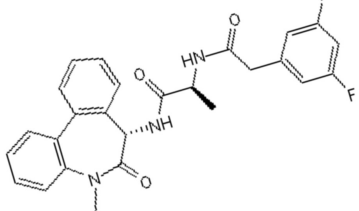
Beige/Brown adipocyte

- ❖ Stores energy
- ❖ Low number of mitochondria
- ❖ Secretes Adipokines
- ❖ In excess associated with obesity, diabetes and CV disease

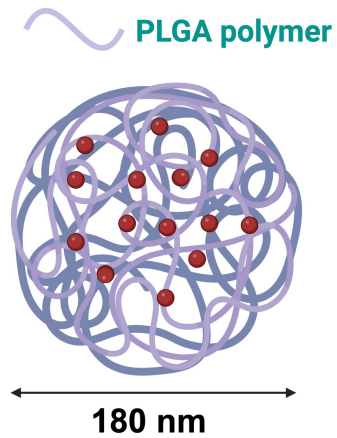
- ❖ Increases energy expenditure
- ❖ High number of mitochondria
- ❖ Secretes BATokines
- ❖ Associated with improved insulin sensitivity, decreased risk for diabetes and CV disease

ADPO-002 belongs to γ -secretase inhibitor class blocking the Notch-signaling pathway

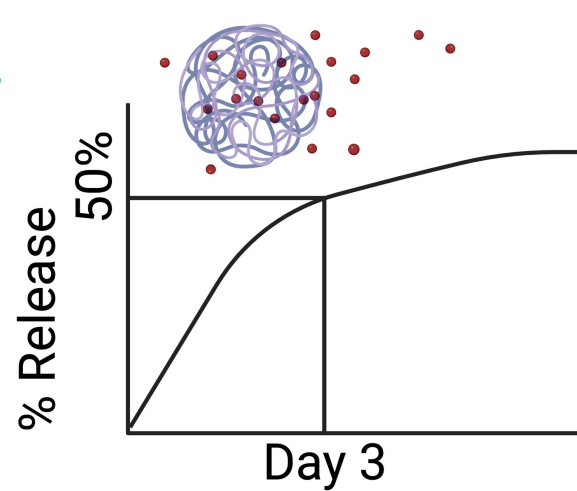
Dibenzazepine



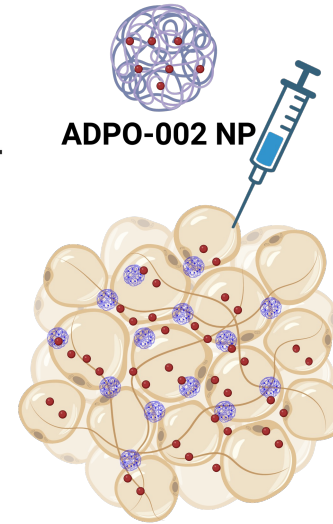
ADPO-002
(MW:463.5)



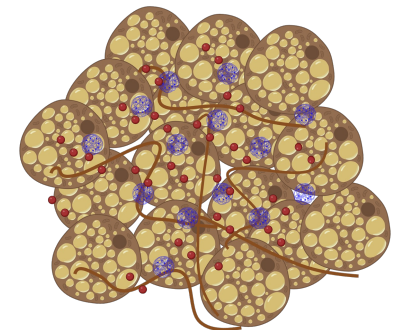
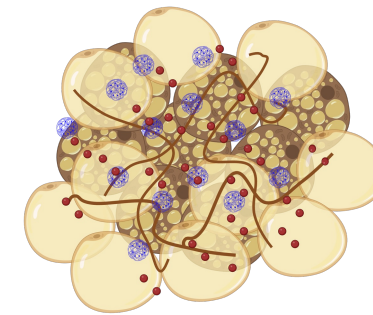
ADPO-002 encapsulated
PLGA nanoparticle
(ADPO-002 NP)



