

Anti-fibrotic effect of a novel long-acting GLP-1/GIP/Glucagon triple agonist (HM15211) in BDL-induced liver fibrosis mice

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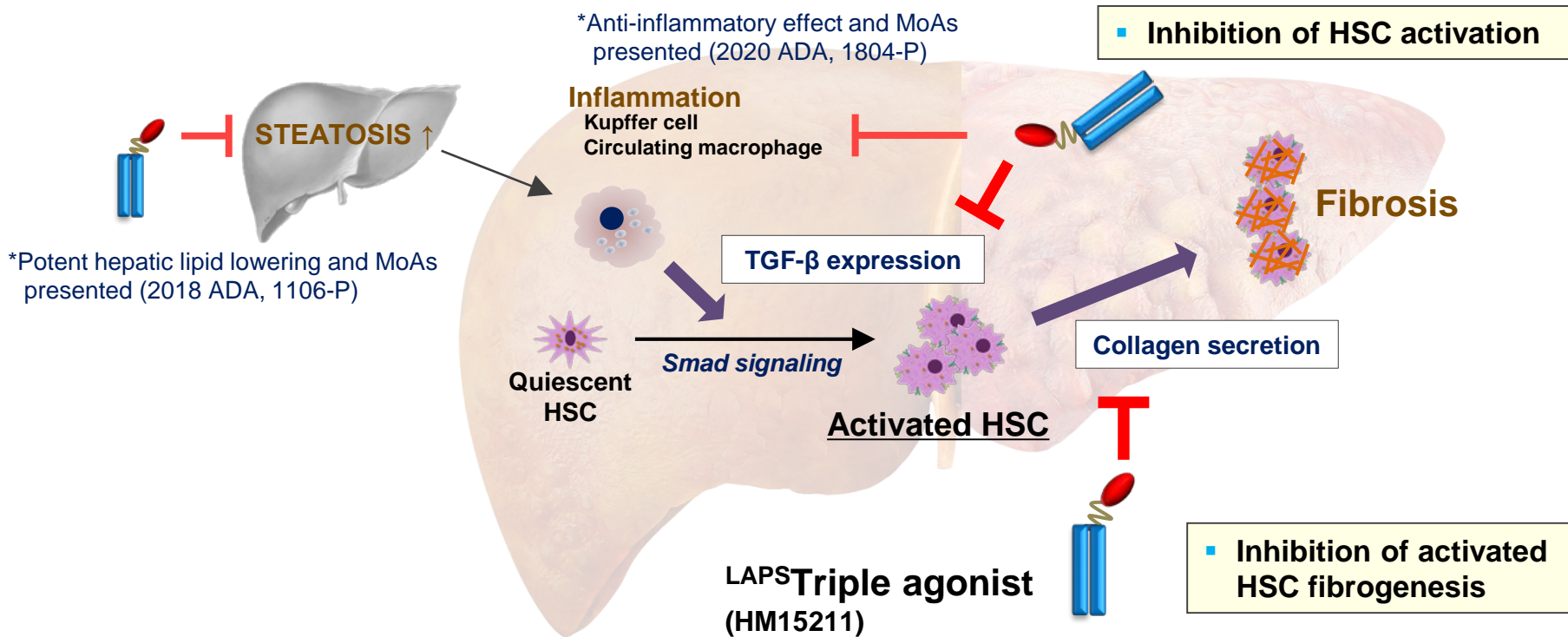
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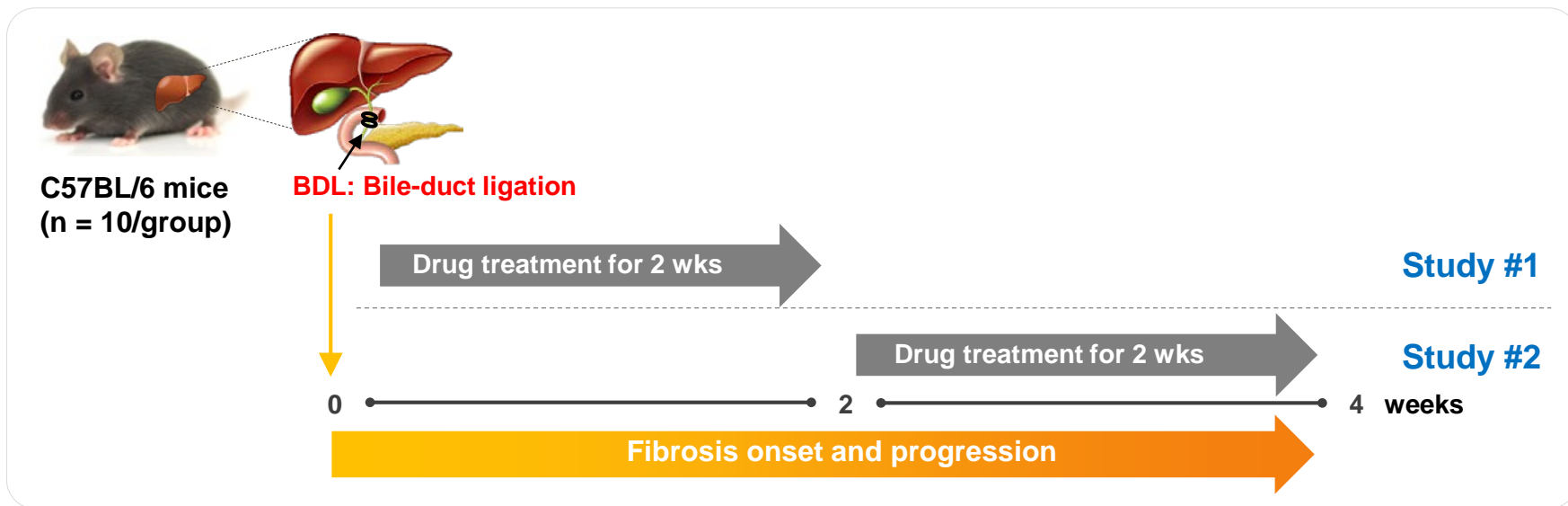


