



Anti-inflammatory and anti-fibrotic effects of a novel long-acting Glucagon/GIP/GLP-1 triple agonist, HM15211, in TAA induced mouse model of liver injury and fibrosis

Jung Kuk Kim, Jong Suk Lee, Yohan Kim, Seon Myeong Lee, Hyunjoo Kwon, Eun Jin Park, Jae Hyuk Choi, Sung Min Bae, Dae Jin Kim, Sang Hyun Lee, In Young Choi

Hanmi Pharm. Co., Ltd., Seoul, Republic of Korea

Hanmi

Employee of Hanmi Pharm. Co., Ltd.

GLP-1

- Insulin resistance improvement
- Glycemic control
- Weight loss by appetite regulation
- Anti-inflammation

GIP

Glucagon

- Glucose production
- Weight loss by energy expenditure

[Liver targeting]

- Favorable lipid metabolism reprogramming
- Bile acid production ↓
- Anti-inflammation
 - Lipotoxicity and liver injury ↓
- TGF-β production ↓
- Smad signaling ↓ in HSC
 - HSC activation and fibrogenesis ↓

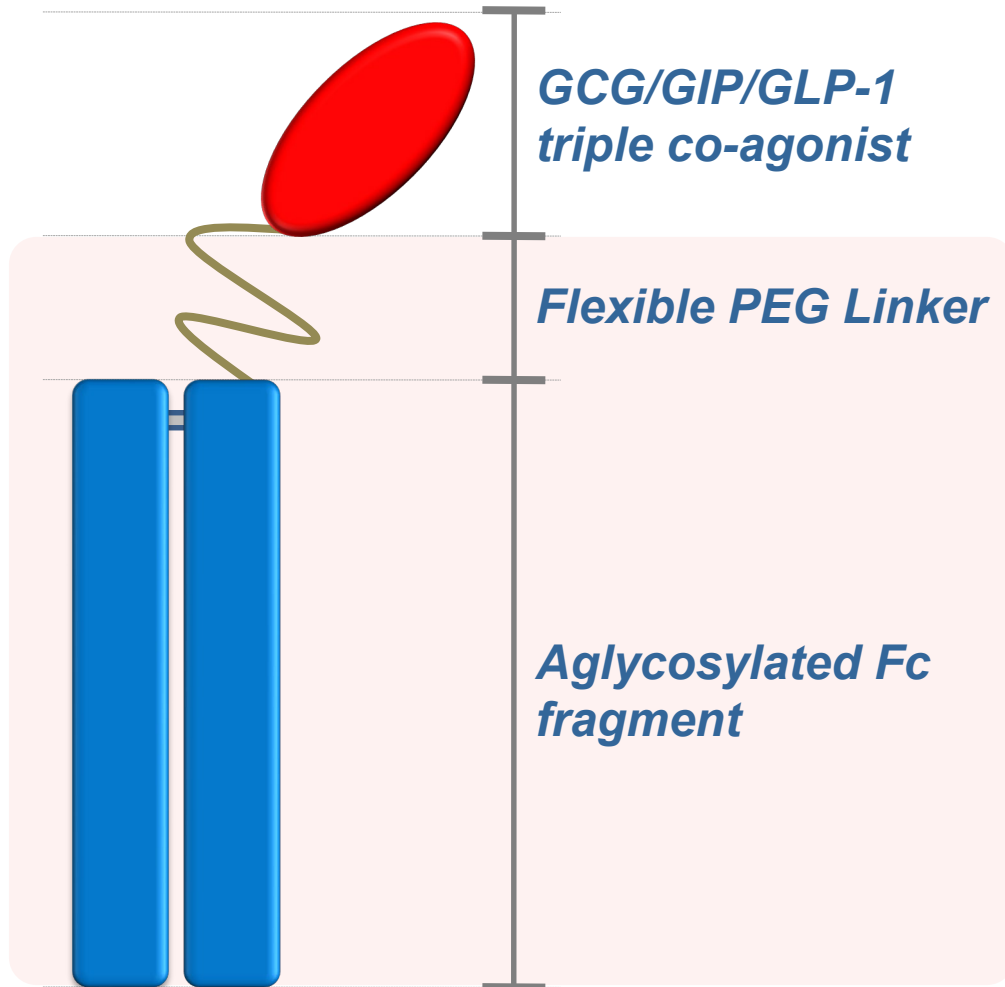
May be
