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ePoster [217-LB]

A Novel GPR119 Agonist, DA-1241 Improves Hepatic Inflammation and Fibrosis in Ob-NASH Mice.

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Dong-A ST Co., Ltd., Republic of Korea

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A Virtual Experience

SCIENCE THAT MATTERS TO LIFE

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Declaration

All authors are employees of Dong-A ST Co., Ltd.

Background

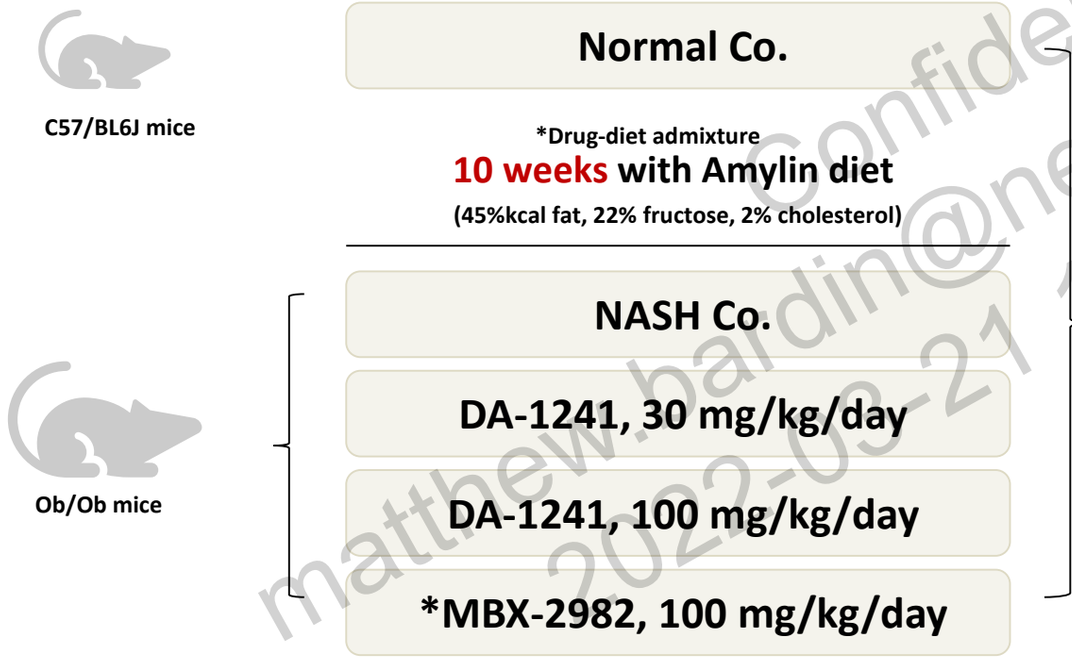
- **Non-alcoholic steatohepatitis (NASH) is characterized by steatosis, inflammation, and fibrosis in the liver**
- **Nearly 30% of adults have fatty liver and around 20% of them are progressed to NASH**
- **There is no FDA-approved drug for NASH treatment yet**

- **DA-1241, a novel GPR119 agonist, is currently underway of early clinical development for the treatment of type 2 diabetes**
- **DA-1241 is the most advanced GPR119 agonist with unique characteristics**

- **GPR119 activation inhibits *de novo* lipogenesis in the liver** (*Kang et al., FASEB J. 2016, 30(1):324-35*)
- **APD668 alleviated fatty liver in STAM mice and Amylin-diet fed mice** (*Nemmani et al., Med Mol Morphol. 2019, 52(1):36-43; Biochem Biophys Res Commun. 2018 Jan 8;495(2):1608-13; Eur J Pharmacol. 2017, 15;801:35-45*)
- **DA-1241, our novel GPR119 agonist reverted hepatic steatosis in high fat/high fructose-fed mice** (*Kim et al., 2017 ADA, 161-LB*)

