HEPION PHARMACEUTICALS

4th Annual NASH Summit 2020 DIGITAL

Pleiotropic Actions of the Cyclophilin Inhibitor, CRV431, in Preclinical Models

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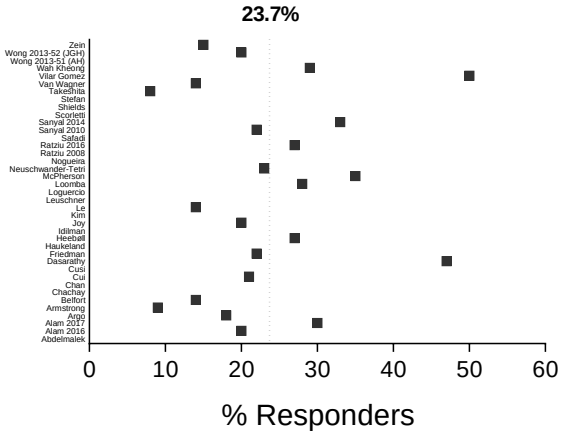
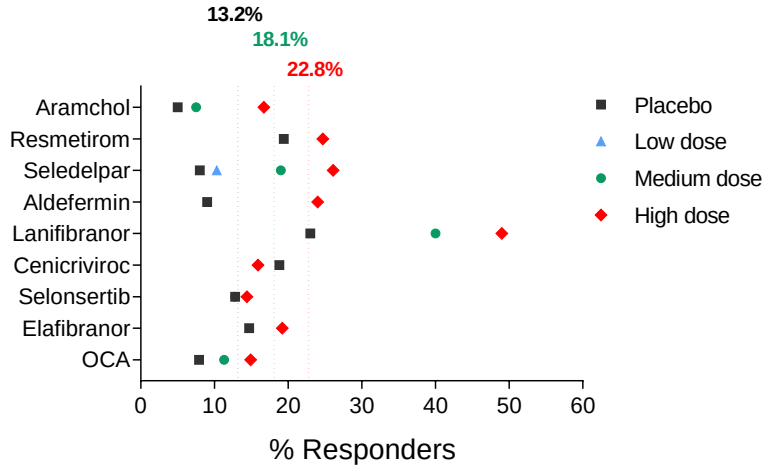
NASH Clinical Trial Outcomes

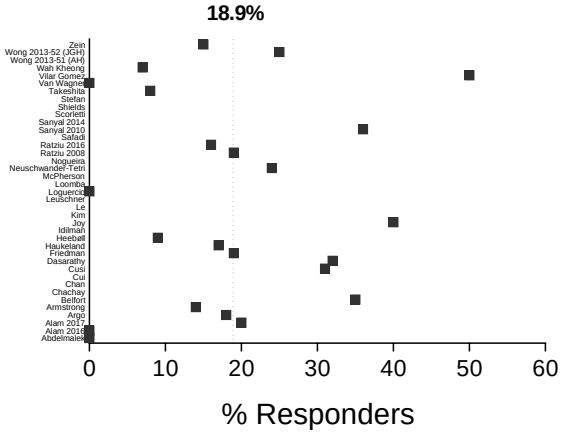
Han et al (2019) Placebo Responders
≥2-point Improvement in NAS Score



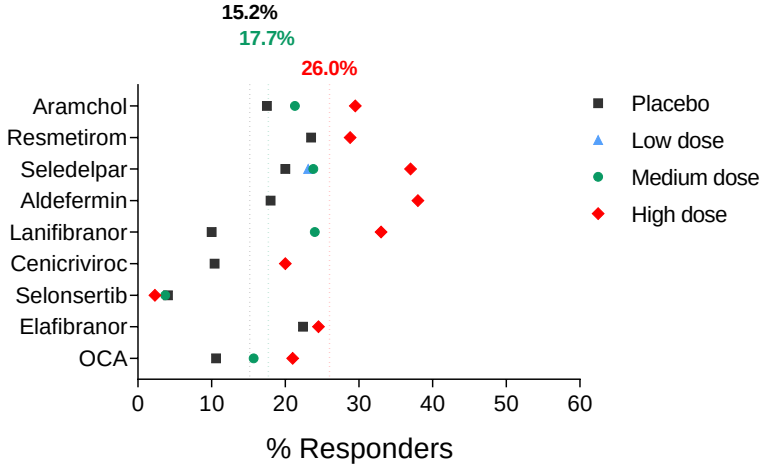
NASH Resolution and No Worse Fibrosis



Han et al (2019) Placebo Responders
Improvement in Fibrosis



Fibrosis Improvement and No Worse NASH



What can we learn from placebo and treatment responses in NASH trials?

