Therapeutic effect of a novel long-acting GLP-1/GIP/Glucagon triple agonist (HM15211) in NASH and fibrosis animal models

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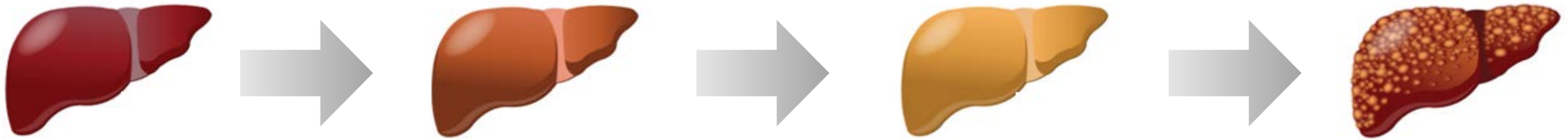
Presenter Disclosure

Employee of Hanmi Pharm. Co., Ltd.

NASH progression

Normal ***NAFL*** ***NASH*** ***Cirrhosis***



Hepatocyte lipotoxicity

- Obesity;
  Dyslipidemia;
  Insulin resistance and T2DM

→ **Liver fat accumulation**

Inflammation

- Lipid peroxidation ↑
- Oxidative stress ↑

→ **Liver cell apoptosis**

Inflammatory cytokine

Resident / infiltrated macrophage activation

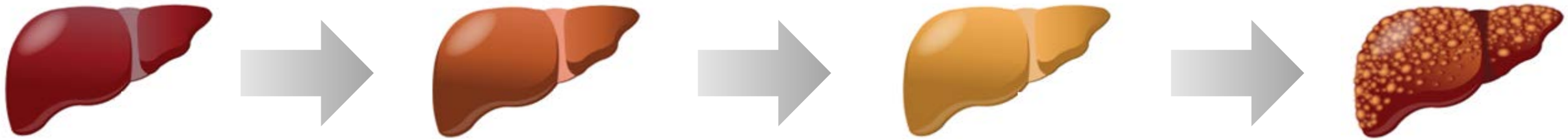
Fibrosis

- Inflammatory tissue injury
- HSC activation
- Fibrogenic component ↑

→ **Scar replaces damaged liver cells**
→ **Liver function failure**

NASH progression and potential drug candidates

Normal ***NAFL*** ***NASH*** ***Cirrhosis***



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  Dyslipidemia;
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Inflammatory cytokine

Resident / infiltrated macrophage activation

Fibrosis

- **Inflammatory tissue injury**
- **HSC activation**
- **Fibrogenic component ↑**

→ **Scar replaces damaged liver cells**
→ **Liver function failure**

GLP-1RA
√Liraglutide; semaglutide (P2, Novo)

ACC inhibitor
GS-0976 (P2, Gilead)

PPAR agonist
Elafibranor (P2, GENFIT)

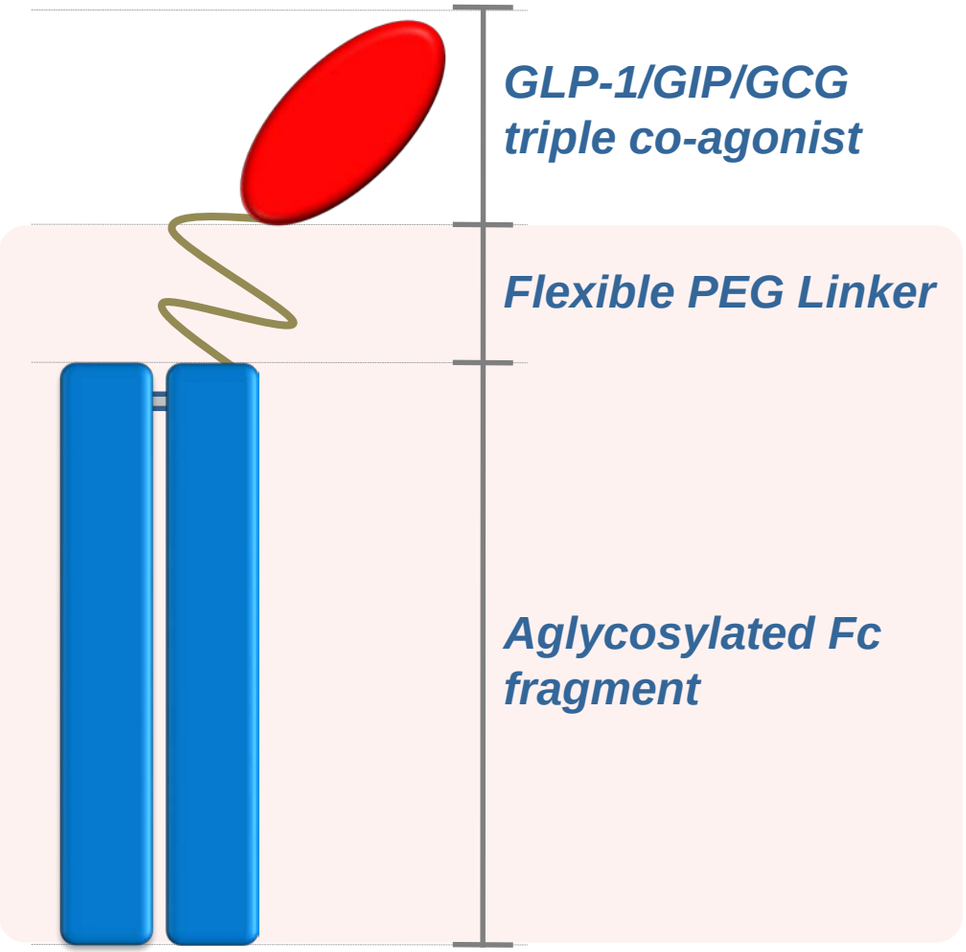
FXR agonist
√Obeticholic acid (P3, Intercept.)
GS-9674 (P2, Gilead)

ASK1 inhibitor
√Selonsirtib (P3, Gilead)

Drug candidates (selected)

Note. √ Indicated compounds were used as active comparators in efficacy studies

What is long-acting GLP-1/GIP/Glucagon triple agonist?



Hanmi's GLP-1/GIP/GCG triple co-agonist is conjugated with a human IgG Fc fragment *via* flexible linker

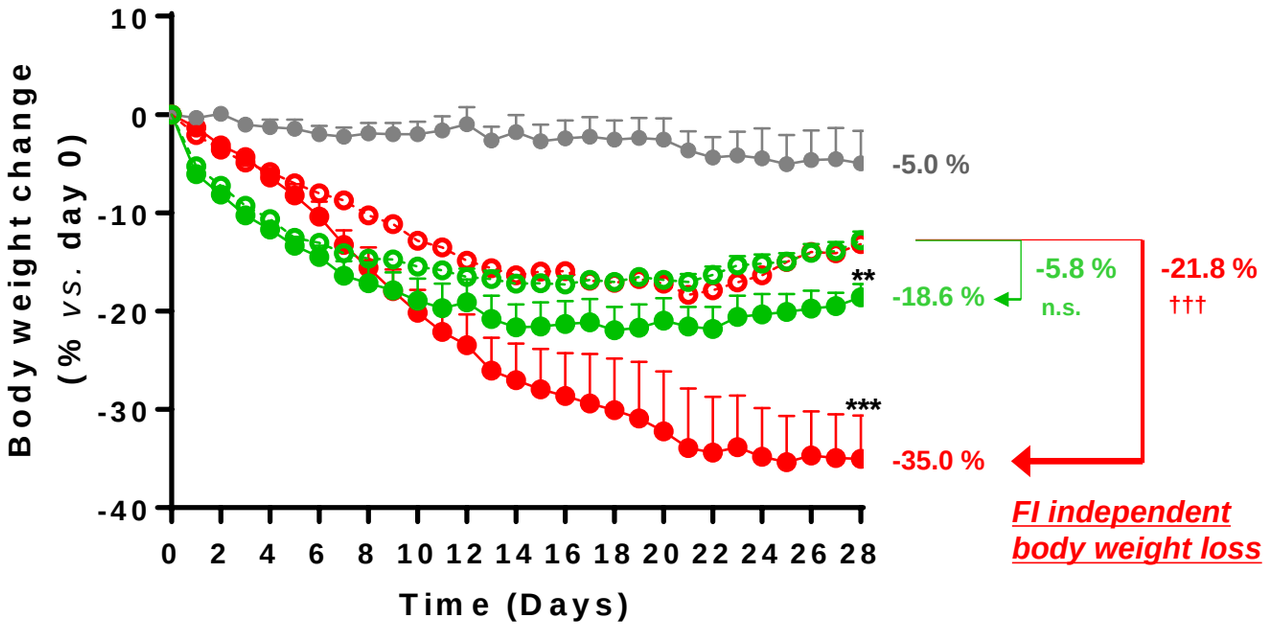
[General profile]

- **Extended half-life ($t_{1/2}$ = 42.7 ~ 55 hrs in mice; 82.8 ~ 85.7 hrs in rats)**
- **High glucagon (GCG) activity suitable for obesity treatment**
- **Balanced GLP-1 and GIP activity to neutralize hyperglycemic risk of high GCG**
- **Anti-inflammatory effect by GIP activity**
- **Recently completed FIH clinical study in healthy obese subjects**