indirect benefits

- NASH resolution
- Fibrosis improvement
- Off-set blood glucose elevation

HM15211 [Ph2b, US, KR]

Direct benefits

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



Hanmi's Glucagon/GIP/GLP-1 triple co-agonist (HM15211) is conjugated with a human IgG Fc fragment *via* flexible linker

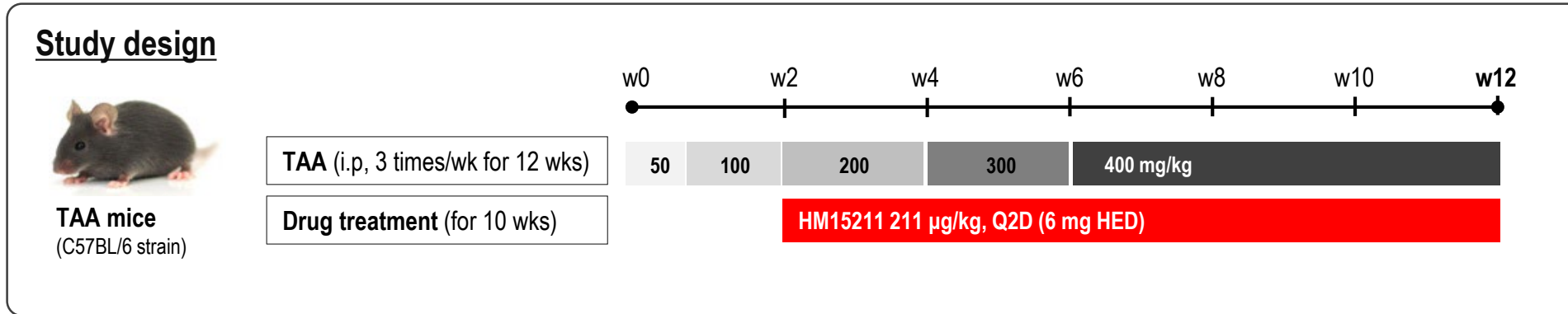
[General profile]

- Single drug moiety with triple activity
- Extended half-life allows once weekly dosing
- Rationally designed triple agonist optimized for liver targeting
- Rapid & potent liver fat reduction both in animal and human (*12 weeks MAD trial results in obese NAFLD subjects presented at 2020 EASL)
- Multiple MoAs exist for managing inflammation and fibrosis
- On-going for P2b study in biopsy-proven NASH subjects

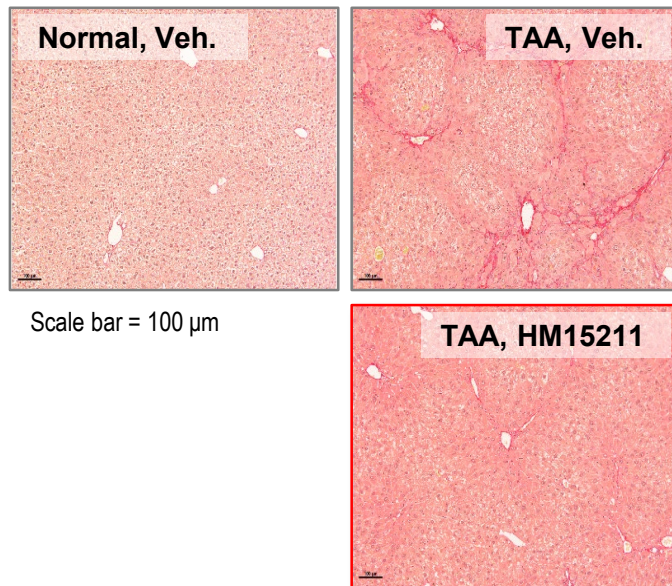
LAPSCOVERY : Long Acting Peptide/Protein DiSCOVERY Technology