High placebo responses:

- malleable, regenerative liver?
  (but why low treatment responses?)

Low treatment responses:

- wrong targets?
- too few targets?

THESIS

NASH livers will benefit most by targeting multiple pathophysiologic pathways.

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Cyclophilins

Pleiotropic effects arising from multiple cyclophilin isoforms

- Enzymes that accelerate proline peptide bond *cis-trans* isomerization
- *cis-trans* switching = regulation of protein interactions and functions
- 17 human isoforms in all major cellular compartments and tissues
- 30 years of research and 4000+ papers

EXPERT OPINION ON INVESTIGATIONAL DRUGS (2019)

Cyclophilin inhibition as a potential treatment for nonalcoholic steatohepatitis (NASH).

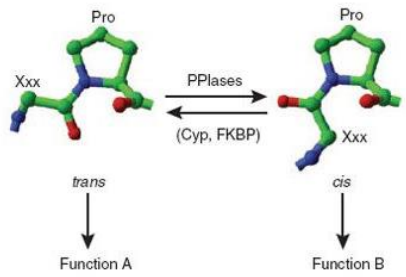
Daren R. Ure, Daniel J. Trepanier, Patrick R. Mayo and Robert T. Foster

CYCLOPHILIN(s) DELETION OR INHIBITION ATTENUATES DISEASE PROCESSES IN MANY EXPERIMENTAL MODELS

metabolism, inflammation, necrosis, fibrosis, carcinogenesis, virulence, etc.

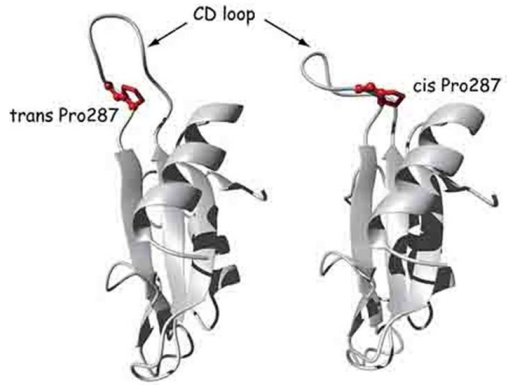
ischemia-reperfusion injuries • myocardial infarction • stroke • chronic asthma • arthritis • atherosclerosis • acute pulmonary embolism • thrombosis • aortic aneurysm • coronary artery disease • pulmonary arterial hypertension • ALS • Alzheimers disease • multiple sclerosis • muscular dystrophies • traumatic CNS injury • tumorigenesis • metastasis • viral hepatitis

Proline Peptide Bond *cis-trans* Isomerization



Lu et al. (2007) Prolyl cis-trans isomerization as a molecular timer. Nature Chem Biol 3 (10): 619-629.

EXAMPLE



Itk kinase SH2 domain: cis-trans conformational changes regulate Itk activity

Andreotti (2003) Native state proline isomerization: an intrinsic molecular switch. Biochemistry 42(32):9515-24.

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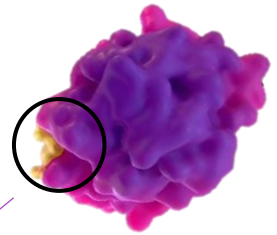
CRV431 Modes of Action

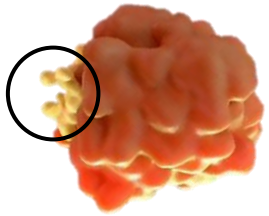
CRV431 blocks cyclophilin participation in several disease processes

CRV431
Pan-Cyclophilin Inhibitor
(Ki ≈ 1 nM)



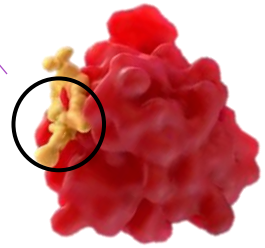
Cyclophilin A
(cytosol and secreted)

Secreted from injured cells and acts as proinflammatory cytokine by binding to CD147



