Combination therapy using semaglutide-loaded lipid nanocapsules and a peptidomimetic against integrin α5 in the treatment of metabolic dysfunction-associated steatotic liver

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CONTROLLED RELEASE SOCIETY
CRS 2024 Annual Meeting AND Exposition
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INTEGRATING
Delivery Science
ACROSS DISCIPLINES

What is MASLD?

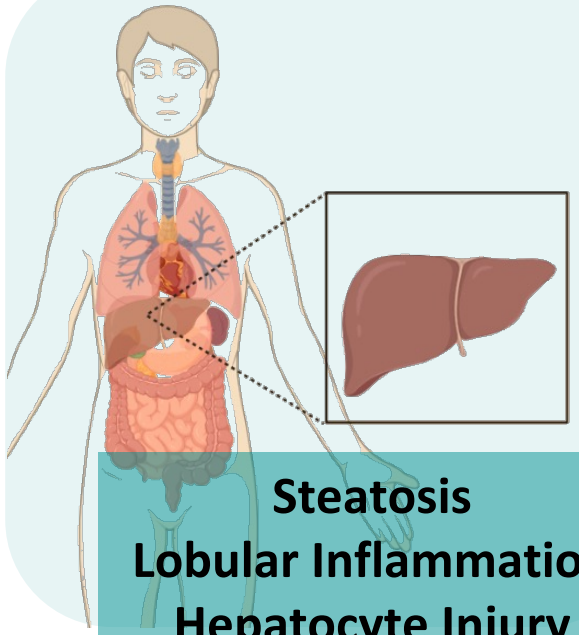
Prevalence

Highly prevalent chronic liver disease

Affects **30%** of the adult global population

Slow progressing disease

MASLD



Steatosis
Lobular Inflammation
Hepatocyte Injury
Fibrosis

Metabolic Syndrome

Obesity
Hyperglycaemia
Insulin Resistance
Dyslipidemia
Hypertension

Domingues I, et al. J Control Release 2023; 363:415-434
Younossi ZM, et al. Hepatology. 2023 Apr 1;77(4):1335-1347

MASLD: Metabolic dysfunction-associated steatotic liver

What is MASLD?

Treatment

Lifestyle modifications (exercise and energy caloric restrictions)

One pharmacological treatment approved (Rezdiffra®)

Clinical Trials – GLP-1 analogs

MASLD is the **Hepatic Manifestation** of the **Metabolic Syndrome**

Liraglutide and **Semaglutide**

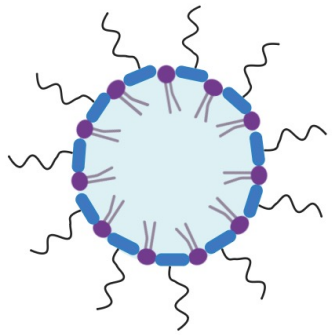
Improvement in hepatic steatosis without worsening of fibrosis

(ClinicalTrials.gov, numbers NCT01237119 and NCT02970942)

Domingues I, et al. J Control Release 2023; 363:415-434
S.A. Harrison, et al. N Engl J Med 2024; 390:497-509

GLP-1: Glucagon-like peptide 1
MASLD: Metabolic dysfunction-associated steatotic liver

