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

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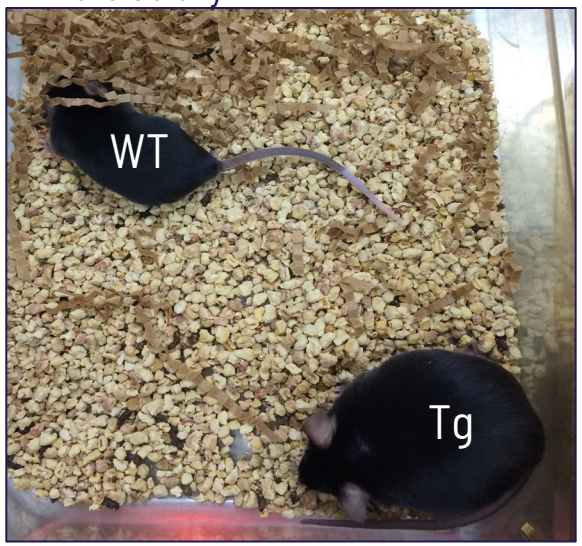
Disclosure

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

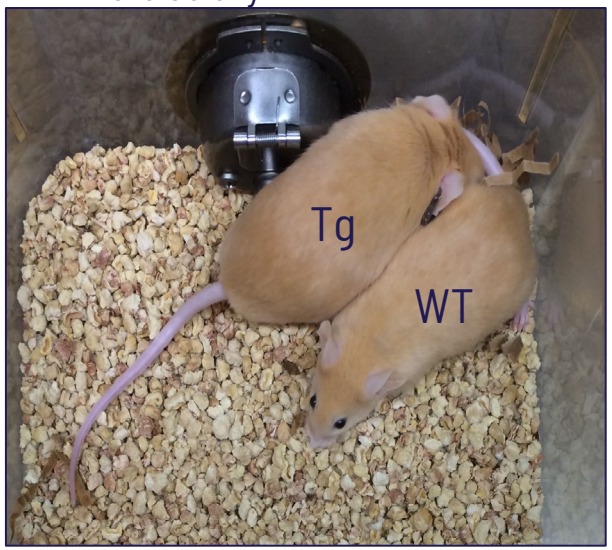
I am an inventors of patents and patents related to miR-22 in cancer and metabolism, owned by Beth Israel Deaconess Medical Center-Harvard Medical School and Aalborg University and licensed to Resalis Therapeutics srl.

