Anti-miR-22 therapy for obesity and MAFLD: from target discovery to clinical development

Riccardo Panella, PhD
Associate Professor
Center for RNA Medicine
Aalborg University
Copenhagen

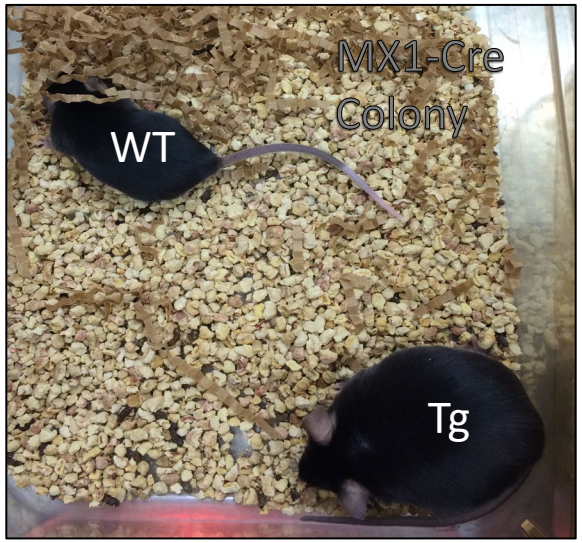
International Congress on Obesity
Sao Paulo- Brazil
29/6/24

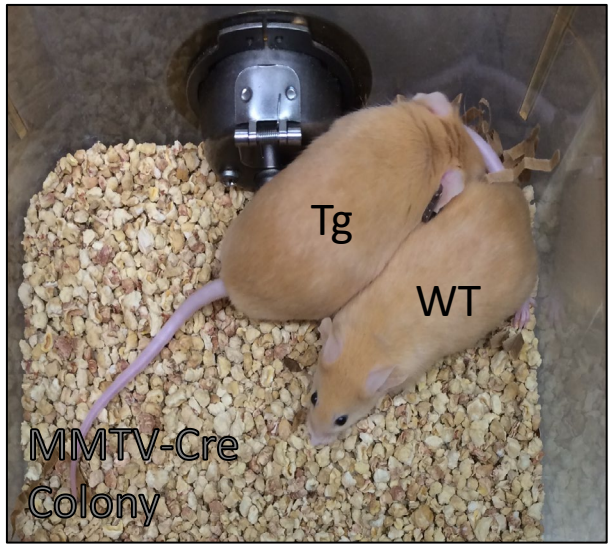
Disclosure

I am a founder, shareholder, and CSO of Resalis Therapeutics srl

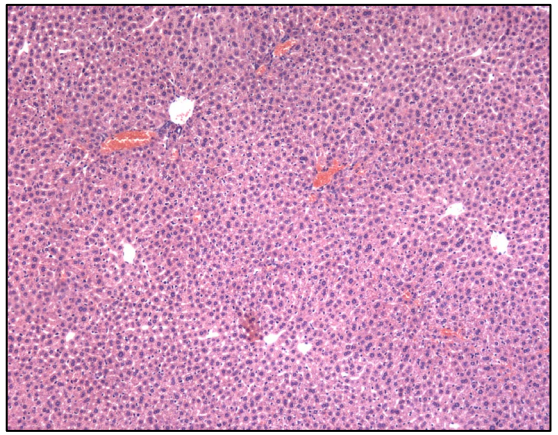
I am an inventors of patents and patents related to miR-22 in cancer and metabolism, owned by Beth Israel Deaconess Medical Center-Harvard Medical School and Aalborg University and licensed to Resalis Therapeutics srl.

miR-22 overexpression increases mice weight and liver steatosis

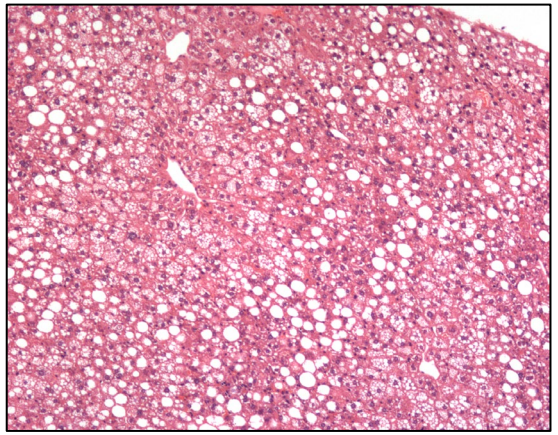




WT Liver

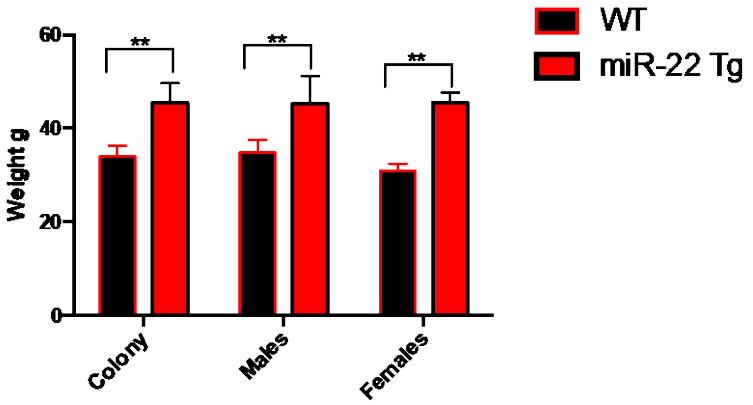


miR-22 Tg Liver

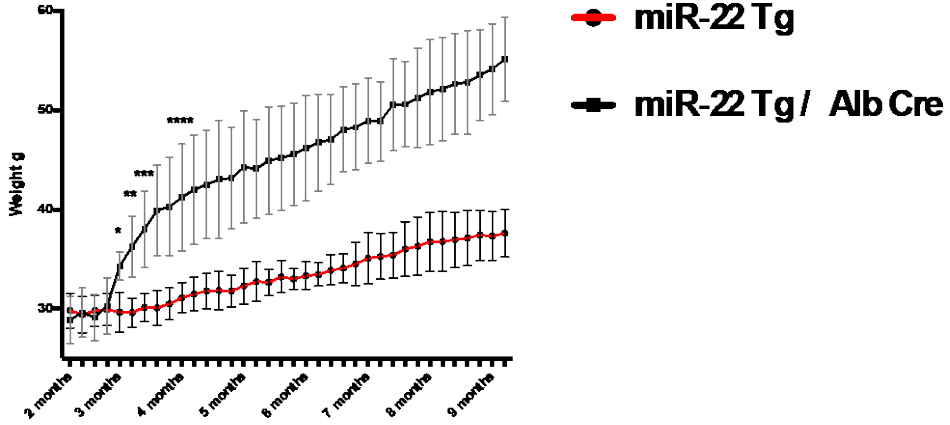


10 months old

Weight miR-22 Tg Colony vs WT



Weight over time



Genetic loss-of-function of miR-22 results in profound metabolic changes in mice

Reduced lipid biosynthesis

- KO models maintain their body weight on HFD with no change in food consumption.
- Echo MRI revealed that miR-22 genetic ablation is reducing fat mass deposition.

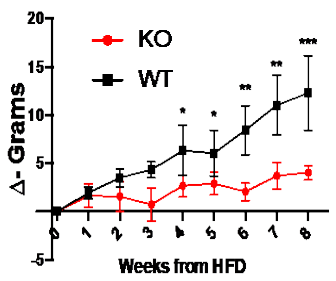
Increased energy expenditure via Brown Adipose Tissue (BAT) activation

- Thermal pictures of WT and KO after 8 weeks on HFD show increased signal in the intrascapular area where BAT is located.
- Metabolic cages show increased oxigen consumption.

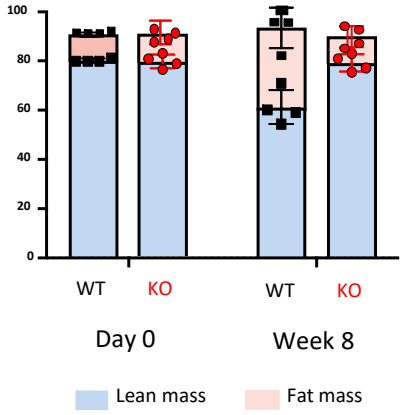
Increased transformation of White Adipose Tissue into BAT

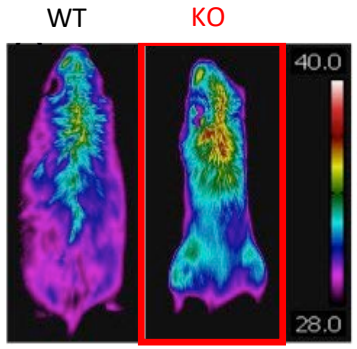
- White adipose tissue (WAT) show signs of brownization.