Experimental Design

- To explore if and how a novel GPR119 agonist affect the pathogenesis of hepatic inflammation and fibrosis in NASH

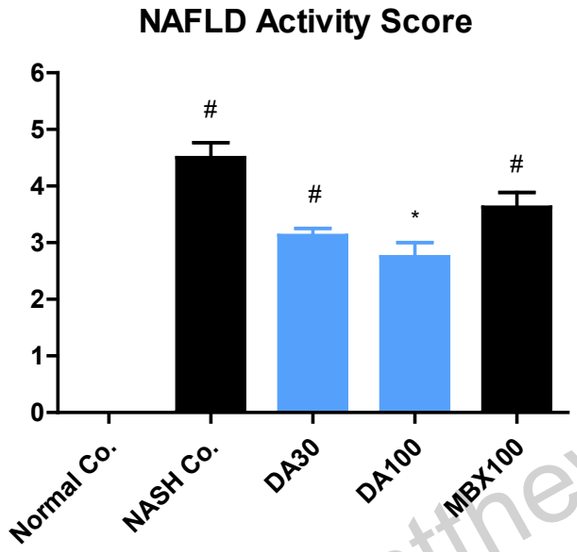


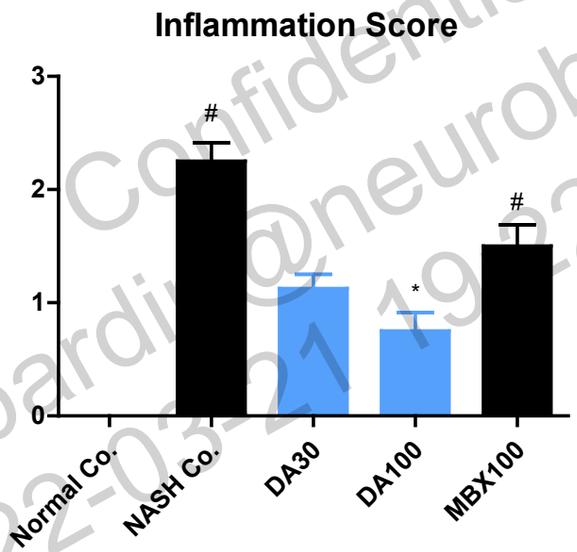
- Liver histology (HE/Masson Trichrome staining)
- Plasma total GLP-1 & TIMP-1
- Plasma ALT/AST
- Liver protein & mRNA

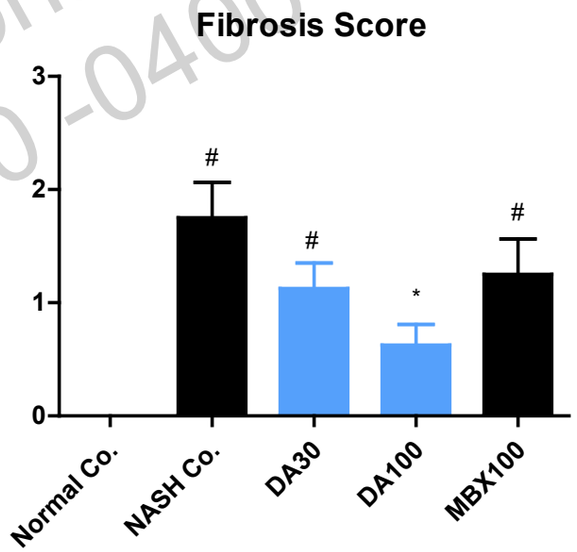
*MBX-2982: GPR119 agonist, previous clinical candidate of CymaBay (halted at Phase 2a)

DA-1241 Attenuated Hepatic Histological Changes

- DA-1241 inhibited the progression to hepatic inflammation and fibrosis compared to NASH control
- DA-1241 was superior to MBX-2982 at the same dosage







Kruskal-Wallis test

#, p<0.05 vs. Normal Co.

