The Effect of Rencofilstat on the Multi-Omics of Biomarker Assessed F2/F3 NASH Subjects

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Background

To date, the pharmacotherapy for Non-alcoholic steatohepatitis (NASH) has proven elusive. This may be due in part to heterogeneity in the disease which may require multiple treatment modalities including polypharmacy. However, drugs with pleotropic effects in NASH potentially offer treatment advantages. Rencofilstat (RCF, CRV431) inhibits multiple isoforms of the peptidyl prolyl isomerases known as cyclophilins (CyP's). Cyclophilins are a ubiquitous family of isomerases which catalyze the isomerization of peptide bonds from trans to cis at proline residues.

Introduction

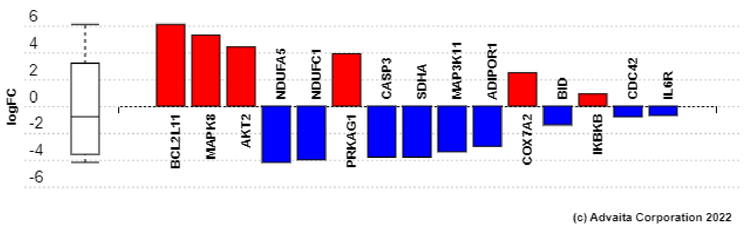
The progression of liver fibrosis in Non-Alcoholic Steatohepatitis (NASH) has been directly linked to increased mortality and morbidity. Rencofilstat (RCF, formerly CRV431), is a non-immunosuppressive cyclophilin (CyP) inhibitor that has demonstrated anti-fibrotic effects in numerous pre-clinical models and in precision cut human liver slices. A multi-omics analysis of transcriptomics and lipidomics was performed to further elucidate the action of RCF in subjects with biomarker defined F2/F3 NASH and explore biomarkers markers for clinical responsivity.

Methods and Materials

RNA sequencing data with serum lipid analysis was obtained from 27 patients on active treatment, with biomarker confirmed F2/F3 NASH participating in a 28-day, Phase 2a trial of RCF (NCT04480710). A total of 43 subjects were administered RCF 75 mg, 225 mg, or placebo orally once daily for 28 days. RNA was stabilized and isolated from whole blood on Day 1 and Day 28. RNA sequencing transcripts were evaluated using FastQC, with quantification in Salmon v1.4.0. Differential expression analysis (DEA) was performed using edgeR and Advaita Bioinformatics iPathway. Serum lipid levels were quantitated by Owl metabolomics. Multi-omic analysis was performed using a projection to latent structures (PLS) method as implemented in the Bioconductor package, mixOmics. Lipid/transcriptomics were evaluated in terms of clinical outcome traits measures including ALT, AST, ProC3, C3M, C6M, PLT, and FIB4. Final lipid-gene networks were identified to determine exposure to RCF and ProC3 reduction. ProC3 response was taken as any reduction in from baseline in ProC3 by at least 2 ng/mL. The final gene network was analyzed using weighted key driver analysis as implemented in Bioconductor package, Mergeomics.

Results

Figure 1. Differential Gene Expression



Results

Figure 2. Differential Gene Expression: Effects of RCF on NASH KEGG Pathway

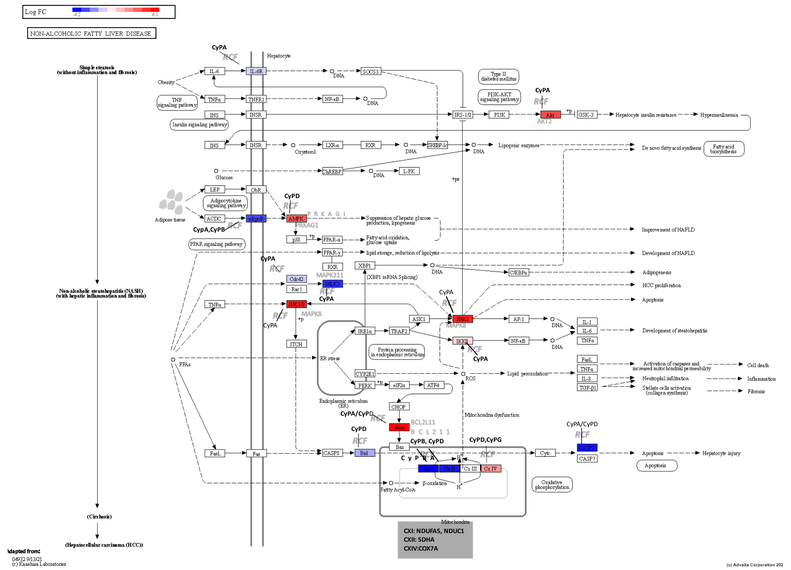


Figure 3: ProC3 Responder Multi-omics Clinical Traits-Transcriptomics-Lipidomics Component 1