Weight gain on HFD

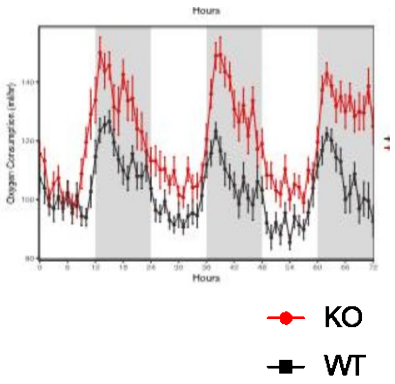


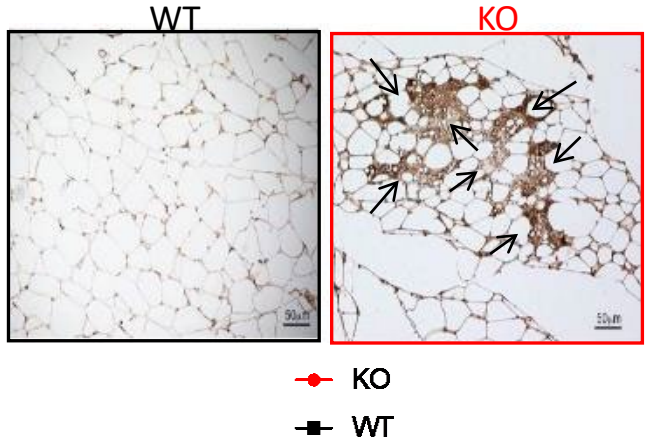
Body composition on HFD





Oxygen consumption

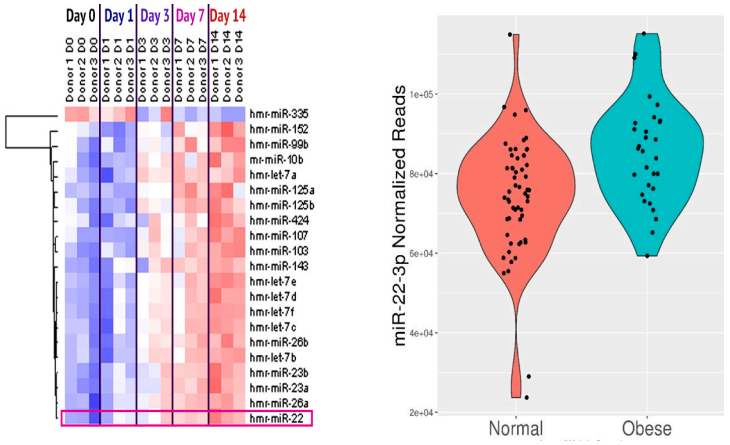




Ref: Panella et al: Int. J. Mol. Sci. 2023, 24, 12870. https://doi.org/10.3390/ijms241612870

Role of miR-22 in fat and liver tissues in human subjects

miR-22 is upregulated in human abdominal subcutaneous adipose tissue samples in subjects fed with HFD and is overexpressed in obese subjects



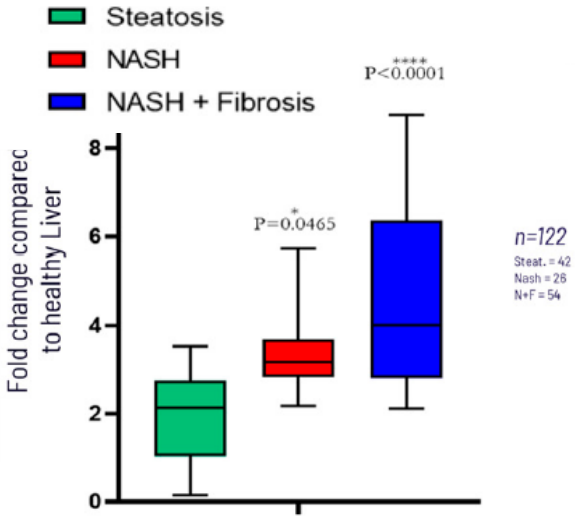
Adapted from Oskowitz et al. PNAS, 2008

Abdominal subcutaneous fat tissue miR-22 expression correlates with metabolic and anthropometric characteristics.

Parameter	Spearman's ρ	Storey's q-value
Waist-Hip Ratio	0.38	0.0027
BMI	0.36	0.0047
TRGs	0.34	0.008
Alanine Aminotransferase	0.31	0.015
ApoB	0.31	0.015
Creatinine Clearance	0.3	0.015
HDL cholesterol	-0.29	0.016
HOMAIR	0.28	0.017
Muscle Mass	-0.28	0.017
sCRP	0.28	0.017
OGTT Fasting Plasma Insulin	0.29	0.017
Matsuda Insulin Sensitivity Index	-0.27	0.019
HOMAIS	0.26	0.022
OGTT 120' Plasma FFA	0.25	0.025
Fat Mass	0.25	0.028
Insulin AUC	0.21	0.05
OGTT 30' Plasma Insulin	0.25	0.028
Adiponectin	-0.24	0.03
ApoA1	-0.22	0.04

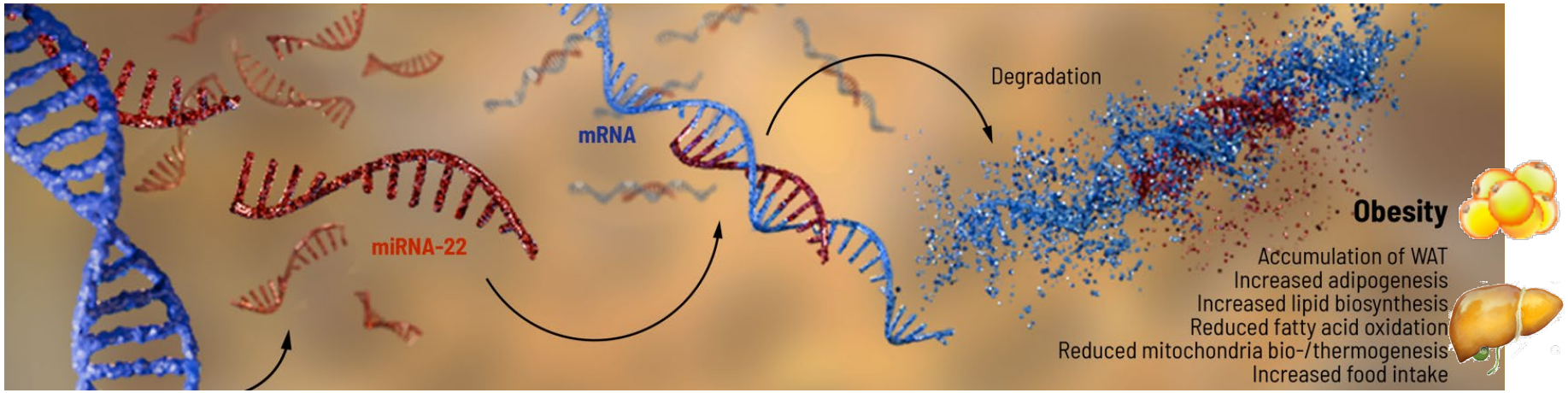
Ref: Civelek et al: Hum. Mol. Genet. 2013, 22, 3023

miR-22 level directly correlates with disease progression in human patients, from steatosis to F1-F2 to F3-F4 fibrosis stage