LAPSCOVERY : Long Acting Peptide/Protein DiSCOVERY Technology

Efficient weight loss by HM15211 and related MoA

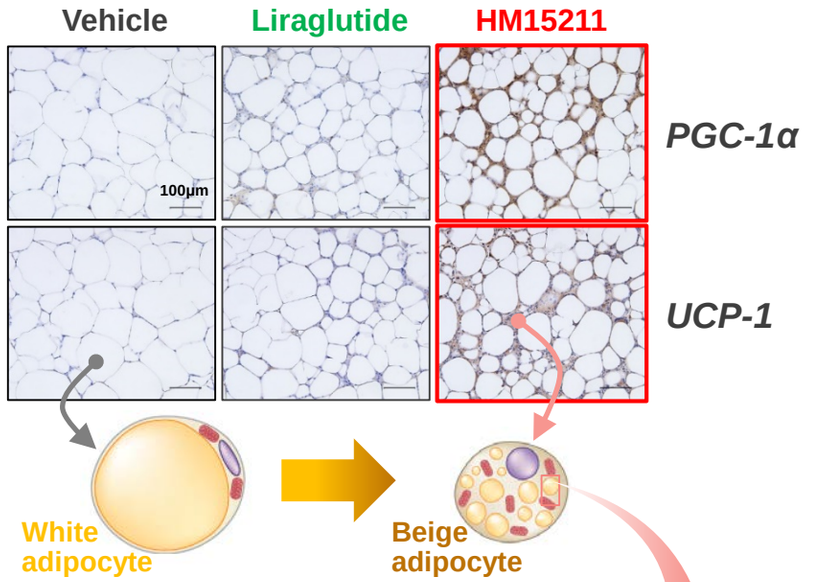
Weight change in pair-fed controlled DIO mice



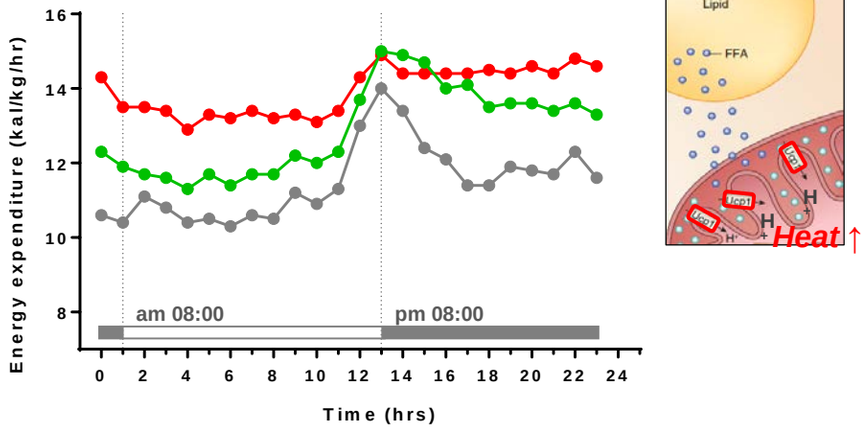
Vehicle
Liraglutide 50 nmol/kg, BID (3 mg/day in human)
HM15211 1.44 nmol/kg, Q2D (2 mg/week in human)
Pair-fed for liraglutide
Pair-fed for HM15211

** ~ ***p<0.01 ~ 0.001 *vs.* vehicle by One-way ANOVA , †††p<0.001 *vs.* pair-fed by One-way ANOVA

❖ White adipose tissue browning

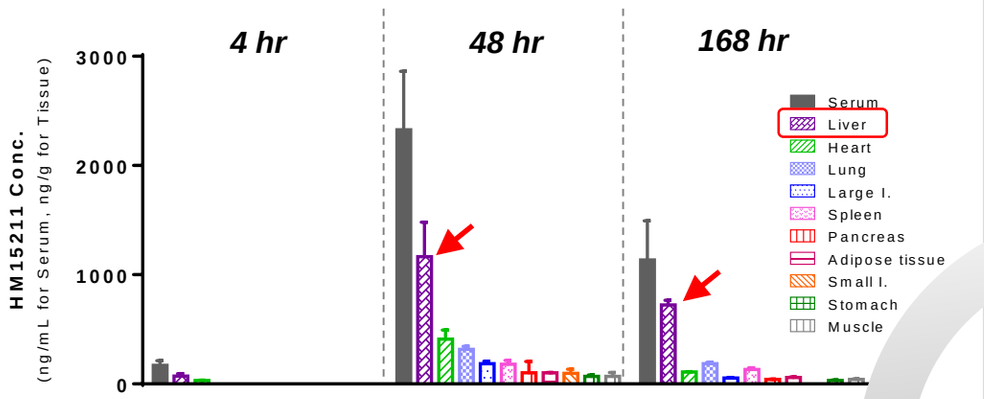


❖ Enhanced energy expenditure

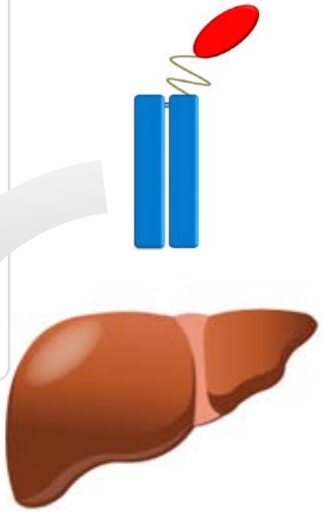


Efficient hepatic fat reduction by HM15211 and related MoA

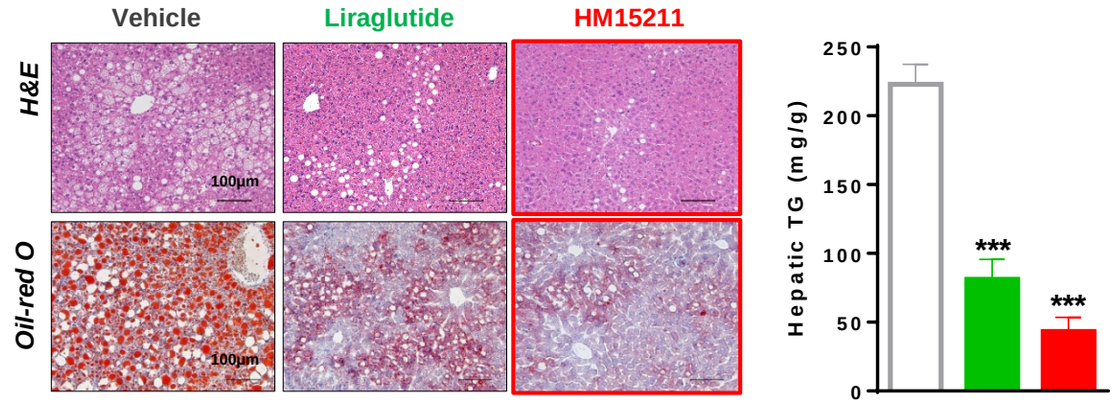
1) Liver preferential distribution



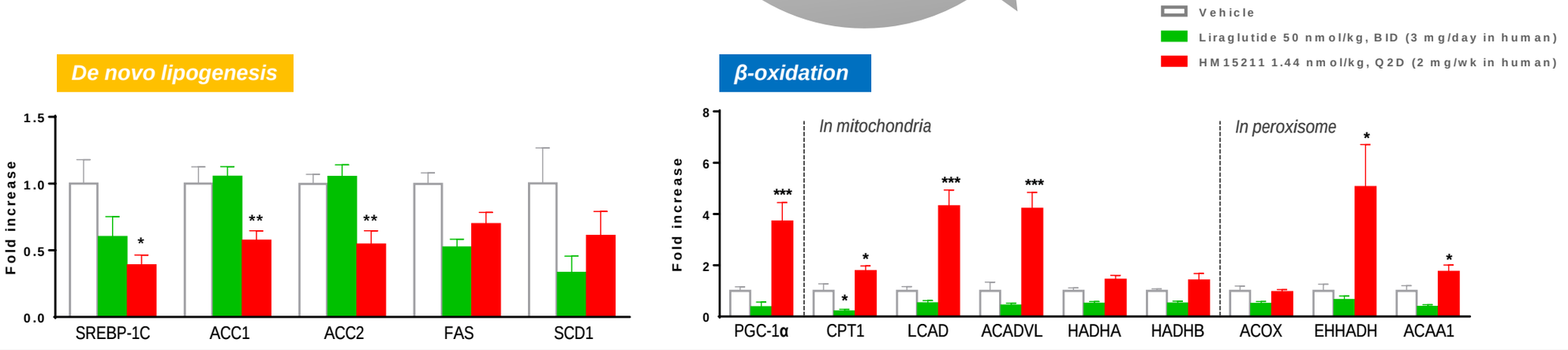
HM15211



3) Enhanced hepatic fat reduction in DIO mice

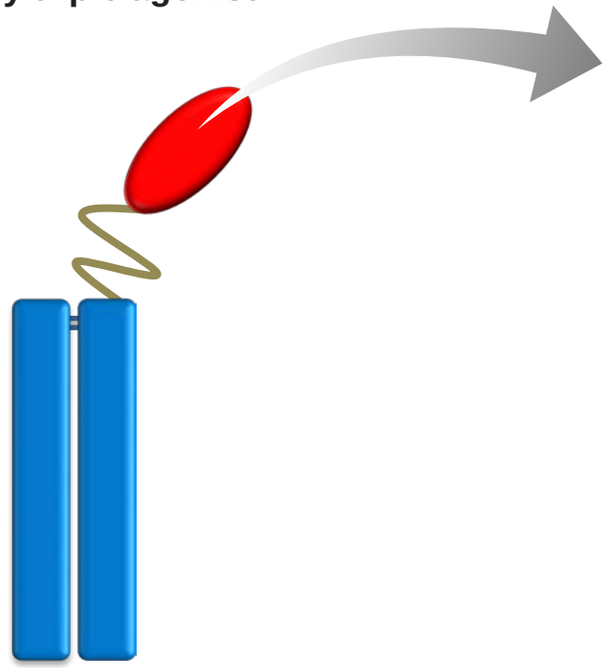


2) Hepatic lipid metabolism reprogramming



Hypothesis

Weekly triple agonist



Glucagon
- Browning of WAT
  : Energy expenditure ↑
- Liver targeting
  : Lipolysis ↑ & lipogenesis ↓