Controlled release of
ADPO-002



ADPO-002 NP injection
in white adipose tissue depot



Local conversion into
brown adipose tissue

• ADPO-002



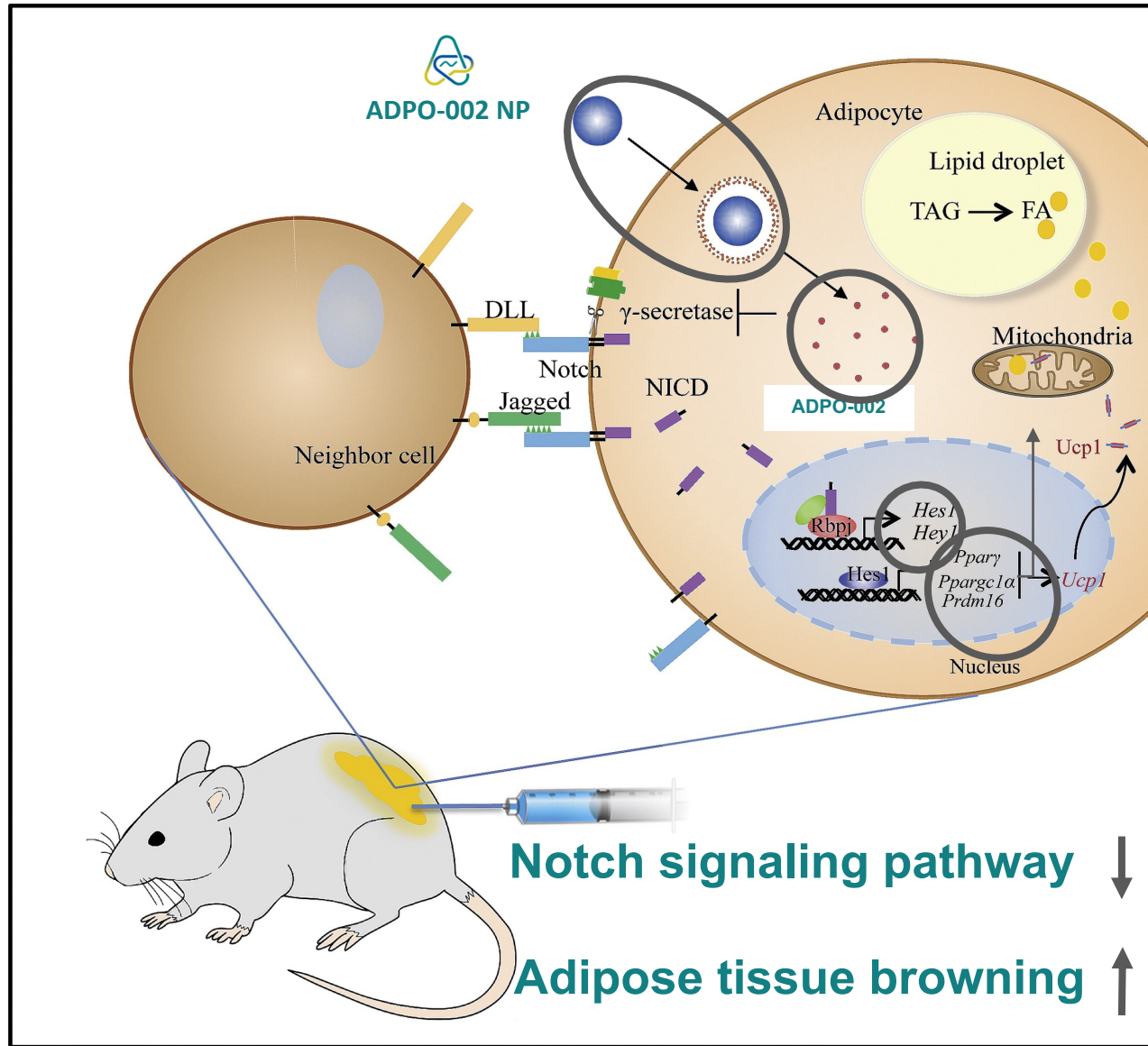
PLGA polymer



ADPO-002 NP

- Bi, Pengpeng, et al. Nature Medicine (2014)*
- Jiang, Chunhui, et al. Frontiers in Endocrinology (2015)*
- Jiang, Chunhui, et al. Molecular Therapy (2017)*
- Huang, Di, et al. Trends in Endocrinology & Metabolism (2019)*
- Huang, Di, et al. iScience (2020)*
- Huang, Di, et al. Pharmaceutical Research (2020)*
- Sharifi, Farrokh, et al. Obesity 30 (2022)*

Notch-inhibition pathway signaling promotes browning of white adipose tissue



Local internalization of ADPO-002 NP by the adipose tissue

Controlled release of ADPO-002- γ -secretase inhibitor

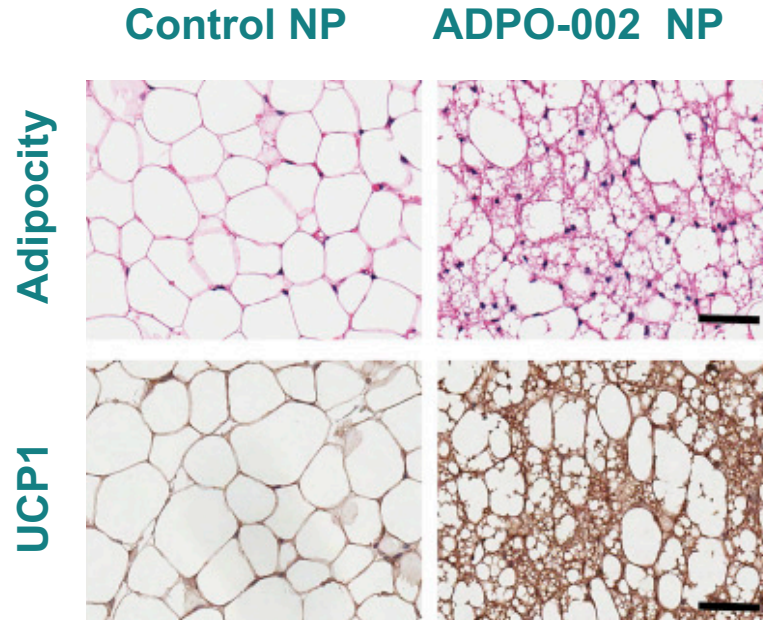
Inhibition of Notch signaling target genes Hes1, Hey1

Upregulation of browning marker genes PRDM16, PGC1A

Jiang, Chunhui, et al. Molecular Therapy (2017)