miR-22 overexpression affects mice weight and liver steatosis

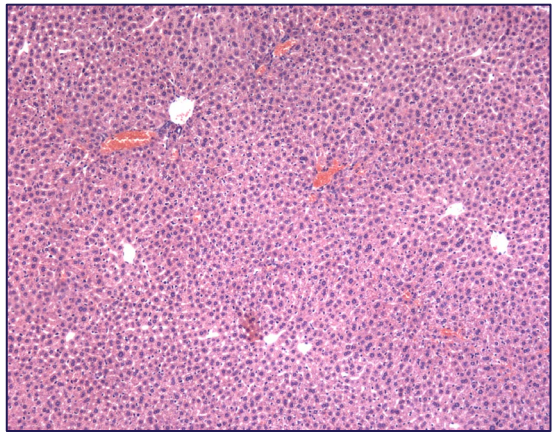
MX1-Cre Colony



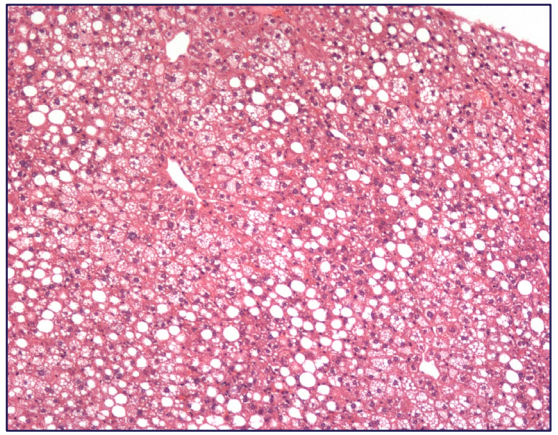
MMTV-Cre Colony



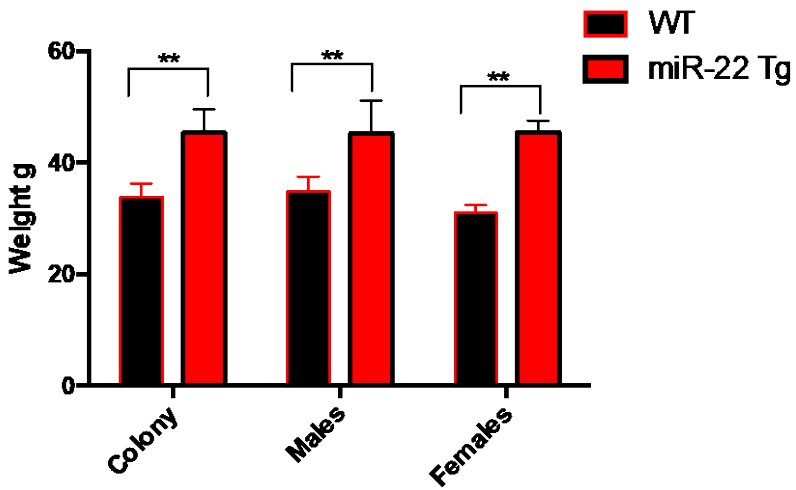
WT Liver



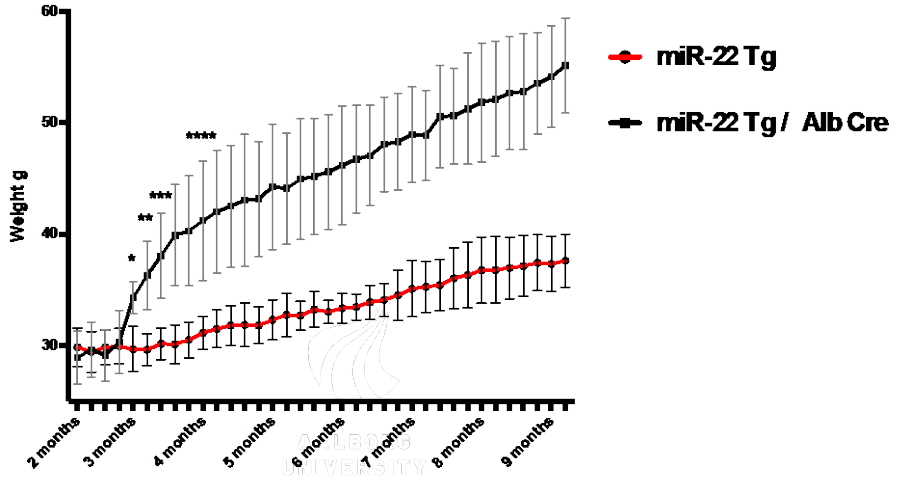
miR-22 Tg Liver



Weight miR-22 Tg Colony vs WT



Weight over time



10 months old

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

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 affecting fat mass deposition.

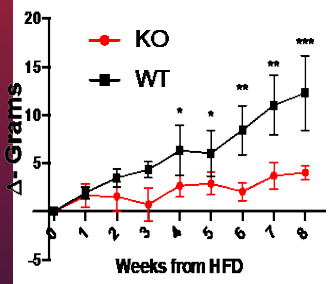
Increased energy expenditure via BAT activation and increased mitochondrial biogenesis

- Thermal pictures of WT and KO after 8 weeks on HFD, increased signal in the intrascapular area where BAT is located while Oxigen consumption increased.

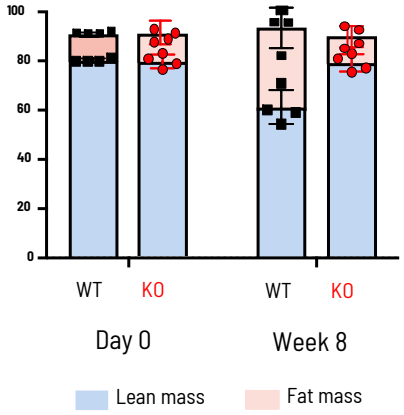
Increased transformation of White Adipose Tissue into Brown Adipose Tissue

- Increased BAT and sign of brownization of WAT.

