

**HM15211, a novel long-acting GLP-1/GIP/Glucagon triple agonist,
exhibits anti-inflammatory and –fibrotic effects in AMLN/TAA
induced liver inflammation and fibrosis mice**

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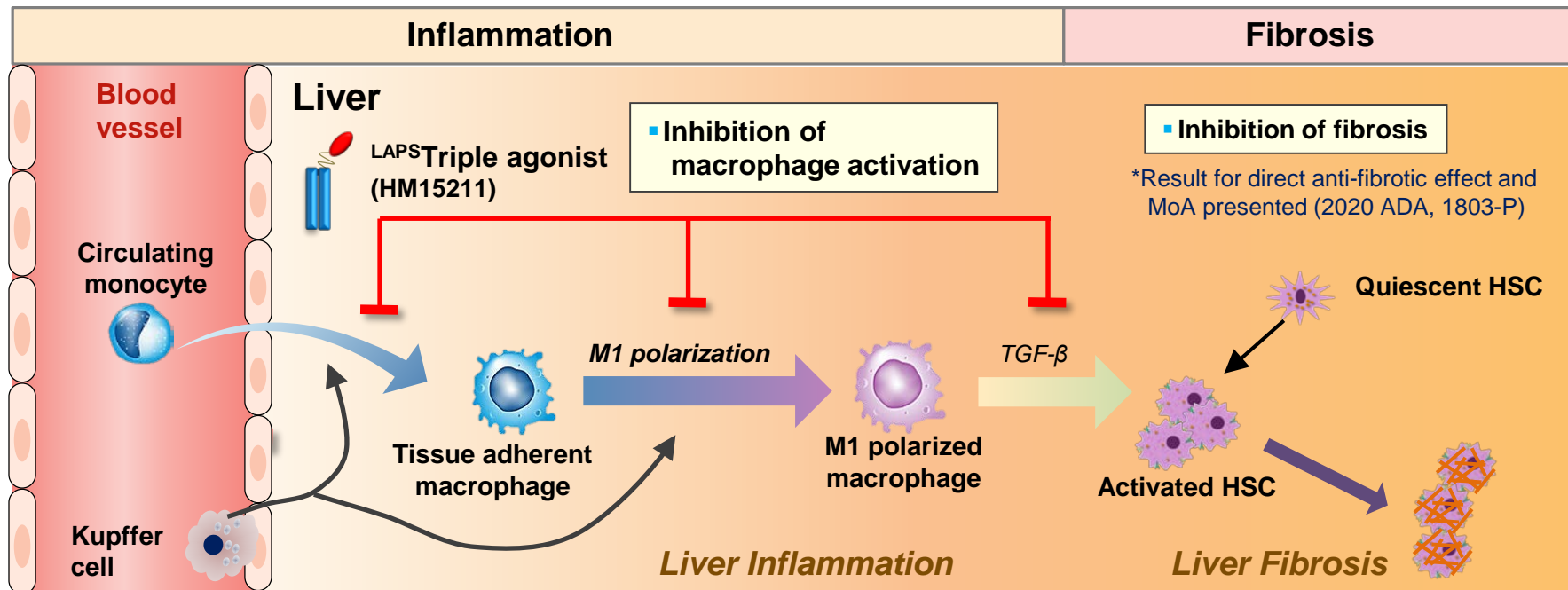
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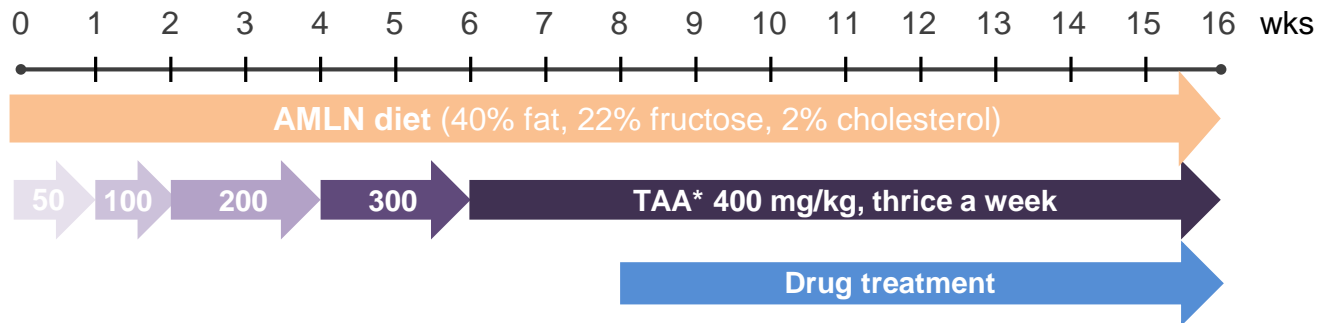
Essential role of macrophage in liver inflammation and fibrosis