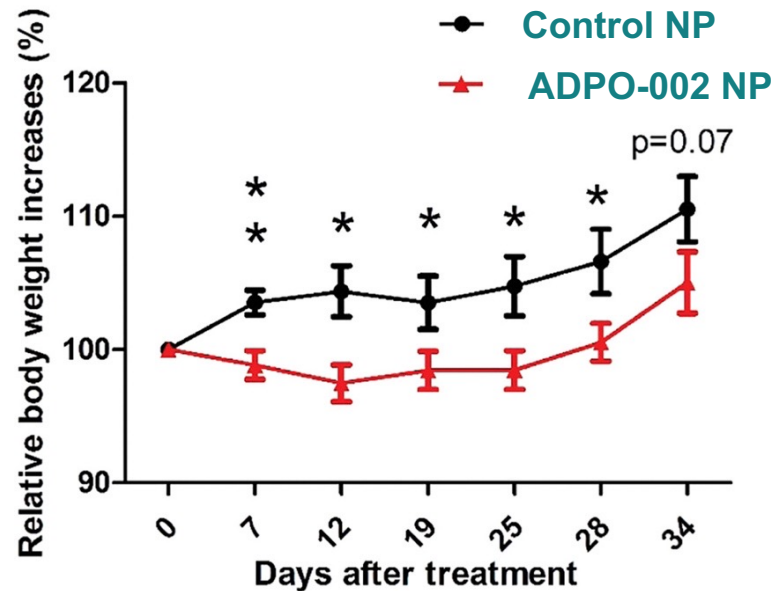
ADPO-002 NP demonstrated browning efficacy in rodents and pigs

The local retention of ADPO-002 NPs promotes browning of inguinal white adipose tissue (WAT) in mice

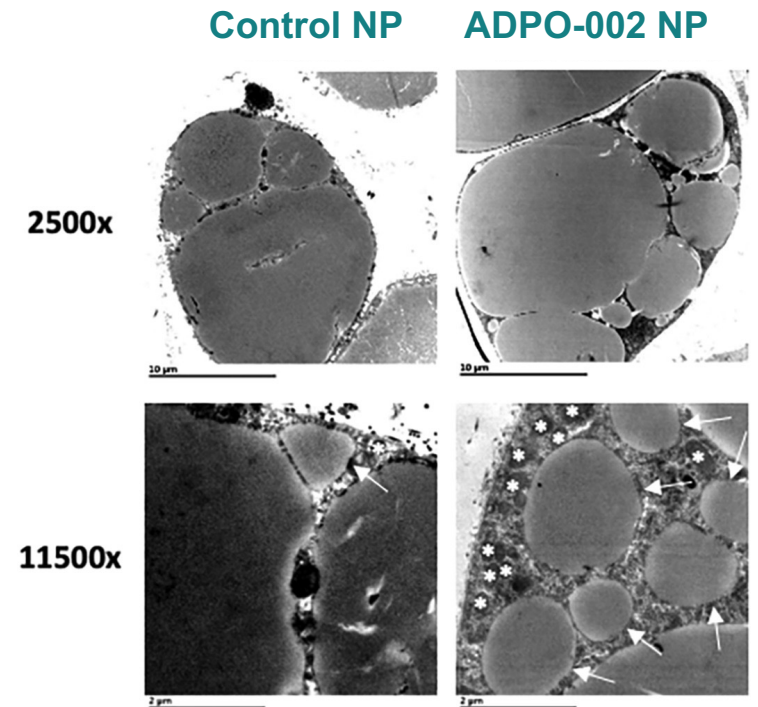


ADPO-002 NPs prevent HFD induced obesity in mice

Relative weight gain after 4 weekly injections



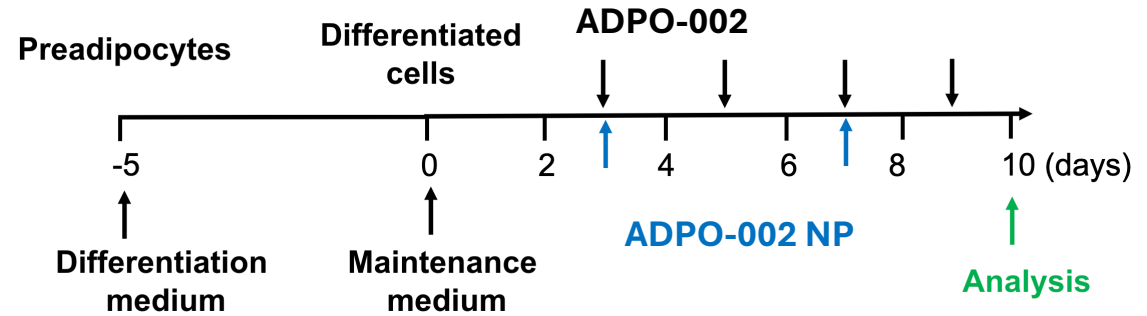
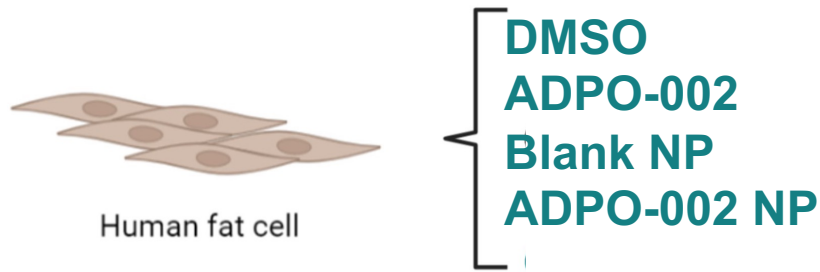
ADPO-002 NPs increases the number of mitochondria and multilocular lipid droplets in WAT in Pigs