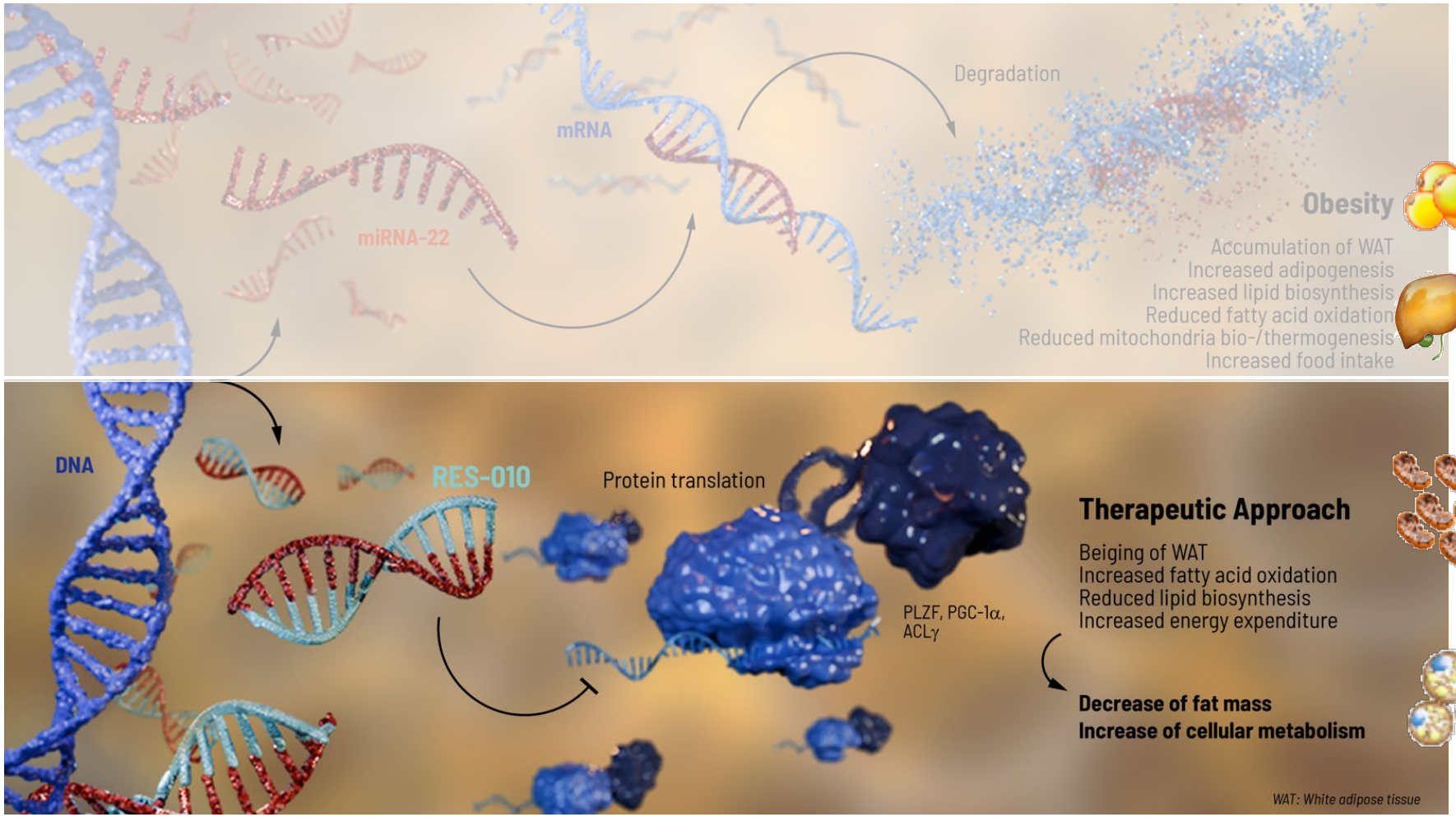


Ref: Panella et al: Int. J. Mol. Sci. 2023, 24, 12870

miR-22 triggers a transcriptional status that is promoting obesity



miR-22 inhibition can represent a valid strategy to restore a metabolic healthy status



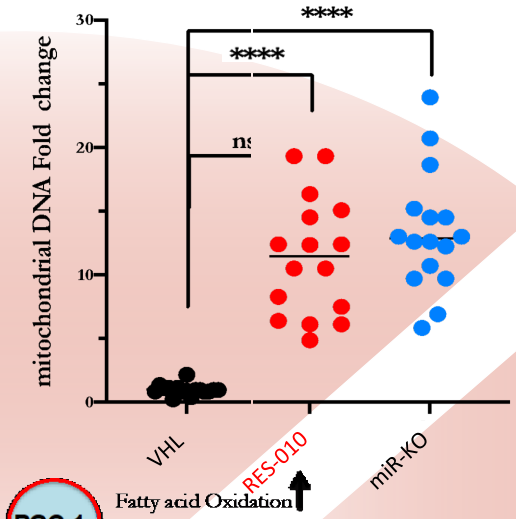
RES-010 is an ASO targeting miR-22 seed sequence lead compound

- RES-010 is a LNA/DNA mixmer antisense oligonucleotide (ASO) designed to specifically target miR-22
- The locked nucleic acid (LNA) chemistry provides increased binding affinity to target without affecting bioavailability

RES-010 inhibition of miR-22 affects multiple metabolic pathways

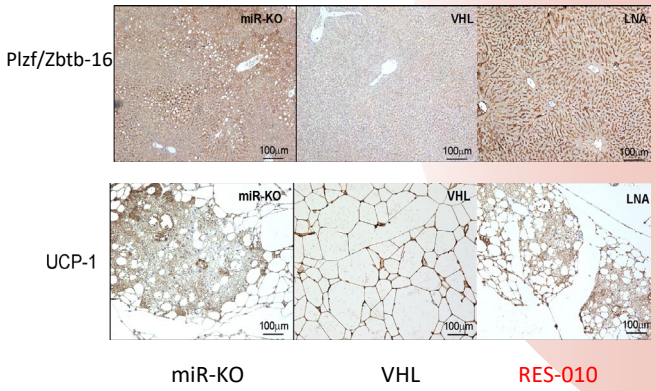
Increased mitochondria biogenesis and fatty acid oxidation

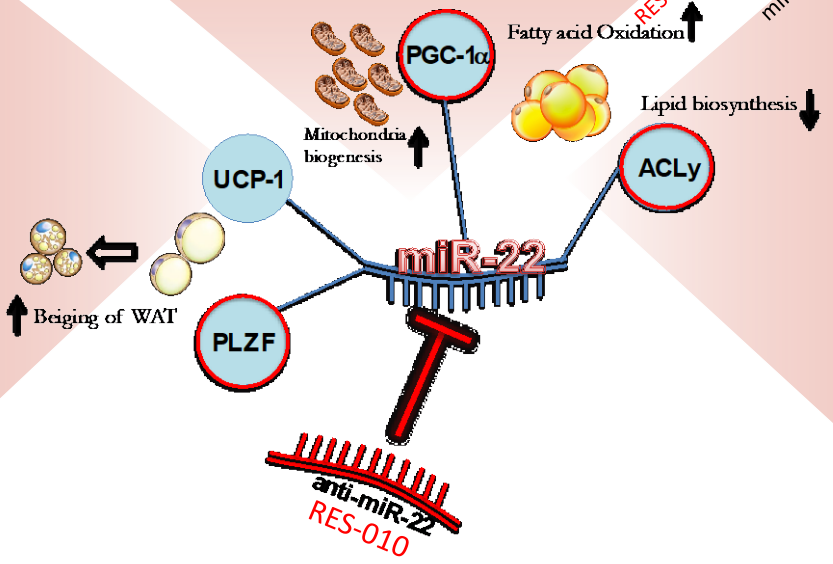
- More mitochondria, more energy expenditure, as in the KO model



Increased transformation of White Adipose Tissue into Brown Adipose Tissue

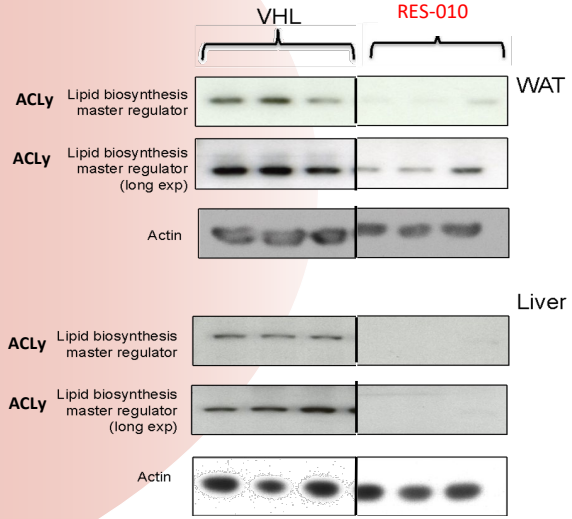
- Strong signs of browning in WAT, as in the miR-22 KO model





Reduced lipid biosynthesis

- Impaired lipid biosynthesis, as in the miR-22 KO model

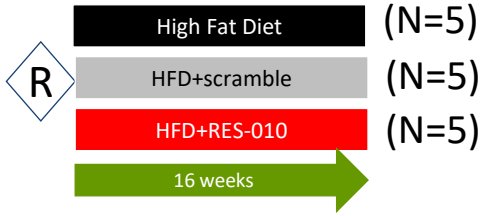


Ref: Panella et al: Int. J. Mol. Sci. 2023, 24, 12870. https://doi.org/10.3390/ijms241612870

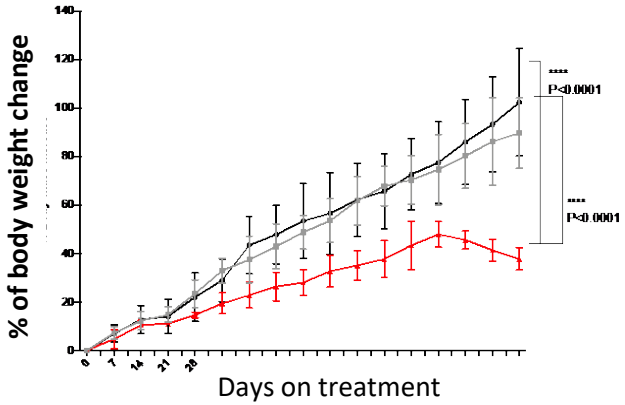
RES-010 induces weight loss only in overweight and obese animals