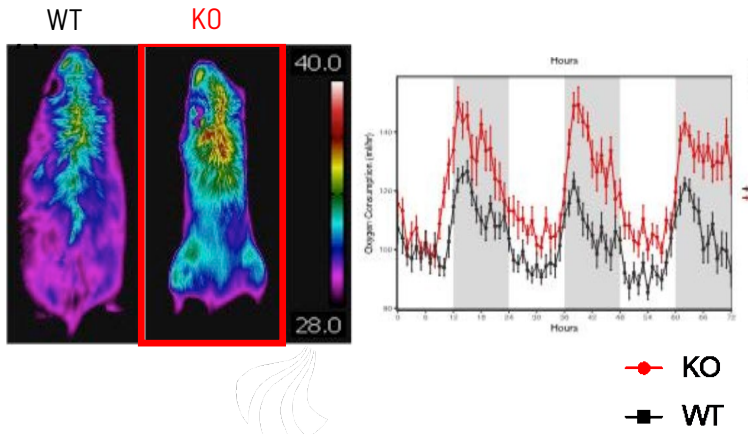
Weight gain on HFD

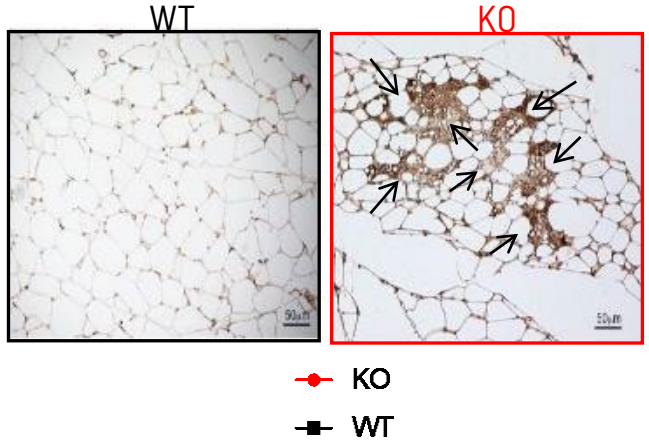


Body composition on HFD



Oxygen consumption





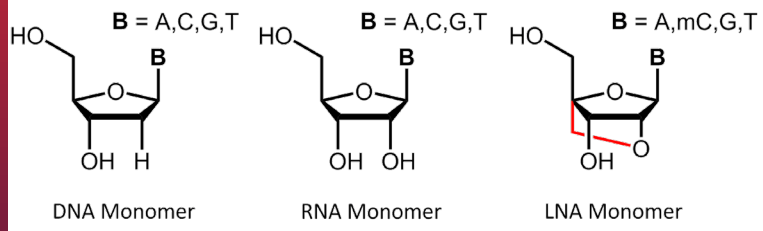
Ref: Panella et al: Int. J. Mol. Sci. 2023, 24, 12870

miR-22 KO mouse was a kind gift from Da-Zhi Wang lab, BCH

miR-22 pharmacological inhibition

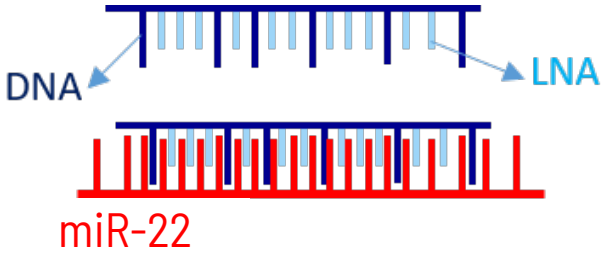
- ☑ Identification of target RNA (miR-22)
- ☑ Target validation
- ☑ Silencing

LNA (Locked Nucleic Acid)

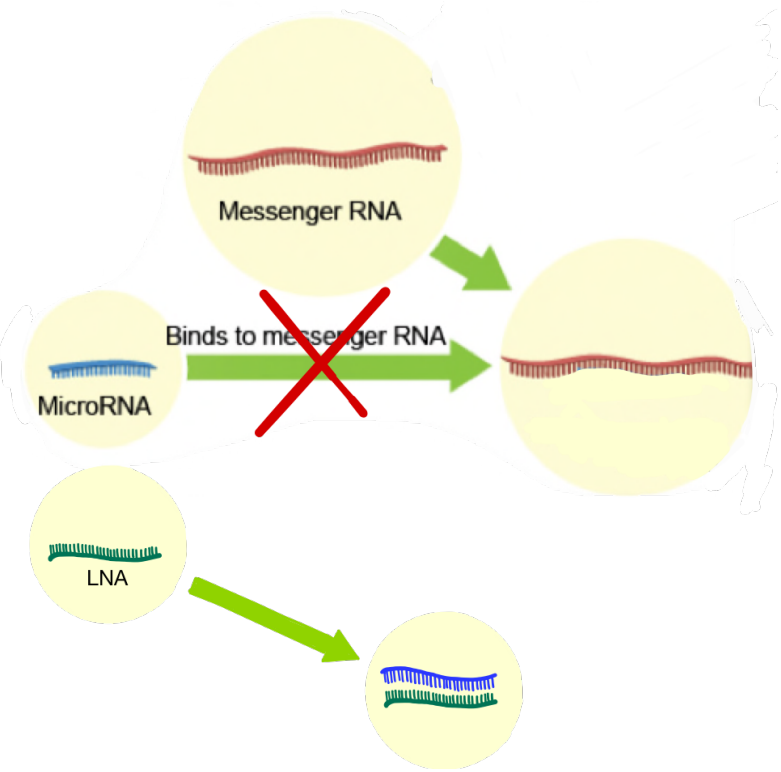


LNA is a high-affinity RNA analog perfectly suited for miRNA inhibition

Our lead anti-miR compound



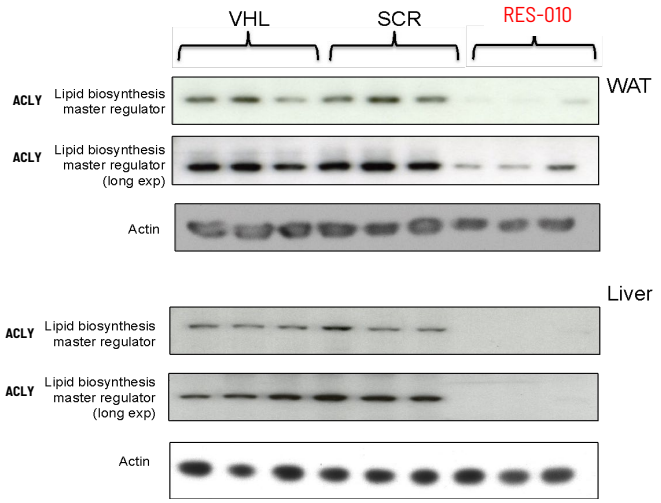
Granted in USA ane EU
Pending in JP and CN