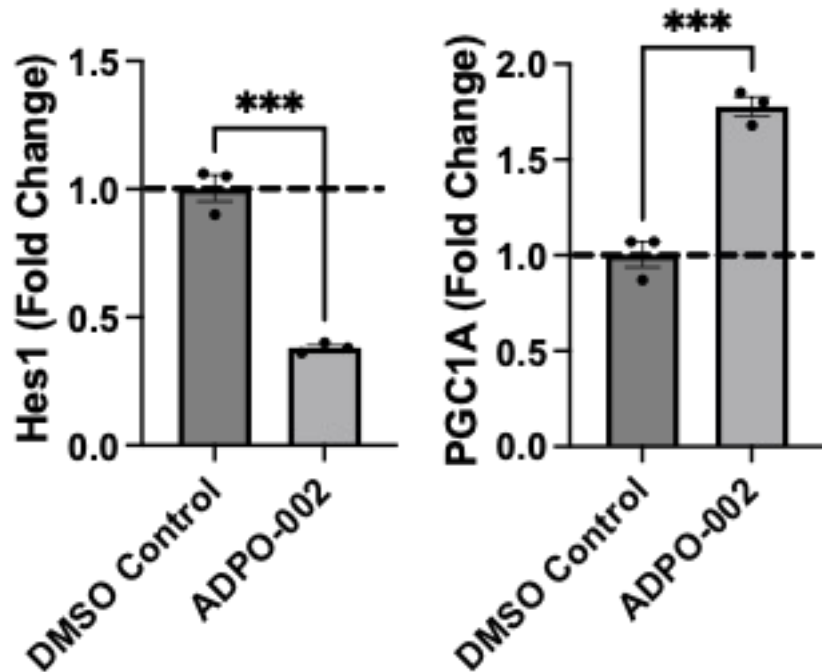
Jiang, Chunhui, et al. *Molecular Therapy* (2017)

Huang, Di, et al. *iScience* (2020)

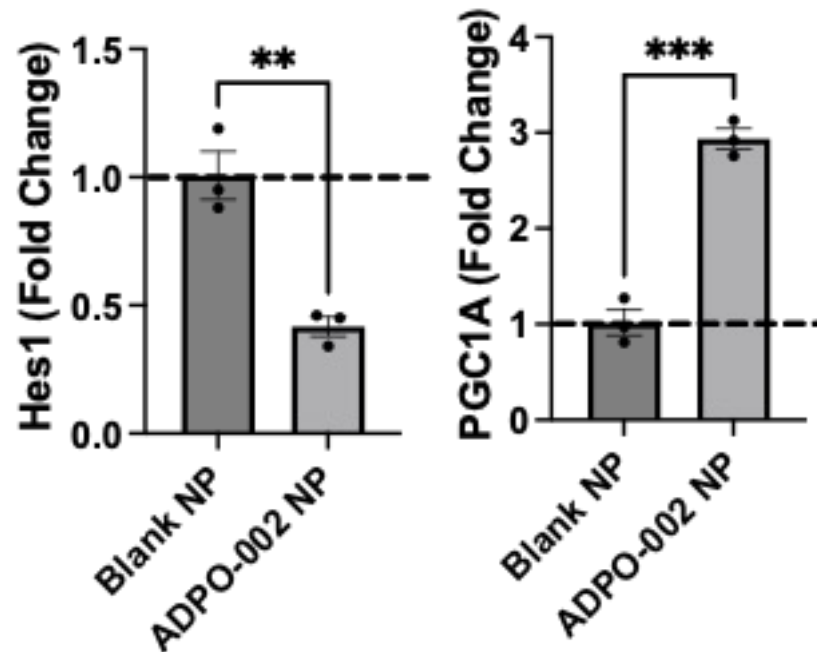
Delivery of ADPO-002 and ADPO-002 NP promote higher expression of browning markers in human adipose cells *in vitro*



ADPO-002



ADPO-002 NP



Collaborator: Dr. Shihuan Kuang, PhD
 Purdue University, IN
 Dr. Frank Greenway, MD
 Pennington Biomedical Research Center
 Louisiana State University, LA

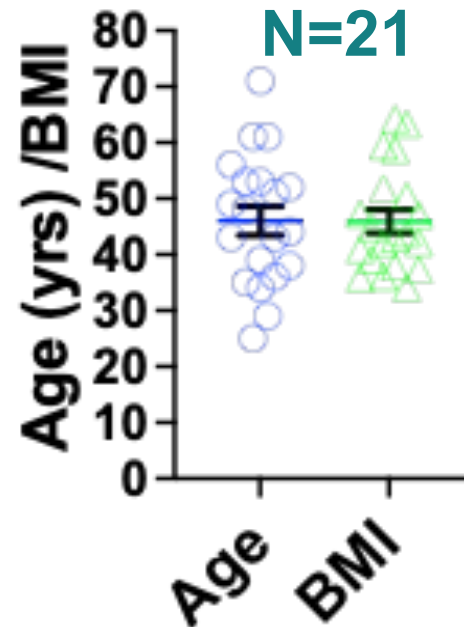
Human adipose tissue study objectives

To confirm that treatment of human adult fat with ADPO-002 induces browning as demonstrated by key gene markers PRDM16 and PGC1A

