A Novel New Chemical Entity, Gemcabene, Shows Significant Lipid Regulation in PPAR_α Knock-out Mice, Supporting a Mechanism Independent of PPAR_α

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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 \textit{de novo} Synthesis of Both Cholesterol and Triglycerides

Inhibition of Cholesterol and Triglyceride Synthesis from $[^{14}\text{C}]-\text{Acetate in Primary Rat Hepatocytes}$

Gemcabene inhibits \textit{de novo} synthesis of both cholesterol and triglycerides.

- Gemcabene at 10 µM
- Gemcabene at 30 µM
- Atorvastatin at 1 µM
- CE 156860 (3 µM, ACC Inhibitor)
Gemcabene has **Little or No** Direct PPAR Agonist Activity

**Mouse**

- GW590735 (Lot 1)
- GW590735 (Lot 2)
- Muraglitzaar
- WY-14653
- Gemcabene
- Fenofibric Acid
- Gemfibrozil

**Rat**

- GW590735 (Lot 1)
- GW590735 (Lot 2)
- Muraglitzaar
- WY-14653
- Gemcabene
- Fenofibric Acid
- Gemfibrozil

**Human**

- GW590735 (Lot 1)
- GW590735 (Lot 2)
- Muraglitzaar
- WY-14653
- Gemcabene
- Fenofibric Acid
- Gemfibrozil

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**Mouse**

- GW0742 (Lot 1)
- GW0742 (Lot 2)
- GW501516
- L165041
- Gemcabene
- EPA

**Rat**

- GW0742 (Lot 1)
- GW0742 (Lot 2)
- GW501516
- L165041
- Gemcabene
- EPA

**Human**

- GW0742 (Lot 1)
- GW0742 (Lot 2)
- GW501516
- L165041
- Gemcabene
- EPA

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**Mouse**

- Rosiglitazone (Lot 1)
- Rosiglitazone (Lot 2)
- Muraglitzaar
- Gemcabene
- Indomethacin

**Rat**

- Rosiglitazone (Lot 1)
- Rosiglitazone (Lot 2)
- Muraglitzaar
- Gemcabene
- Indomethacin

**Human**

- Rosiglitazone (Lot 1)
- Rosiglitazone (Lot 2)
- Muraglitzaar
- Gemcabene
- Indomethacin
Gemcabene is **NOT** a PPAR Antagonist

**Mouse**

- PPARα
- PPARβ
- PPARγ

**Rat**

- PPARα
- PPARβ
- PPARγ

**Human**

- PPARα
- PPARβ
- PPARγ
Effect of Gemcabene on Hepatic ApoC-III mRNA Levels and Plasma Lipids in PPAR_α Knock Out Mice

- **Hepatic ApoC-III mRNA/Actin mRNA**:
  - Control: 160 ± SEM
  - Gemfibrozil (0.3%): 140 ± SEM, -8%
  - Gemcabene (0.3%): 140 ± SEM
  - Wy 14643 (0.1%): 128 ± SEM, -47%

- **Triglycerides (mg/dL)**:
  - Control: 120 ± SEM
  - Gemfibrozil (0.3%): 100 ± SEM, -46%
  - Gemcabene (0.3%): 100 ± SEM
  - Wy 14643 (0.1%): 84 ± SEM, -47%

- **VLDL-C (mg/dL)**:
  - Control: 6 ± SEM
  - Gemfibrozil (0.3%): 4 ± SEM, -47%
  - Gemcabene (0.3%): 4 ± SEM
  - Wy 14643 (0.1%): 3 ± SEM, -47%

- **LDL-C (mg/dL)**:
  - Control: 15 ± SEM
  - Gemfibrozil (0.3%): 10 ± SEM, -22%
  - Gemcabene (0.3%): 10 ± SEM
  - Wy 14643 (0.1%): 10 ± SEM, -22%
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\textsubscript{α}, PPAR\textsubscript{β} or PPAR\textsubscript{γ} receptors.
- Gemcabene can lower plasma triglycerides, VLDL-C and LDL-C in the PPAR\textsubscript{α} knockout mouse.

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