miR-22 pharmacological inhibition is mimicking genetic ablation

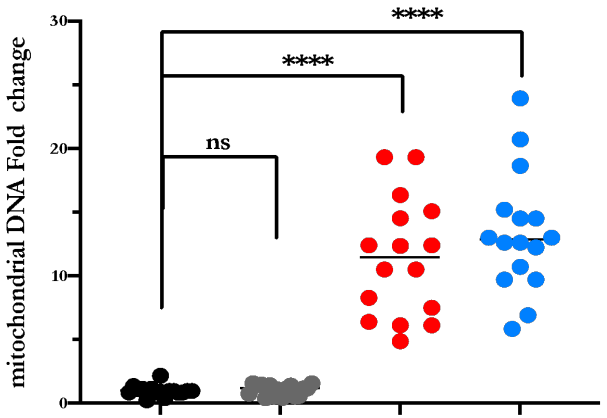
Reduced lipid biosynthesis

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



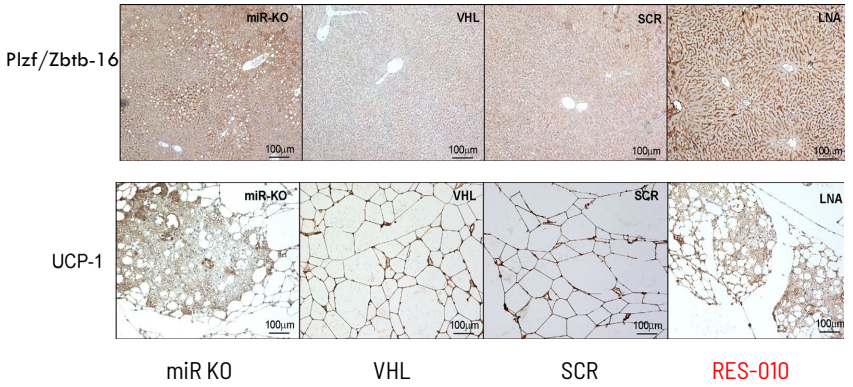
Increased mitochondria biogenesis and fatty acid oxidation

- More mitochondria, more energy expenditure, as in the miR-22 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.

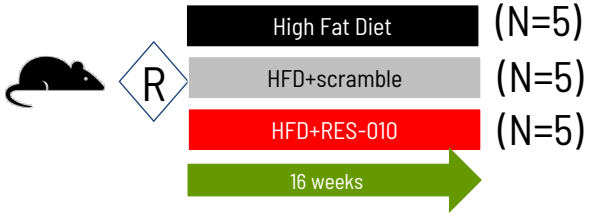


Ref: Panella et al: Int. J. Mol. Sci. 2023, 24, 12870

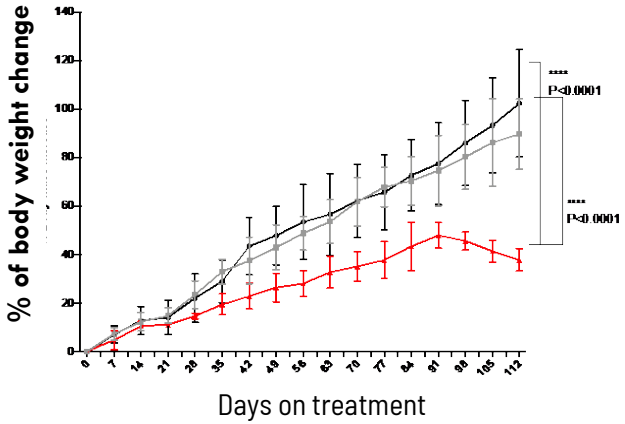
RES-010 induces weight loss only in overweight and obese animals

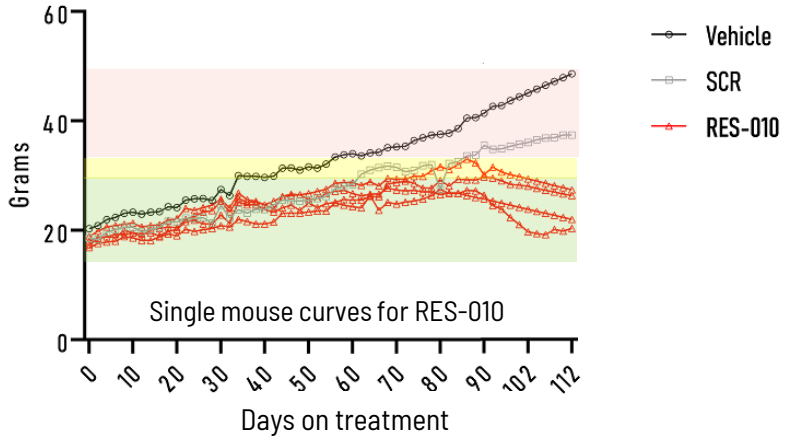
PREVENTIVE

Study design



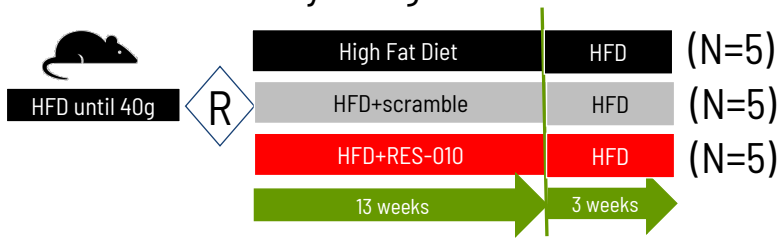
Lean mice do not lose weight. Only after gaining a sufficient amount of weight as fat mass, mice treated with RES-010 lose weight despite being on high fat diet.