GLP-1
- Appetite ↓
- Inflammation ↓

- Body weight ↓
- Fat mass, blood lipid ↓
- Liver fat ↓

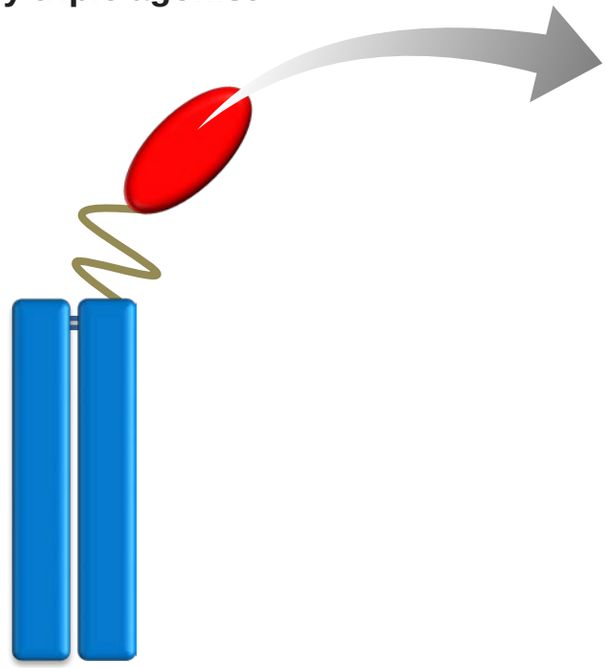
HM15211 [Ph1, US]
- Expected for once-weekly regimen
- Completed for P1 SAD study in healthy obese subjects

→ **NASH improvement: Steatosis ↓, Inflammation ↓**

→ **Insufficient for fibrosis improvement**

Hypothesis

Weekly triple agonist



Glucagon
- Browning of WAT
  : Energy expenditure ↑
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  : Lipolysis ↑ & lipogenesis ↓

GLP-1
- Appetite ↓
- Inflammation ↓

GIP
- Inflammation ↓

- Body weight ↓
- Fat mass, blood lipid ↓
- Liver fat ↓

- Liver inflammation ↓

HM15211 [Ph1, US]
- Expected for once-weekly regimen
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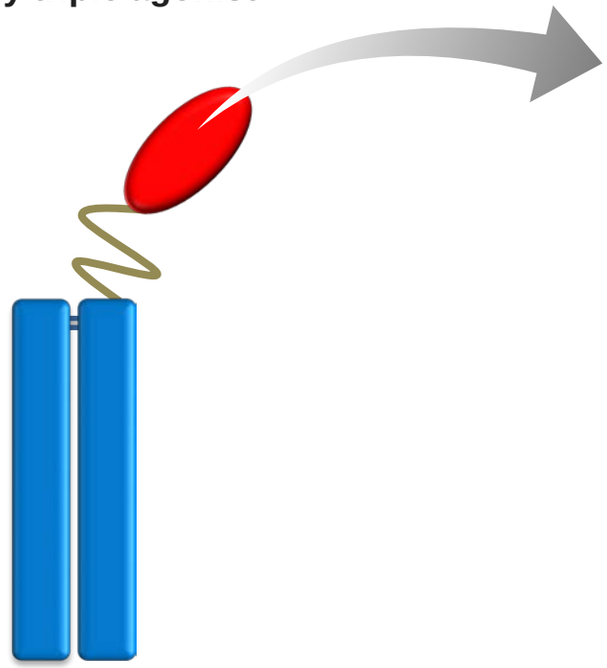
→ **NASH improvement: Steatosis ↓, inflammation↓, ballooning↓**

→ **Fibrosis improvement**

Hypothesis

Weekly triple agonist



Glucagon
- Browning of WAT
  : Energy expenditure ↑
- Liver targeting
  : Lipolysis ↑ & lipogenesis ↓
- BG increasing risk ↑

GLP-1
- Appetite ↓
- Inflammation ↓
- INS secretion ↑

GIP
- Inflammation ↓
- INS secretion ↑

- Body weight ↓
- Fat mass, blood lipid ↓
- Liver fat ↓

- Liver inflammation ↓

HM15211 [Ph1, US]
- Expected for once-weekly regimen
- Completed for P1 SAD study in healthy obese subjects

→ **NASH improvement: Steatosis ↓, inflammation↓ ballooning↓**

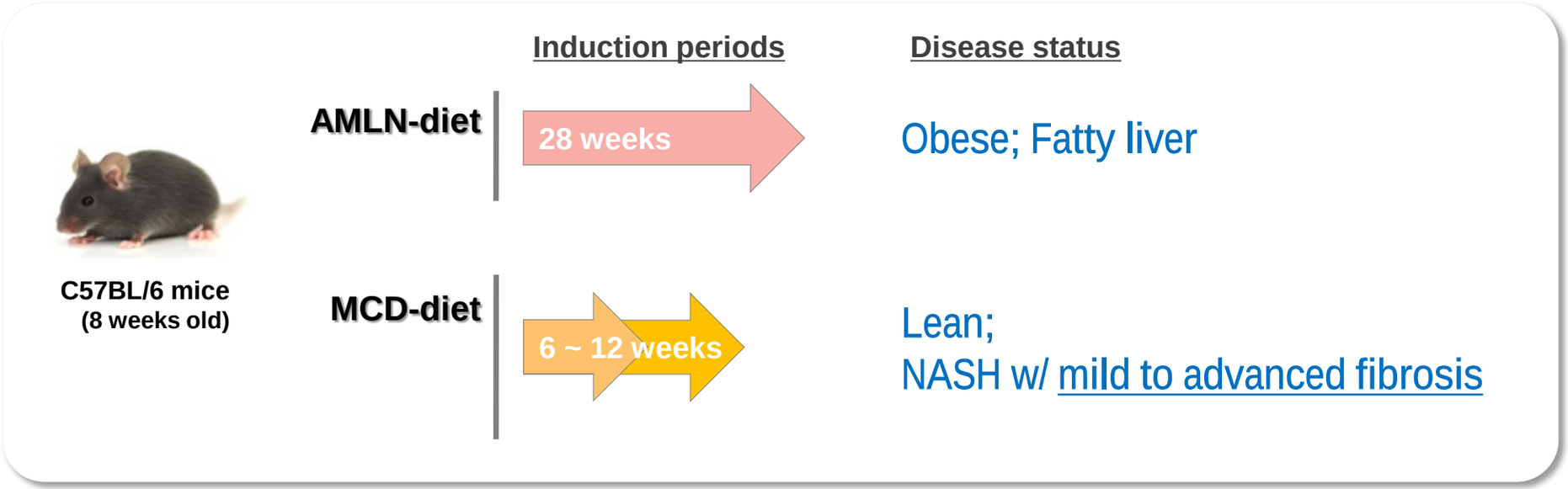
→ **Fibrosis improvement**

→ Hyperglycemic risk of glucagon use ↓

Objective & study strategies

HM15211, long-acting GLP-1/GIP/Glucagon triple agonist, might have therapeutic potential in NASH and fibrosis as well as obesity

- **The efficacy was evaluated in rodent disease models**



Change of weight and steatosis score in AMLN-diet mice

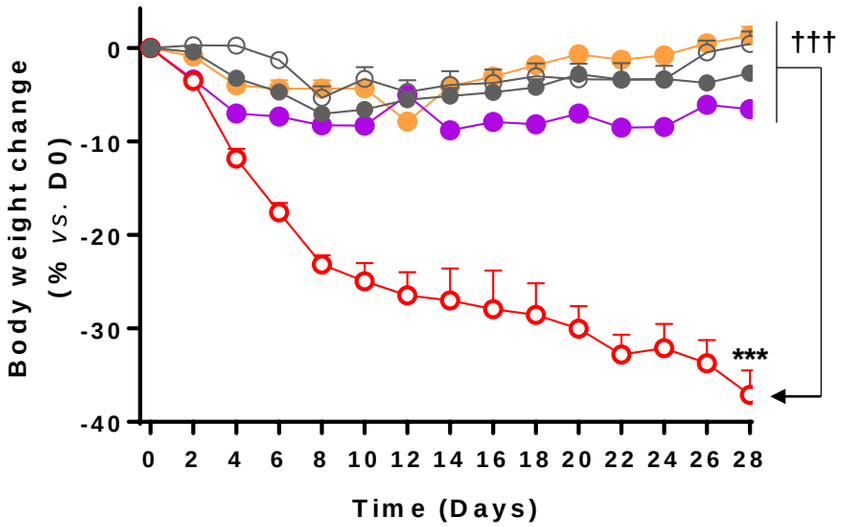
Experimental scheme

C57BL/6 mice
(8 weeks old)

AMLN-diet

Model induction	Drug treatment	Analysis
28 weeks	4 weeks	Body weight Hepatic TG Steatosis score