Fat tissue from adult human with obesity



Subjects with obesity demographics



Age 46.0 ± 11.6

BMI 45.9 ± 9.2

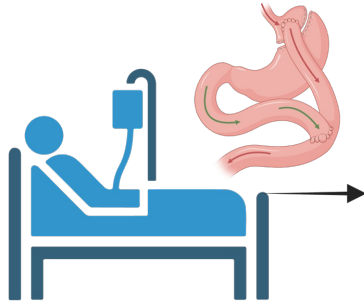
Diabetic : 08 (38%)

Female: 18 (86%)

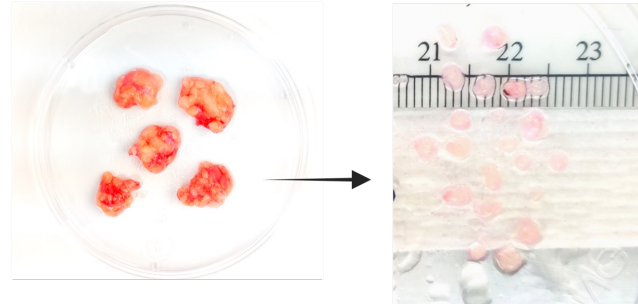
Male: 03 (14%)

Methodology of human adipose tissue explant study

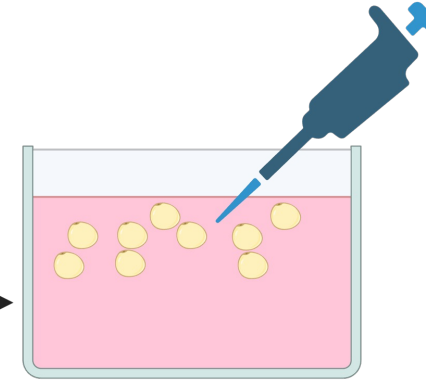
Subcutaneous and omental tissue collected from adult patients with obesity undergoing bariatric surgery



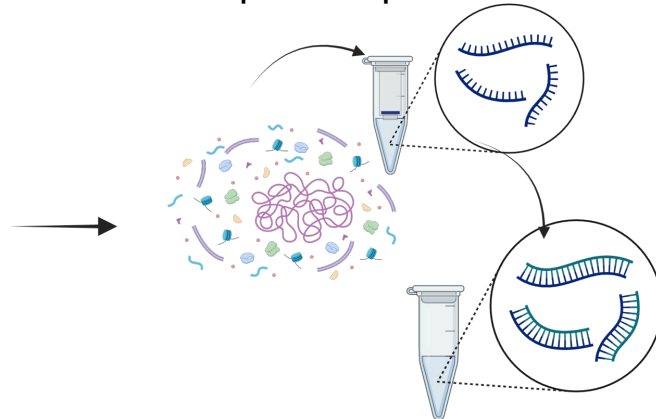
Tissue samples cut into small pieces (5-10 mg) using surgical scissors



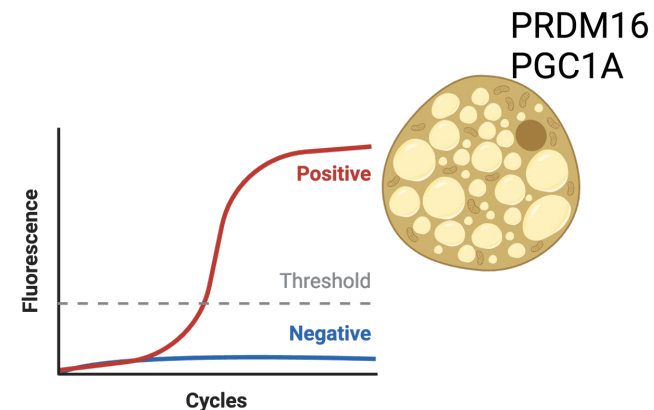
Adipose tissue were transferred into a well plate and treated with ADPO-002



Tissue harvested on day 7, RNA extraction and cDNA synthesis steps were performed

