Superior Antifibrotic Efficacy of CRV431 in Human Precision Cut Liver Slices

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BACKGROUND

CYCLOPHILINS: multi-isoform family of enzymes that regulate proline peptide bond isomeric structure and in turn regulate protein conformation, activity, trafficking, and molecular interactions

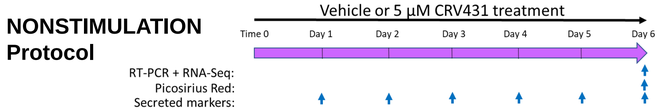
CRV431: a non-immunosuppressive analog of cyclosporine A with high potency, pan-cyclophilin inhibition. Currently in the AMBTION, Phase 2a NASH clinical trial.

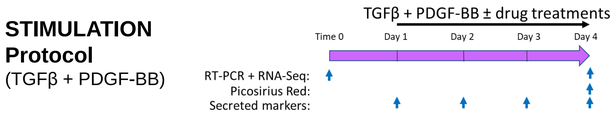
AIMS

Investigate the effects of CRV431 on human precision cut liver slices in comparison to other NASH drug candidates.

METHODS

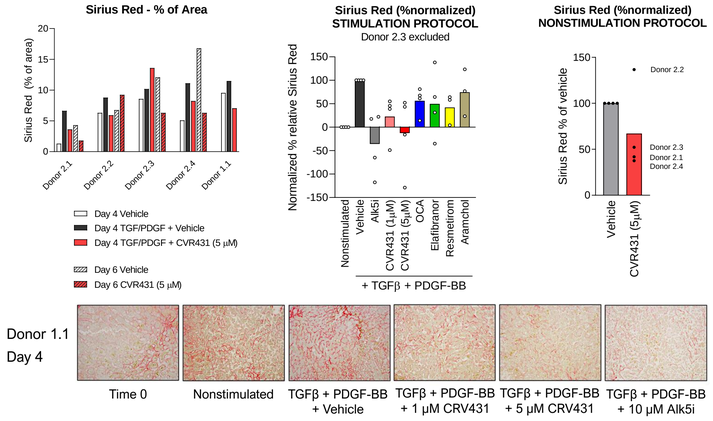
- Precision cut liver slices obtained from non-cancerous margins of tumor resections from five human donors (FibroFind Ltd)
- Nonstimulated and Stimulated (TGFβ + PDGF-BB) protocols
- CRV431 (1 and 5 µM) compared to 5 µM obeticholic acid, elafibranor, resmetirom, Aramchol or 10 µM Alk5i (positive control inhibitor of TGFβ receptor-1).



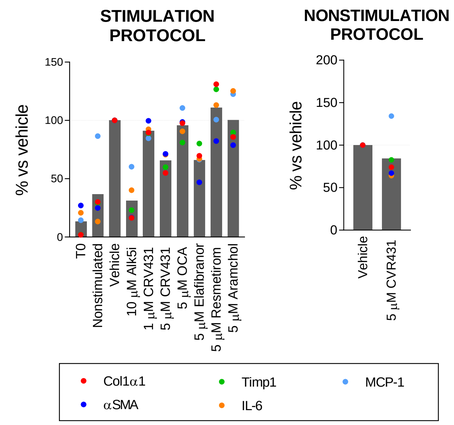


RESULTS

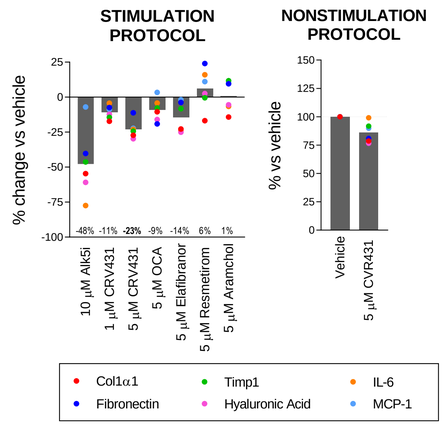
Sirius Red (Fibrosis)



Gene Expression – Inflammatory and Fibrotic Markers

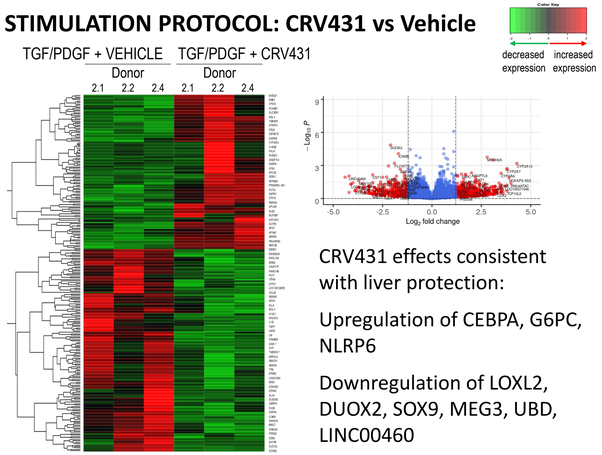


Secreted Markers of Inflammation and Fibrosis (daily average % change)



RNA-Seq / Differentially Expressed Genes

STIMULATION PROTOCOL: CRV431 vs Vehicle

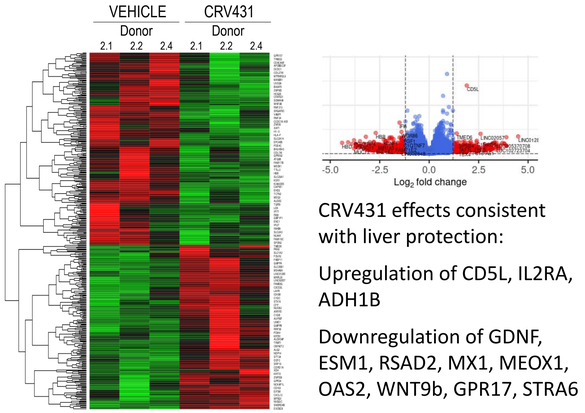


CRV431 effects consistent with liver protection:

Upregulation of CEBPA, G6PC, NLRP6

Downregulation of LOXL2, DUOX2, SOX9, MEG3, UBD, LINC00460

NONSTIMULATION PROTOCOL: CRV431 vs Vehicle



CRV431 effects consistent with liver protection:

Upregulation of CD5L, IL2RA, ADH1B

Downregulation of GDNF, ESM1, RSAD2, MX1, MEOX1, OAS2, WNT9b, GPR17, STRA6

CONCLUSIONS

- CRV431 decreased tissue fibrosis, gene expression, and secretion of inflammatory and fibrotic markers to a greater extent than equimolar concentrations of obeticholic acid, elafibranor, resmetirom, and Aramchol.
- Whole genome analysis demonstrated significant diversity among donors in transcriptional responses to TGFβ + PDGF-BB and CRV431.
- CRV431 induced many statistically significant changes in gene expression that are reported to associate with decreased fibrosis, HCC, and other liver-protective activities.