Rencofilstat, a pan-cyclophilin inhibitor, exerts diverse metabolic and transcriptional anti-tumor activities in a murine NASH-HCC model

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INTRODUCTION

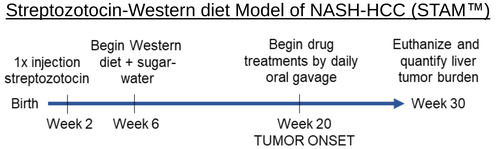
Cyclophilins are protein folding and regulatory enzymes that have been shown in preclinical studies to contribute to progression of several types of cancer, including hepatocellular carcinoma (HCC). They are elevated in most types of cancer, and overexpression is prognostic of shorter survival. Therefore, cyclophilin inhibition is proposed to have anti-cancer activities. Rencofilstat (CRV431) is a second-generation, clinical phase cyclophilin inhibitor being investigated in NASH and HCC.

AIM

To investigate the cyclophilin inhibitor, rencofilstat (CRV431) in a murine NASH-HCC model and conduct multi-omic analyses to identify mechanistic pathways through which rencofilstat affected HCC.

METHODS

Streptozotocin-Western diet Model of NASH-HCC (STAM™)



Drug Treatments

Daily oral gavage of Vehicle or 3 different cyclophilin inhibitors from Weeks 20-30 of age

- Rencofilstat – clinical phase nonimmunosuppressive cyclosporin
- Debio-025 – 1st generation nonimmunosuppressive cyclosporin
- NV556 – nonclinical sangamide

Multi-Omics Analyses of Tumor and NASH Liver Tissue

- Whole exome sequencing: 36 samples
- RNA sequencing: 47 samples
- Untargeted metabolomics: 36 samples

CONTACT INFORMATION

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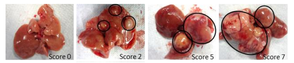
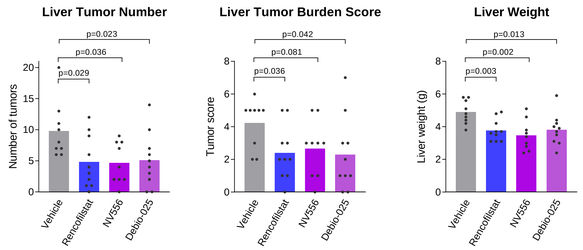
RESULTS

Cyclophilin Inhibitors Decrease Tumor Burden

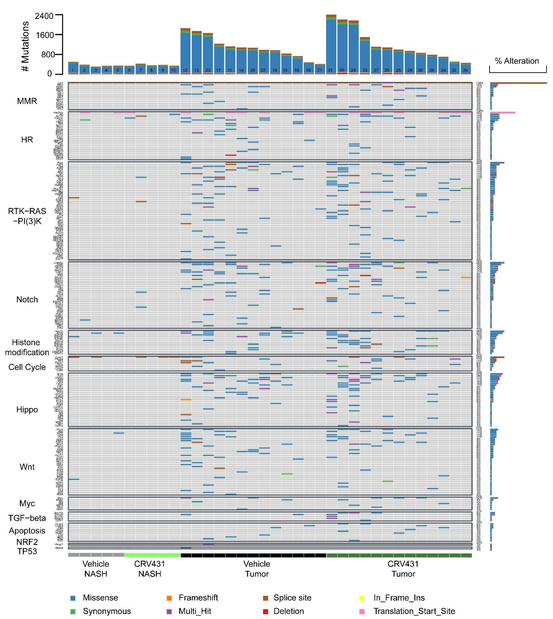


Fewer liver tumors developed in mice treated with cyclophilin inhibitors.



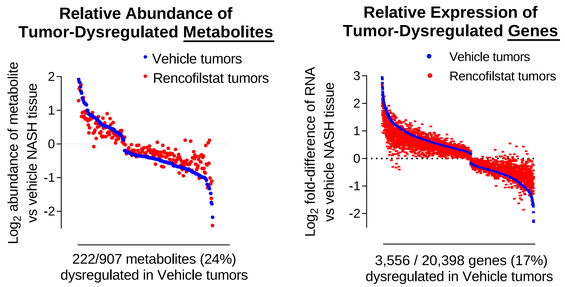
Mutation Analysis of Tumors and NASH Tissue

Tumors from vehicle-treated and rencofilstat-treated mice contained similarly high numbers of nonsynonymous DNA mutations in a diversity of human cancer driver genes. Mean tumor masses of analyzed tumors were 64 mg (Vehicle) and 65 mg (Rencofilstat).