Lipid Nanocapsules as a Therapeutic Agent

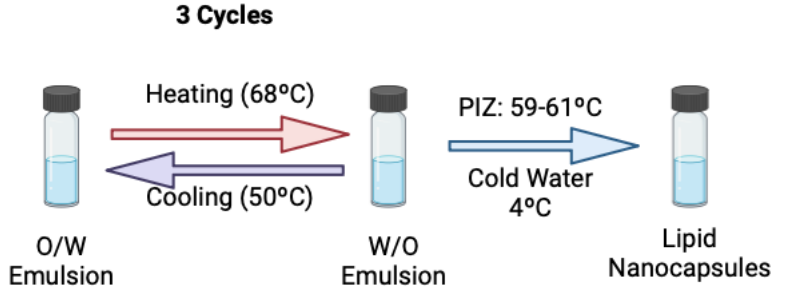


Koliphor® HS15

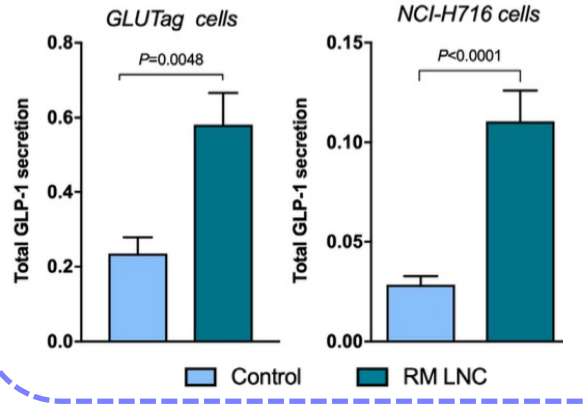
Lipoid® S100

Labrafac® WL 1349/Peceol ®

Phase Inversion Temperature



In vitro Studies



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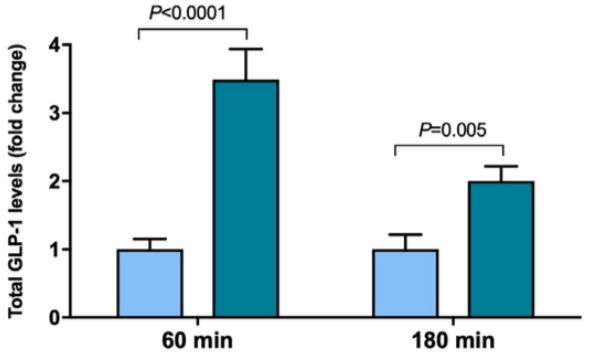
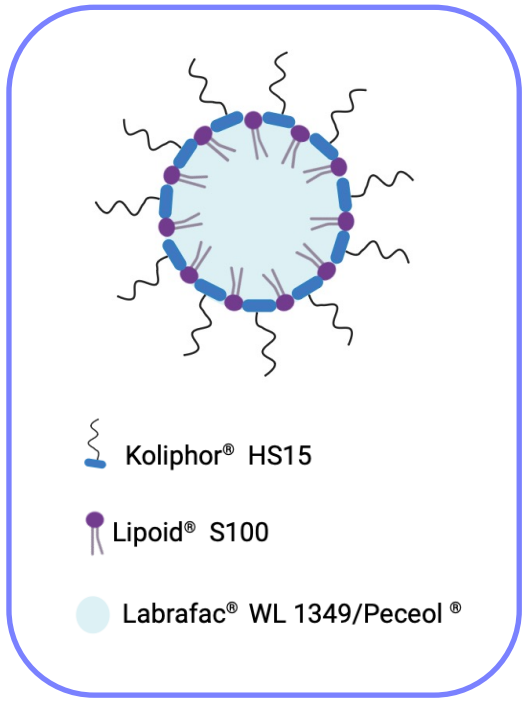


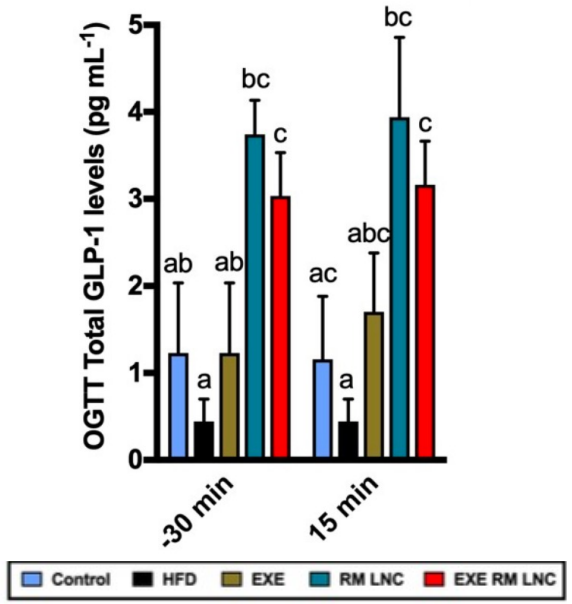
Xu Y, Van hul M, suriano F, *et al*. *Gut* 2020;69:911–919

LNC: Lipid nanocapsules

Lipid Nanocapsules as a Therapeutic Agent



T2DM mouse model



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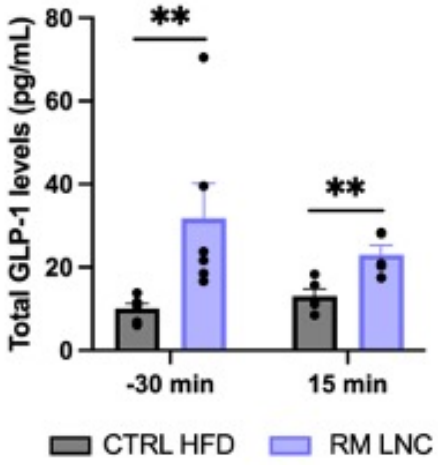
MASLD mouse model