Proposed modes of action (MoA) for anti-inflammatory effect of HM15211





**C57BL/6 mice
(n = 5/group)**



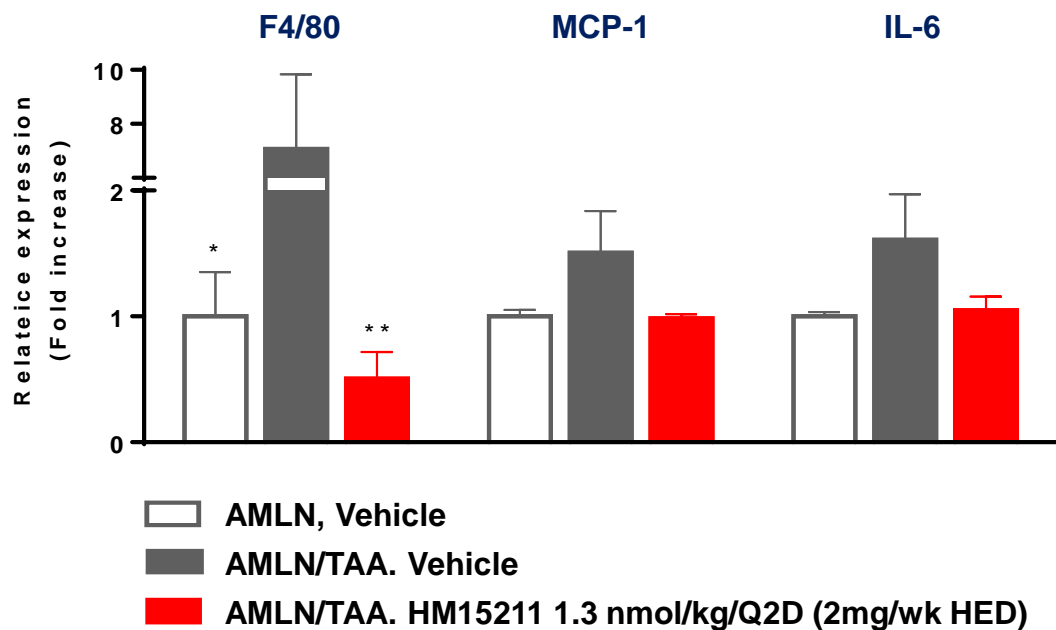
*TAA (Thioacetamide) → Necrotic liver inflammation ↑ → HSC activation → Fibrosis ↑

| 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 liver inflammation

➤ Normalization of hepatic inflammatory marker gene expression and lobular inflammation score by HM15211 treatment in AMLN/TAA mice

(a) Hepatic inflammation gene expression



(b) Lobular inflammation score

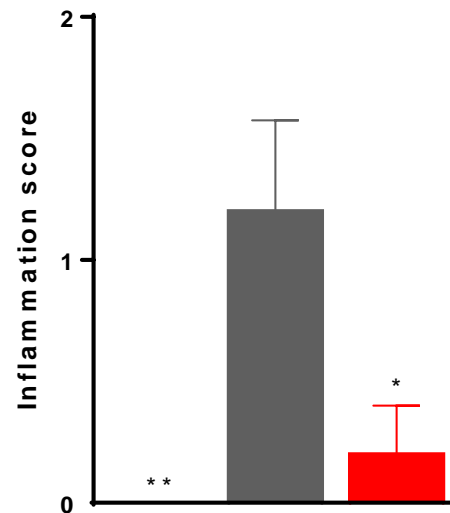


Figure 2. HM15211 effect on cytokine secretion in THP-1 macrophage

- Mechanistically, HM15211 significantly inhibited LPS-induced pro-inflammatory cytokine secretion in THP-1 macrophage, demonstrating direct inhibitory effect of HM15211 on macrophage polarization