Weight change (AMLN mice, n=7)



Normal, Vehicle
AMLN-mice, Vehicle
Selonsertib 30 mg/kg, QD (250 mg/day in human)
Obeticholic acid 30 mg/kg, QD (250 mg/day in human)
HM15211 2.87 nmol/kg, Q2D (4 mg/week in human)

*~***p<0.05 ~ 0.001 *vs.* AMLN mice, vehicle by One-way ANOVA
†††p<0.001 *vs.*selonsirtib or OCA One-way ANOVA

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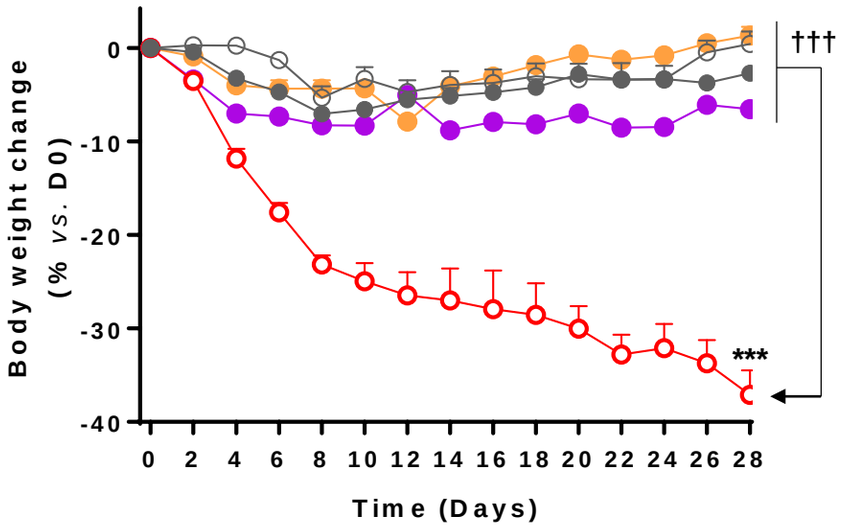
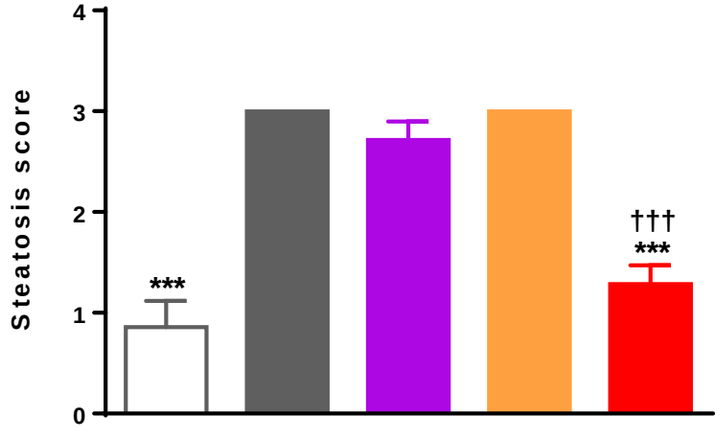
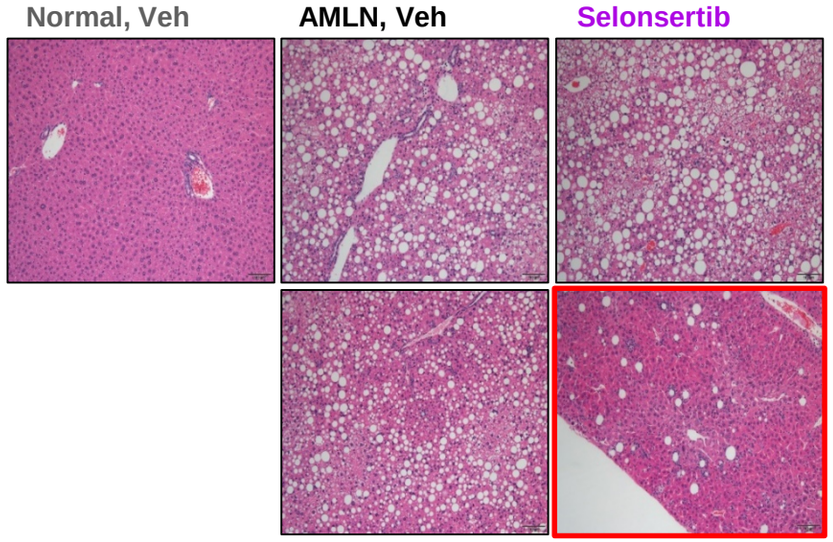


Steatosis score (AMLN mice, n=7)



H&E staining (AMLN mice, representative image)



Normal, Vehicle
AMLN-mice, Vehicle

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Change of hepatic fat content in MCD-diet mice

Experimental scheme

C57BL/6 mice
(8 weeks old)

MCD-diet

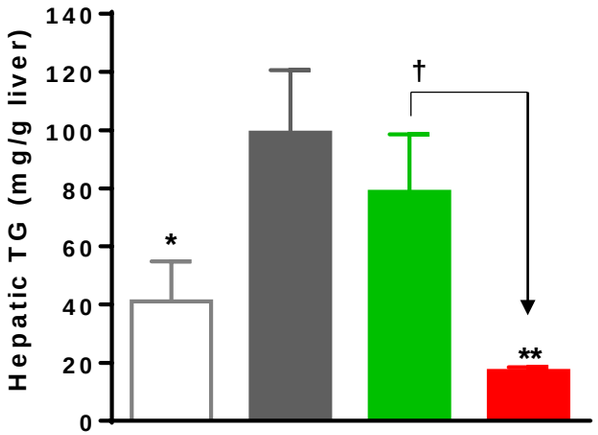
Model induction | Drug treatment | Analysis

6 weeks | 4 weeks

MRI MRI MRI

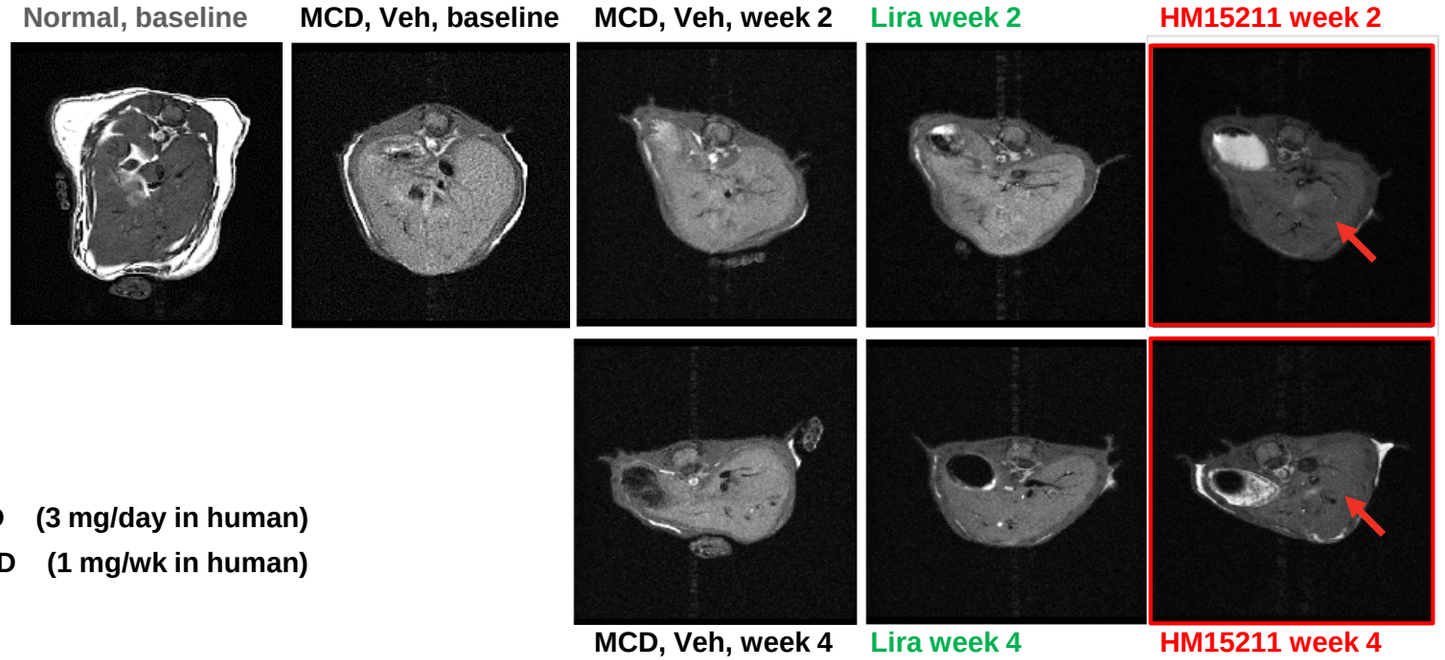
Hepatic TG, TBARS
Blood liver function marker
Marker expression (qPCR, IHC)
NAS

Hepatic TG (MCD mice, n=7)



Normal, Vehicle
MCD mice, Vehicle
Liraglutide 50 nmol/kg, BID (3 mg/day in human)
HM15211 0.72 nmol/kg, Q2D (1 mg/wk in human)