**, p<0.05 vs. NASH Co.*

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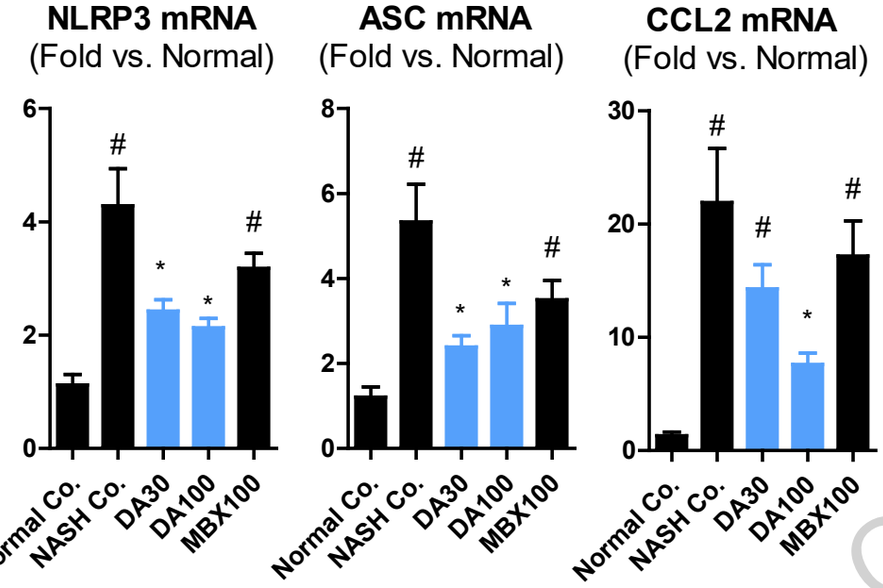
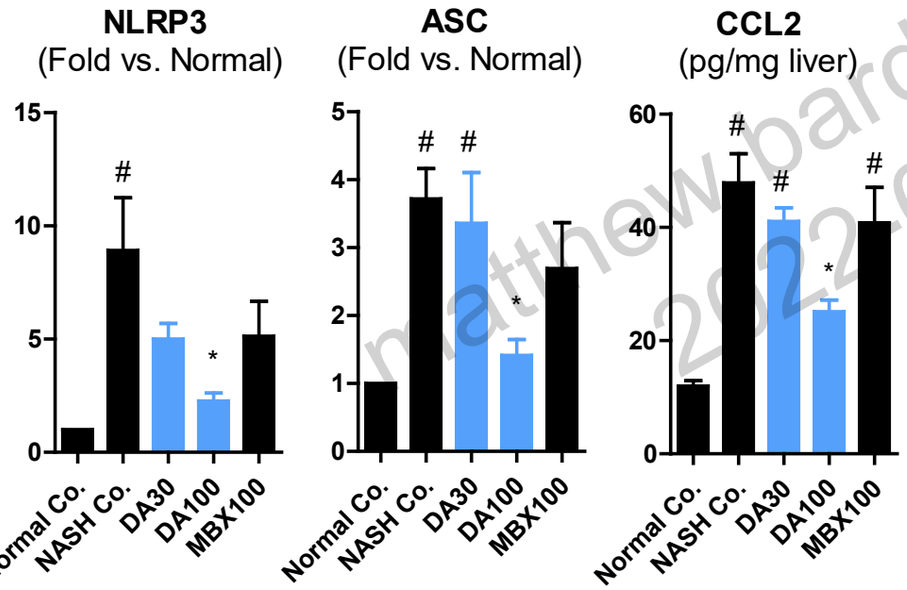
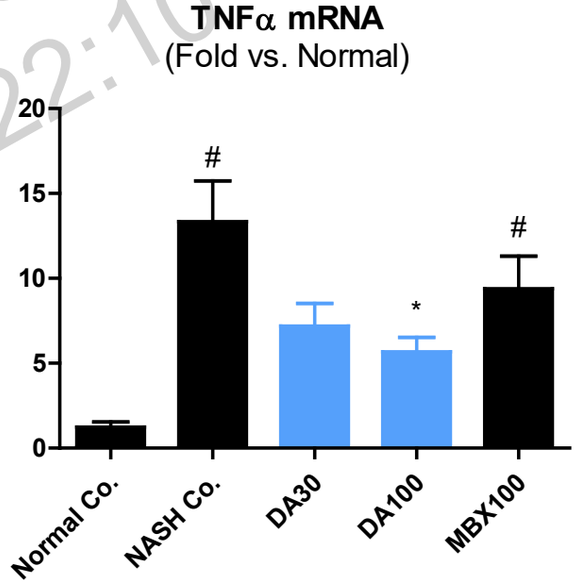
DA-1241 Reduced Hepatic Expression of Inflammation-Related Targets