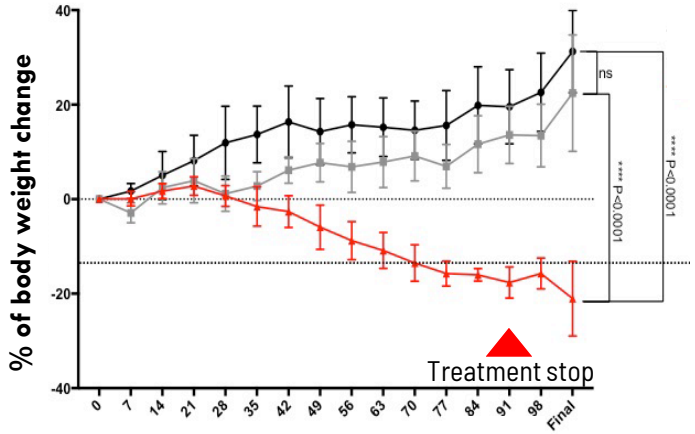


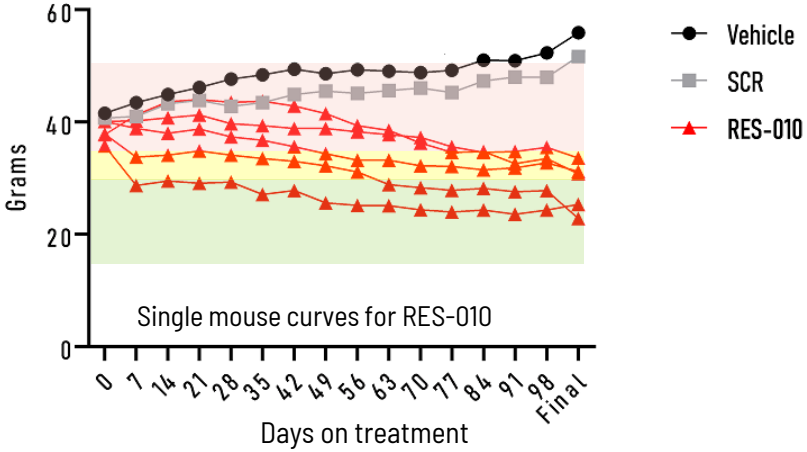
CURATIVE

Study design

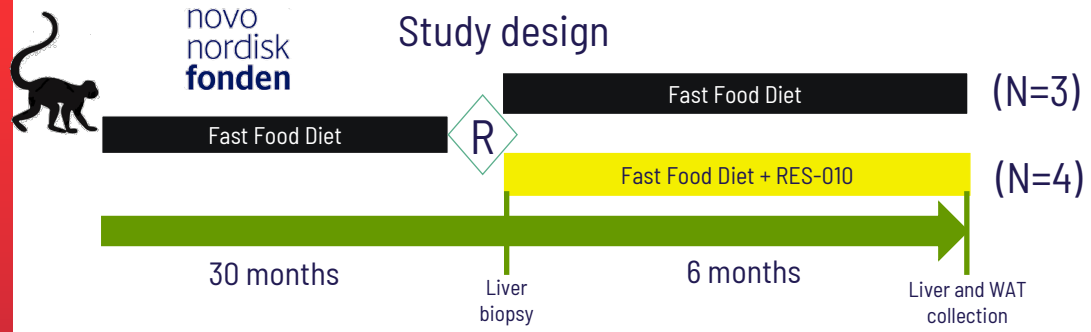


Obese mice on high fat diet lose weight within few weeks: miR-22 pharmacological inhibition induces a statistically significant weight loss in obese mice under a DIO protocol (-20% vs baseline)





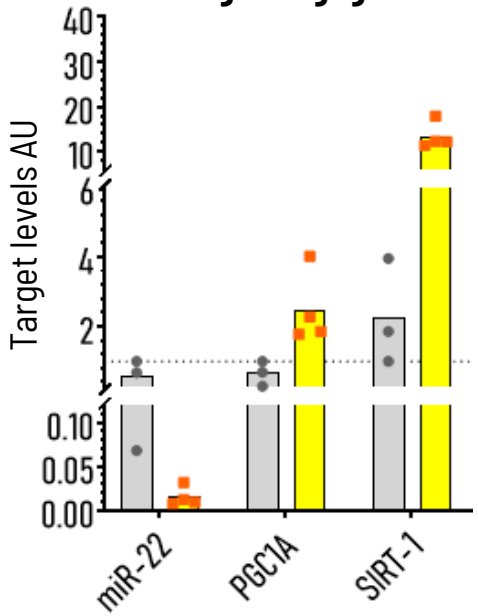
Six-months treatment with RES-010 confirms safety and MoA in Fast Food Diet-fed Non Human Primates (NHP)



