

Itemized Response to Reviewer comments

Reviewer #1:

Specific Comments to Authors: In this minireview, the authors discussed the current drug development pipeline of NASH, target pathways associated with NASH pathogenesis, and evaluated the multimodal combination strategy. Since NASH is a complex disease, the combination strategy might be superior to mono-therapeutic options, and represent new direction for NASH treatment.

No changes required.

Reviewer #2:

Specific Comments to Authors: In this minireview the authors discuss the role of combination therapeutics in treating nonalcoholic steatohepatitis. Overall the review is informative and well-written but would benefit from a number of improvements.

Introduction: - NASH definition, include other important factors such as excluding excessive alcohol consumption >20g/day women or >30g/day men, and excluding other causes of liver disease.

ADDED: "The definition of NAFLD includes the lack of secondary causes of hepatic steatosis such as alcohol consumption, steatogenic medication or hereditary liver disease."

-"Liver specific targets aimed at decreasing histologic inflammation or fibrosis such as farnesoid X receptor (FXR) agonists or peroxisome proliferator-activated receptor (PPAR) agonists." This is not a complete sentence and needs to be rephrased.

EDITED: "Liver specific targets aimed at decreasing histologic inflammation or fibrosis such as farnesoid X receptor (FXR) agonists or peroxisome proliferator-activated receptor (PPAR) agonists are currently being evaluated for the treatment of NASH."

-Where is the figure mentioned in-text, figure 1, table 1 etc.? These are not included in the manuscript.

EDITED: All tables and figures now included within the body of the manuscript.

-"As such, it was no surprise that a previously terminated clinical trial attempted to combine the effects of pioglitazone and roflumilast, a potent anti-inflammatory drug used in chronic pulmonary disease trials. " Please could the authors clarify what they mean by this statement?

EDITED: Statement removed.