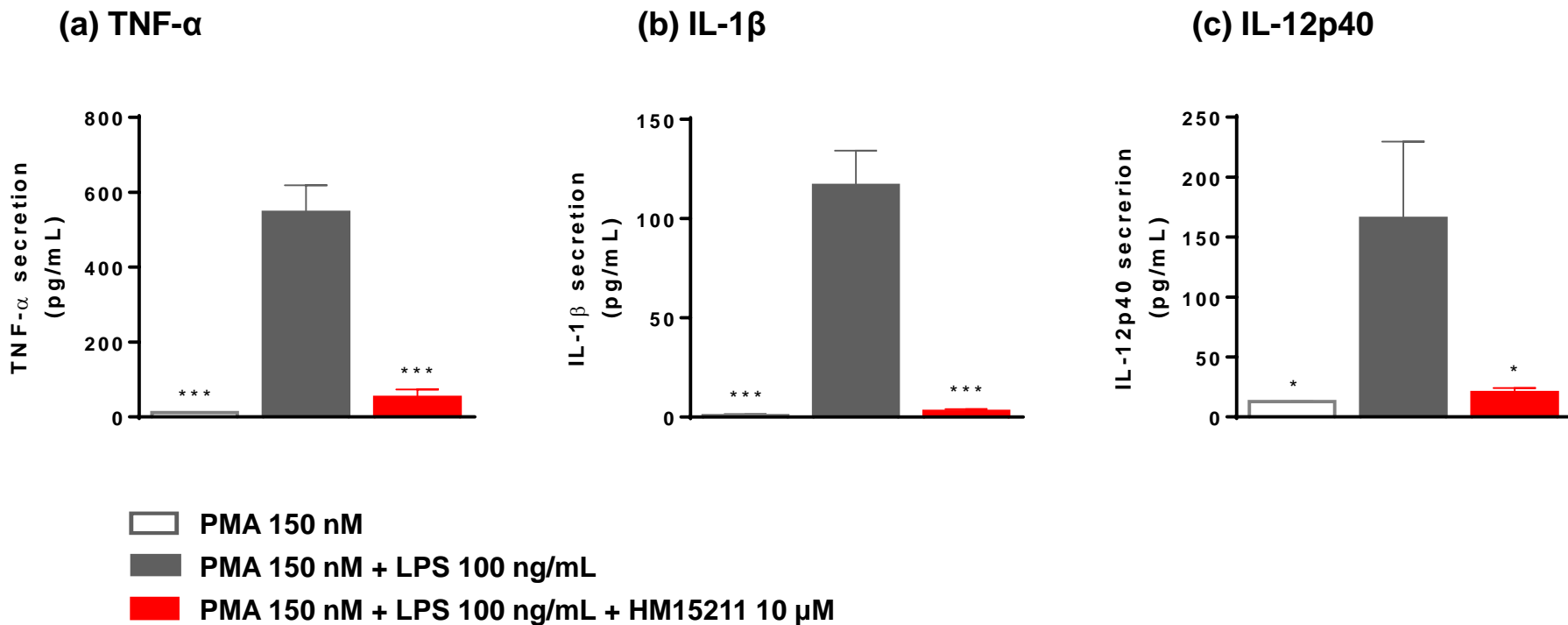
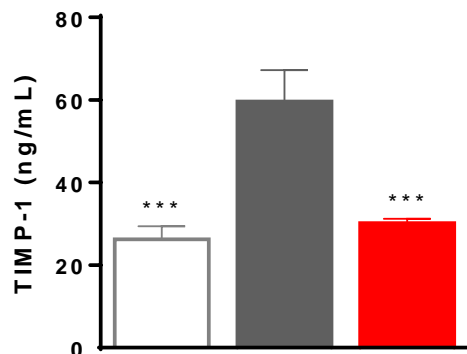


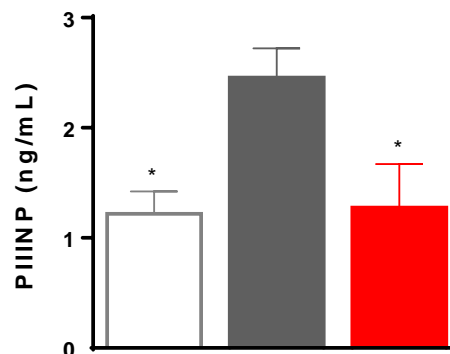
Figure 3. HM15211 effect on blood surrogate marker level