Figure 1. HM15211 effect on hepatic fibrosis in TAA mice

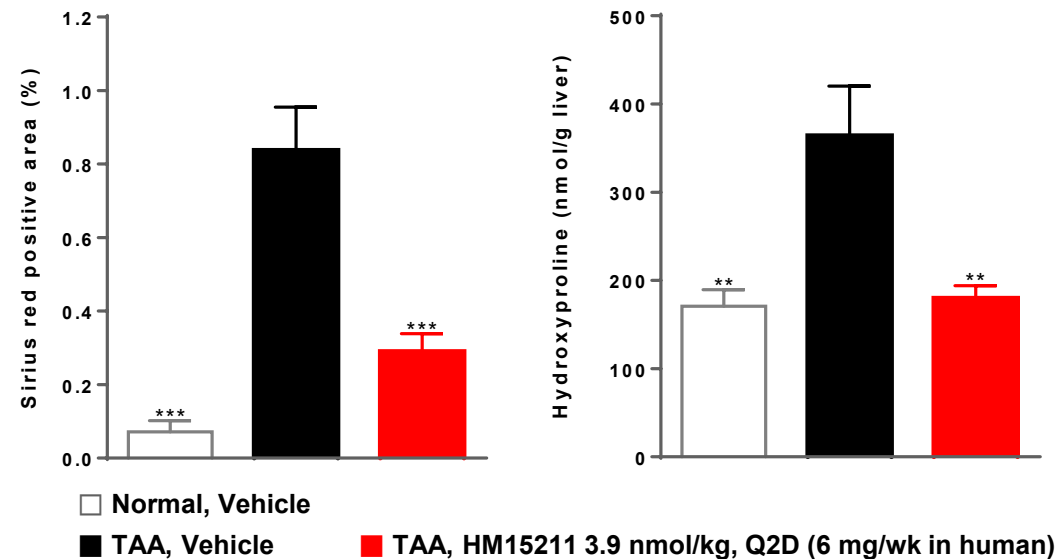
➤ HM15211 treatment led to histological improvement of liver fibrosis in TAA mice. Reduction effect of fibrosis score is correlated with that of Sirius red positive area and hepatic hydroxyproline



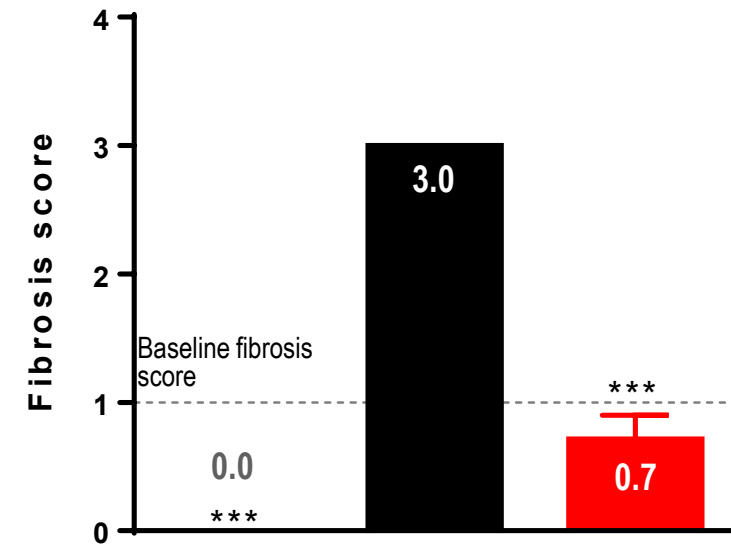
(a) Sirius red staining and positive area