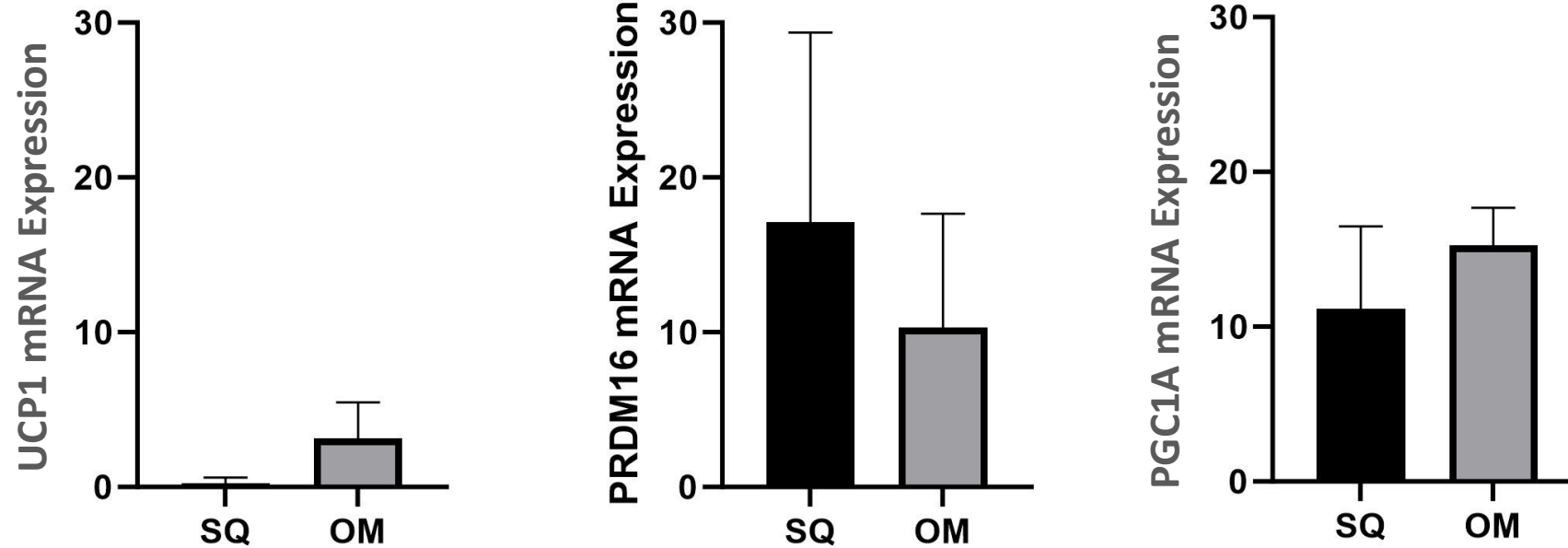


RT-qPCR performed for browning marker genes PGC1A and PRDM16



Gene expression in untreated human *ex vivo* fat

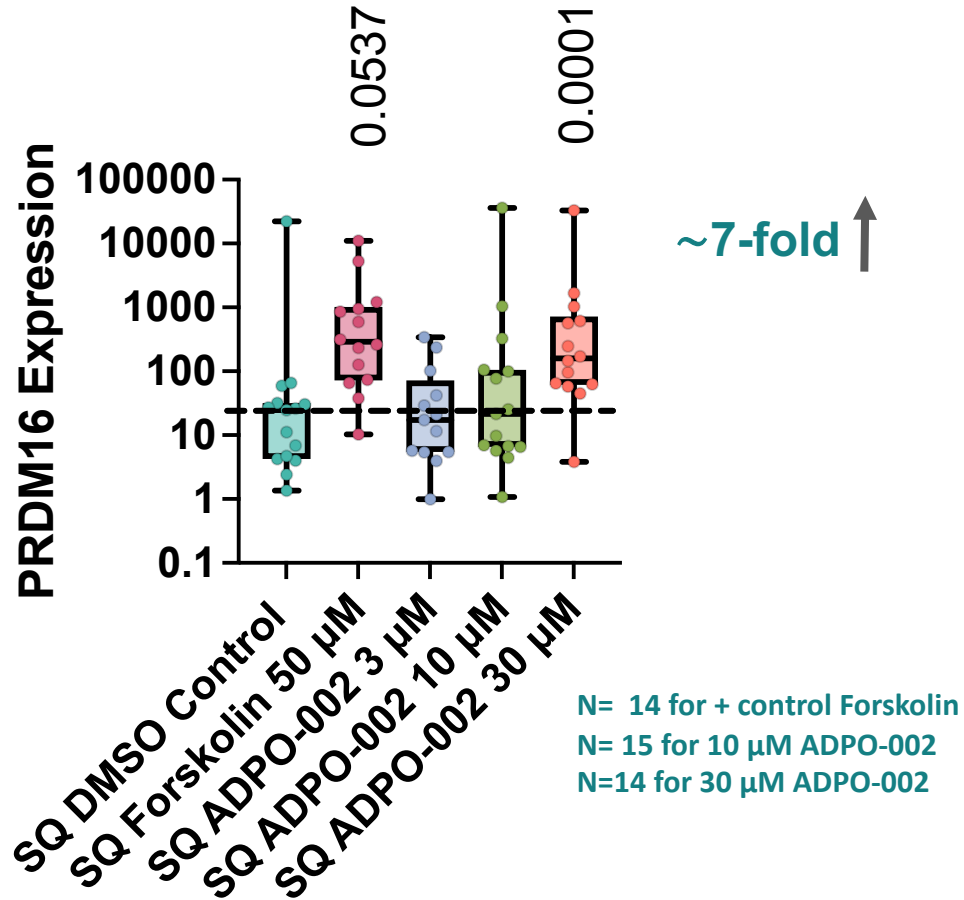
Untreated tissue mitochondrial gene expression (N= 6)