Cyclophilin B
(endoplasmic reticulum)

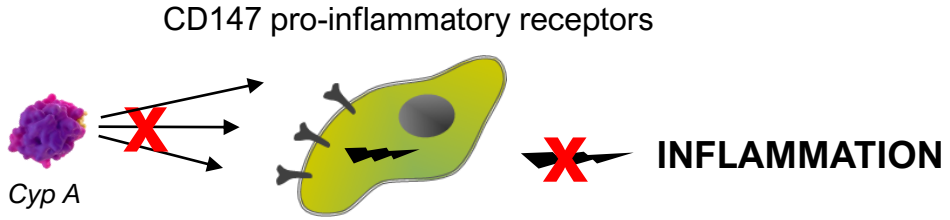
Promotes fibrotic scarring by controlling collagen production

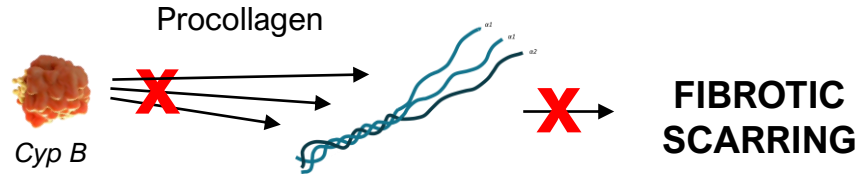


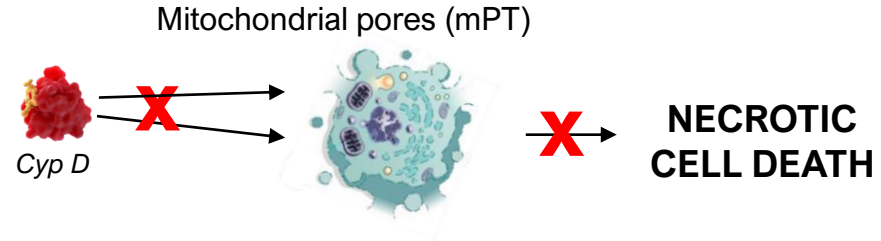
Cyclophilin D
(mitochondria)

Regulates mitochondrial metabolism

Promotes mitochondrial pore opening leading to mitochondrial and necrotic cell death







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MetaCore Biological Systems Database (2.6M+ curated interactions)

CRV431 predicted to inhibit diversity of cyclophilin-protein interactions

Target	Type	Total protein and gene interactions	Protein binding interactions	Transcription regulated by "#" genes/proteins	Regulates expression transcription of "#" genes/proteins
Cyclophilin A	enzyme	280	160	78	4
Cyclophilin B	enzyme	174	116	33	0
Cyclophilin D	enzyme	153	49	34	0
All CYCLOPHILINS	enzyme	**902**	**518**	279	4
CCR2	receptor	**156**	**40**	82	16
CCR5	receptor	**205**	**89**	91	10
FGF21	ligand	**371**	15	79	**164**
FXR	nuclear receptor	**1200**	401	110	**482**
PPAR alpha	nuclear receptor	**609**	58	73	**462**
PPAR beta-delta	nuclear receptor	**299**	29	10	**210**
PPAR gamma	nuclear receptor	**1549**	17	13	**1187**
THR beta	nuclear receptor	**26**	10	6	**6**
THR (alpha+beta)	nuclear receptor	**243**	43	2	**198**

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CRV431 – Pan-Cyclophilin Inhibitor

- Cyclophilin inhibitor (Ki ≈ 1 nM)
- Non-immunosuppressive analog of cyclosporine A
- Oral, once daily
- Concentrates in liver
- Completed Phase 1 (SAD, MAD, DDI)
- Currently in Phase 2a NASH
- No dose-related toxicities observed in preclinical/toxicology or Ph1 clinical

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Anti-Fibrotic and Additional CRV431 Effects in Diverse Preclinical Models

Human Cell Cultures		CRV431 Effects
Hepatic stellate cells, fibroblasts (multiple organs)	TGFβ or endogenous stimulation	▼fibrotic gene expression ▼procollagen and fibronectin secretion
Blood platelets	Collagen and thrombin stimulation	▼procoagulant platelet formation