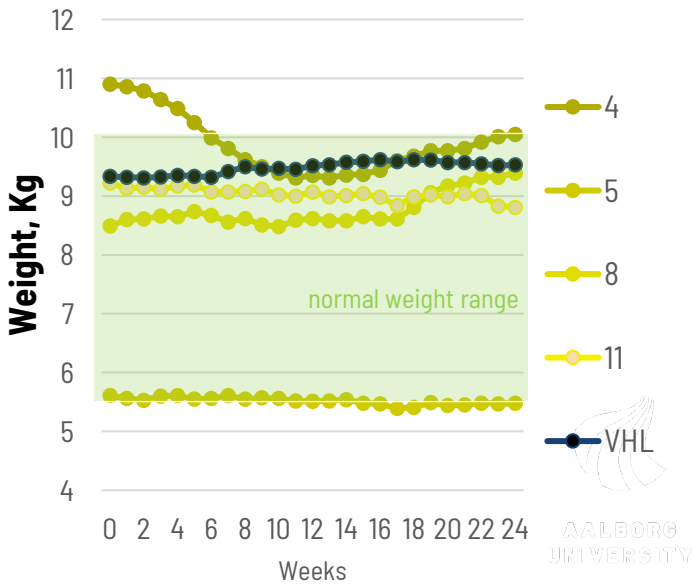
RES-010 in NHP fed with Fast Food Diet confirmes findings in mice:

- No safety issues observed during the 6-month treatment at 5 mg/kg/week.
- All treated monkeys show a strong ininhibition of miR-22 in the liver while PGC1α and SIRT-1 are de-repressed.
- Body weight: RES-010 works on animals with high BMI.
- Triglycerides: consistend downregulation in all treated animals.
- WAT: relevant brownisation detected in treated primates.

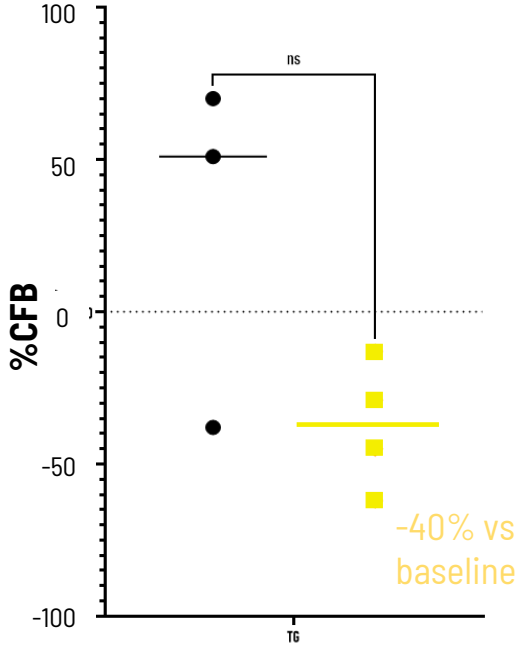
Target engagement



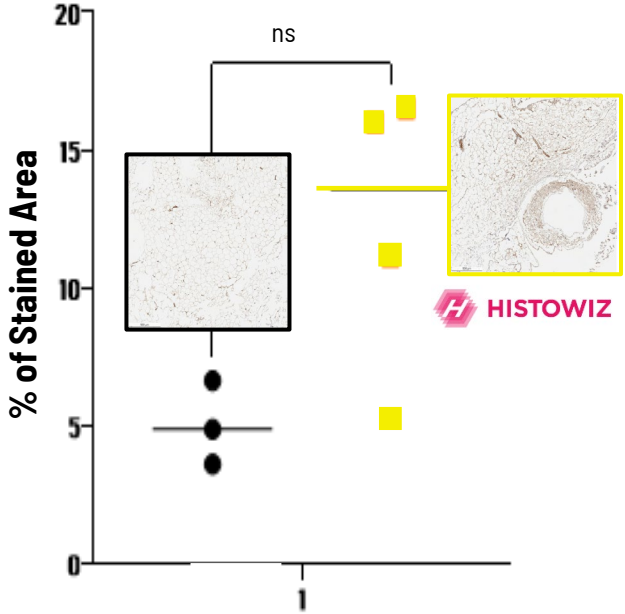
Body weight



Triglycerides

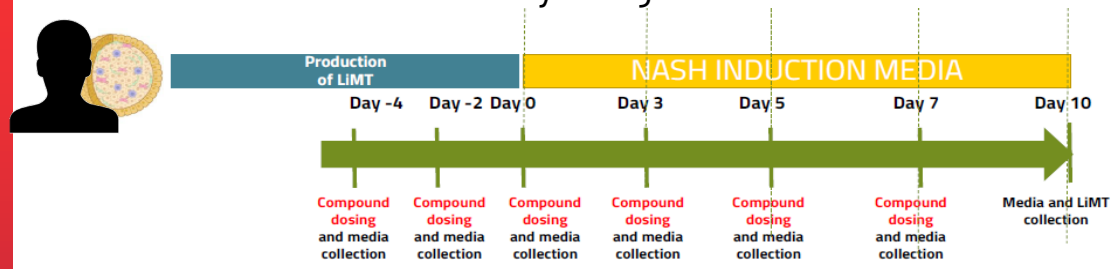


Staining of UCP-1 in WAT



Efficacy study of RES-010 in 3D liver human organoids confirms activity in a human NASH model

