A Novel New Chemical Entity, Gemcabene, Shows Significant Lipid Regulation in PPAR$_\alpha$ Knock-out Mice, Supporting a Mechanism Independent of PPAR$_\alpha$

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Background

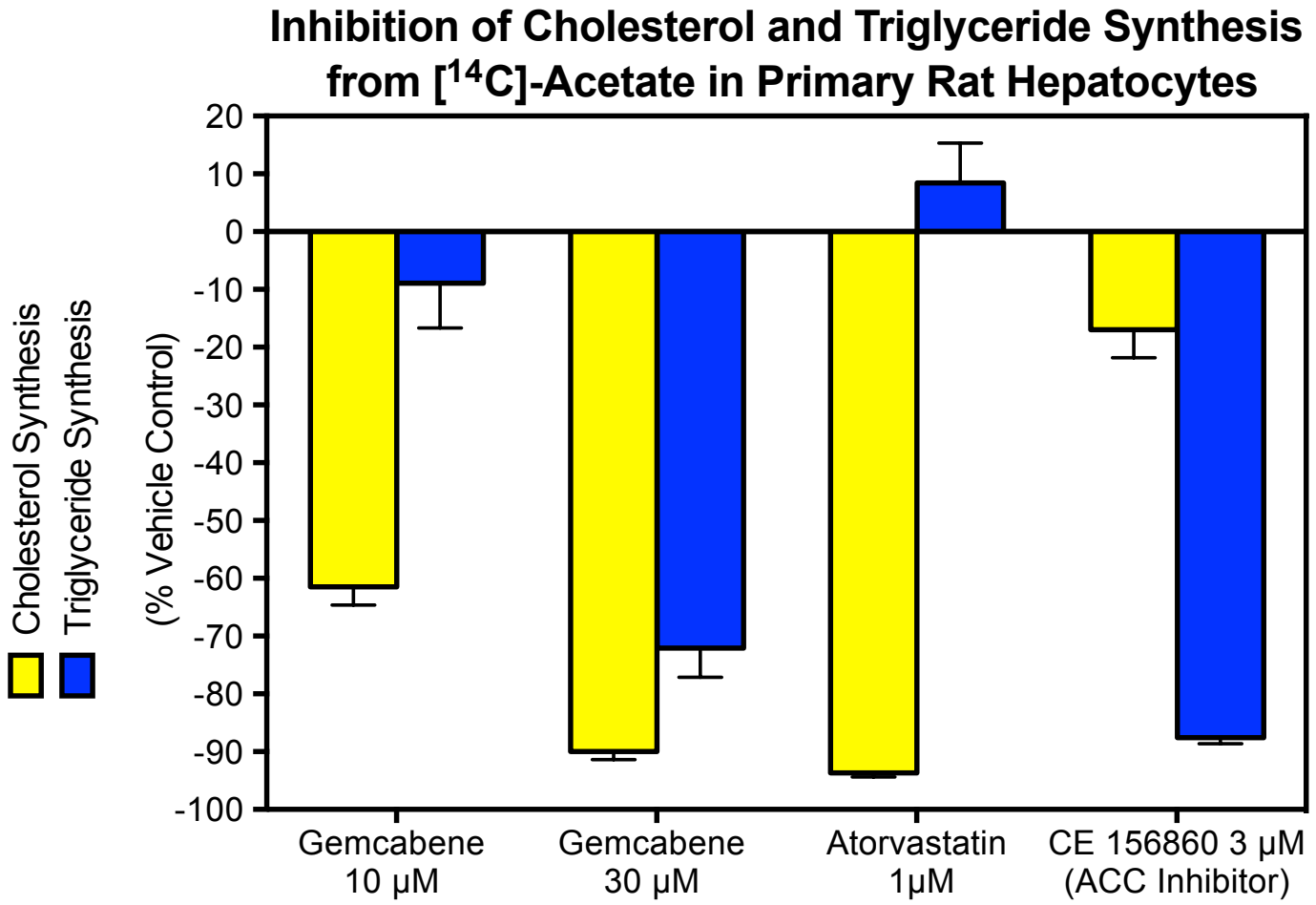
- Gemcabene is an orally administered lipid regulating agent in phase 2 clinical development for dyslipidemia patients
- Early preclinical studies conducted in chow-fed Sprague Dawley rats showed gemcabene markedly reduces hepatic apoC-III mRNA levels and plasma apo C-III, triglycerides, apoB, VLDL-C, LDL-C and caused a marked elevation in HDL-C and apoE levels.
- The agent also showed dose- dependent increases in liver weight and peroxisomal enzyme levels in rodents
- These data suggest that the compound may be a $PPAR_{\alpha}$ agonist
- The current work addresses whether the agent is a direct $PPAR_{\alpha}$ agonist and if lipid regulating effects can be dissociated from its activation of $PPAR_{\alpha}$ receptor responses.