- DA-1241 suppressed the gene expression of innate immune response (NLRP3, ASC) and inflammatory cytokines (CCL2, TNFα) in the liver
- Protein levels of NLRP3, ASC, and CCL2 in DA-1241-treated mice were also lower than NASH control and MBX100-treated group



Tukey's multiple comparison
#, p<0.05 vs. Normal Co.
**, p<0.05 vs. NASH Co.*

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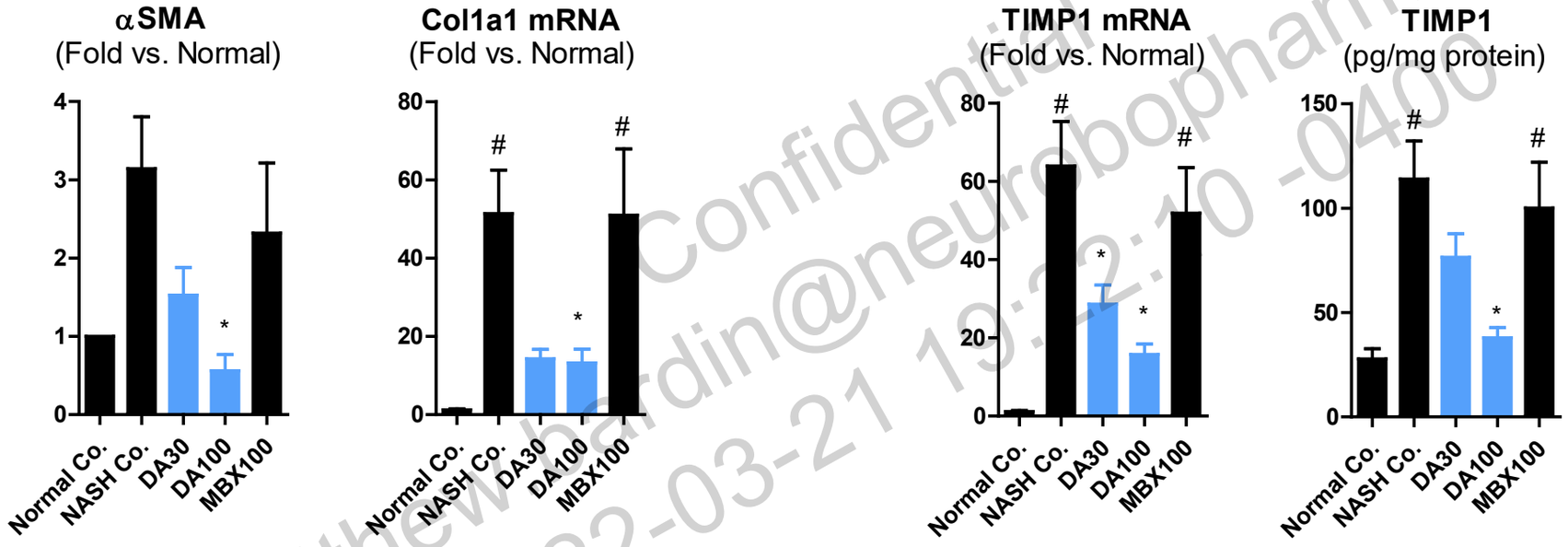
DA-1241 Reduced Hepatic Expression of Fibrosis-Related Targets