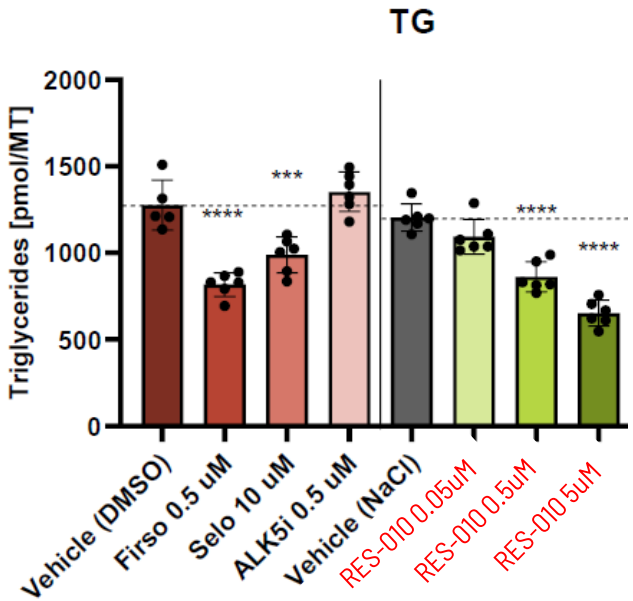
Study design



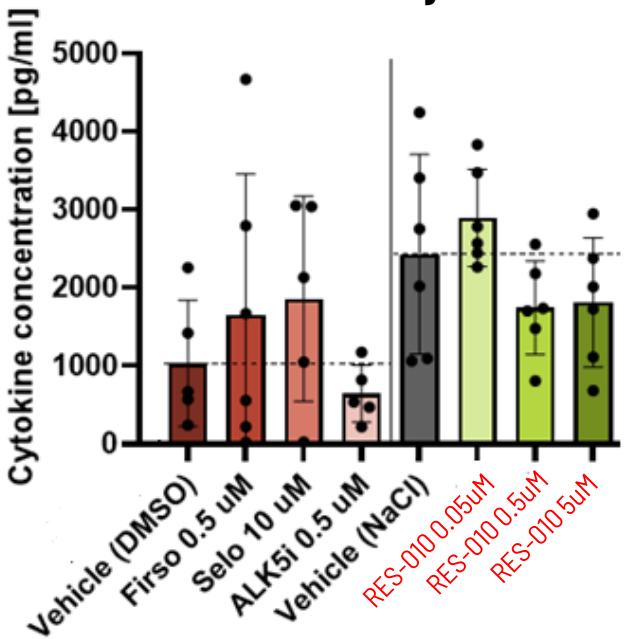
3D human liver model (Co-culture of primary human hepatocytes, stellate cells, Kupffer Cells and Liver Endothelial Cells) treated with RES-010 show:

- Significant reduction in intracellular triglycerides at day 10.
- Trend in reduction of inflammatory marker IL-6 at day 5.
- Reduction in the fat accumulation and in the deposition of fibrosis on stained histology slides in the lean and NASH conditions.