(b) Hepatic hydroxyproline



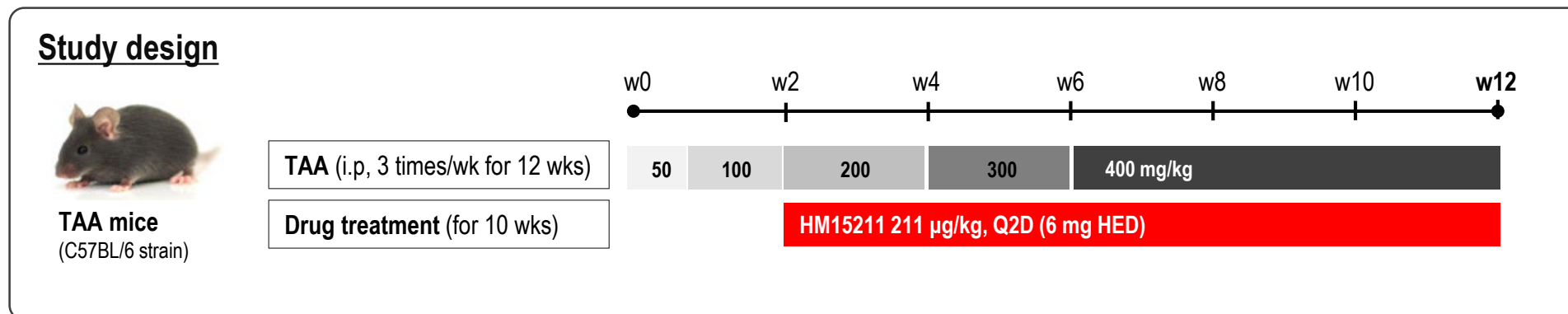
(c) Fibrosis score



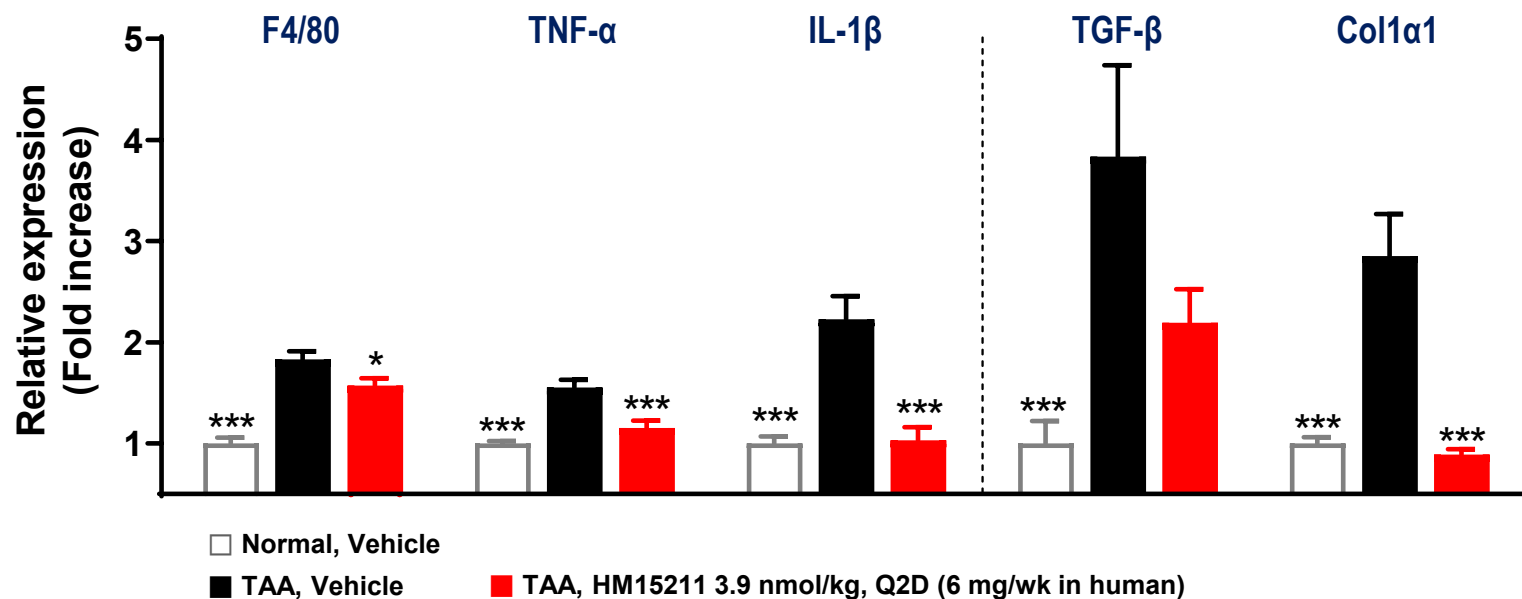
~* $p < 0.01 \sim 0.001$ vs. TAA, vehicle by One-way ANOVA