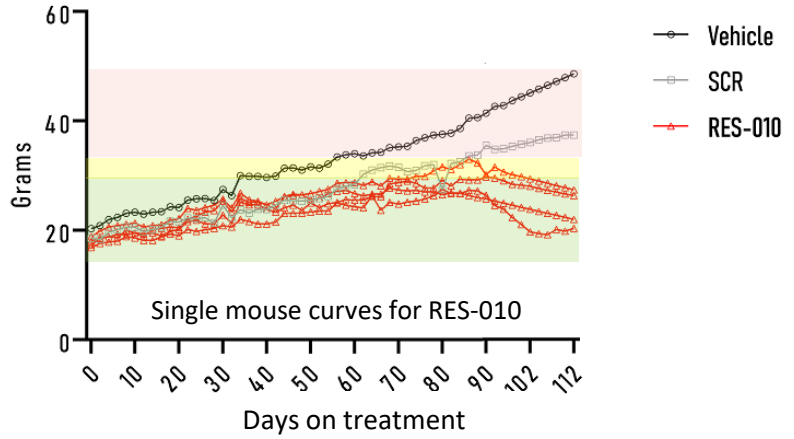
PREVENTIVE

Study design



Lean mice do not lose weight. Only after having gained a sufficient amount of weight as fat mass, RES-010 promotes weight lost

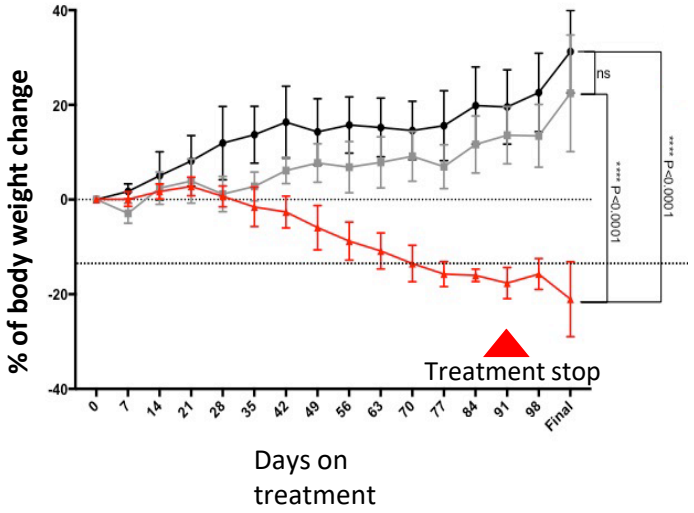


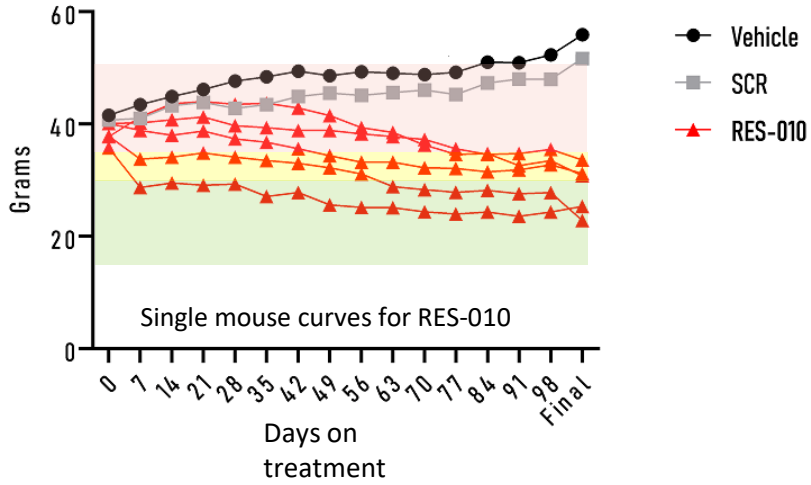


CURATIVE

Study design

Obese mice on high fat diet lose weight within few weeks: miR-22 pharmacological inhibition induces a statistically significant weight loss in obese mice under a DIO protocol
(-20% vs baseline)



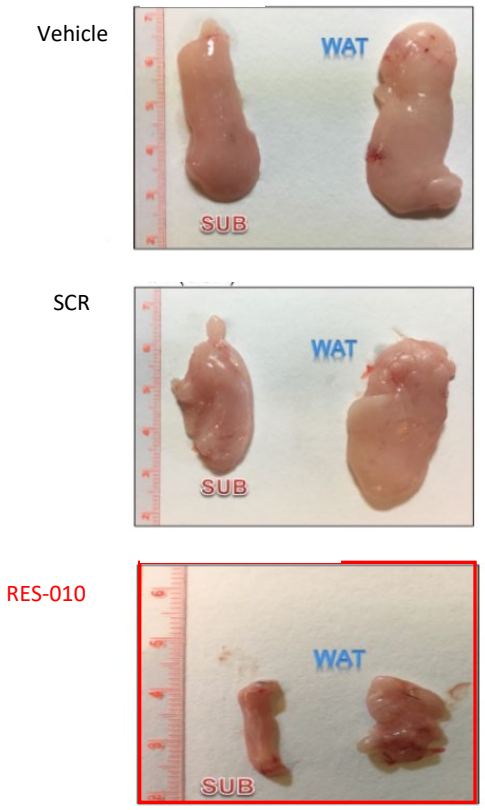


Ref: Panella et al: Int. J. Mol. Sci. 2023, 24, 12870

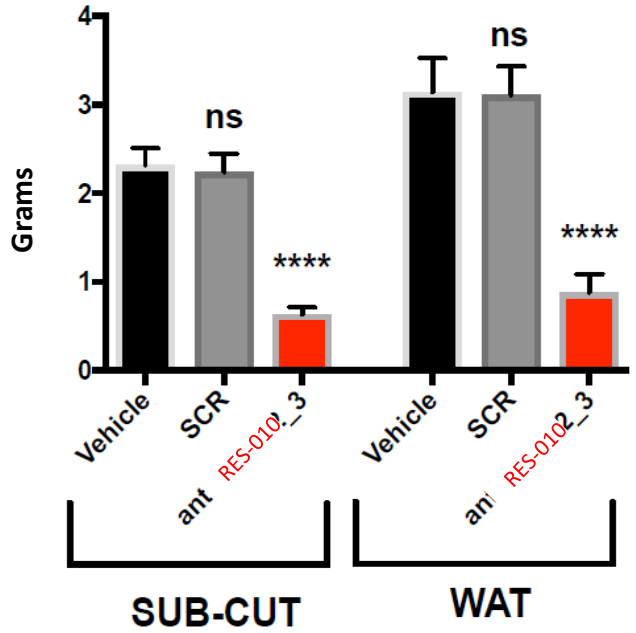
Inhibition of miR-22 leads to fat reduction

Weight decrease is independent from food intake

RES-010 treated mice show reduction in fat pad size



RES-010 treated mice show reduction in fat pad weight that correlates with body weight loss

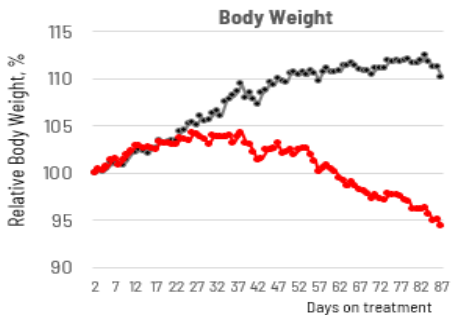


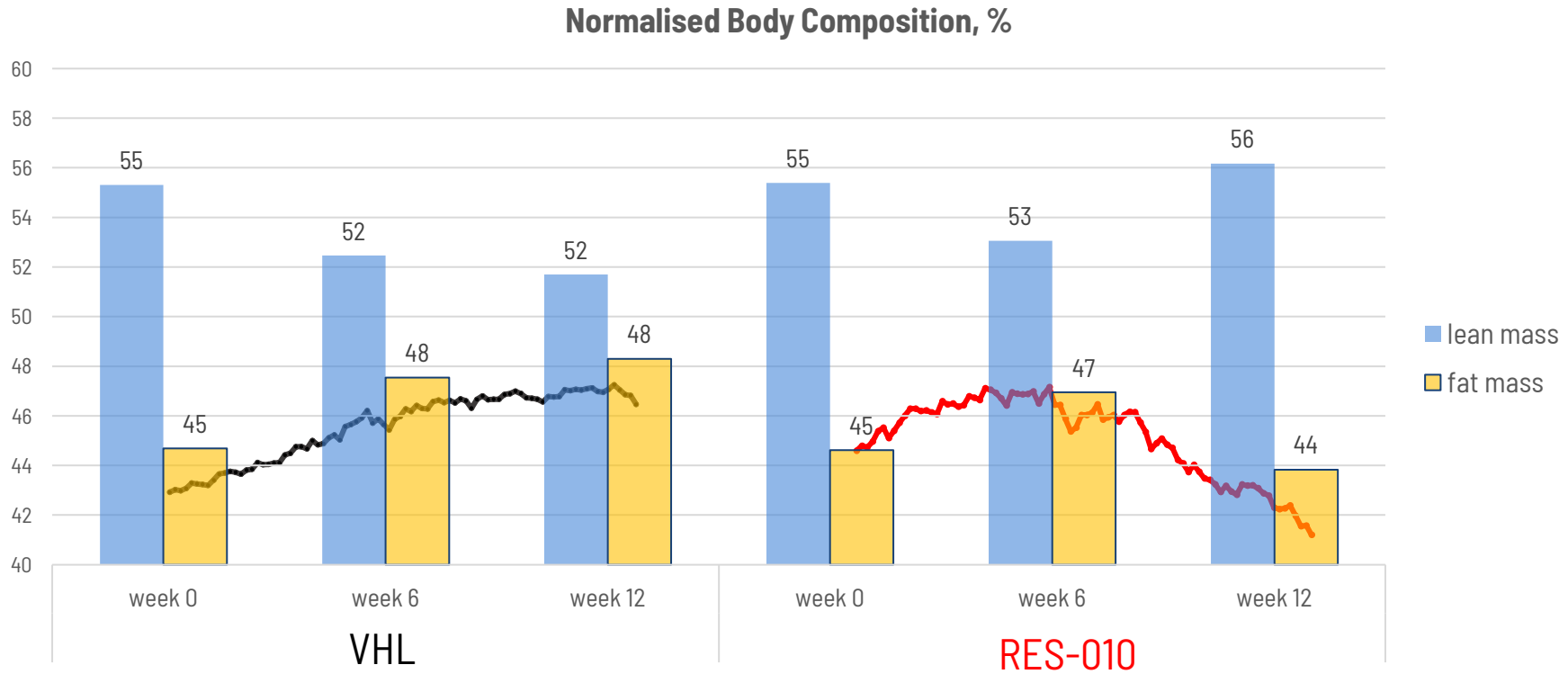
Ref: Panella et al: Int. J. Mol. Sci. 2023, 24, 12870. https://doi.org/10.3390/ijms241612870