Human Tissue Explants (Precision Cut Slice Cultures)		CRV431 Effects
Liver explants (4 donors)	TGFβ+PDGF-BB or endogenous stimulation	▼ inflammatory/fibrotic gene expression ▼ inflammatory/fibrotic protein secretion ▼ tissue fibrosis
IPF lung explants (1 donor)	Endogenous stimulation	

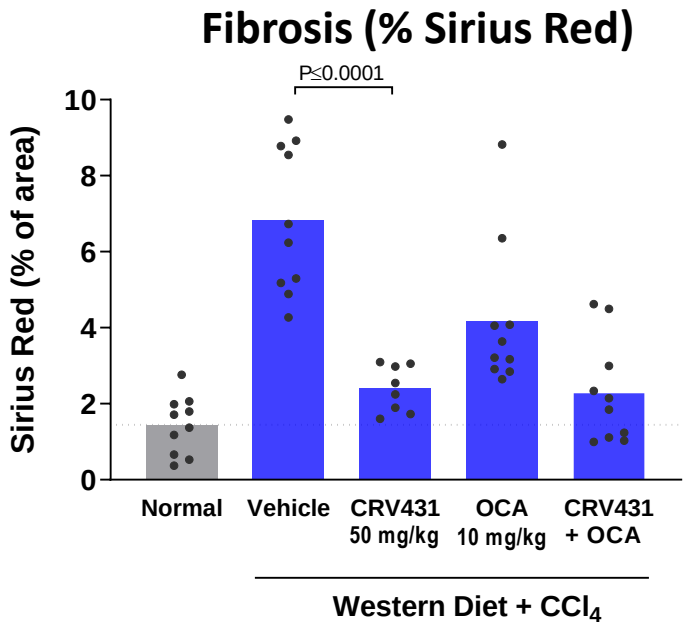
Animal Models		CRV431 Effects
Mice (NASH)	Western diet + carbon tetrachloride	82%▼ fibrosis; ▼weight gain
Mice (NASH)	High fat diet + early STZ (4 studies)	37-57%▼fibrosis; ▼weight gain; 50%▼liver tumors
Mice (liver fibrosis)	Carbon tetrachloride	44%▼ fibrosis
Mice (kidney fibrosis)	Unilateral ureter obstruction	42%▼ fibrosis
Rats (liver fibrosis)	Thioacetamide	48%▼ fibrosis; prevented cirrhosis
Mice (acute lung injury)	Lipopolysaccharide inhalation	▼BAL fluid inflammatory cytokines, neutrophils
Mice (diabetes)	High fat diet + late STZ	▼adiposity; ▼weight gain

Preclinical Models: Diet and Toxin Induced Liver Fibrosis in Rodents

Western Diet + CCl_4 (Mice)

12 weeks diet + CCl_4

6 weeks vehicle, CRV431, or OCA

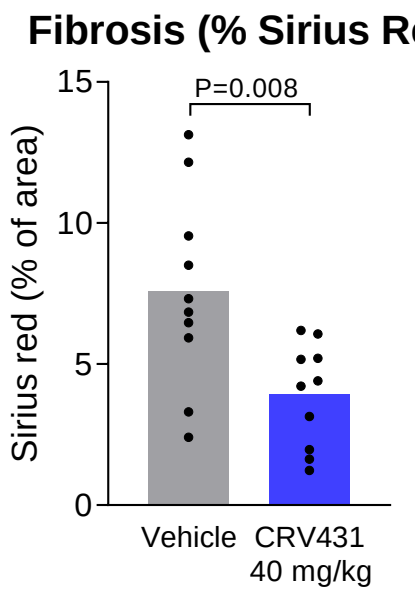


6 weeks treatment:
82% reduction in fibrosis

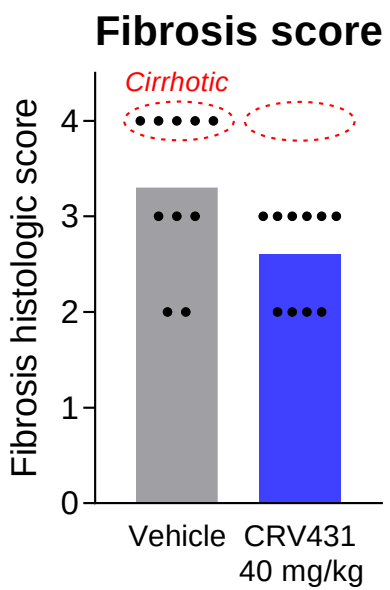
Thioacetamide (Rats)