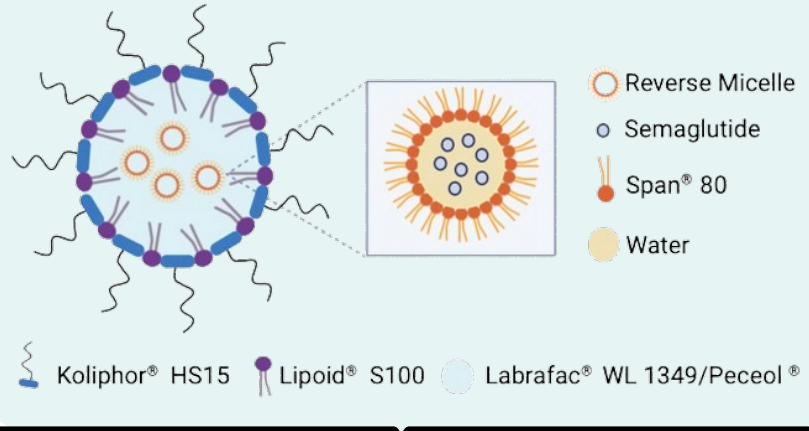


Xu Y, Van hul M, suriano F, *et al*. *Gut* 2020;69:911–919
Domingues I, et al. J Control Release 2023;356:542-553

LNC: Lipid nanocapsules
T2DM: Type 2 diabetes mellitus
MASLD: Metabolic dysfunction-associated steatotic liver

Lipid Nanocapsules: therapeutic agents and drug delivery systems!

Lipid Nanocapsules



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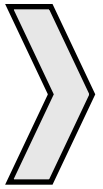
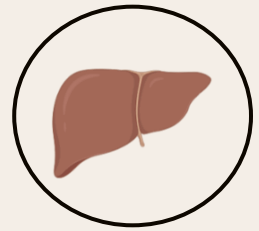
Anti-Fibrotic Peptide

Peptidomimetic against Integrin α5

SC – 3x/week





Metabolic Syndrome
Inflammation
Fibrosis

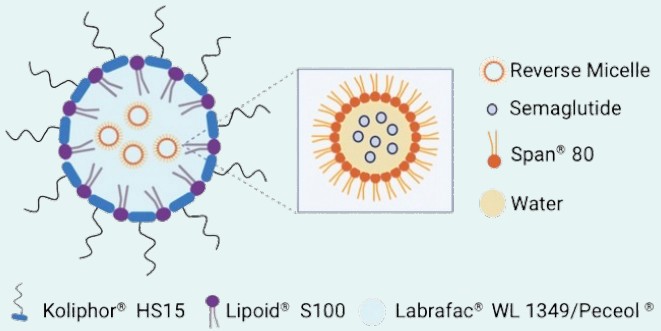
DUAL-ACTION

Increased **GLP-1 secretion** + Increased **GLP-1 analog absorption**

GLP-1: Glucagon-like peptide 1

In vivo: Combination therapy efficacy in Fibrotic MASH

Lipid Nanocapsules



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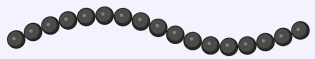
Anti-Fibrotic Peptide



Peptidomimetic against Integrin $\alpha 5$

SC – 3x/week

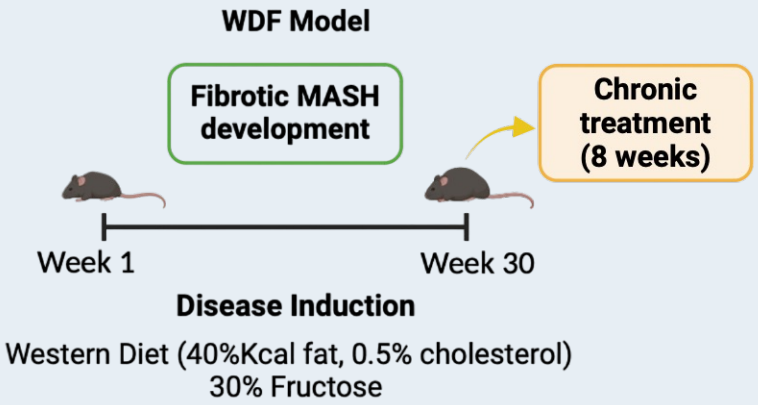
Oral/Once daily:

Semaglutide oral: **500 µg/kg**
CTRL groups: MilliQ water

SC/3x Week:

Peptidomimetic: **20 mg/kg**

***In vivo* Study**



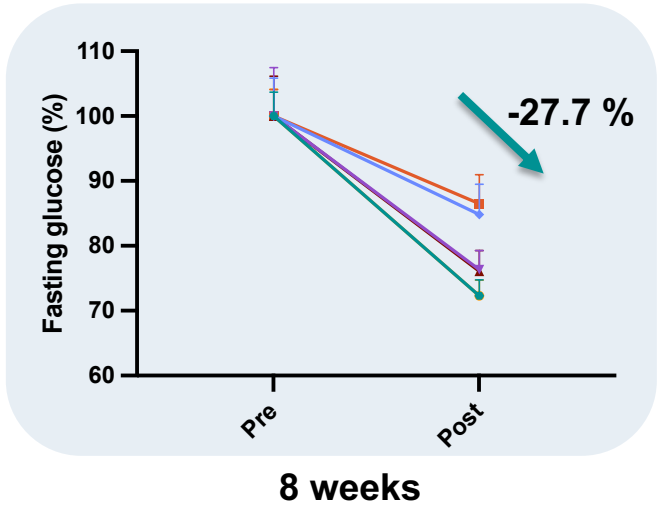
Groups

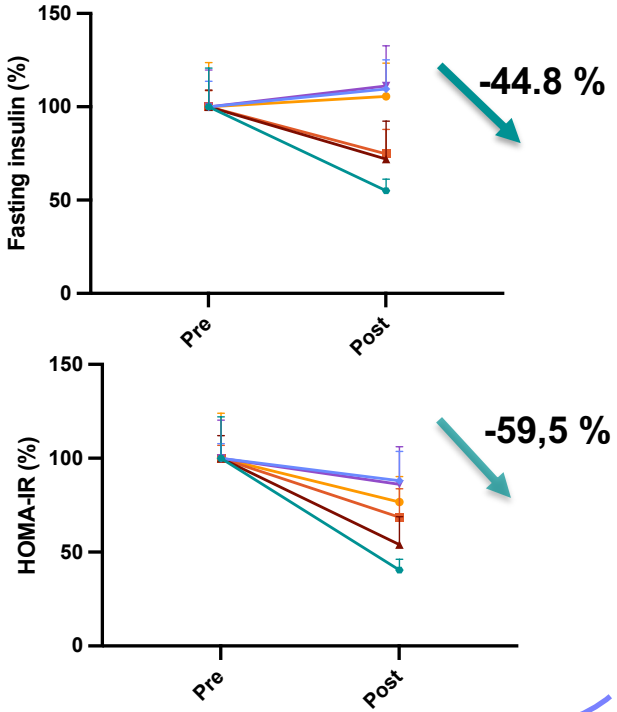
Healthy Control (CTRL ND)
Diseased Control (CTRL WDF)
Blank LNC (RM LNC)
Loaded LNC (SEMA RM LNC)
Anti-fibrotic peptide (α5-PEPTIDE SC)
Combination therapy (SEMA RM LNC + α5-PEPTIDE SC)

MASH: Metabolic dysfunction-associated steatohepatitis

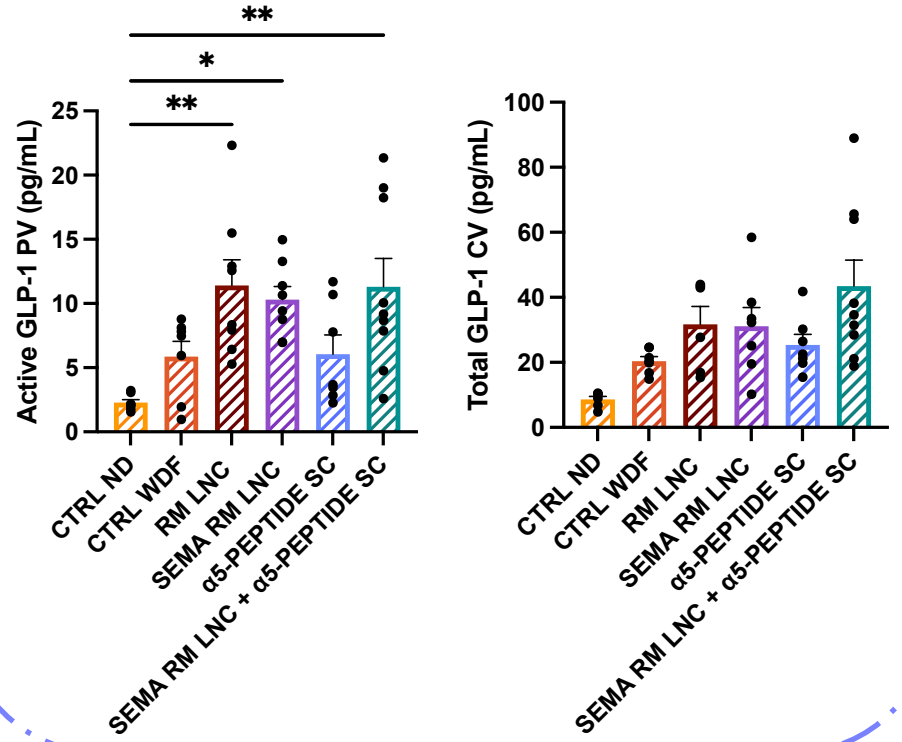
Combination therapy positively impacted the metabolic syndrome