Body composition analysis shows that RES-010 causes fat mass loss

12-weeks DIO male mice on HFD diet in thermoneutrality (Effect on body mass change, body composition, food and energy consumption)

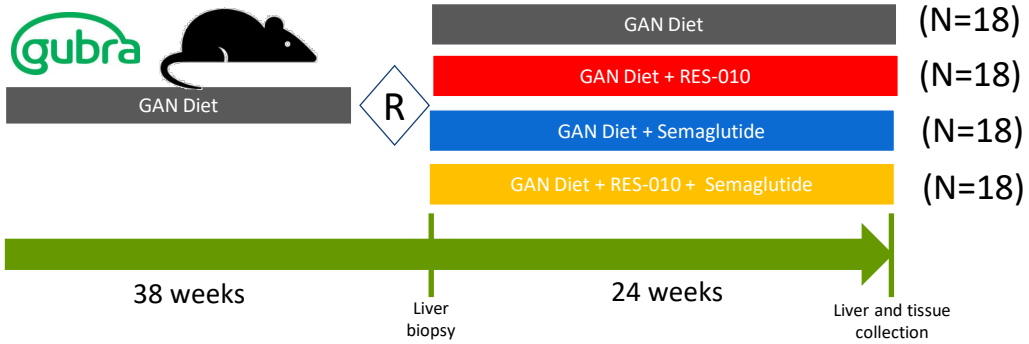
- The weight loss observed between weeks 6 and 12 results in substantial fat mass reduction while the muscles are preserved
- The percentage of fat mass goes parallel with the total body weight





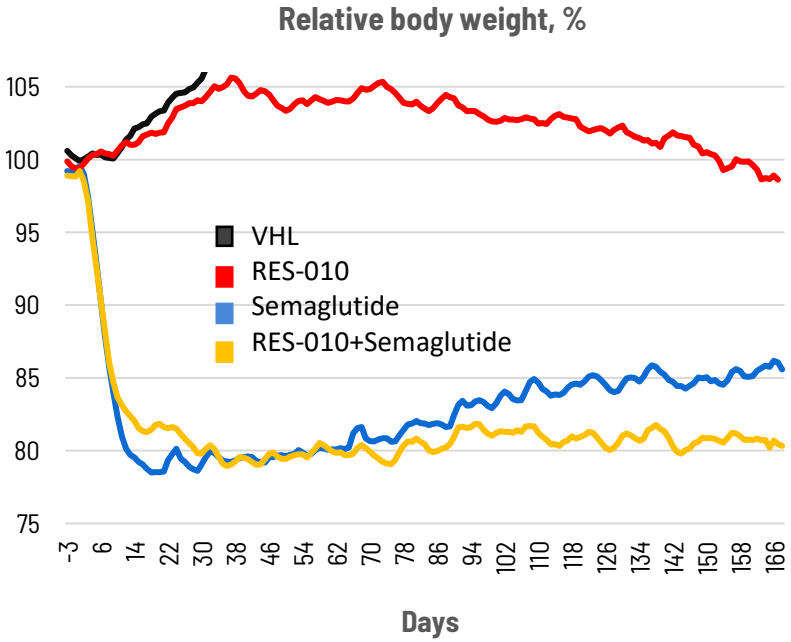
RES-010 has an additive effect with semaglutide on body weight

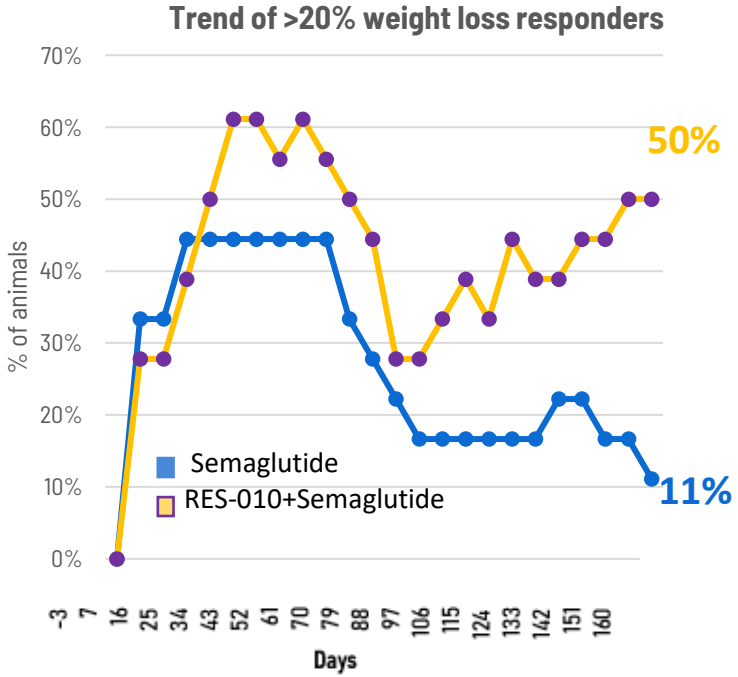
Study design

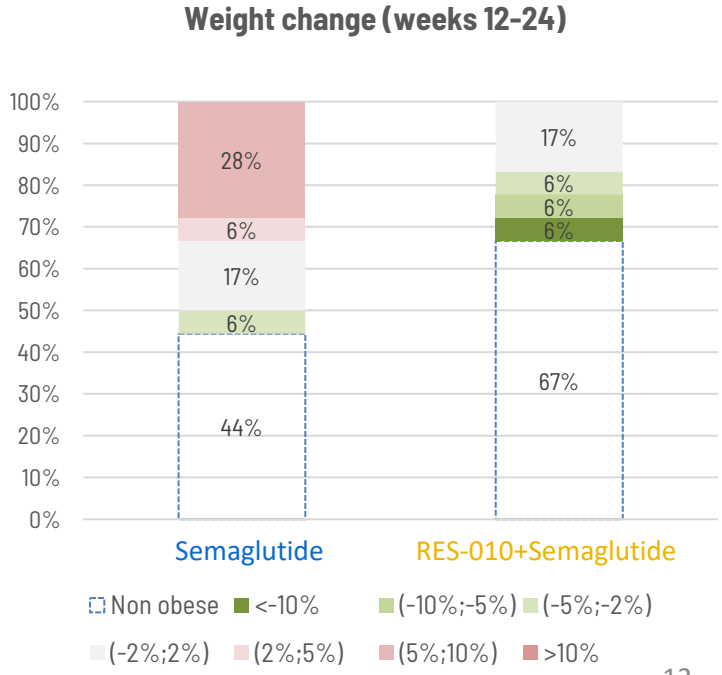


24-weeks DIO-MASH male Mice on GAN diet (Effect on % body mass change)

- The combination RES-010+semaglutide shows better results vs semaglutide in terms of weight loss
- Better response at 24 weeks is experienced in all mice with the combination
- After 12 weeks of treatment, many more mice on combination are no longer obese; and animals treated with the combination keep losing weight in the following 12 weeks of treatment