Figure 2. HM15211 effect on surrogate markers in TAA mice

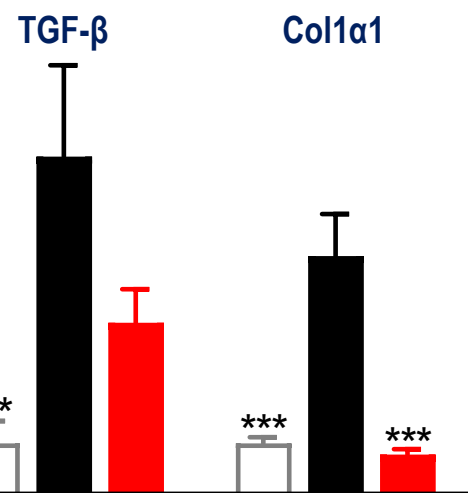
➤ Consistent with histologic results, robust improvement effects of HM15211 were observed for efficacy surrogate measurement such as hepatic marker gene expression and blood liver enzyme level



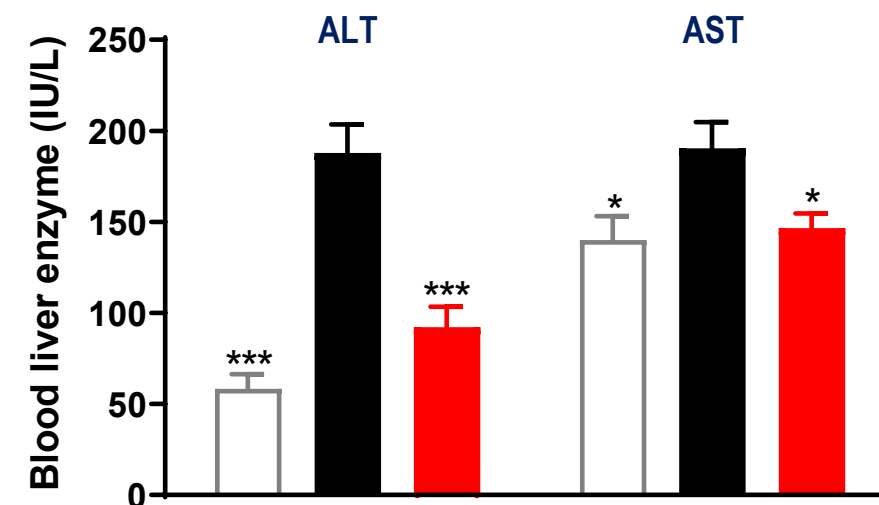
(a) Inflammation marker gene



(b) Fibrosis marker gene



(c) Blood liver enzyme