Fasting Conditions - Glycemia





GLP-1 Secretion



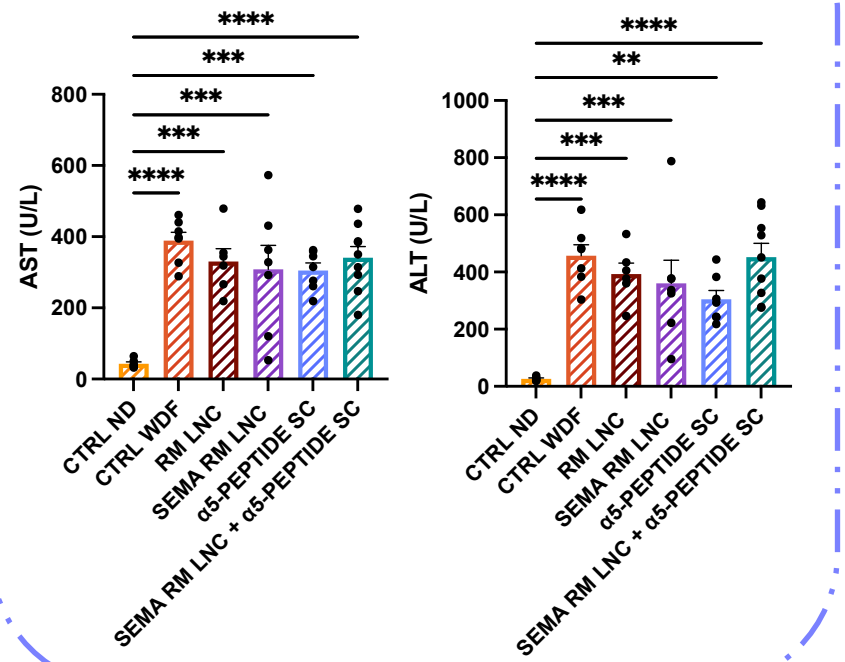
CTRL ND — CTRL WDF — RM LNC — SEMA RM LNC — α5-PEPTIDE SC — SEMA RM LNC + α5-PEPTIDE SC

Statistics: One-way ANOVA or Two-Way ANOVA. Data: mean ± SEM (n=7-9/group)

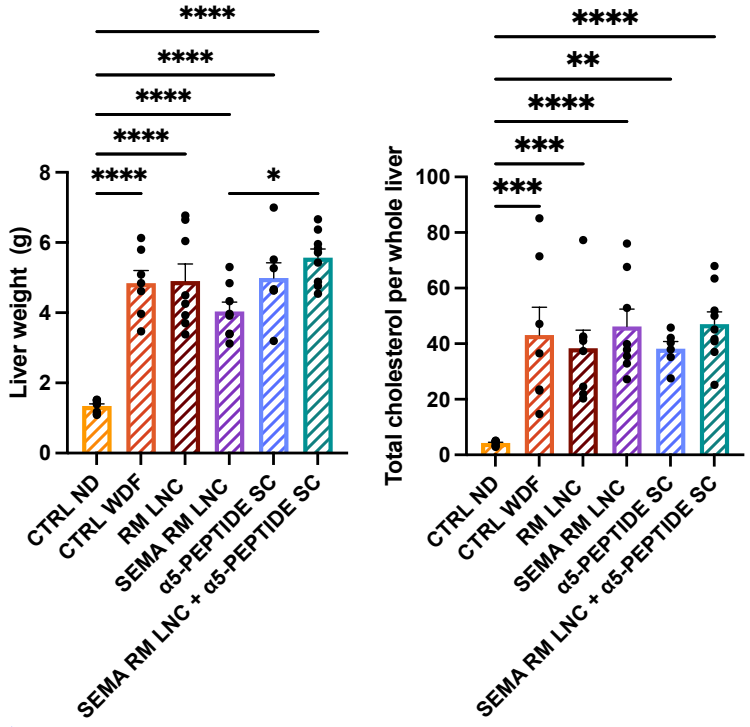
GLP-1: Glucagon-like peptide 1

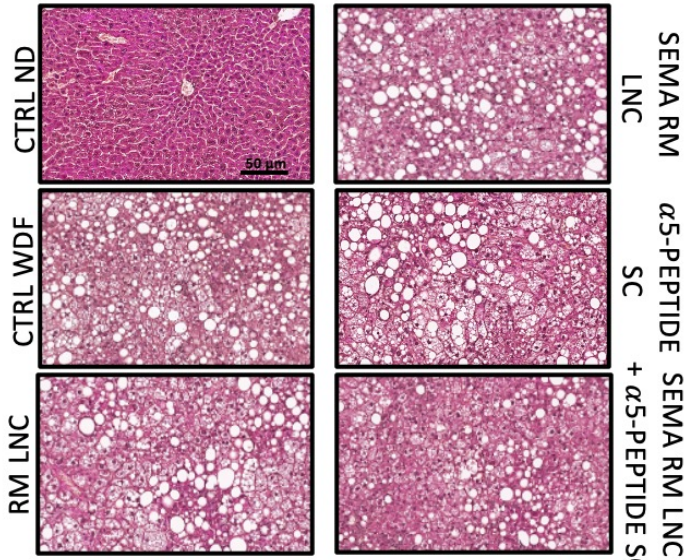
Liver injury & Steatosis: No significant impact