Employee of Hanmi Pharm. Co., Ltd.

Essential role of hepatic stellate cell (HSC) in liver fibrosis

Proposed modes of action (MoA) for direct anti-fibrotic effect by HM15211



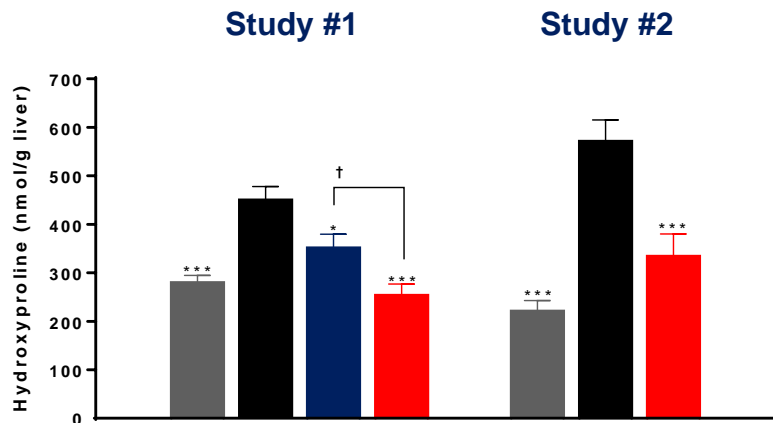


Model	Key highlights	Poster #
AMLN/TAA mice	Anti-inflammatory effect and MoA; Anti-fibrotic effect	1804-P
BDL mice	Direct anti-fibrotic effect and MoA	1803-P
CDHFD mice	BW loss-independent efficacy in NASH and fibrosis	1830-P