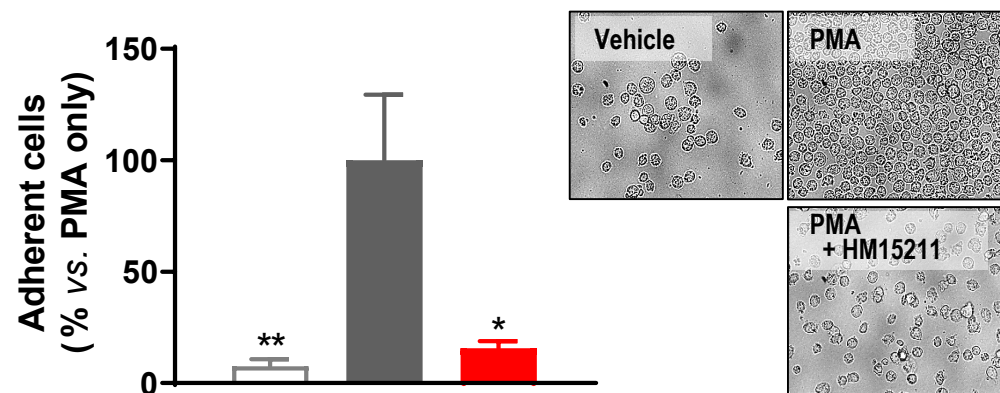


*~***p<0.05~0.001 vs. TAA, vehicle by One-way ANOVA

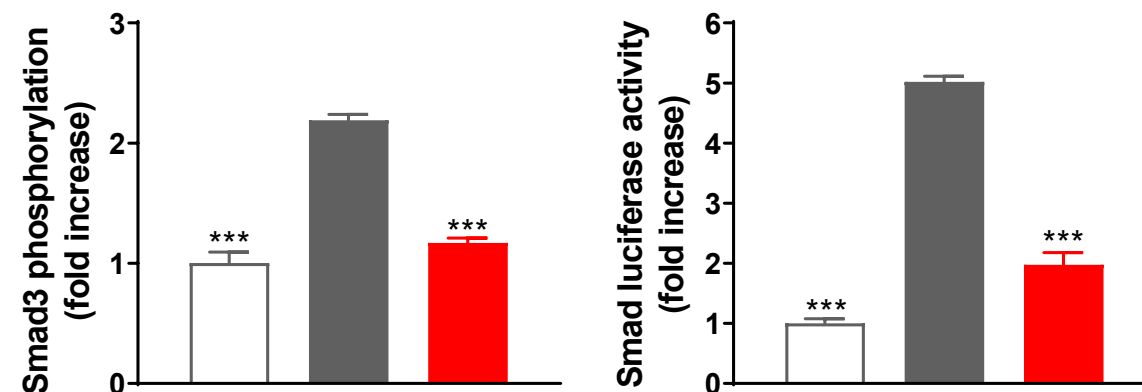
Figure 3. MoAs for anti-inflammatory and anti-fibrotic effects

➤ Inhibitory effects on activation of macrophage and HSC demonstrate direct anti-inflammatory and anti-fibrotic effects of HM15211

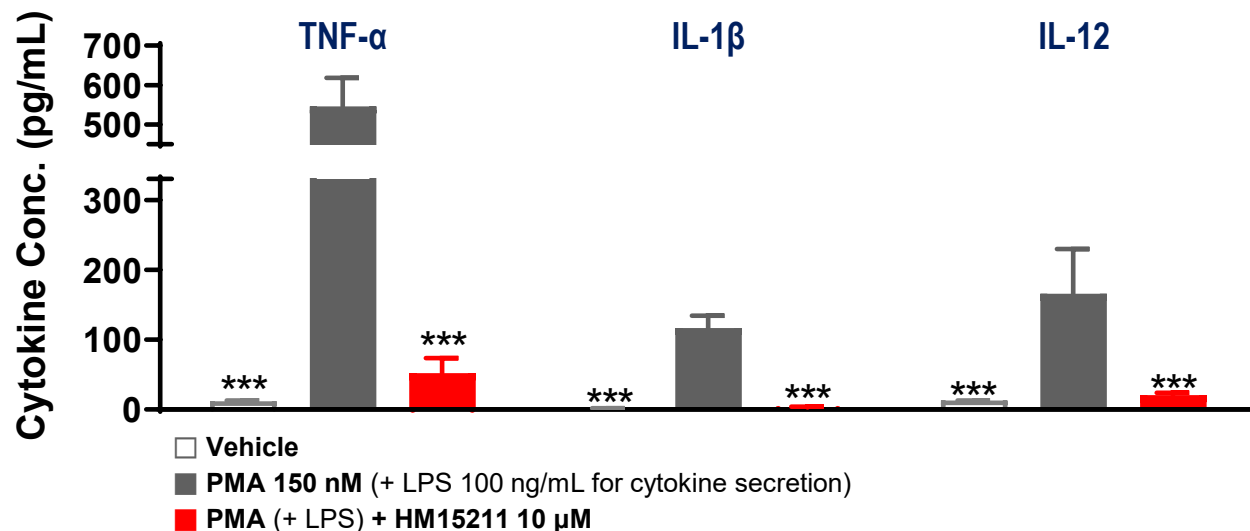
(a) PMA-induced cell adhesion in THP-1 cells (monocyte to macrophage differentiation)