Method of Investigation

We investigated whether gemcabene can:

- Directly inhibit acetate incorporation in to hepatic cholesterol and triglycerides in primary rat hepatocytes
- Is a $PPAR_{\alpha}$, $PPAR_{\delta/\beta}$ or $PPAR_{\gamma}$ agonist or antagonist to the mouse, rat and human PPAR receptors.
- Regulate hepatic apo C-III mRNA and plasma lipids in a $PPAR_{\alpha}$ knock-out mouse.

Gemcabene Inhibits *de novo* Synthesis of Both Cholesterol and Triglycerides



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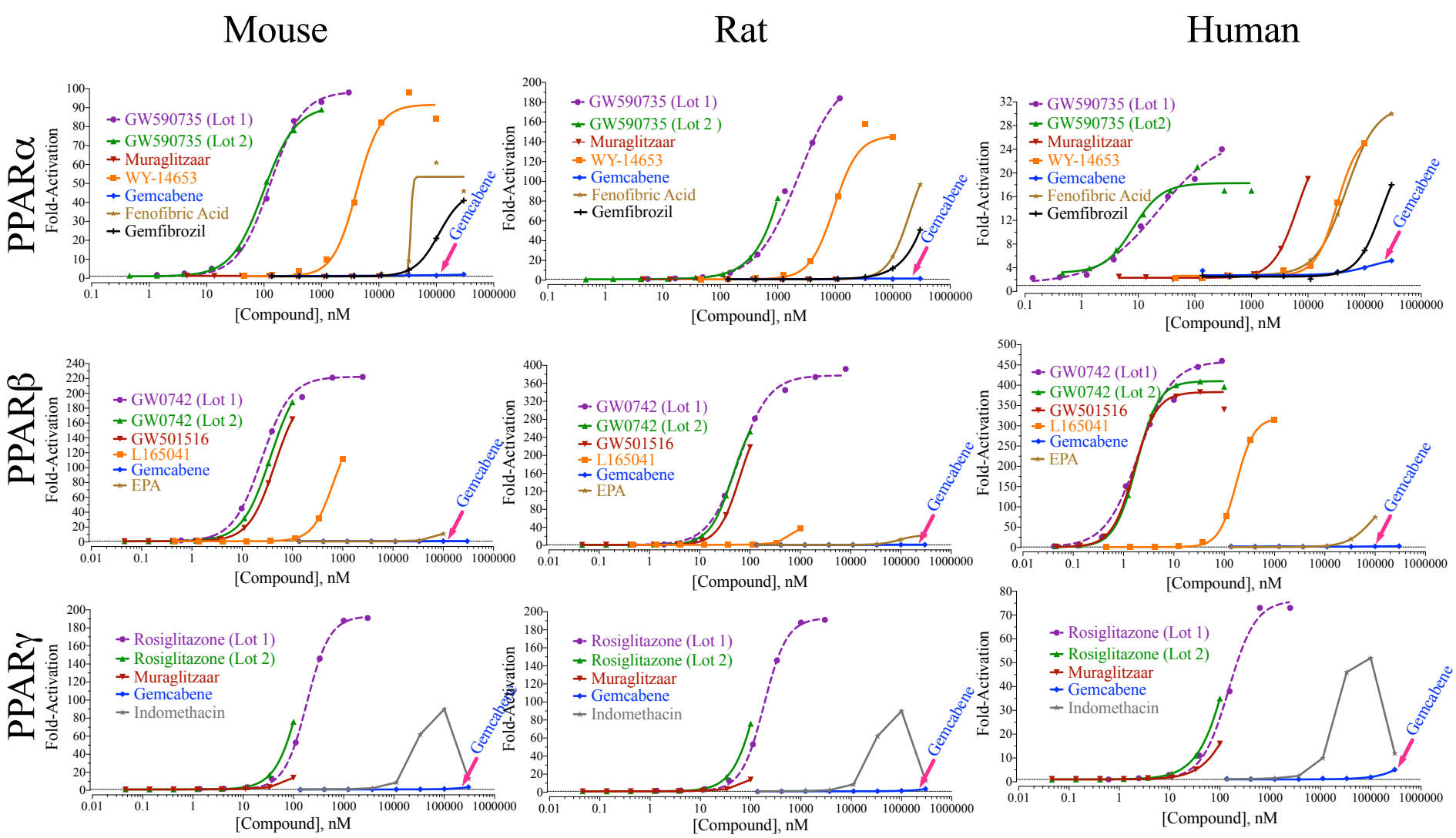
Gemcabene has Little or No Direct PPAR Agonist Activity