9 weeks thioacetamide

9 weeks vehicle or CRV431



9 weeks treatment
48% reduction in fibrosis



No cirrhotic livers
in CRV431 treatment group

(Study performed by Physiogenex)

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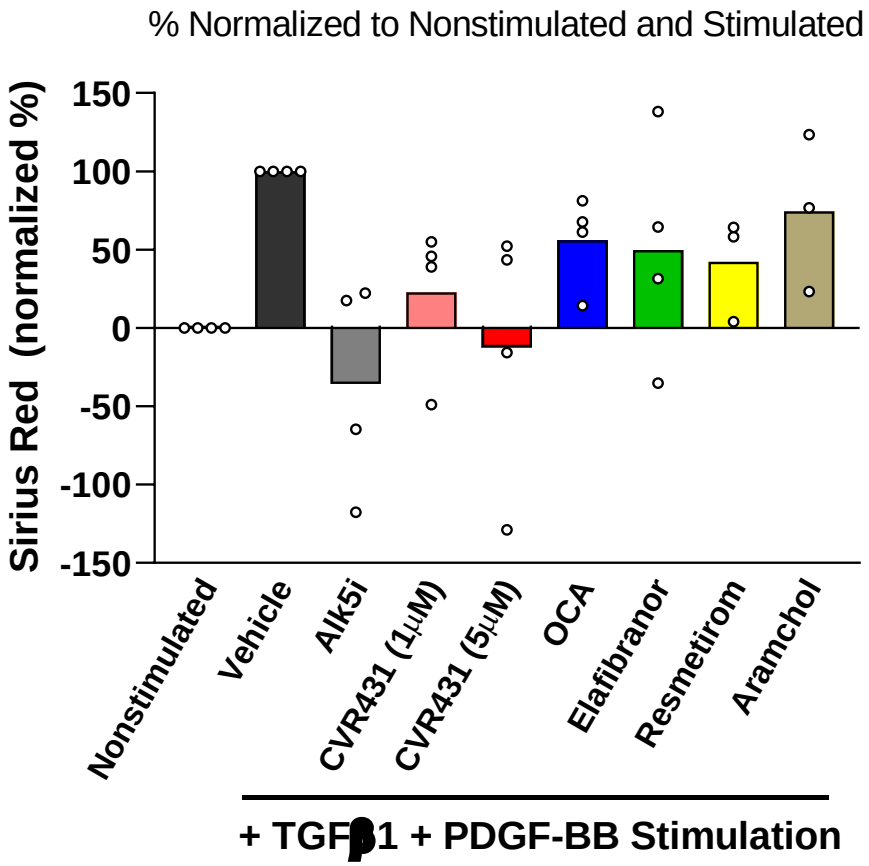
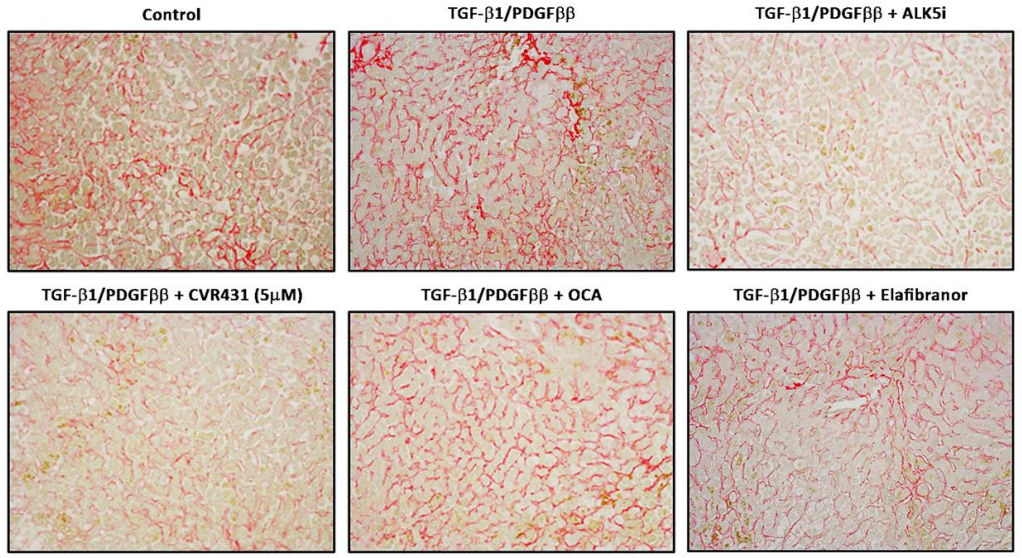
CRV431 on Human Precision Cut Liver Slices (FibroFind, UK)