Liver Injury (liver enzymes)



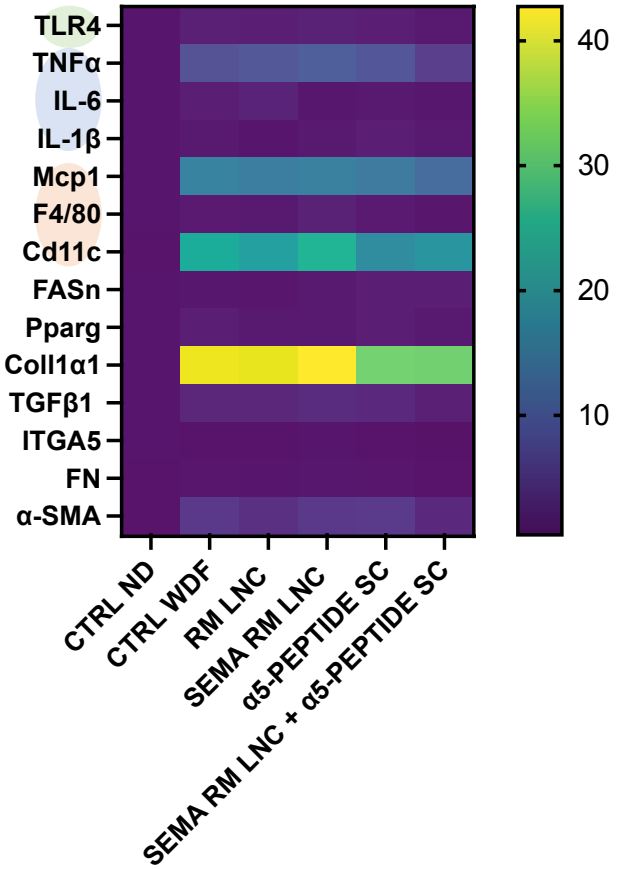
Steatosis (liver weight, total cholesterol, H&E)



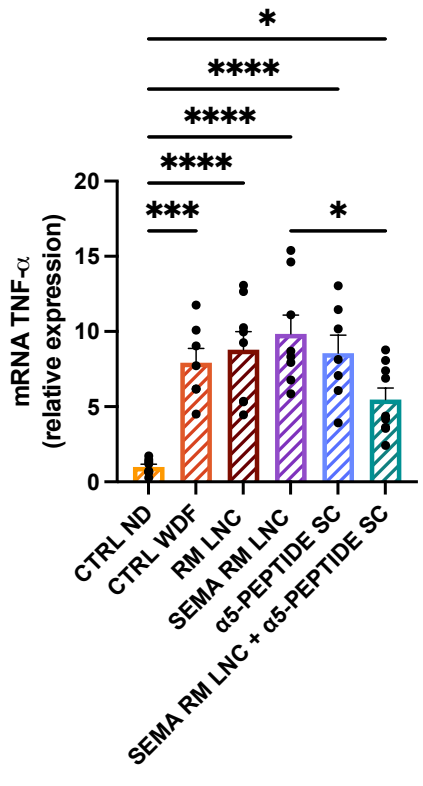


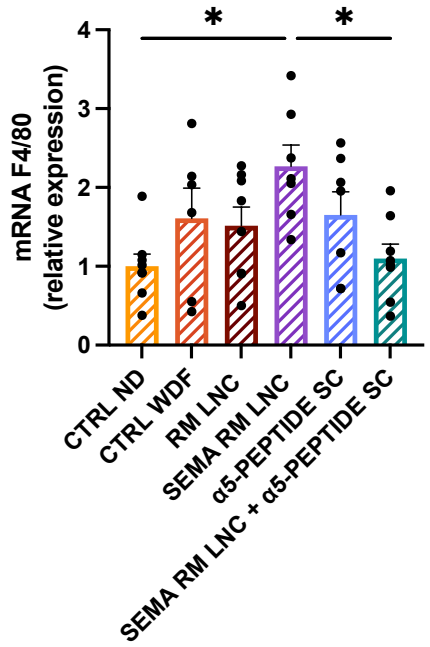
Statistics: One-way ANOVA. Data: mean ± SEM (n=7-9/group)