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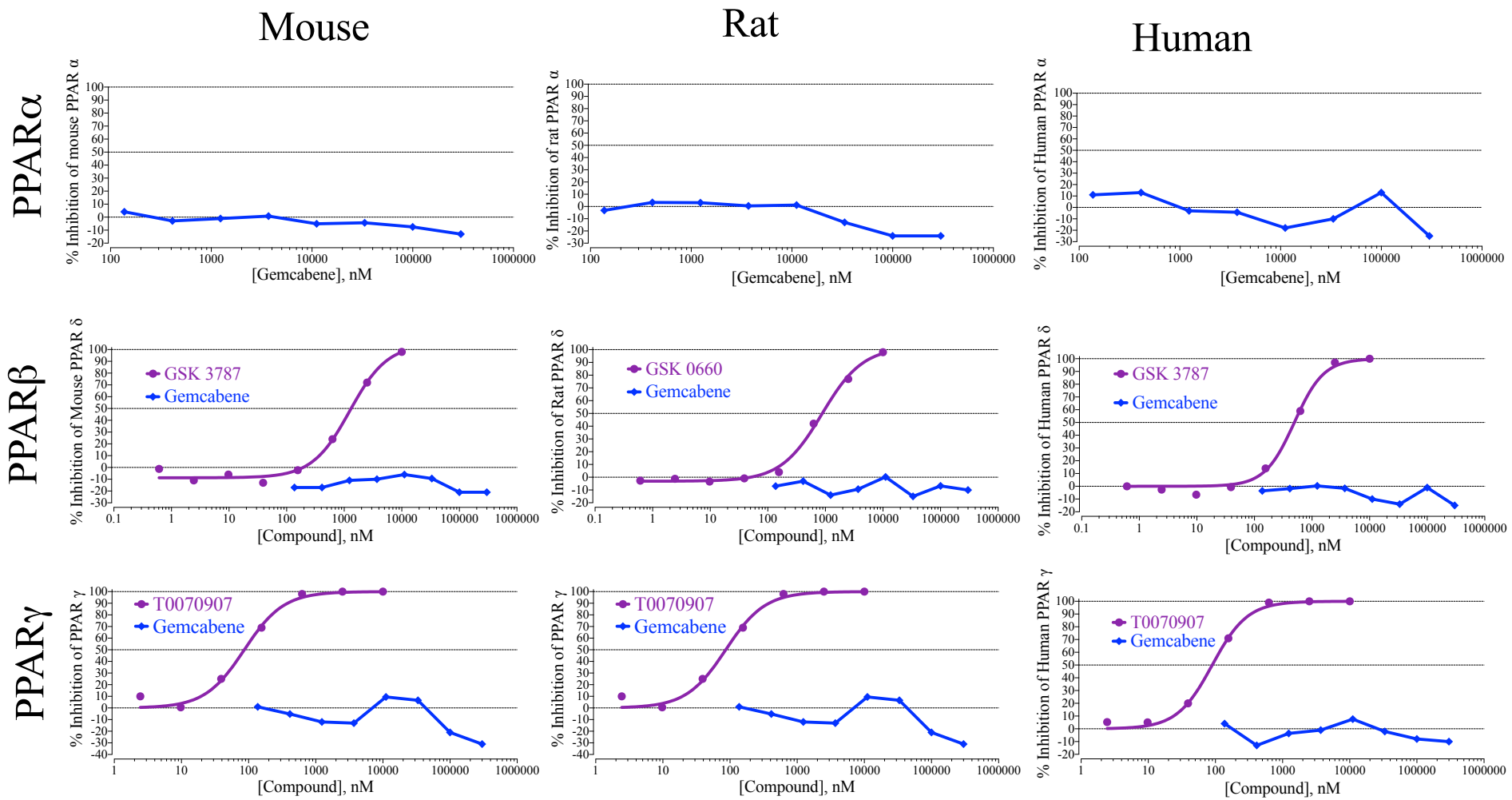
Gemcabene is NOT a PPAR Antagonist