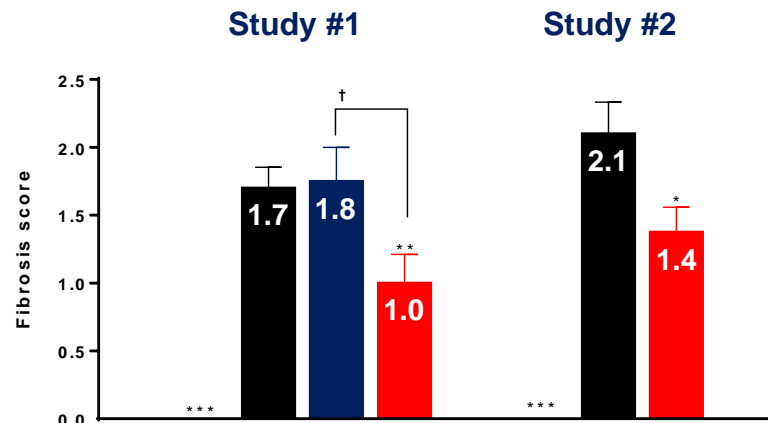
Figure 1. HM15211 effect on hepatic hydroxyproline and fibrosis score

- Significant reduction both in hepatic hydroxyproline contents and fibrosis score by HM15211 in BDL mice
- Greater efficacy than obeticholic acid (OCA) suggests more therapeutic benefits of HM15211 in fibrosis

(a) Hepatic hydroxyproline contents



(b) Fibrosis score

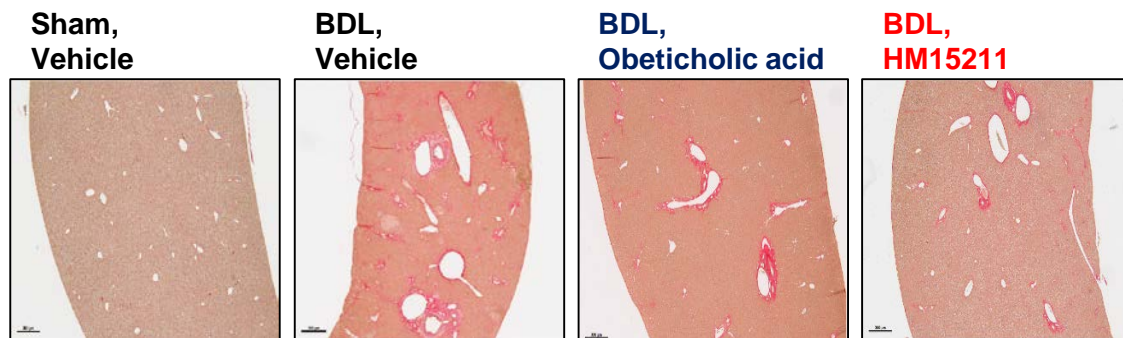


- Sham, Vehicle
- BDL, Vehicle
- BDL, Obeticholic acid 30 mg/kg, QD
- BDL, HM15211 1.3 nmol/kg, Q2D (2 mg/wk in human)

Figure 2. HM15211 effect on hepatic collagen deposition (study #1)

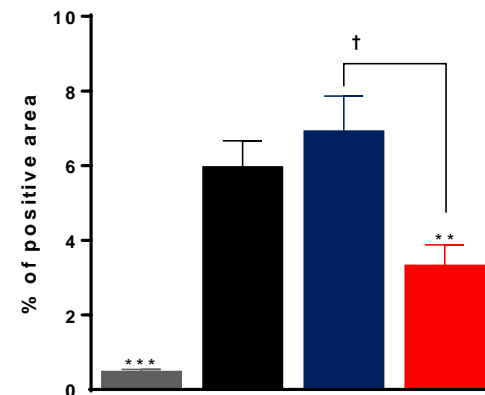
➤ HM15211 treatment was associated with greater reduction in Sirius red positive area than OCA, confirming anti-fibrotic effect of HM15211 in BDL mice

(a) Representative image for Sirius red staining



[Scale bar: 300 μm]

(b) Sirius red positive area



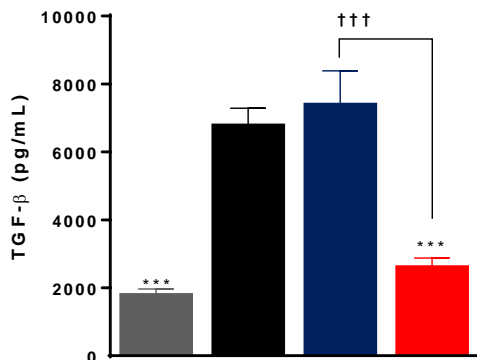
‡ Similar reduction in Sirius red positive area was observed in study #2 (data not shown)