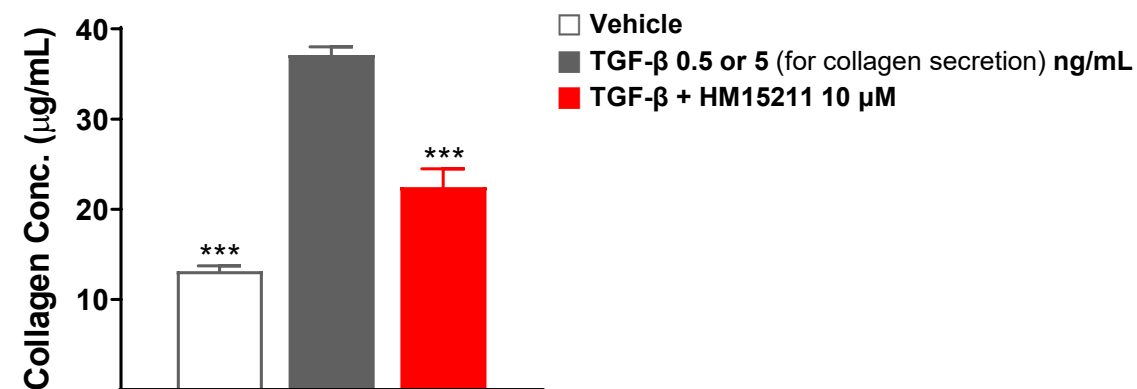
(c) TGF-β-induced Smad3 activation of LX-2 cells



(b) Inflammatory cytokine secretion (M1 polarization)



(d) Collagen secretion



*~***p<0.05~0.001 vs. Stimulation by One-way ANOVA

- **HM15211 is Glucagon/GIP/GLP-1 triple agonist with unique activity features designed to treat NASH and fibrosis by targeting multiple aspects of this disease**
- **In previous studies, robust therapeutic benefits were observed in animal models of NASH and/or liver fibrosis (e.g. MCD mice, CDAHFD mice, AMLN mice, and BDL mice)**
- **In the current study, direct anti-inflammatory and anti-fibrotic effects of HM15211 were further confirmed in TAA mice**
- ***In vitro* mechanistic studies revealed that HM15211 could inhibit monocyte differentiation and M1 polarization (pro-inflammation cytokine secretion), and HSC activation (collagen secretion)**

**HM15211 might provide improved efficacy for the treatment of NASH and fibrosis
Fast-track granted and P2b clinical study is on-going in biopsy-proven NASH subjects (US, KR)**

Please note oral presentation reporting more information about HM15211:

#838: Anti-fibrotic potential of a novel long-acting Glucagon/GIP/GLP-1 triple agonist (HM15211) in preclinical models of idiopathic pulmonary fibrosis

Contact information: kjk515@hanmi.co.kr