Fibrosis: Picrosirius Red



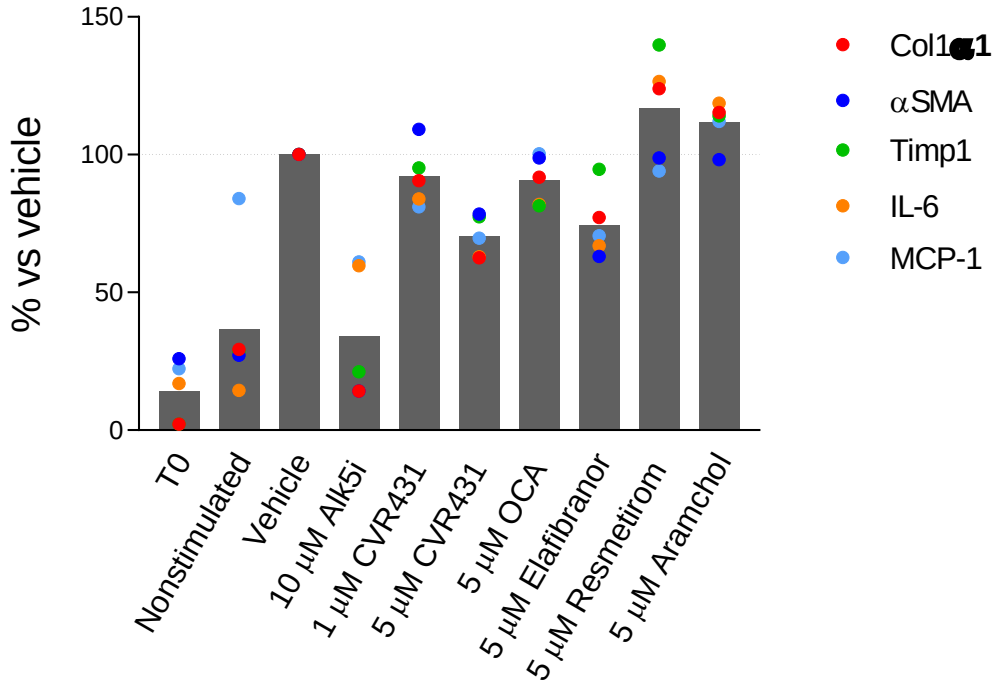
Summary

- Precision cut liver slices from 4 human donors
- Sirius red baseline (1.3 - 9.5%) increased with TGFβ + PDGF-BB stimulation for 3 days to 6.6 - 11.5%
- Alk5i (inhibitor of TGFβ receptor signaling) blocked fibrosis induced by exogenous (TGFβ + PDGF-BB) and endogenous stimulation as suggested by negative, normalized value