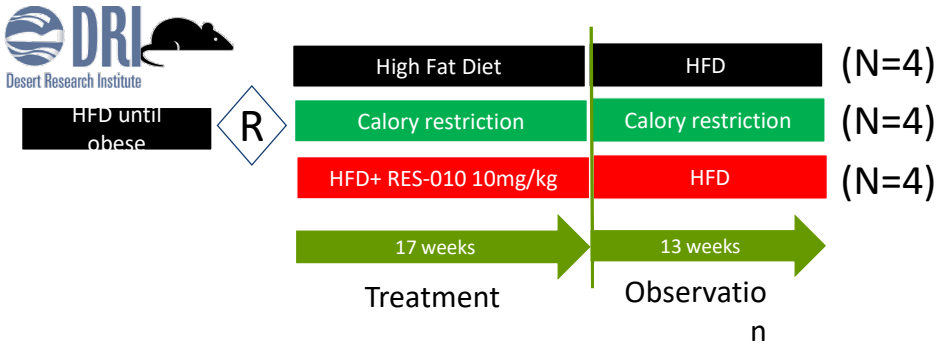






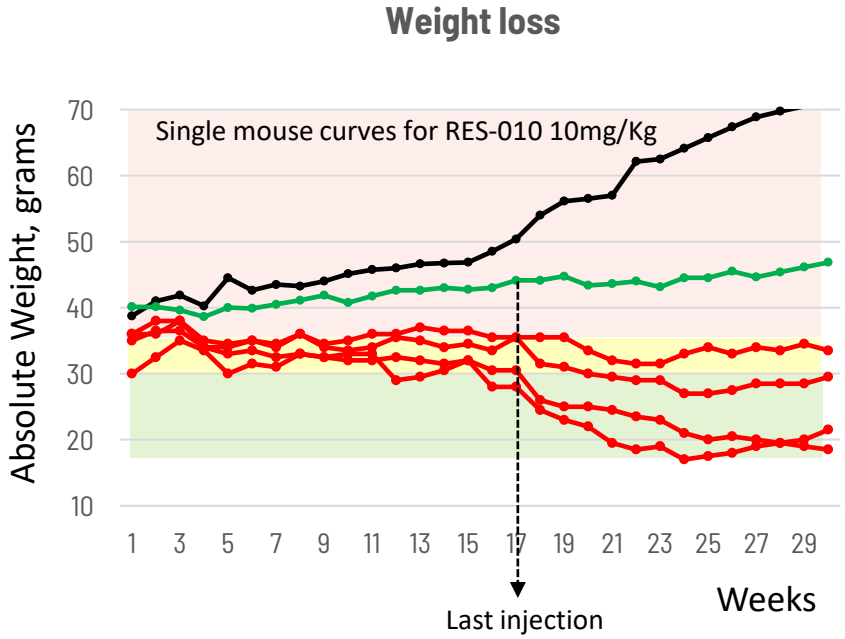
RES-010 disease modifying effect is maintained after treatment interruption

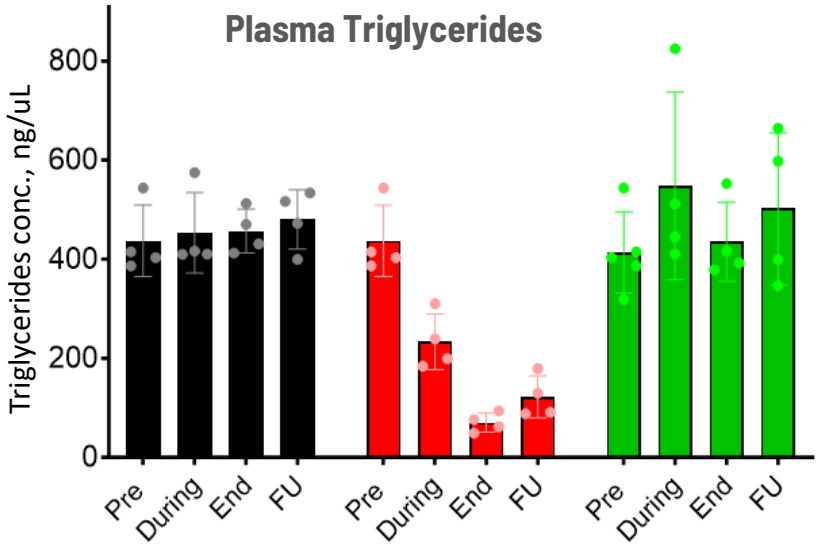
Study design

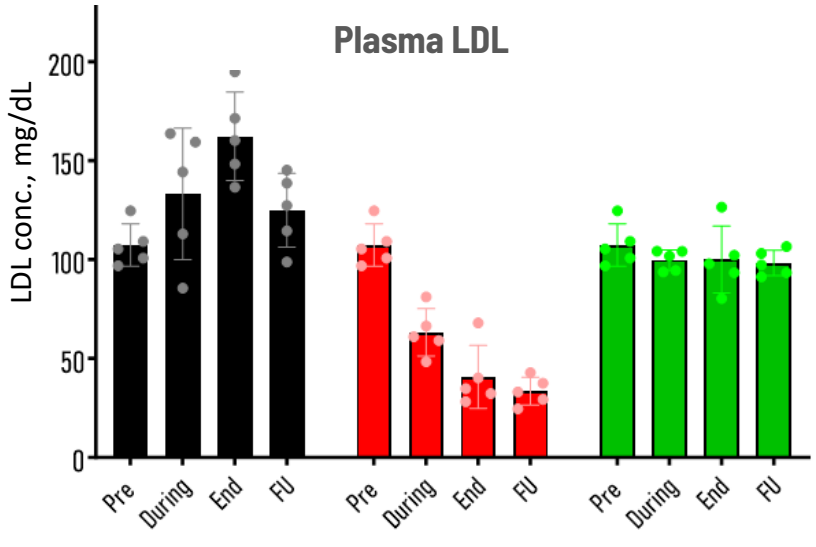


30-weeks DIO female mice on HFD diet (Effect on body mass change and lipid profile)

- During the treatment phase, RES-010 induces weight loss despite HFD, showing a better performance than a calory restricted diet
- Once interrupted the treatment with RES-010, the mice keep losing weight for other 8 weeks while on HFD and then the weight is stabilised
- Plasma lipids (Triglycerides and LDL) are reduced by the treatment and remain low for several weeks after treatment discontinuation





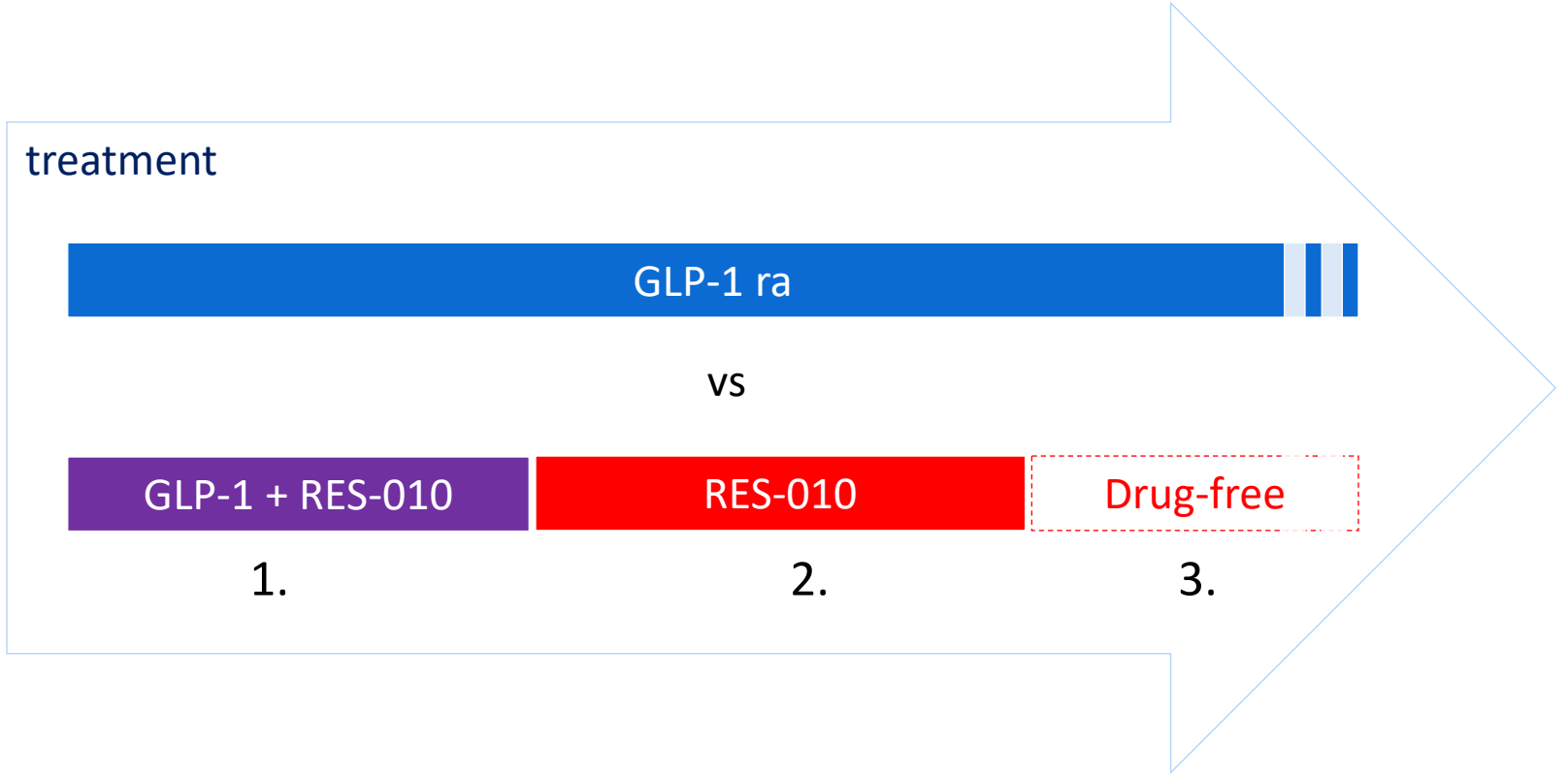


Vehicle RES-010 Calory restriction

Our studies indicate a new treatment approach based on combination of GLP-1 agonist and RES-010