➤ HM15211 treatment significantly reduced blood fibrosis surrogate marker level, suggesting anti-fibrotic potential of HM15211 in addition to anti-inflammatory effect

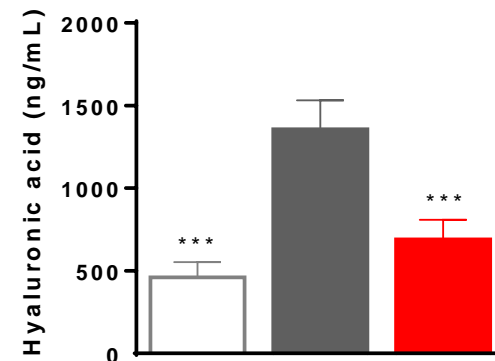
(a) TIMP-1



(b) PIIINP



(c) Hyaluronic acid

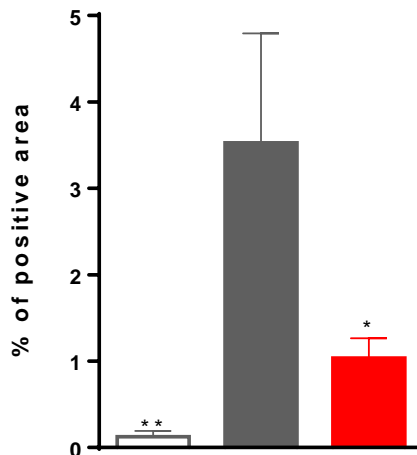
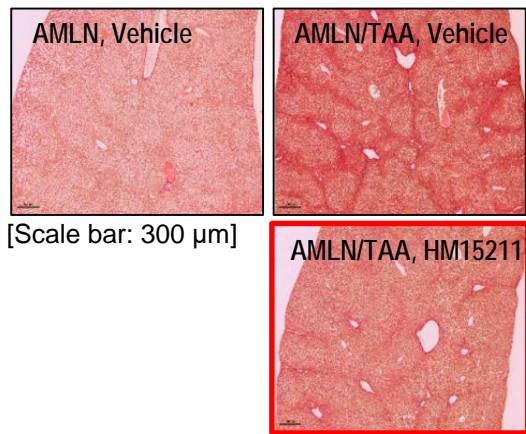


- AMLN, Vehicle
- AMLN/TAA, Vehicle
- AMLN/TAA, HM15211 1.3 nmol/kg/Q2D (2mg/wk HED)

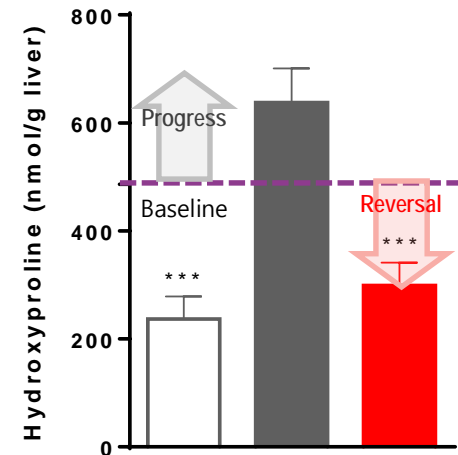
Figure 4. HM15211 effect on liver fibrosis

➤ Consistently, HM15211 treatment not only reduced Sirius red positive area, but also reversed hepatic hydroxyproline contents even below the baseline, demonstrating fibrosis improvement by HM15211

(a) Representative image for Sirius red staining and positive area



(b) Hepatic hydroxyproline



- AMLN, Vehicle
- AMLN/TAA, Vehicle
- AMLN/TAA, HM15211 1.3 nmol/kg/Q2D (2mg/wk HED)

- **HM15211, a novel long-acting GLP-1/GIP/Glucagon triple agonist, is designed to treat NASH and fibrosis by targeting multiple aspect of the disease**
- **In AMLN/TAA mice, HM15211 confers significant improvement in inflammation**
- **Mechanistically, HM15211 inhibits pro-inflammatory cytokine secretion in THP-1 macrophage, clarifying the direct anti-inflammatory effect of HM15211**
- **Hence, HM15211 treatment significantly reverses hepatic collagen deposition in AMLN/TAA mice, demonstrating additional benefits in fibrosis improvement in addition to anti-inflammatory effect**
- **For human efficacy translation, clinical studies in biopsy-proven NASH and fibrosis patients are on-going**