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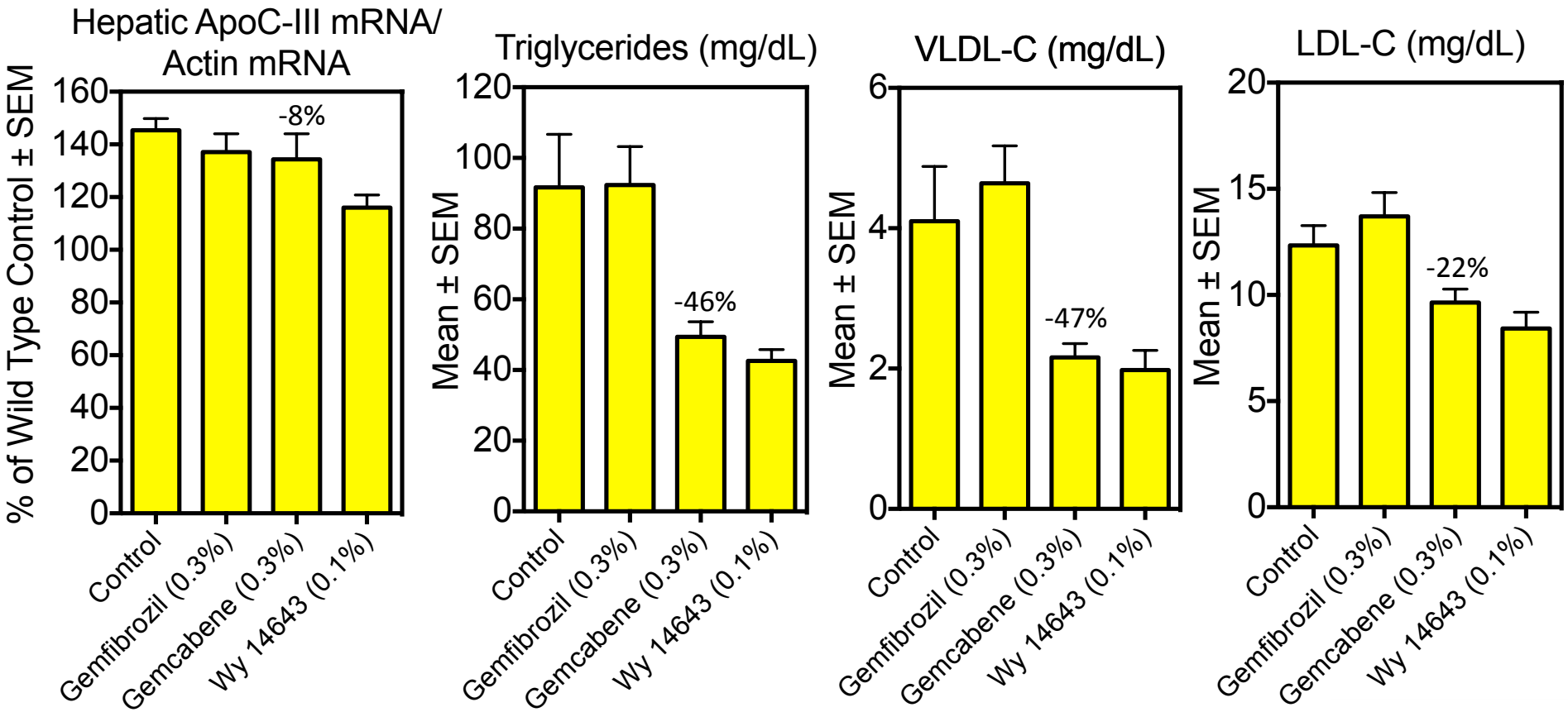
Effect of Gemcabene on Hepatic ApoC-III mRNA Levels and Plasma Lipids in PPAR$_\alpha$ Knock Out Mice



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Results and Conclusions

- Gemcabene is a dual inhibitor of cholesterol and triglyceride synthesis
- Gemcabene shows essentially no direct binding or antagonism to the mouse, rat or human $PPAR_{\alpha}$, $PPAR_{\beta}$ or $PPAR_{\gamma}$ receptors.
- Gemcabene can lower plasma triglycerides, VLDL-C and LDL-C in the $PPAR_{\alpha}$ knockout mouse.

These data suggest gemcabene can lower lipids independent $PPAR_{\alpha}$. Gemcabene effects seen in rodents are likely secondary to direct binding to $PPAR_{\alpha}$. Perhaps gemcabene mobilizes an endogenous ligand that acts on $PPAR_{\alpha}$.