Our proposed approach includes:

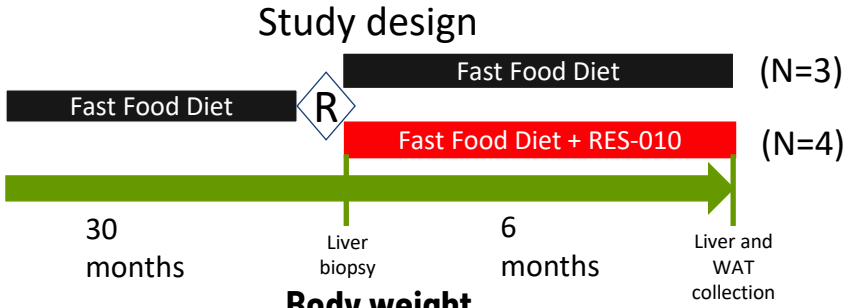
1. initial induction phase with RES-010 in combination with a GLP-1
2. followed by chronic consolidation with RES-010 monotherapy
3. with potential drug-free periods

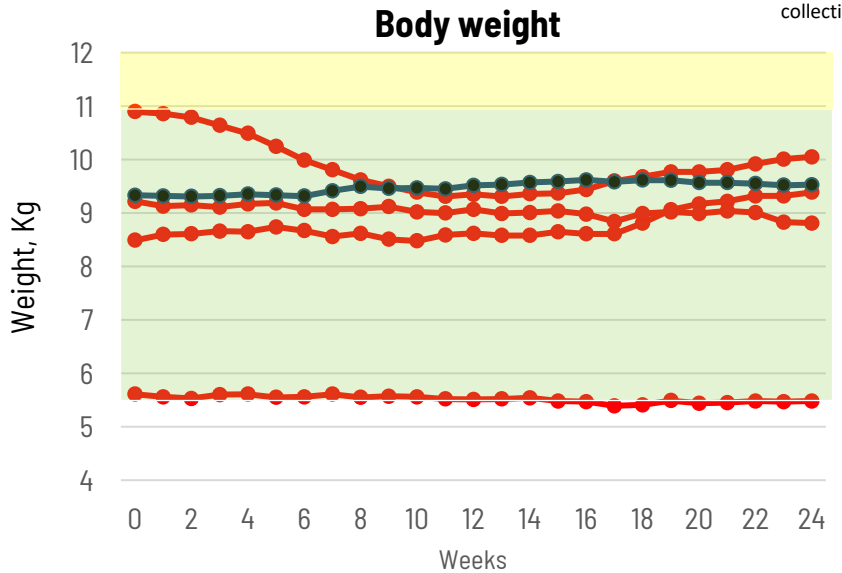


RES-010 effect on body weight loss is confirmed in NHP studies

24-weeks NHP in different HFD diets (Effect on body mass change and lipid profile)

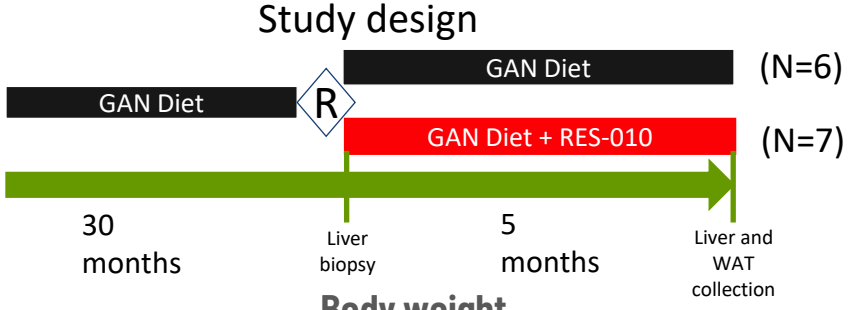
- Two different long-lasting experiments in superior species with two different diets confirm no safety issues observed during the up to 6-month treatment at 5 mg/kg/week
- RES-010 selectively acts on those subjects which suffer from an excessive amount of fat and works as long as this condition remains

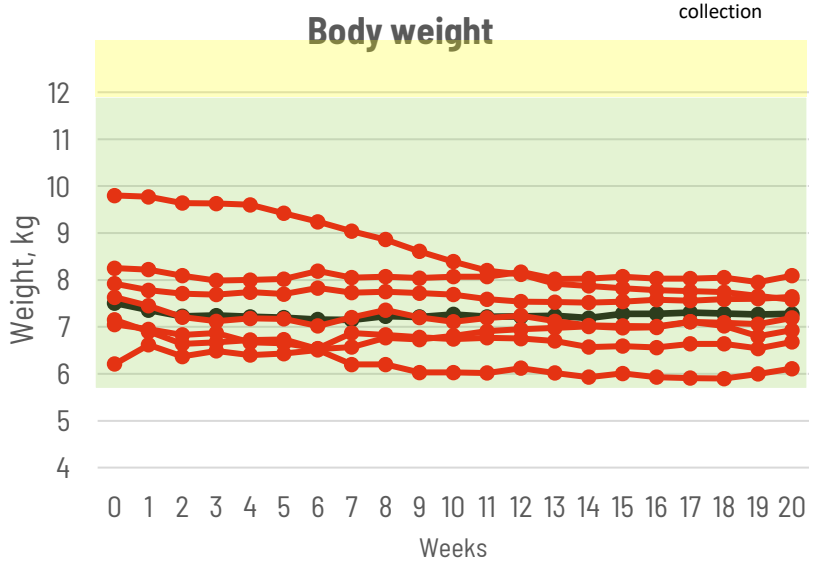




VHL
RES-010 5mg/kg

Single NHP curves for RES-010 5mg/kg/w



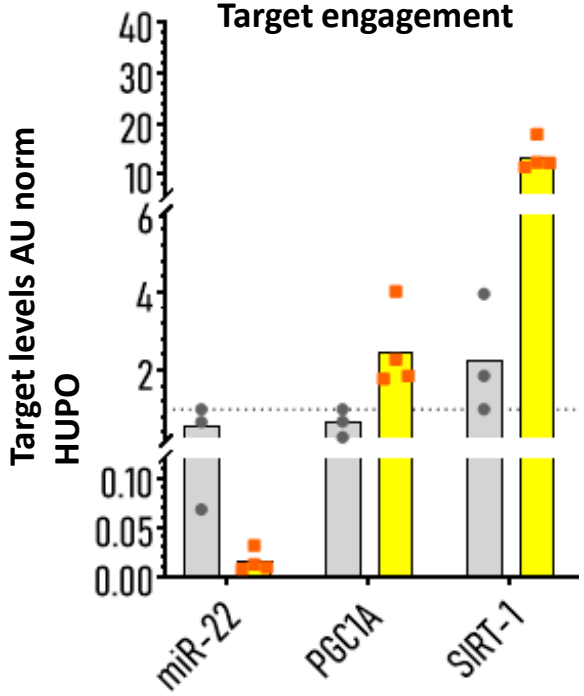


Six-months treatment in NHP confirms safety and MoA

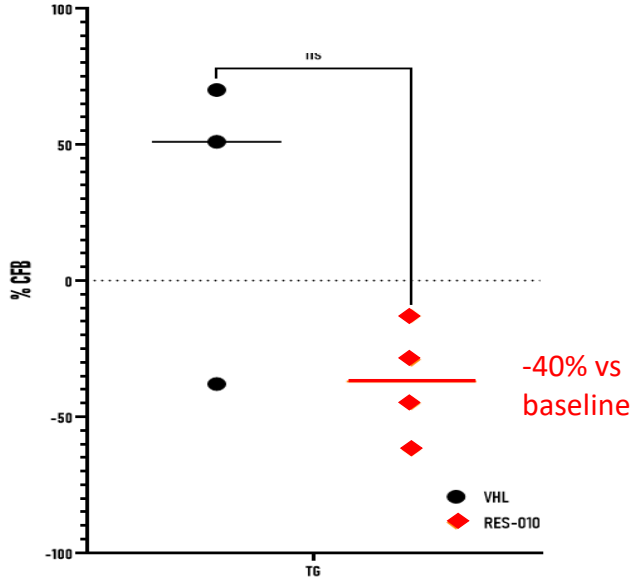
RES-010 in NHP fed with Fast Food Diet confirmes what recorded in mice:

- All treated monkeys show very low levels of miR-22 in the liver while PGC1α and SIRT-1 are activated
- Triglycerides: well controlled in all treated animals
- WAT: relevant brownisation detected in treated primates

