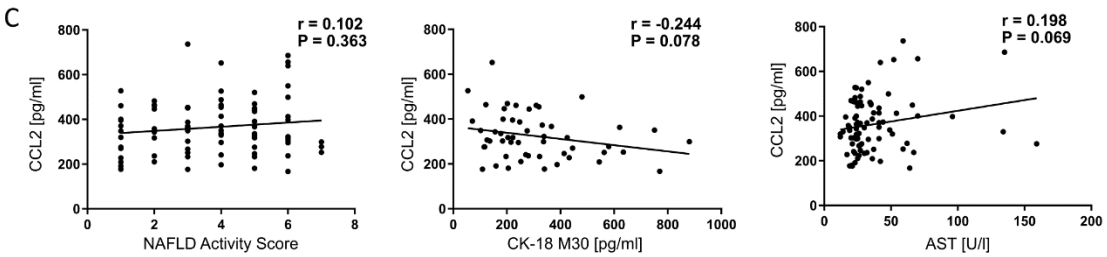
Point-to-point Responses to the Reviewers' Comments

Reviewer 2

To explore the pathogenesis and treatment of NASH are liver diseases research hotspot. NASH are charactered by steatosis and hepatitis, and some cases could develop to fibrosis/cirrhosis and HCC. In this article, CDAHFD was used to set up mice NASH plus fibrosis model. Authors set up the combined therapy with CCR2/CCR5 antagonist (BMS-687681) and FGF21 analogue synergizes PEG-FGF21 variant (BMS-986171) to inhibit inflammatory reaction and reduce lipid deposition in liver. HE, IHC of F4/80 and Sirius Red were used to observe liver pathological changes. FACS was used to check inflammatory cells changes in peripheral blood and liver. Combined therapy ameliorated steatohepatitis and fibrosis, and they are new approaches to treat NASH patients. It is quite an interesting research article and would help us explore the innovative approach to treat the increasing NAFLD and NASH; however, I still have a few concerns regarding the manuscript.

1) For the abbreviated word appearing in the 1st time, the whole name should be shown. For example, the whole name of CDAHFD should be shown in *Abstract* or *Introduction*, not in the legend of Fig 2.
   Response: We thank the reviewer for his/her comment and adjusted the manuscript accordingly.
2) Fig 1 A, human serum CCl2 concentration positively correlated with liver fibrosis level. Whether did liver inflammatory level correlate with serum CCl2?
   Response: We thank the reviewer for his/her expert comment. In this study, we demonstrate that CCL2 serum levels correlate with biopsy proven advanced fibrosis (F3-F4) withstanding multivariate analysis. CCL2 serum levels were also associated with fibrosis based on non-invasive FIB-4 score (not significant for CK-18 M30 levels). On the contrary, there was no significant relationship between CCL2 levels and NASH activity based on NAS (neither for lobular inflammation (p=0.401), nor ballooning (p=0.323). Differently from FGF21 serum levels which correlated with AST and GGT (and non-significantly with CK-18 M30), CCL2 serum concentrations did not correlate with non-invasive biomarkers of steatohepatitis (AST, GGT). We added the analyses to the new

Supplementary Figure 1C and mentioned all results in the revised manuscript (line 123 to 132):



3) In Materials and Methods, *4.5. Flow cytometry of mouse samples*. All used antibodies and their fluorescence color have been listed, but please list the positive and negative marker of each cell, such as KC would be $F4/80^{High}Ly6C^{Low}CD45^{+}$…

Response: We thank the reviewer for his/her suggestion and added an overview as new Supplementary Table S5 demonstrating myeloid and lymphoid immune cells mentioned in the manuscript and their individual expression profiles we employed for identification for FACS analysis.