- DA-1241 suppressed the expression of pro-fibrotic elements (αSMA, type I collagen) including endogenous matrix metalloprotease inhibitor (TIMP1) in the liver through transcriptional down-regulation



Tukey's multiple comparison
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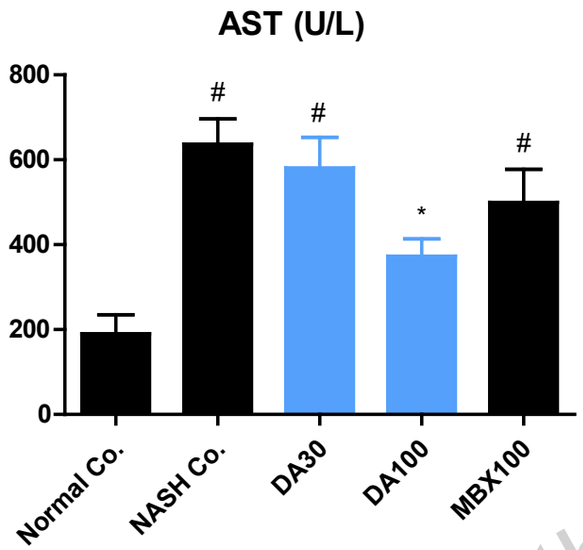
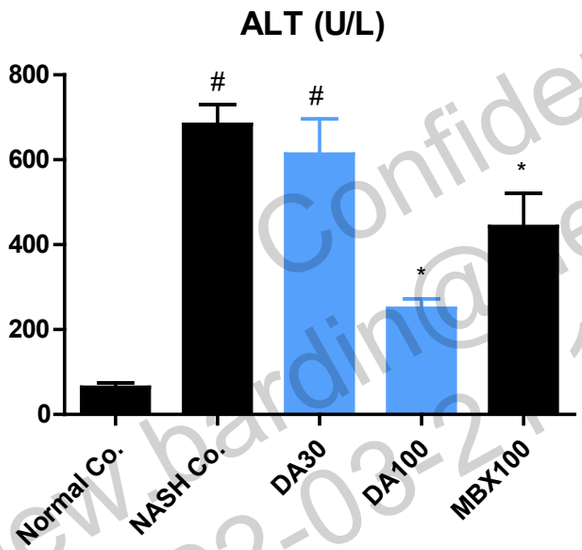
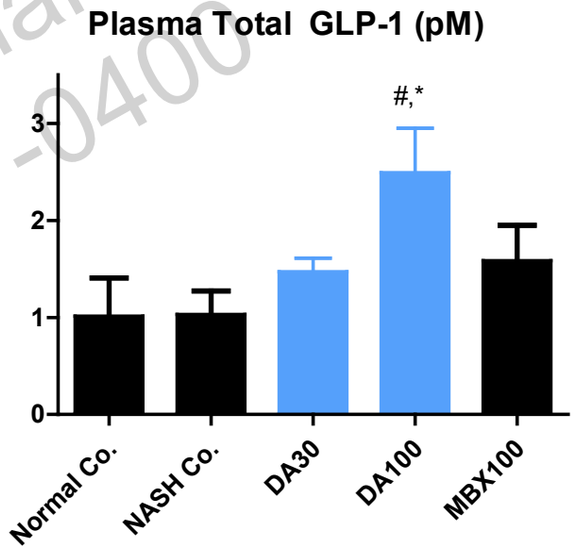
DA-1241 Improved Plasma Parameters Accordingly