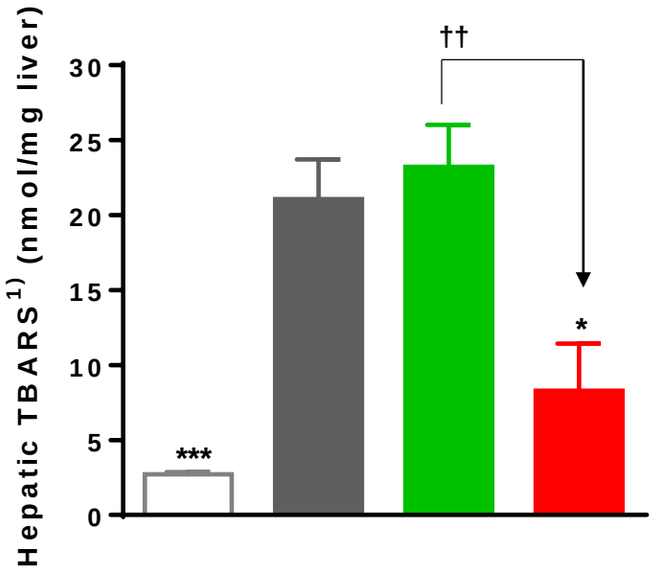
Real-time liver MRI (MCD mice, representative image)



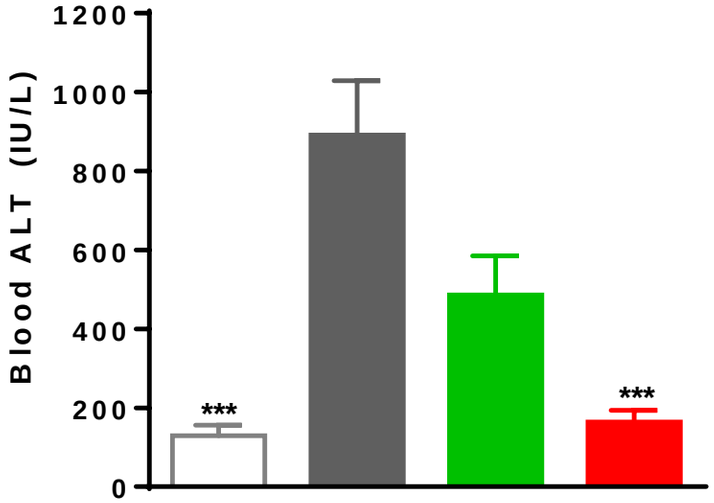
*~**p<0.05 ~ 0.01 *vs.* MCD mice, vehicle by One-way ANOVA; †p<0.05 *vs.* Liraglutide by One-way ANOVA

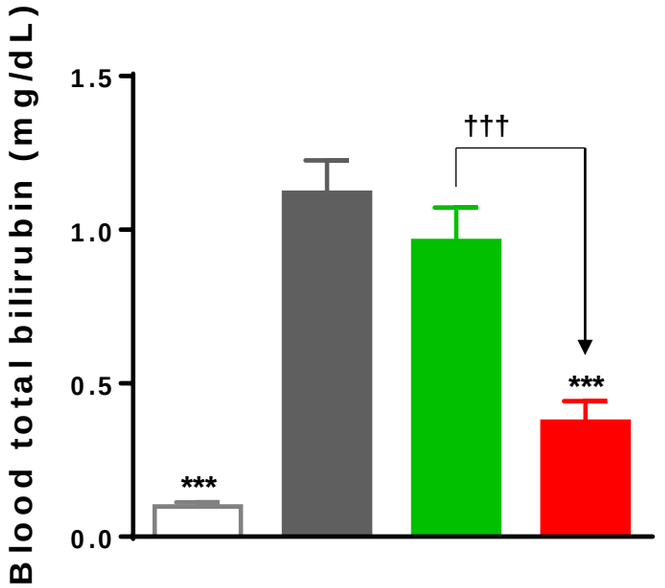
Change of NASH prognosis markers in MCD-diet mice

Hepatic TBARS[1)]
(MCD mice, n=7)



Blood ALT and bilirubin level
(MCD mice, n=7)





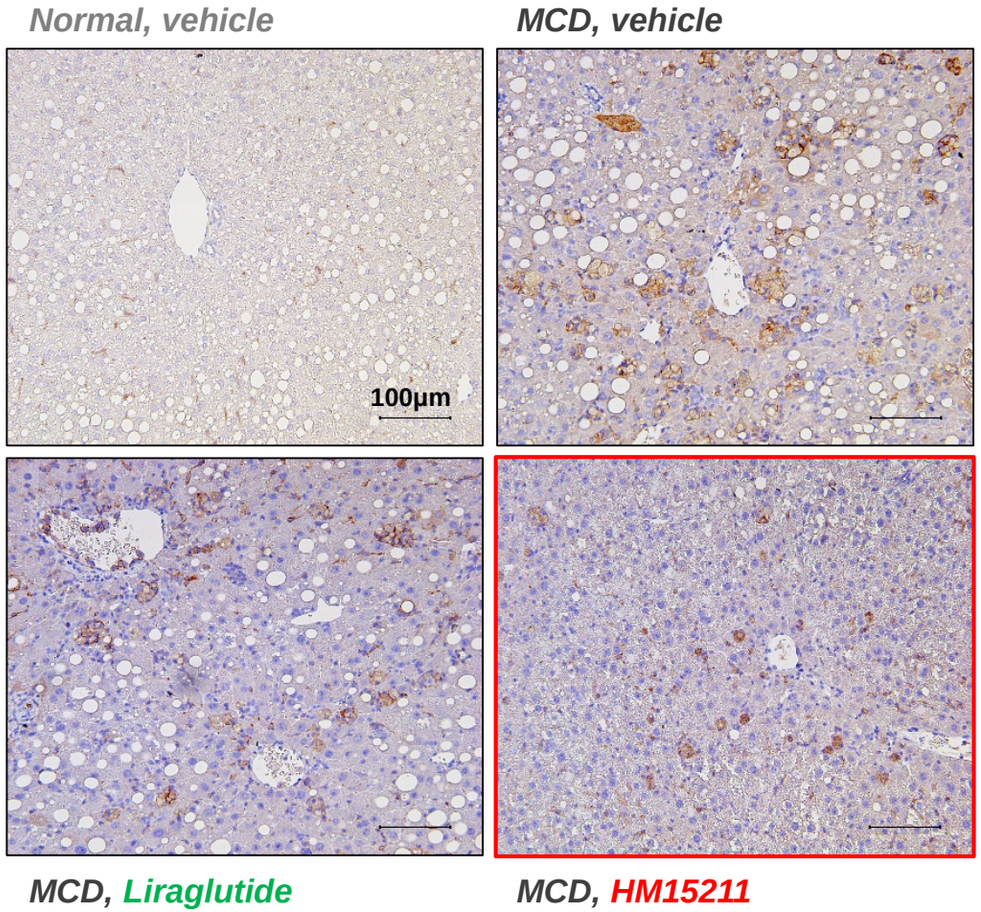
Normal, Vehicle
MCD mice, Vehicle
Liraglutide 50 nmol/kg, BID (3 mg/day in human)
HM15211 0.72 nmol/kg, Q2D (1 mg/wk in human)

*~***p<0.05 ~ 0.001 *vs.* MCD mice, vehicle by One-way ANOVA
††~†††p<0.01 ~ 0.001 *vs.* Liraglutide by One-way ANOVA

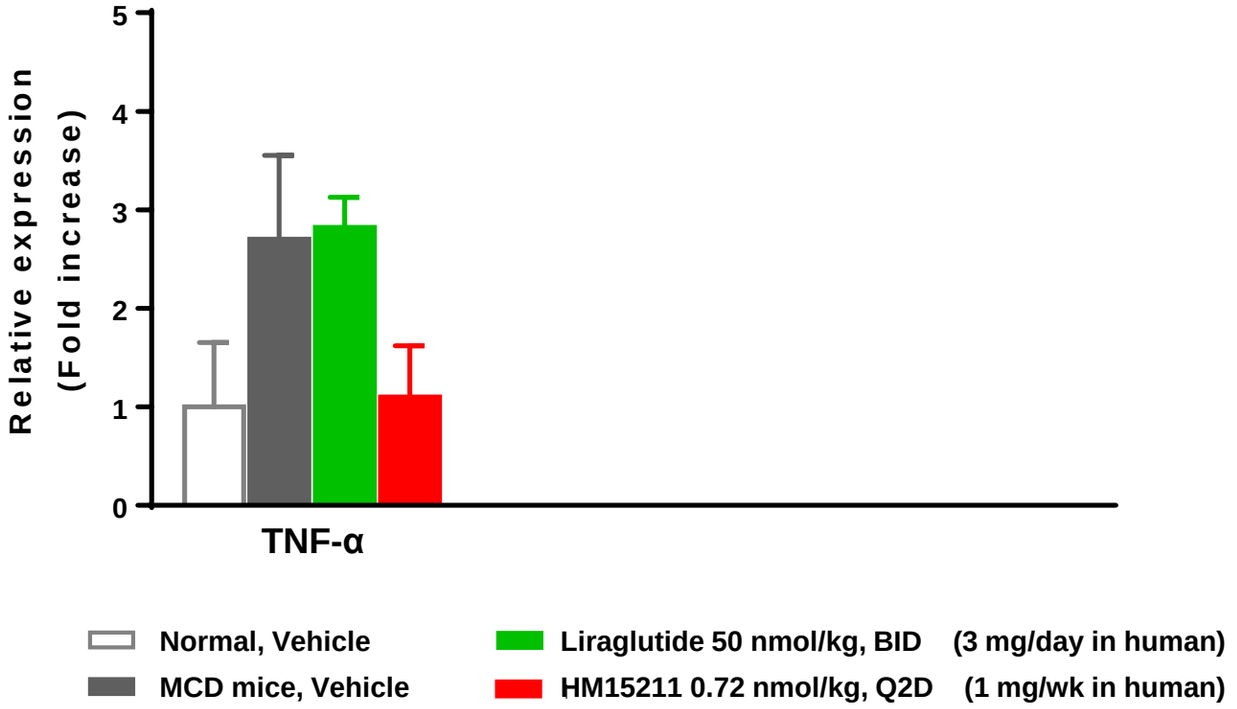
1) TBARS is surrogate of malondialdehyde, the lipid peroxidation product; oxidative stress marker