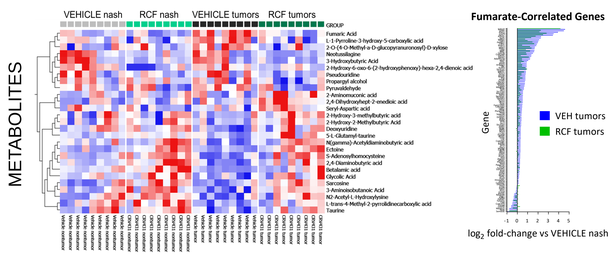
"Normalizing" Effect of Rencofilstat on Metabolomic and Transcriptomic Tumor Signatures

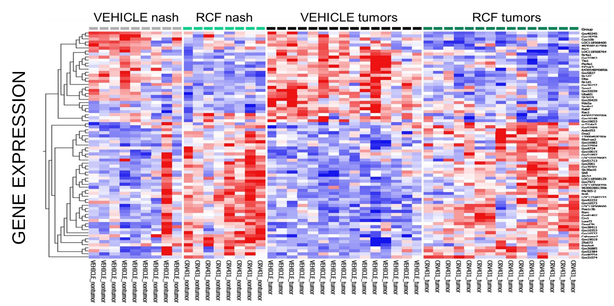
24% of metabolites and 17% of genes were significantly altered in expression in Vehicle tumors compared to Vehicle NASH tissue. Rencofilstat reversed the changes for **47%** of the tumor-signature metabolites and **59%** of the tumor-signature genes (P>0.05 vs Vehicle NASH group).



Hierarchical Clustering of Metabolites and Gene Expression

Hierarchical clustering identified metabolites and genes significantly altered by rencofilstat in tumor and NASH tissue, including the oncometabolite, **fumarate**, and many fumarate-correlated cancer-driving genes.

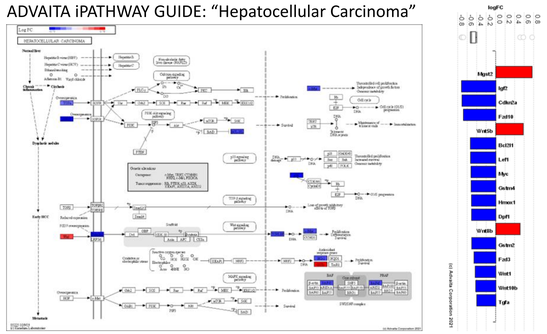




Transcriptomic Pathway Analysis

Rencofilstat effects on gene expression associated significantly with attenuated oncogenic signaling, as in "**Hepatocellular Carcinoma**".

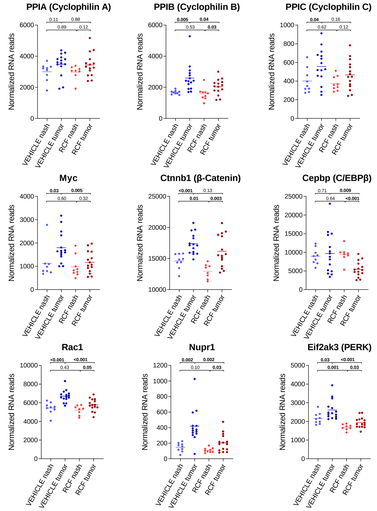
ADVAITA iPATHWAY GUIDE: "Hepatocellular Carcinoma"



Key Changes in Gene Expression

Increased expression of cyclophilins B and C in tumors.

Rencofilstat-induced decrease in cancer-driver and stress-response gene expression in tumors and NASH tissue.



CONCLUSIONS

Rencofilstat decreased liver tumor burden in a chemical/Western diet model of HCC.

The tumor-reducing effect of rencofilstat was associated with attenuation of oncogenic pathways found in human HCC, and with significant normalization of the tumor gene expression signature.