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- BDL, Vehicle
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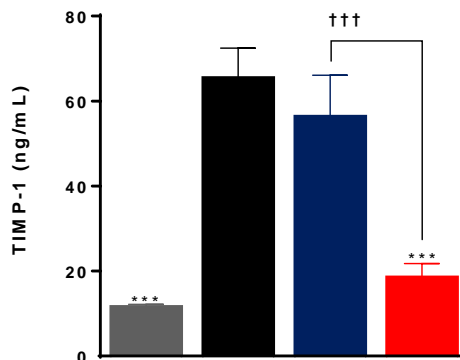
Figure 3. HM15211 effect on blood surrogate marker level (study #1)

- Consistently, improvement at blood fibrosis surrogate markers further supports anti-fibrotic effect of HM15211
- Decrease in blood TGF- β level suggests the mitigation of HSC activation by HM15211

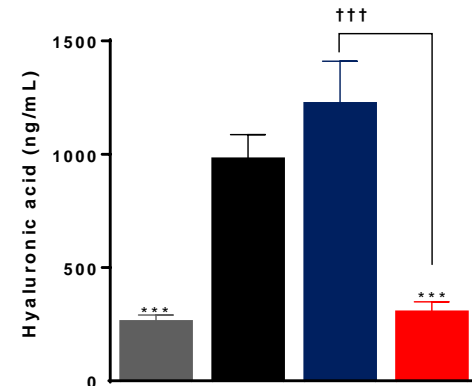
(a) TGF- β



(b) TIMP-1



(c) Hyaluronic acid



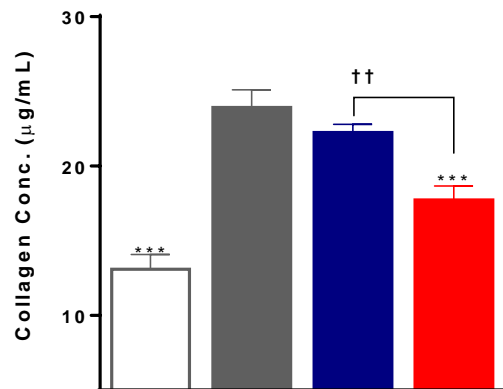
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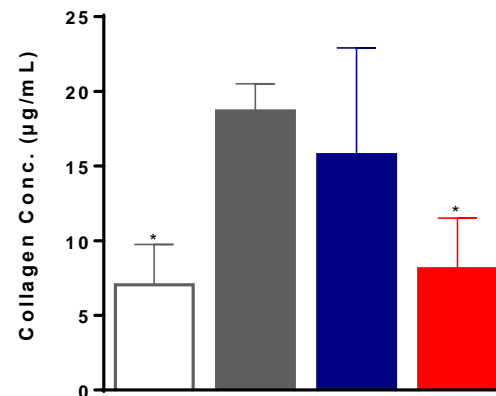
Figure 4. HM15211 effect on collagen secretion in HSC

➤ HM15211, but not OCA, reduced TGF- β induced collagen secretion both in LX2 cells and rat primary HSCs, demonstrating direct inhibitory effect of HM15211 on fibrogenesis of activated HSC

(a) LX2 cells



(b) Rat primary HSCs



□ Vehicle ■ TGF- β 5 ng/mL + Obeticholic acid 10 μM
■ TGF- β 5 ng/mL ■ TGF- β 5 ng/mL + HM15211 10 μM

- **HM15211, a novel long-acting GLP-1/GIP/Glucagon triple agonist, is designed to treat NASH and fibrosis**
- **In BDL mice, HM15211 confers significant improvement in fibrosis regardless of model induction period**
- **Hence, better efficacy than OCA highlights anti-fibrotic effect of HM15211**
- **HM15211, but not OCA, not only reduced TGF- β production, but also inhibited collagen secretion by HSC in the presence of TGF- β , clarifying negative modulation of HSC activation as a MoA for anti-fibrotic effect by HM15211**
- **For human efficacy translation, clinical studies in biopsy-proven NASH and fibrosis patients are on-going**