Change of hepatic marker expression in MCD-diet mice

F4/80 staining (MCD mice, representative image)



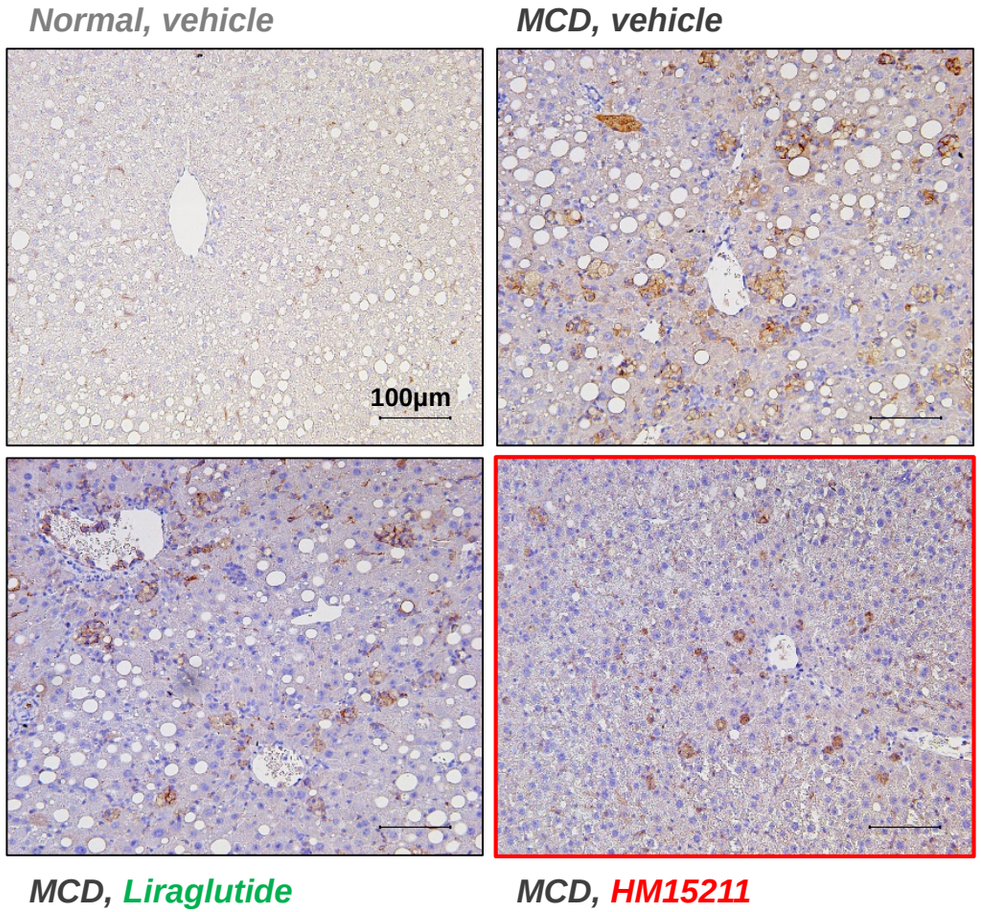
Inflammation & HSC activation marker gene expression (MCD mice, n=7, qPCR)



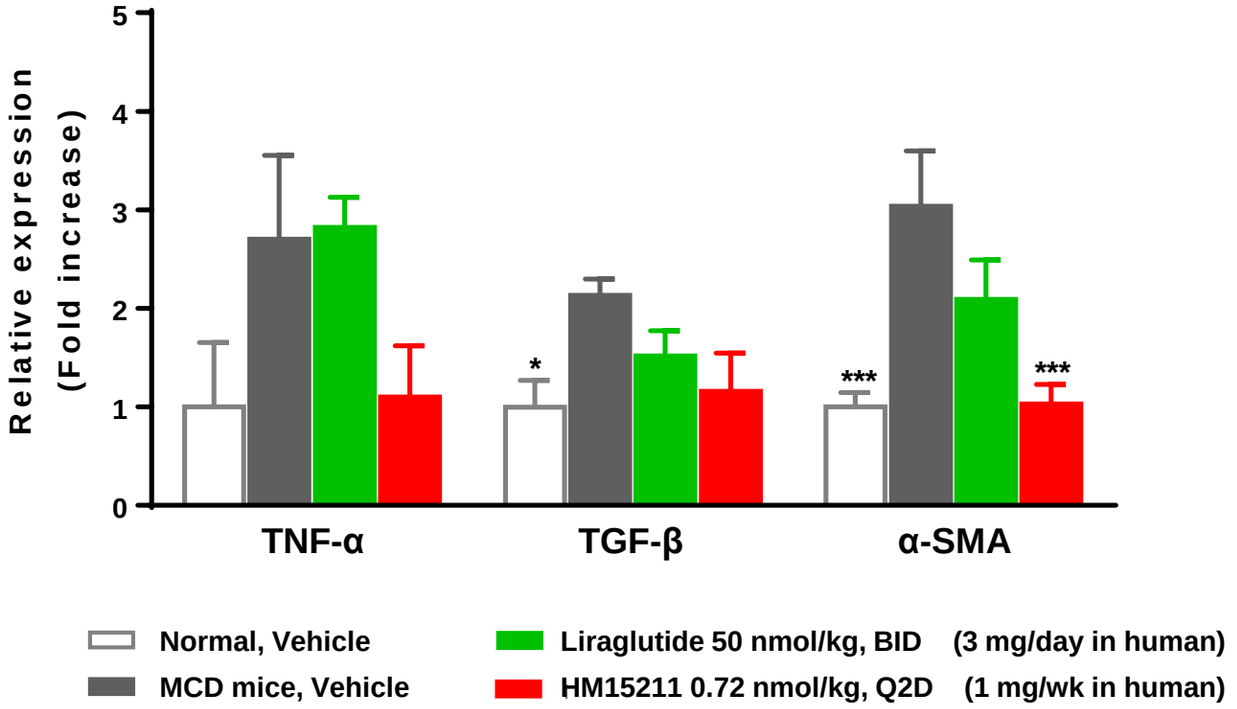
*~***p<0.05 ~ 0.001 *vs.* MCD mice, vehicle by One-way ANOVA

Change of hepatic marker expression in MCD-diet mice

F4/80 staining (MCD mice, representative image)



Inflammation & HSC activation marker gene expression (MCD mice, n=7, qPCR)



*~***p<0.05 ~ 0.001 *vs.* MCD mice, vehicle by One-way ANOVA

Change of NAFLD activity score in MCD-diet mice

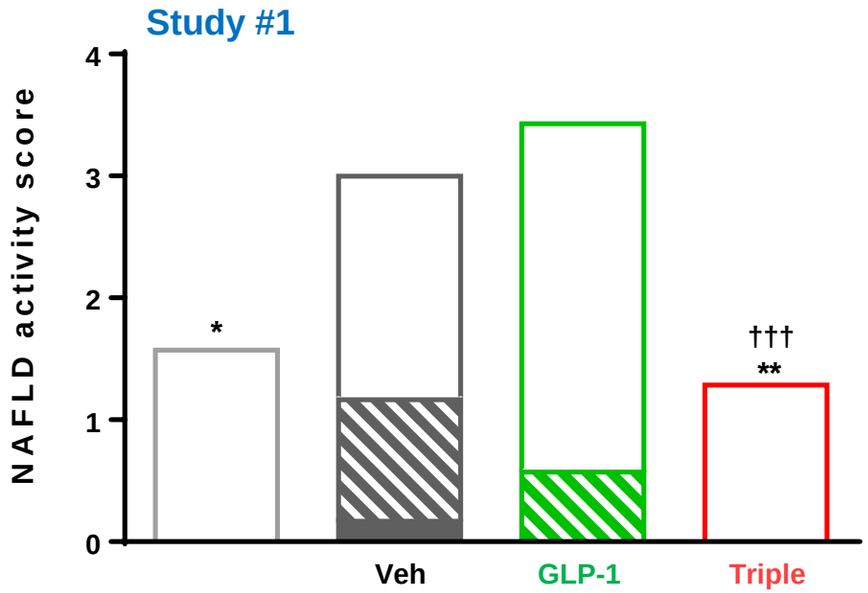
Experimental scheme

C57BL/6 mice
(8 weeks old)

MCD-diet

Model induction	Drug treatment		Expected disease status
6 weeks	4 weeks	Study #1	Liver fat ↑ Inflammation onset

NAFLD activity score (MCD mice, n=7)



Steatosis
Lobular inflammation
Ballooning

Normal, Vehicle
MCD mice, Vehicle
Liraglutide 50 nmol/kg, BID (3 mg/day in human)
HM15211 0.72 nmol/kg, Q2D (1 mg/wk in human)