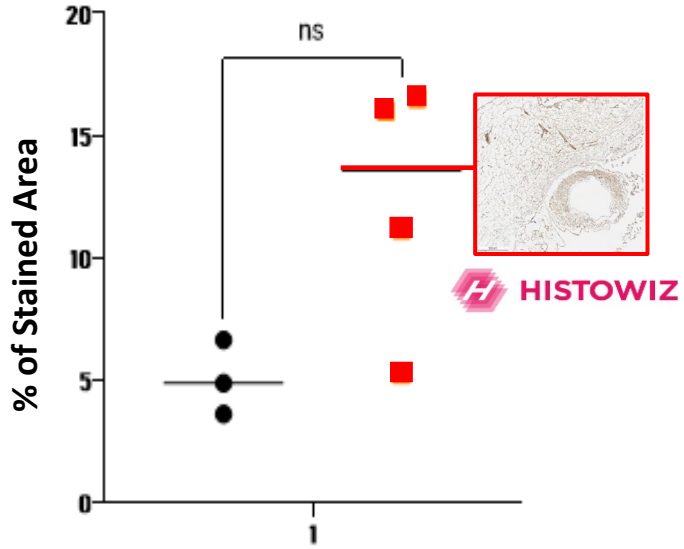
Target engagement



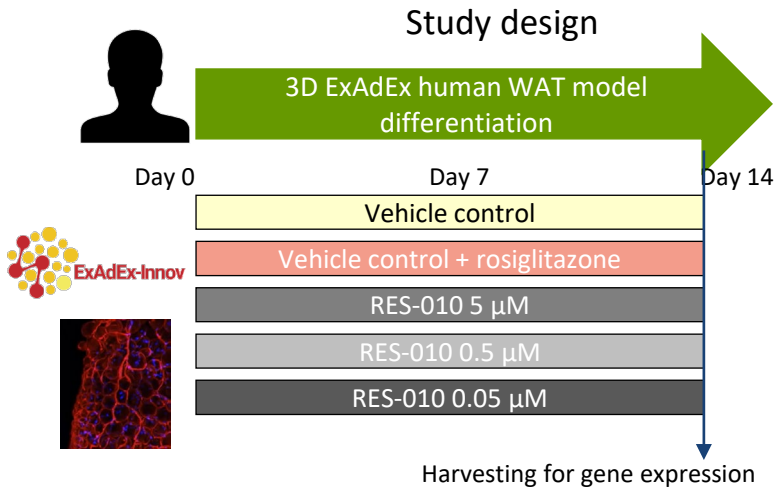
Triglycerides, 6 months



Staining of UCP-1 in WAT



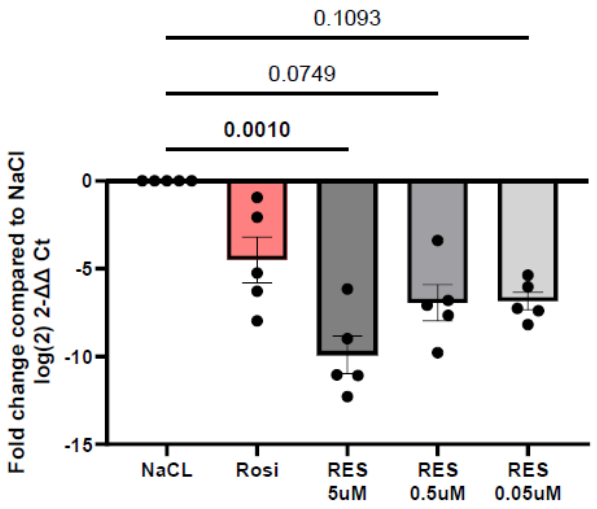
RES-010 shows browning in a 3D human adipose tissue model



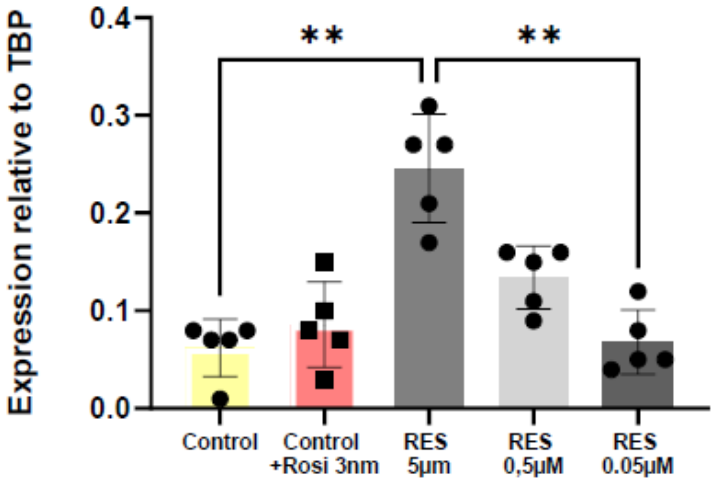
3D ExAdEx human WAT model (Lipoaspirate of subcutaneous human adipose tissue obtained from elective cosmetic surgery from a subcutaneous body fat depot of a donor displaying a BMI=30.7):

- In ex vivo human adipose tissue models, RES-010 was able to induce a statistically significant upregulation of hUCP1 and hPGC1α gene expression, as well as a statistically significant reduction in miR-22 expression.
- Interestingly, while RES-010 induces brownization by reducing the level of miR-22, brownization induced by rosiglitazone results in lower levels of miR-22 as well

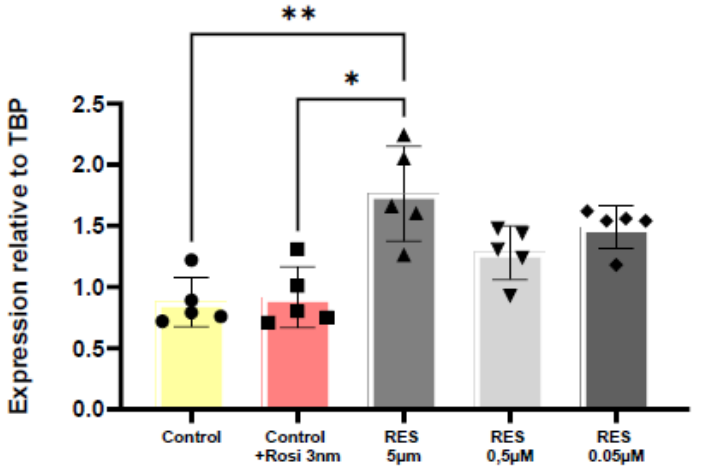
miR-22 expression



UCP1 expression



PGC1α expression



Conclusions

- miR-22 is a master regulator of several metabolic pathways converging into the obese phenotype
- Inhibition of miR-22 is promoting body weight loss via fat mass reduction only in obese animal models
- miR-22 inhibition produce a disease modify effect that last even in absence of treatment for several weeks
- miR-22 inhibition increase the efficacy of GLP-1 RA by prompting further body weight loss in sub-optimal responders
- Metabolic benefits of miR-22 inhibition are confirmed in NHP and 3D human derived organoids

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Sakari Kauppinen
Anja Holm
Mirolyuba Ilieva
Simone Tomasini
Francesco Margiotta
Ulrik Scheele
Anna Altieri
Jens Madsen
Lluis Riera Ponsati
Vibeke Thomsen
Clara Mayer

Alessandro Toniolo
Micheal Hodges
Emanuele Monteleone
Luca Borgio
Barbara Domizi
Almut Nitche

Pesalis THERAPEUTICS

Thank you

riccardop@dcm.aau.dk

Beth Israel Deaconess Medical Center
HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

miR-22 inhibition affects multiple pathways

Mechanistically, we identify 3 major metabolic pathways under miR-22 control converging on obesity phenotype

≥ 2-fold
0,5 to 2-fold
0,5 to 2-fold
≥ 2-fold

Early response

ENHO — Energy homeostasis associated gene, inverse correlation with body weight and liver fat

TIMP3 — Associated with NASH progression

CyP7a1 — Cholesterol processing enzyme, high expressed in NASH

SP1 — Transcriptional regulator of metabolic relevant genes

FASN — Mediates pro-inflammatory and fibrogenic signaling

Late response

Increase mitochondria & energy expenditure (including BAT)

PPARα — Promotes fatty acid oxidation

Sirt1 — Reduces fatty acid metabolism

PLZF (Zbtb16) — Promotes BAT differentiation

PGC-1α — Increases mitochondria biogenesis

Decrease lipid biosynthesis

FOXO1 — Promotes lipolysis and BAT differentiation

Increases initiation of gluconeogenesis

ACLY

SREBP-1c — Stimulates cholesterol biosynthesis

Favours atherosclerotic plaques

Apo B

DGAT2 — Increases last step of gluco-neogenesis

THRβ — Reduces cholesterol

Decrease liver steatosis

Increases fatty acid metabolism — **FGFR1**

FGF21 — Increases fatty acid metabolism

TCF7 — Increases T cell activation, promotes inflammation

HSD17B13 — Reduces hepatic lipids

Source: RNAseq analysis on liver mice tissues treated for 3 or 15 weeks