- DA-1241 lowered plasma liver enzyme levels, indicating reduced liver damage





- DA-1241 increased plasma total GLP-1, a target-related biomarker of GPR119 agonists



Tukey's multiple comparison
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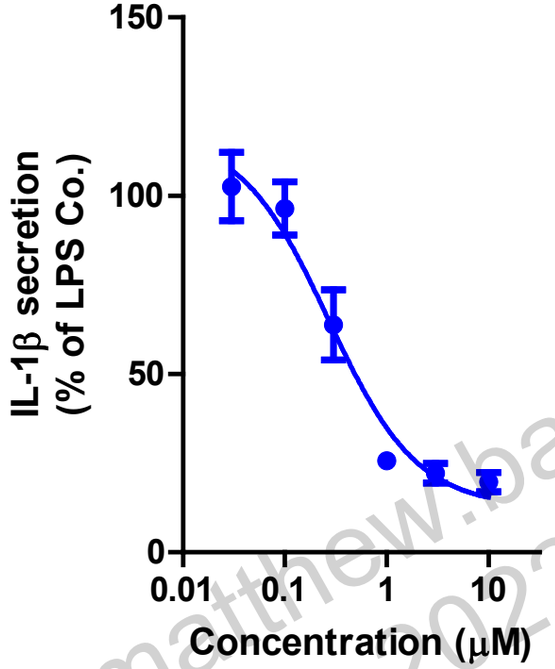
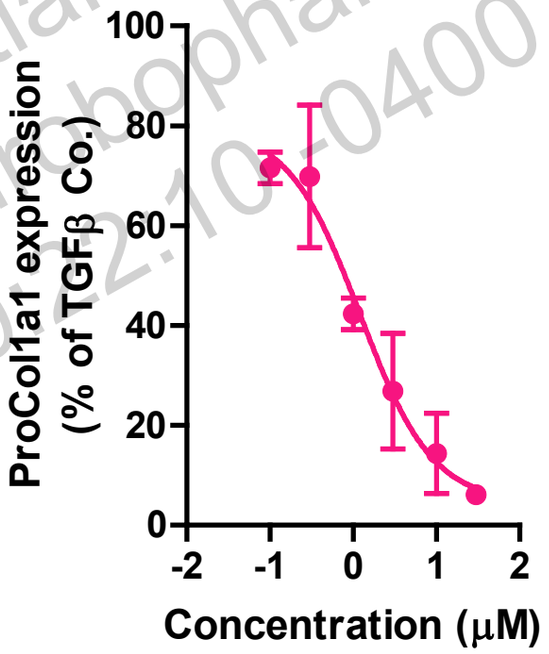
Proposed MOA

- DA-1241 inhibited differentiation of human THP-1 macrophage
- DA-1241 inhibited activation of human primary hepatic stellate cells

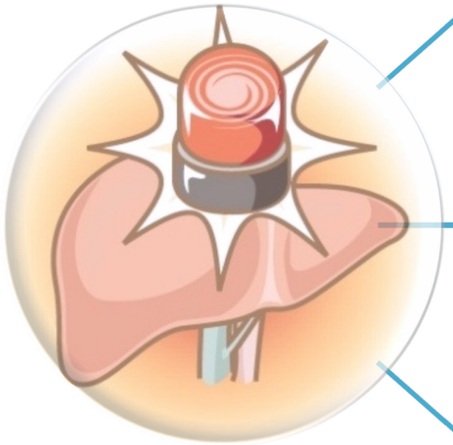
Macrophage Differentiation



Stellate Cell Activation



Summary



- **DA-1241, a novel GPR119 agonist, attenuated the progression of NASH in Ob/Ob mice fed on Amylin diet.**
- **DA-1241 suppressed hepatic expression of inflammation or fibrogenesis-related target elements.**
- **Inhibition of macrophage differentiation and stellate cell activation may contribute to anti-inflammatory and anti-fibrotic effects of DA-1241.**