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Change of NAFLD activity score in MCD-diet mice

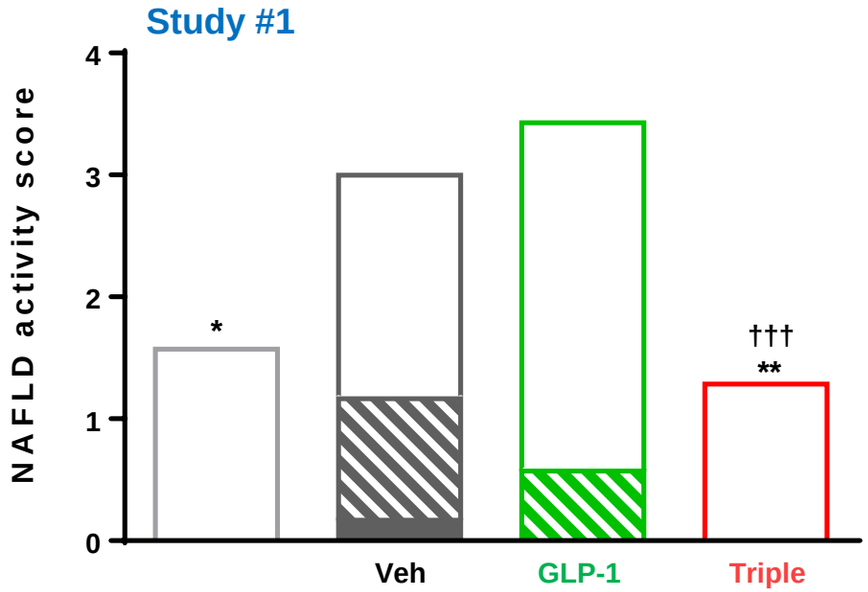
Experimental scheme

C57BL/6 mice
(8 weeks old)

MCD-diet

Model induction	Drug treatment		Expected disease status
6 weeks	4 weeks	Study #1	Liver fat ↑ Inflammation onset
10 weeks	5 weeks	Study #2	Inflammatory liver damage ↑ → liver fat ↓, ballooning ↑

NAFLD activity score (MCD mice, n=7)



Steatosis
Lobular inflammation
Ballooning

Normal, Vehicle
MCD mice, Vehicle
Liraglutide 50 nmol/kg, BID (3 mg/day in human)
HM15211 0.72 nmol/kg, Q2D (1 mg/wk in human)
Selonsertib 30 mg/kg, QD (250 mg/day in human)
Obeticholic acid 30 mg/kg, QD (250 mg/day in human)

*~**p<0.05 ~ 0.01 *vs.* MCD mice, vehicle by One-way ANOVA, ††p<0.01 *vs.* Liraglutide by One-way ANOVA

Change of NAFLD activity score in MCD-diet mice

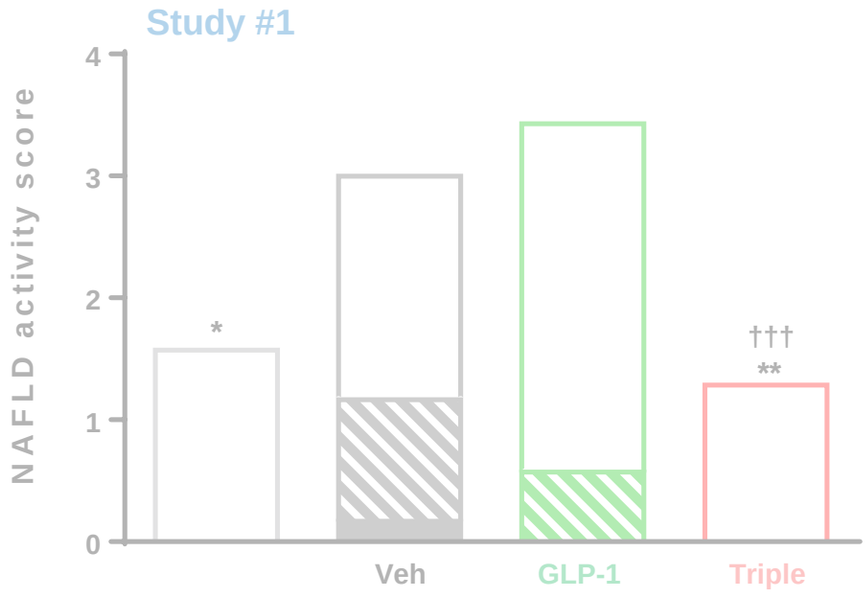
Experimental scheme

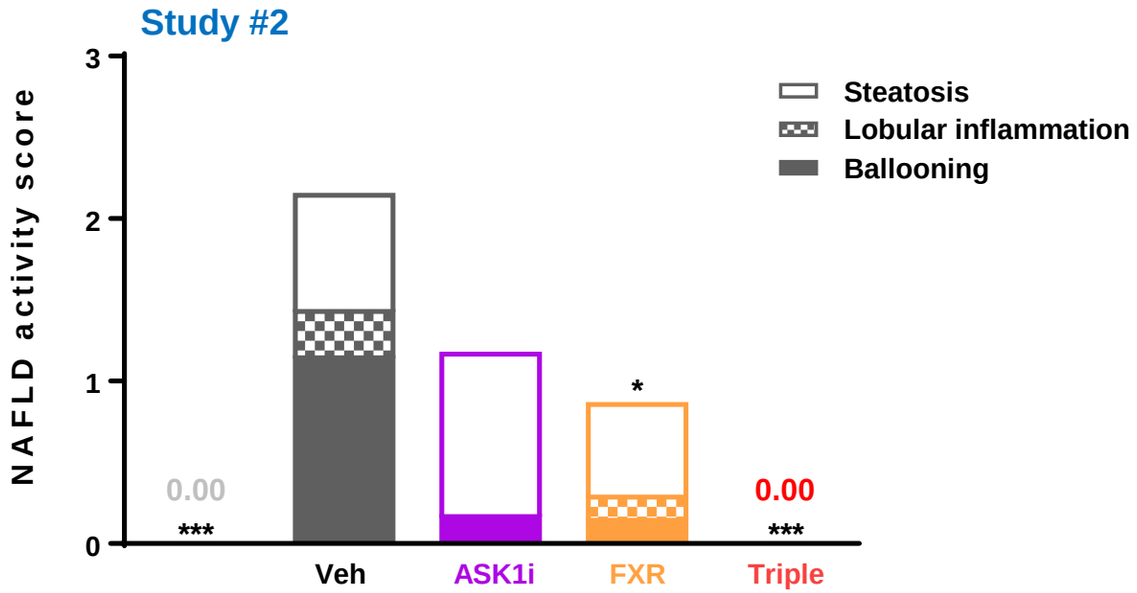
C57BL/6 mice
(8 weeks old)

MCD-diet

	Model induction	Drug treatment		Expected disease status
Study #1	6 weeks	4 weeks	Study #1	Liver fat ↑ Inflammation onset
Study #2	10 weeks	5 weeks	Study #2	Inflammatory liver damage ↑ → liver fat ↓, ballooning ↑

NAFLD activity score (MCD mice, n=7)





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*~**p<0.05 ~ 0.01 *vs.* MCD mice, vehicle by One-way ANOVA, ††p<0.01 *vs.* Liraglutide by One-way ANOVA

Change of hepatic collagen and fibrosis score in MCD-diet mice

Experimental scheme

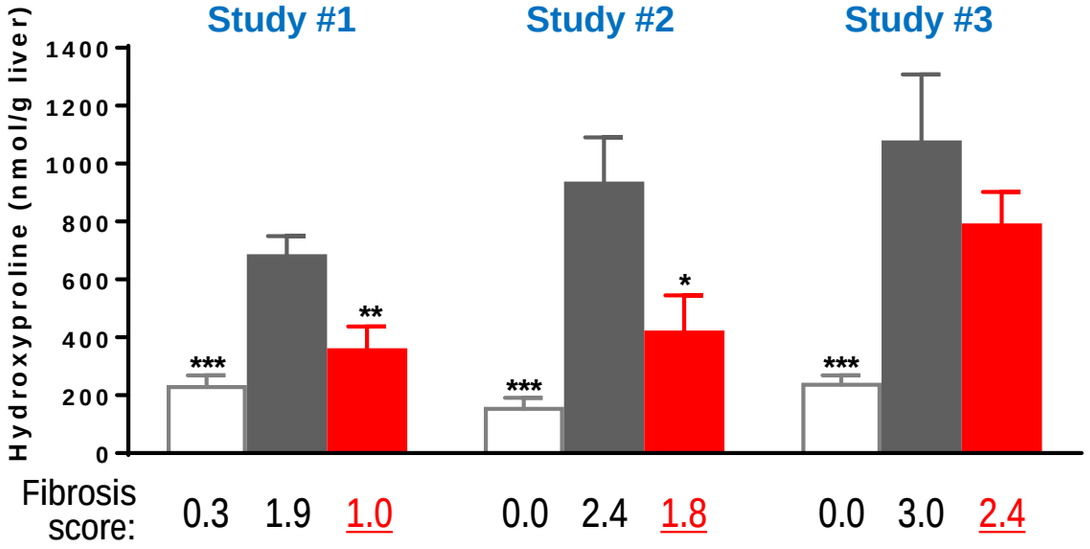
C57BL/6 mice
(8 weeks old)