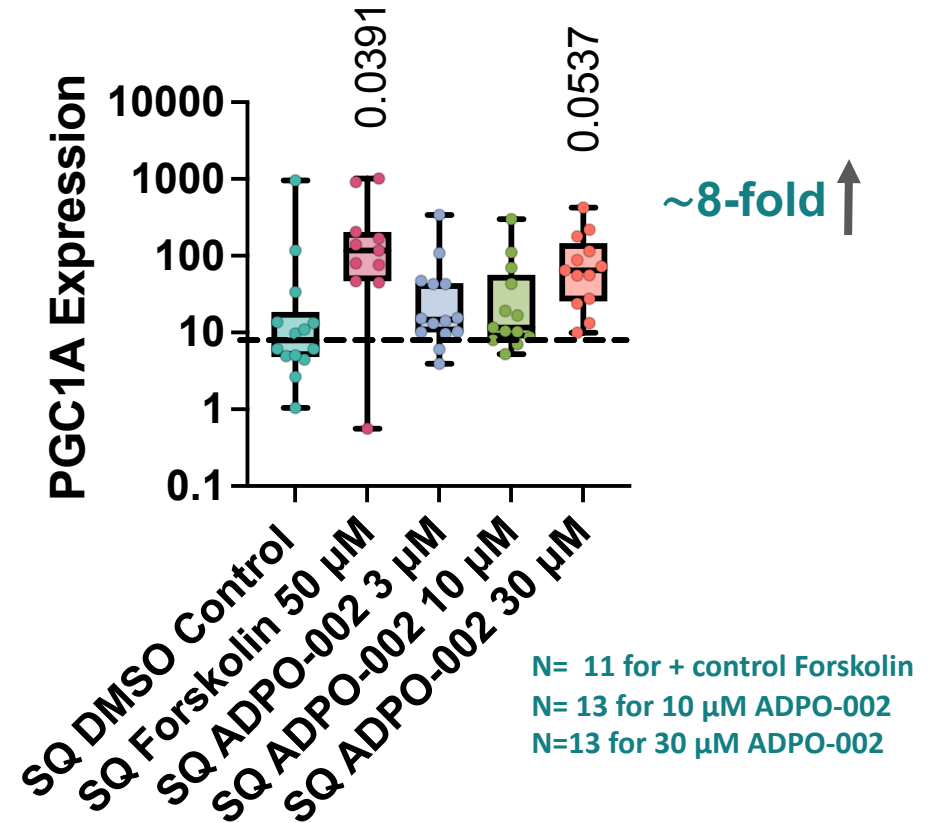
Results of human adipose tissue explant study key browning biomarker expression

Subcutaneous Fat Day 7

30 μ M ADPO-002 Median: 159
DMSO Median: 25



30 μ M ADPO-002 Median: 65
DMSO Median: 08



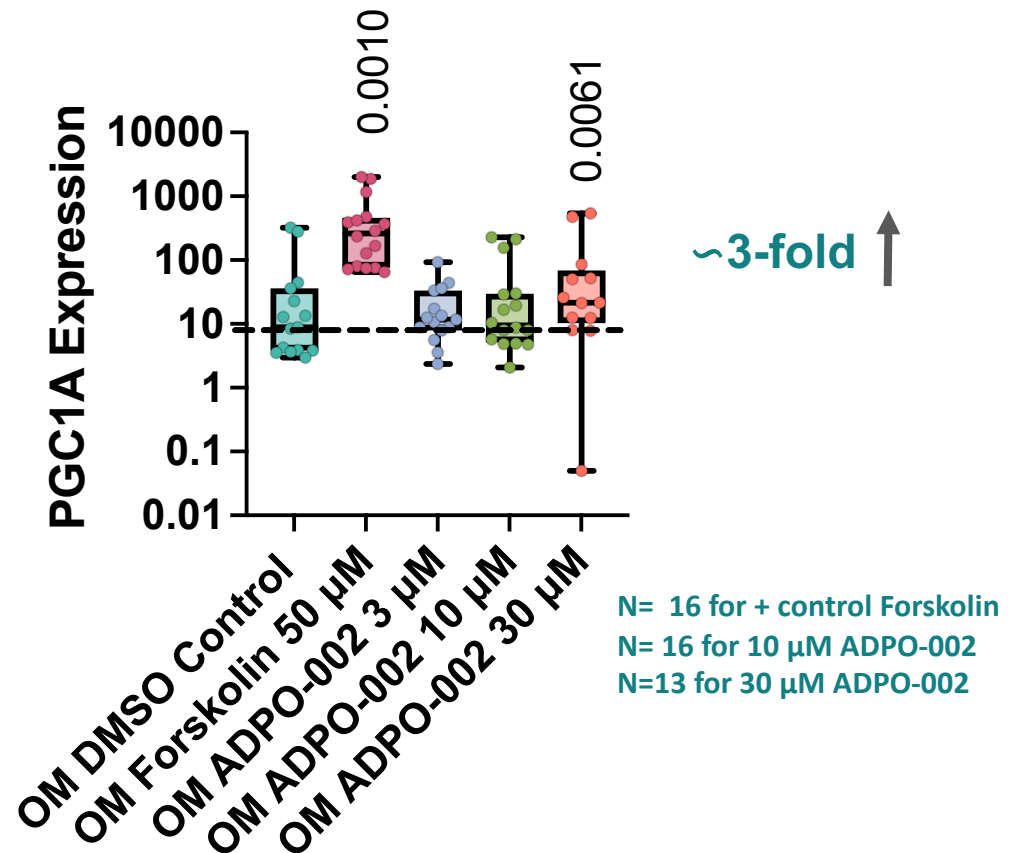
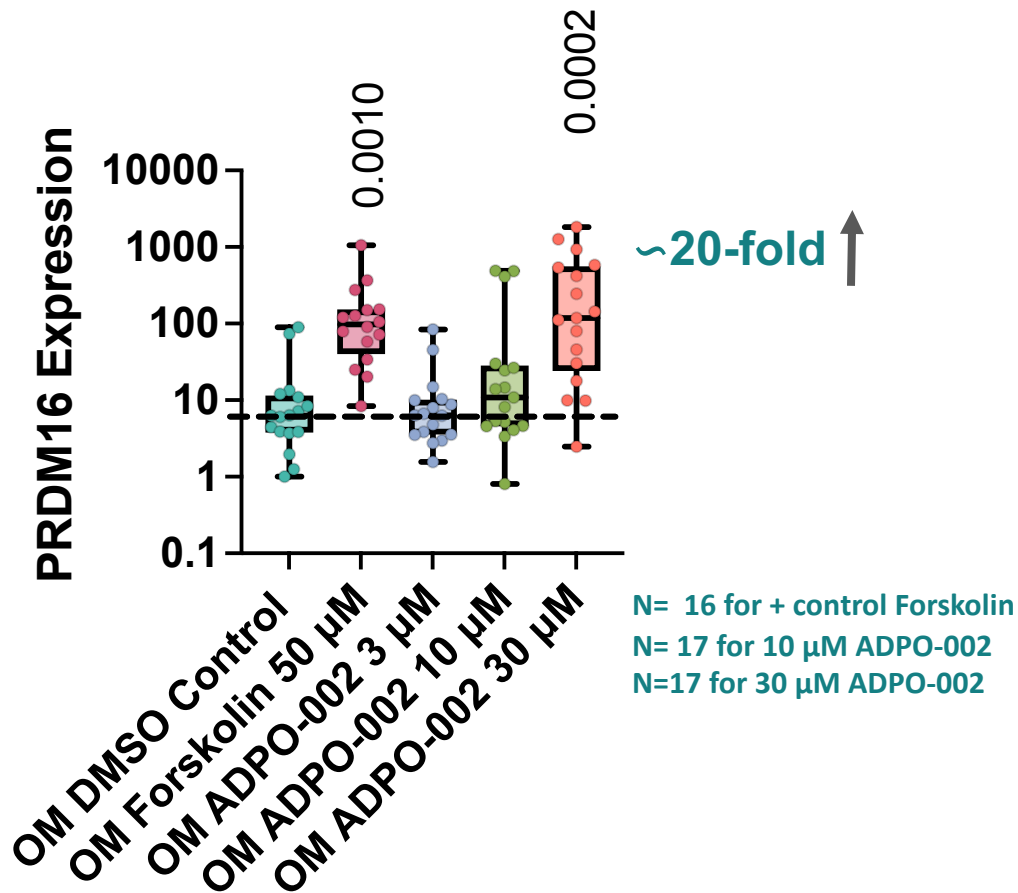
Wilcoxon paired t test