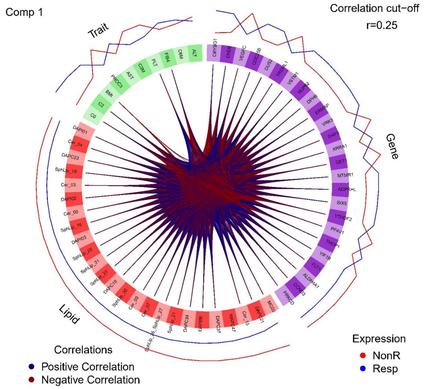
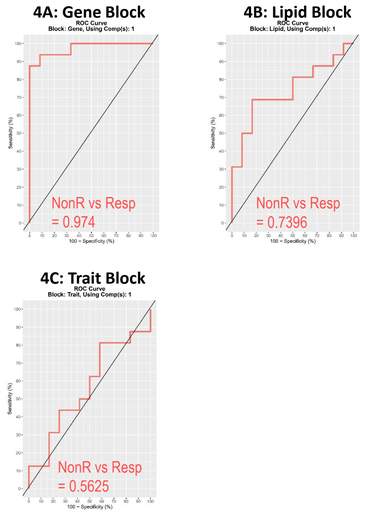
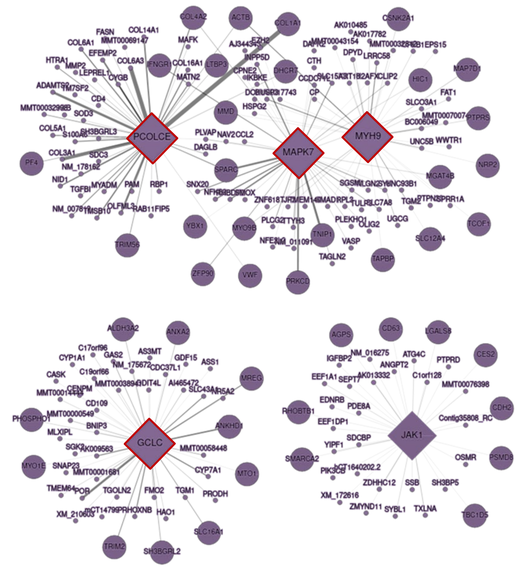


Figure 4: Area-Under-Receiver Operating Curve ProC3 Responder Comp 1



Results

Figure 5: Weighted Key Driver Analysis: Gene Block C1,2,3



Discussion

- CyPA has been shown to be involved in the regulation of JNK/p38-MAPK signaling which is integral to the pathophysiology of NASH.[1]
- RCF treatment in NASH subjects demonstrates anti-inflammatory effects via CyPA and PPAR pathway modulating effects via CyPB and CyPD in the NASH KEGG pathway.
- Downregulation of adipoR1 appears to be offset by upregulation of PRKAG1 (AMPK).
- Multi-Omic analysis demonstrates the greatest accuracy in predicting ProC3 responder status using transcriptomics (Gene Block AUROC=0.9740).
- Clinical traits were not effective in predicting ProC3 response (Trait Block AUROC = 0.5625), while lipids demonstrate a potential biomarker panel (Lipid Block AUROC = 0.7396).
- The top key driver, Procollagen C-endopeptidase Enhancer (PCOLCE) is the gene name for the protein Procollagen C-Proteinase Enhancer 1 (PCPE1) which has been identified as a potential biomarker and/or therapeutic target for fibrosis and liver fibrosis.[2,3]
- MAPK7 is part of the MAPK signaling pathway and has been shown to be modulated by CyPA and CyPD and is involved in NASH pathophysiology.
- JAK1 has been shown to possess both anti-inflammatory and antifibrotic effects in lung liver and lung disease.[4,5]

Conclusions

RCF-treated NASH patients demonstrate anti-fibrotic transcriptomic changes at multiple known sites in the NASH KEGG and other fibrotic pathways . Further research is required to evaluate the full potential of this cyclophilin inhibitor in NASH and other fibrotic diseases.

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References

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