MCD-diet

	Model induction	Drug treatment		Analysis
Study #1	6 weeks	4 weeks		
Study #2	10 weeks	5 weeks	Marker expression (qPCR) Hydroxyproline Sirius red staining	
Study #3	12 weeks	4 weeks		

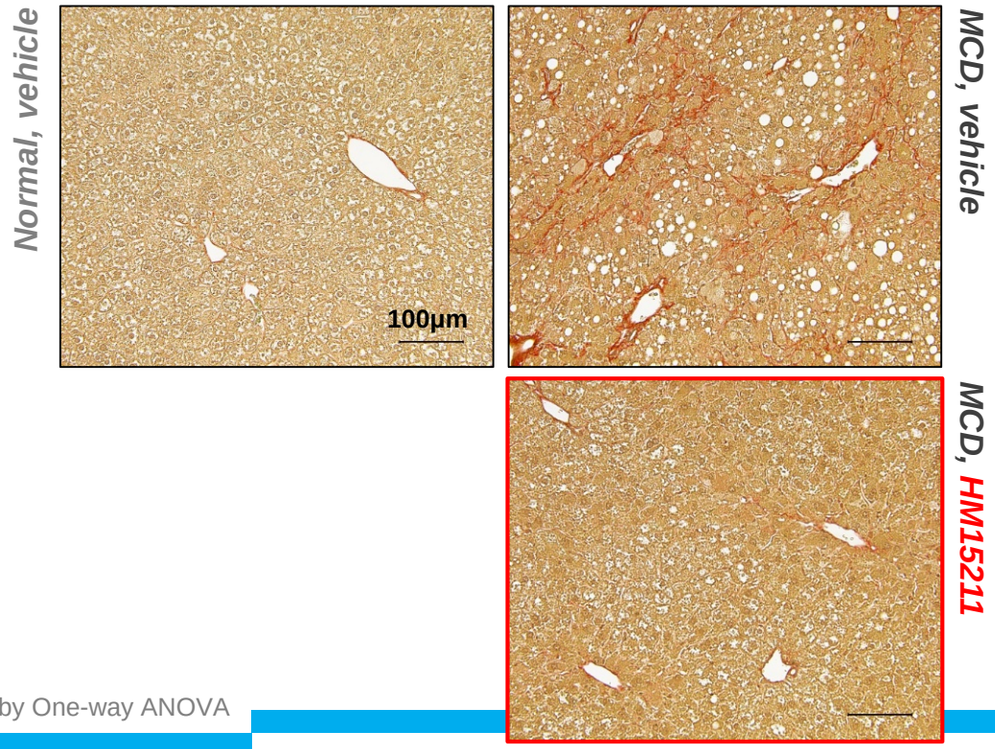
Hepatic hydroxyproline & fibrosis score

(MCD mice, n=7)



*~***p<0.05 ~ 0.001 *vs.* MCD mice, vehicle by One-way ANOVA

Sirius red staining (MCD mice, representative image from study #1)



Change of hepatic fibrosis marker expression in MCD-diet mice

Experimental scheme

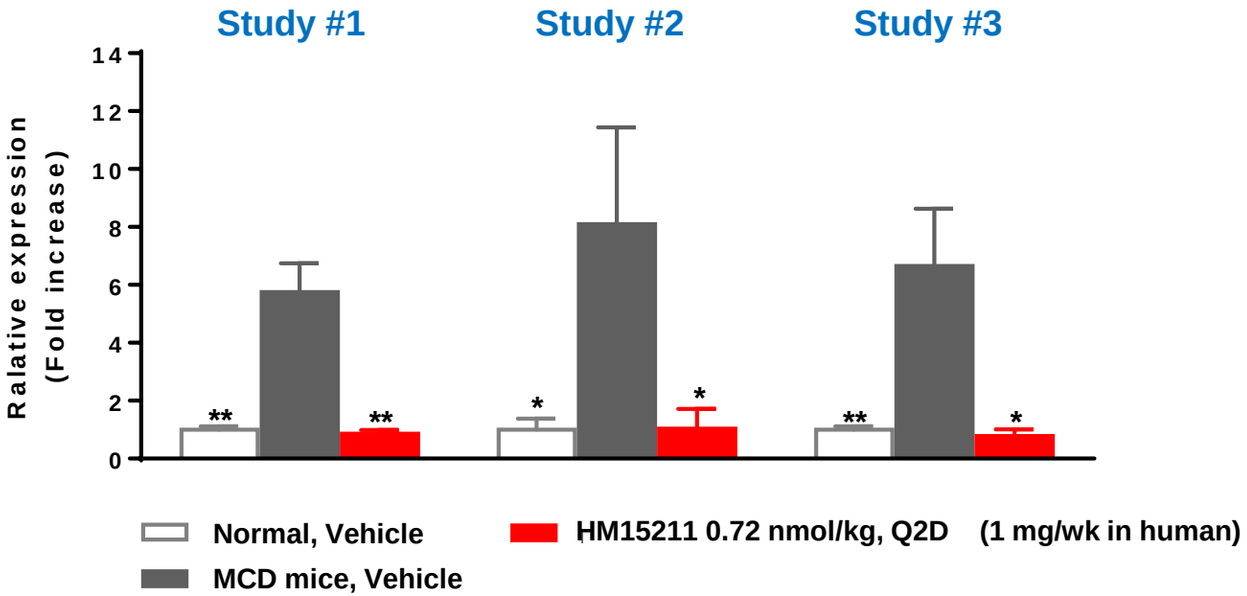
C57BL/6 mice
(8 weeks old)

MCD-diet

	Model induction	Drug treatment	Analysis
Study #1	6 weeks	4 weeks	
Study #2	10 weeks	5 weeks	Marker expression (qPCR) Hydroxyproline Sirius red staining
Study #3	12 weeks	4 weeks	

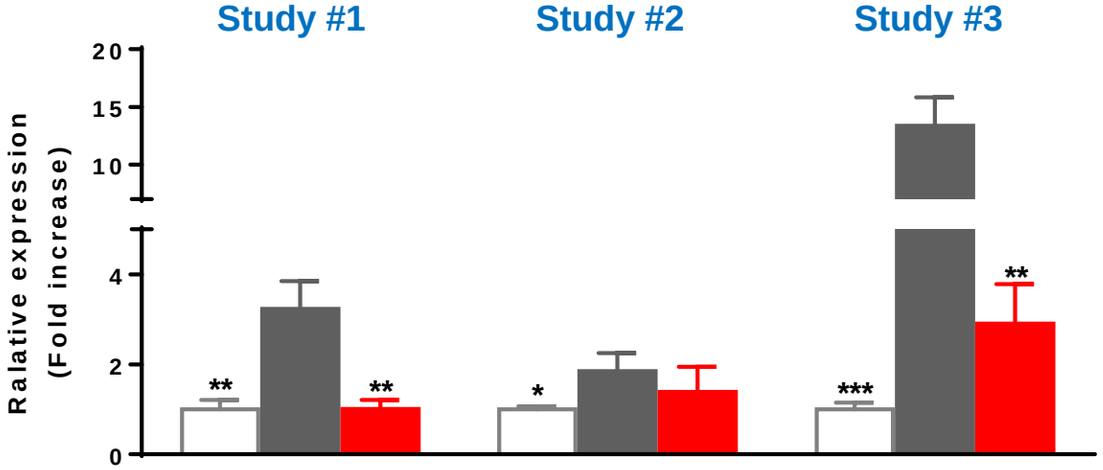
Hepatic collagen-1α1 expression

(MCD mice, n=7, qPCR)



Hepatic TIMP-1[1)] expression

(MCD mice, n=7, qPCR)



Normal, Vehicle
MCD mice, Vehicle
HM15211 0.72 nmol/kg, Q2D (1 mg/wk in human)

*~***p<0.05 ~ 0.001 *vs.* MCD mice, vehicle by One-way ANOVA

1) TIMP-1: Tissue Inhibitor of MetalloProtease-1

Summary & Conclusion

- **Considering the progression of NAFLD from simple steatosis to NASH and fibrosis, recent drug candidates may have limited efficacy because they mainly target one step of disease progression**
- **In addition to efficient weight loss (energy expenditure ↑), the long-acting GLP-1/GIP/Glucagon triple agonist, HM15211, directly reduced liver fat (lipid metabolism reprogramming) and possibly inflammation, suggestive of therapeutic potential in NASH and fibrosis**
- **In AMLN-diet mice, HM15211, but not an ASK1 inhibitor and FXR agonist, provided efficient weight loss and completely reversed steatosis**
- **In MCD-diet mice, HM15211 reduced both 1) liver fat, 2) oxidative stress, and 3) marker gene expression including HSC activation (TGF-β and α-SMA) , resulting in greater NAS reduction than GLP-1RA, ASK1 inhibitor, or a FXR agonist**
- **HM15211 could improve hepatic fibrosis regardless of induction period**

By directly affecting key steps (lipotoxicity and inflammation), HM15211 might provide improved therapeutic efficacy for the treatment of NASH and fibrosis; A Clinical study in NASH patients is planned for human efficacy translation

Please note posters or oral presentation reporting more information about HM15211:

165-OR: Neuroprotective effects of HM15211, a novel long-acting GLP-1/GIP/Glucagon triple agonist in the neurodegenerative disease models
500-P: Bone protective effect of a novel long-acting GLP-1/GIP/Glucagon triple agonist (HM15211) in an animal model
719-P: A novel combination of a long-acting GLP-1/GIP/Glucagon triple agonist and once weekly basal insulin offers improved glucose lowering and weight loss in diabetic animal model