Results of human adipose tissue explant study key browning biomarker expression

Omental Fat Day 7

30 μ M ADPO-002 Median: 119
DMSO Median: 06

30 μ M ADPO-002 Median : 22
DMSO Median : 09



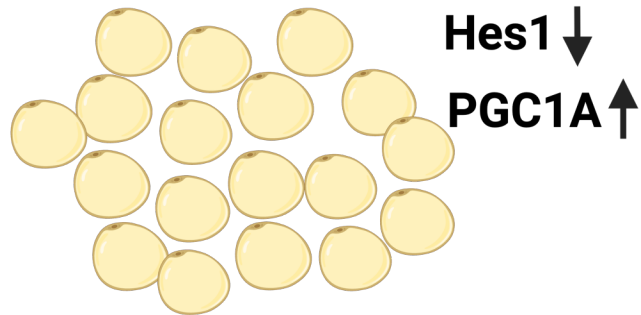
Wilcoxon paired t test

Summary

Human fat cells *in vitro*

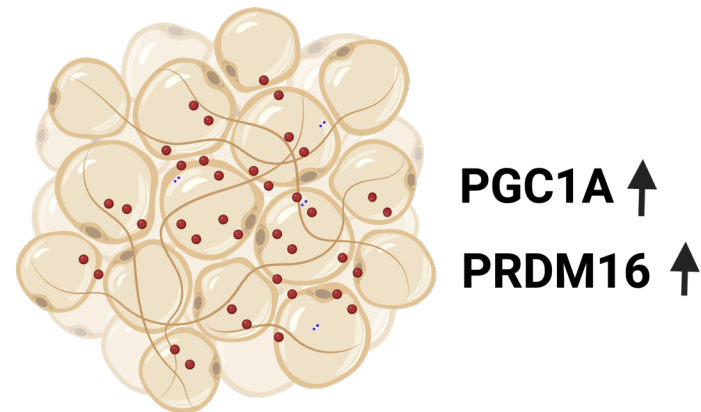
● ADPO-002

 ADPO-002 NP



Human fat tissue *ex vivo*

● ADPO-002



Future work

- Mitochondrial density
- Mitochondrial function
- Establish role in regulation of UCP1

Thank You !

Thanks to the subjects undergoing bariatric surgery who consented to provide white adipose tissue for use in this study

Thanks to the surgeons, nurses and staff at St Vincent Ascension hospital and our colleagues at Indiana Biosciences Research Institute (IBRI) in Indianapolis, IN who assisted with this study

Thanks to the Indiana Innovation Voucher Program for partially funding this study