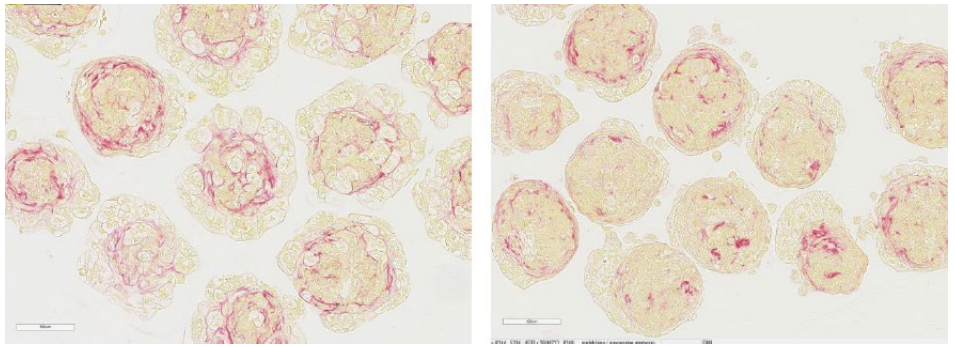
Triglycerides, day 10



IL-6, day 5



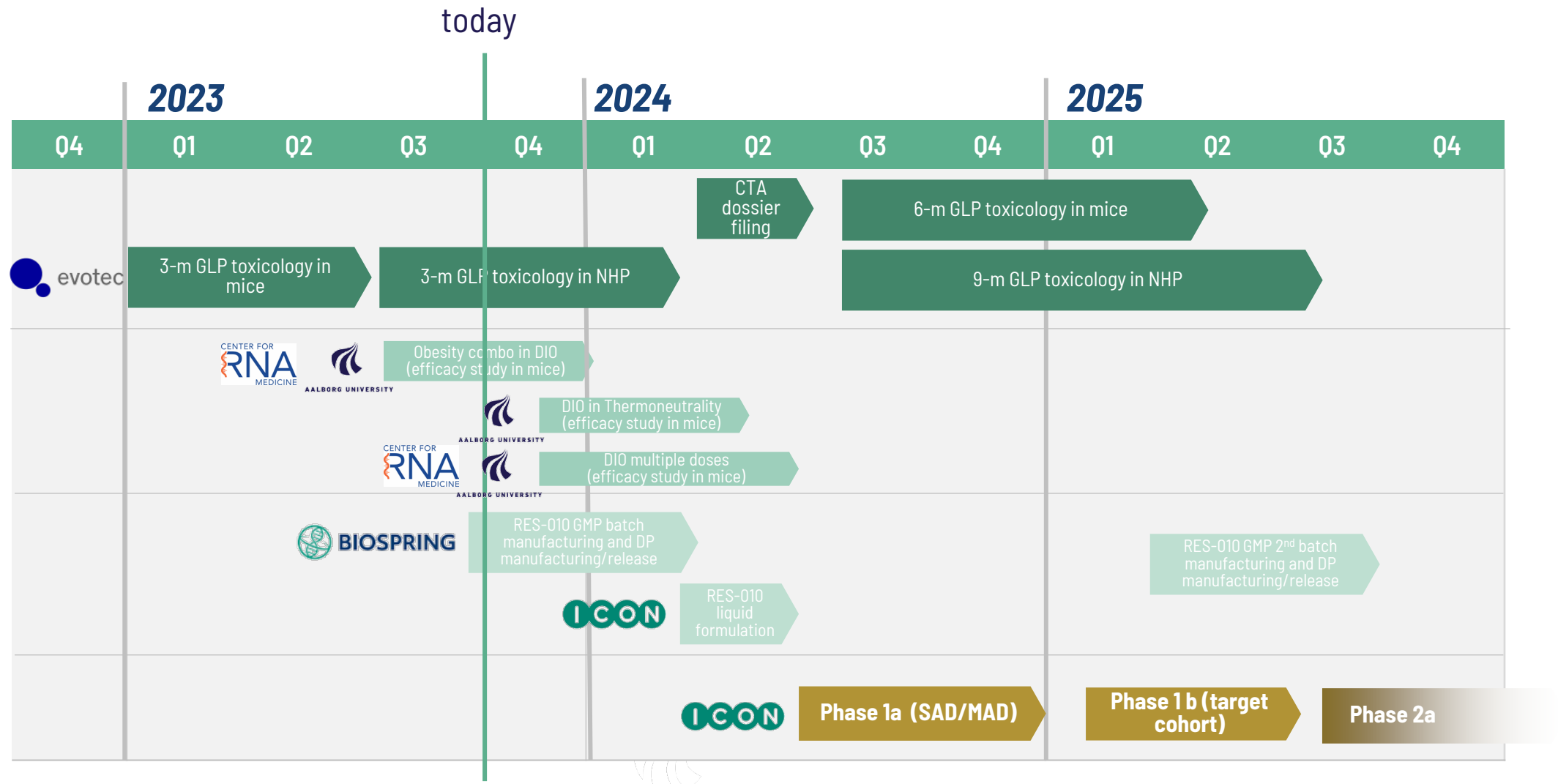
Staining of histology slides, day 10



Vehicle

RES-010 0.05uM

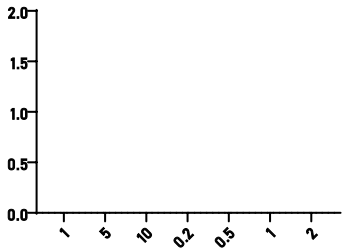
Developmental plan, timelines and future directions



Developmental plan, timelines and future directions

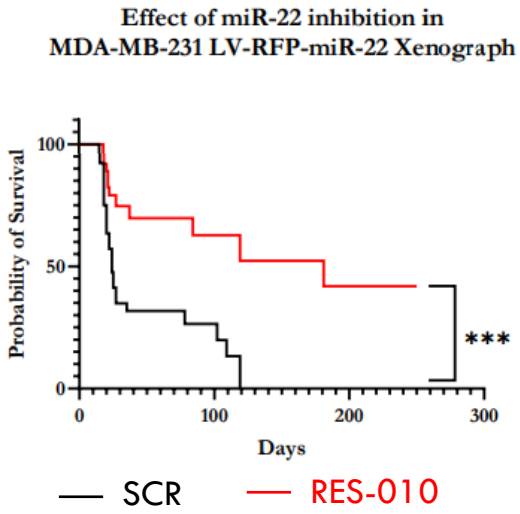
Advancing RES-020 in Obesity

Results show that GalNAc-conjugated RES-010 (RES-020) can achieve the same level of miR-22 inhibition at 1/10 of the dose. RES-020 may represent an ideal solution for long term treatments



PoC of RES-010 in Oncology

miR-22 blockade *in vivo* in mouse models of Triple Negative Breast Cancer was tremendously impactful, resulting in a marked extension in overall survival.
More preclinical trials in model systems (HCC, PC) could confirm the role of RES-010 as effective cancer treatment



Ref: Panella, R. et al; Biomedicines **2023**, 11, 1470.

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