4. Seladelpar target engagement in other liver cell types has not yet been reported.

mediated reductions in bile acid synthesis.

3. Target engagement by seladelpar has been described in hepatocytes with respect to FGF21

Primary Biliary Cholangitis (PBC) and is currently under review at the FDA and EMA.

1. Ppard is the most widely expressed but least studied of the three PPAR isoforms.

Experimental Design and Methods

Assessment of PPARδ target engagement in mouse liver assessed by single nuclei sequencing following a single oral dose of seladelpar

Edward Cable, Yun-Jung Choi, Xia Wu, Jiangao Song, Jeff Johnson, Charles McWherter

Endothelial Cells

Hallmark Analysis FDR<0.25

Notch signaling

Fatty Acid Metabolism

Peroxisomes

Adipogenesis

Oxidative Phosphorylation

Bile Acid Metabolism

Xenobiotic Metabolism

MTORC1 Signaling

Heme Metabolism

Reactive Oxygen Species Pathway

Estrogen Response Late

Unfolded Protein Response

Coagulation

Cholangiocytes

Hallmark Analysis FDR<0.25

Fatty Acid Metabolism

Peroxisomes

Adipogenesis

Xenobiotic Metabolism

Bile Acid Metabolism

Oxidative Phosphorylation

UV Response Down

Kras signaling Up

Estrogen Response Late

Apical Surface

Coagulation

Unfolded Protein Response

Kupffer Cells

Hallmark Analysis FDR<0.25

Fatty Acid Metabolism

Peroxisomes

Adipogenesis

Oxidative Phosphorylation

Xenobiotic Metabolism

Bile Acid Metabolism

Estrogen Response Late

Interferon Alpha Response

Unfolded Protein Response

Coagulation

Stellate Cells

Hallmark Analysis FDR<0.25

Fatty Acid Metabolism

Peroxisomes

Adipogenesis

Oxidative Phosphorylation

Bile Acid Metabolism

Estrogen Response Late

Xenobiotic Metabolism

Epithelial Mesenchymal Transition

Unfolded Protein Response

Kras signaling Down

Unfolded Protein Response

Coagulation

Summary

1. Seladelpar demonstrates Pparδ target engagement in all five liver cell types identified in the study.

2. PSK4 and Arg1, known Pparδ targets, were induced in all liver cell types, but outside the top 20 modulated genes

3. Major metabolic pathways induced by seladelpar include Fatty Acid Metabolism, Peroxisomes, and Adipogenesis.

4. The Unfolded Protein Response is downregulated in all cells, except Hepatocytes

5. The number of inducible or repressed genes varies greatly

6. How these gene changes translate into pharmacodynamic effects requires further study

7. The study only used male mice, whether these changes will occur in female mice, or whether the same changes will occur in disease models requires further study

8. Understanding cell-type specific effects of seladelpar in the liver will be important when integrating mechanisms of action and clinically relevant effects in PBC patients