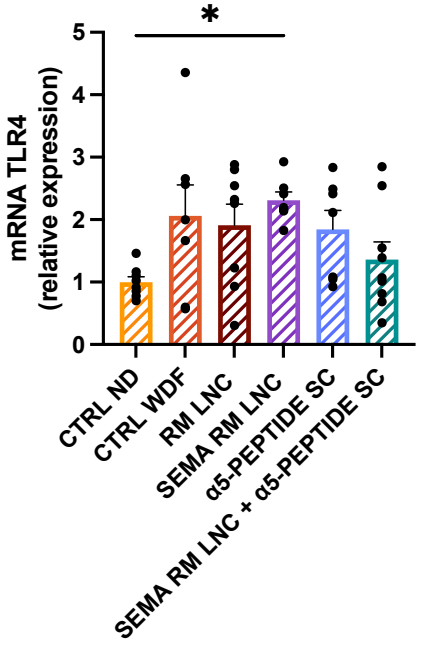
Inflammation: Positive trend



qPCR markers (cytokine expression, immune cell infiltration, endotoxin-mediated inflammation)

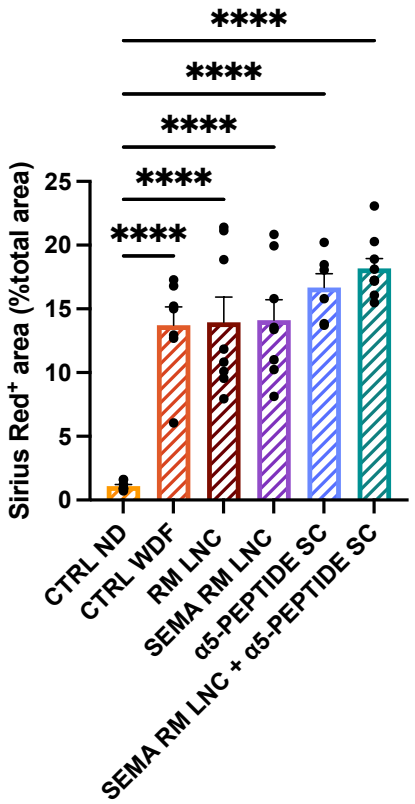


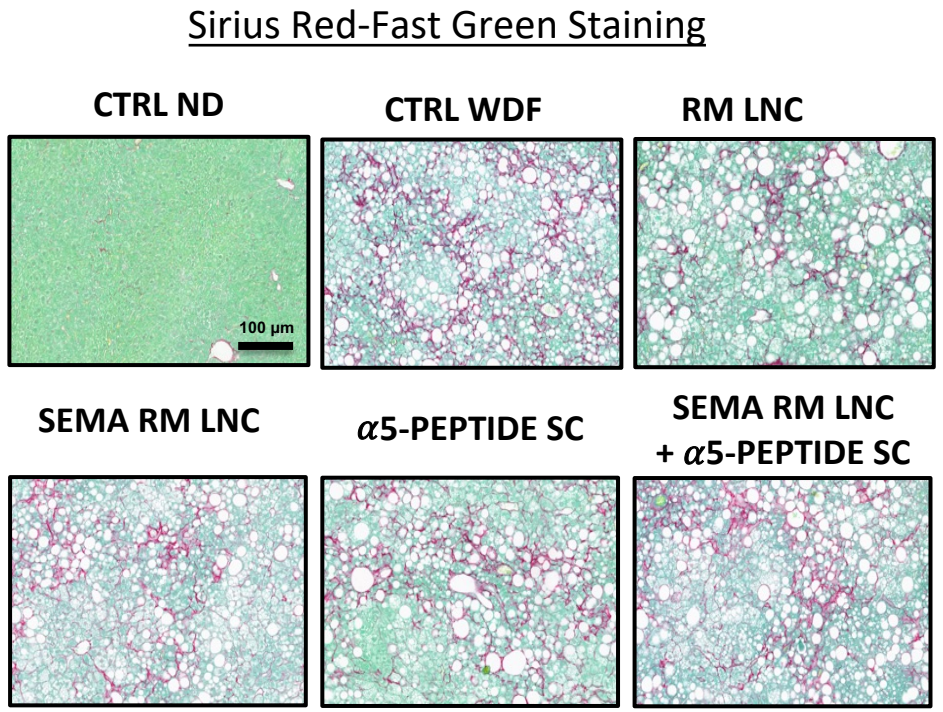




Statistics: One-way ANOVA. Data: mean ± SEM (n=7-9/group)

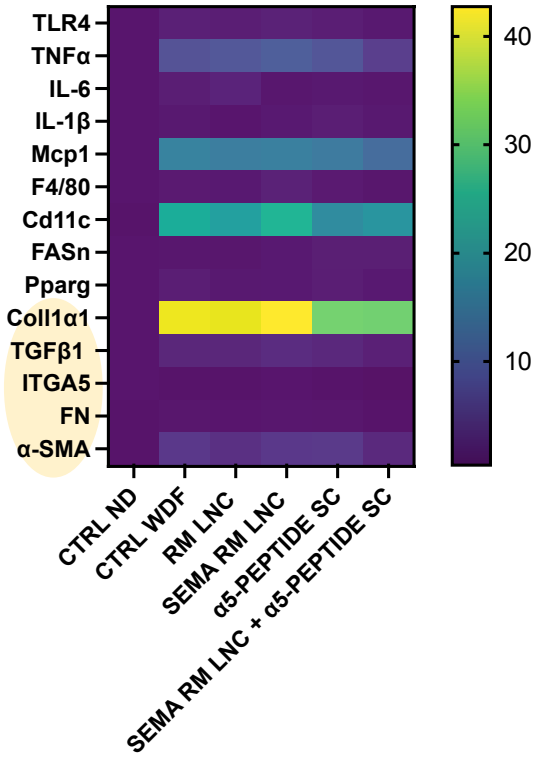
Fibrosis: Positive trend



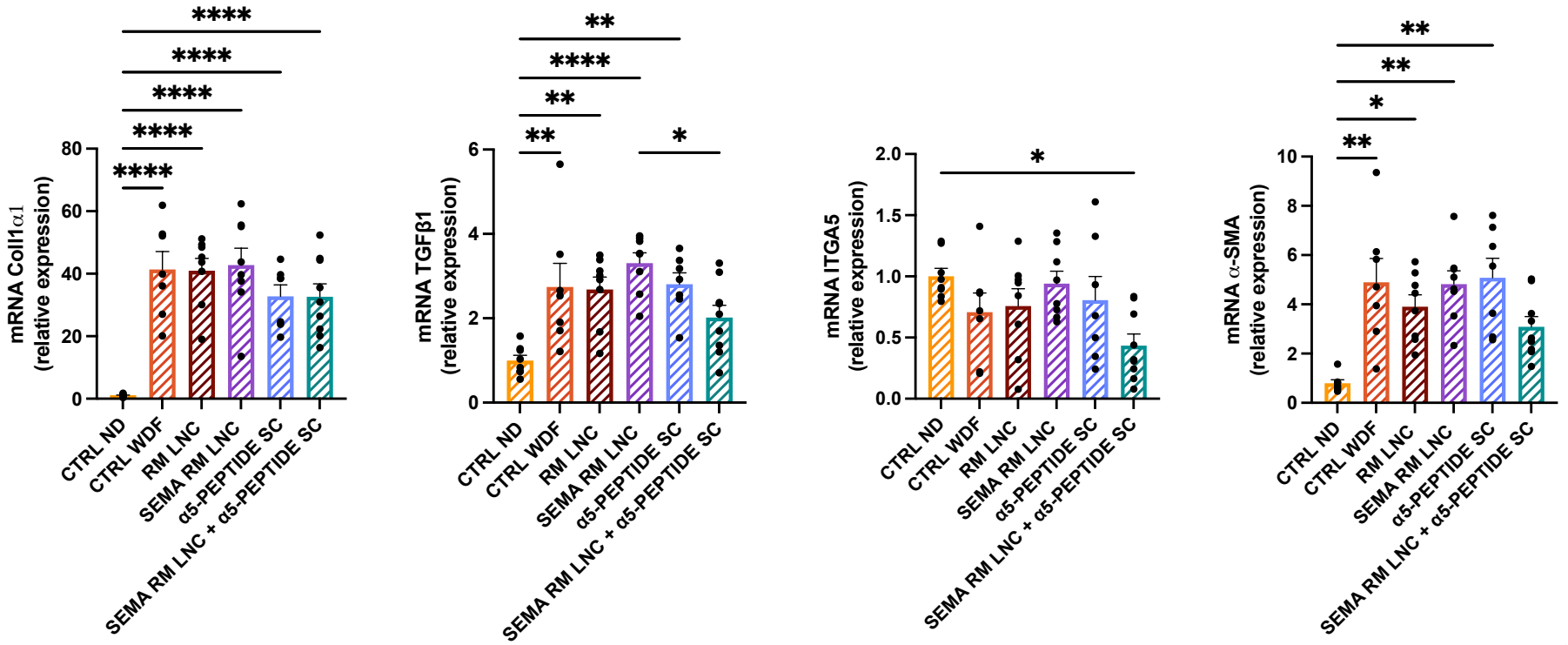


Statistics: One-way ANOVA. Data: mean ± SEM (n=7-9/group)

Fibrosis: Positive trend



qPCR markers (Fibrosis)



Statistics: One-way ANOVA. Data: mean ± SEM (n=7-9/group)

Formulation

- Encapsulation Semaglutide ✓

MASLD (Early MASH & Fibrotic MASH)

MetS

- Glucose homeostasis and insulin resistance ✓
- Combination therapy vs monotherapy ✓

Liver

- Steatosis & Liver Injury ✗
- Inflammation ✓
- Fibrosis ✓

Formulation

- Improve properties of LNC (e.g.: anti-inflammatory oils)
- Tract LNC pathway and accumulation
- Investigate the effect of the LNC components on HSC

MASLD

- IHC ITGA5
- qPCR: EAT

Thank you for your attention!

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