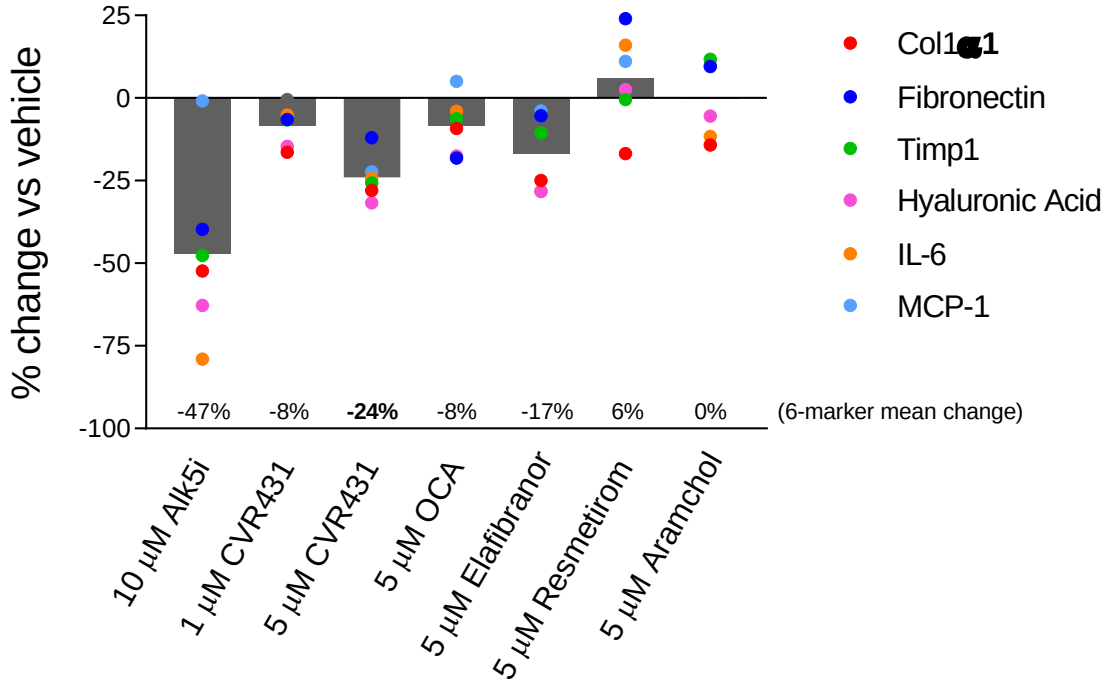


CRV431 on Human Precision Cut Liver Slices (FibroFind, UK)

Gene Expression



Secreted Protein Markers (Daily Average Change)



- Precision cut liver slices obtained from 4 human donors and stimulated with TGFβ + PDGF-BB ± drug treatments
- Alk5i (inhibitor of TGFβ receptor signaling) partly or wholly blocked effects of exogenous TGFβ + PDGF-BB stimulation
- CRV431 (5 µM) was most effective of five NASH drug candidates at equimolar concentrations at reducing gene expression and secretion of fibrotic and inflammatory markers

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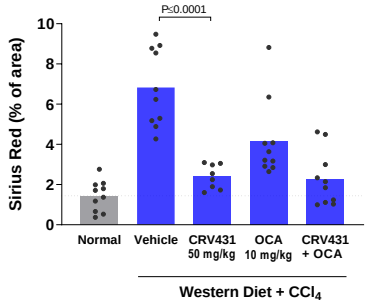
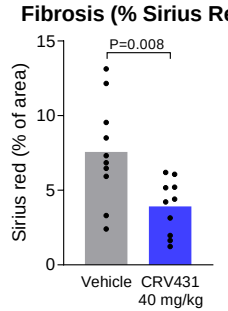
Bioinformatics Analyses - Transcriptomics

Clarivate Metacore and Key Pathway Advisor Platforms

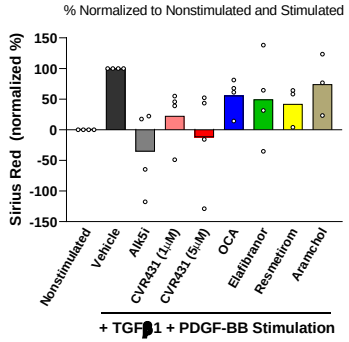
Western Diet/CCl_4 Mice



Thioacetamide Rats



TGFβ + PDGF-BB Human Liver Slices



CRV431 effects on liver <u>transcriptome</u>:

- differentially expressed genes (DEGs) overlap and oppose human NASH DEGs
- hundreds of DEGs map to metabolism, inflammation, extracellular matrix, and other pathways
- causal analyses predict key hub genes such as PPARα, PPARδ, THRβ, and FGF21

(Metacore and Key Pathway Advisor Platforms)

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Processes Regulated by NASH and by CRV431 in Preclinical Models

CRV431 effects on gene expression consistent with human NASH reversal

METABOLISM

Development: Insulin, IGF-1 and TNF-alpha in brown adipocyte differentiation

SCAP/SREBP Transcriptional Control of Cholesterol and FA Biosynthesis

GLP-1 in beta cell apoptosis in type 2 diabetes

Regulation of metabolism: Insulin signaling: generic cascades

Oxidative stress in adipocyte dysfunction in type 2 diabetes and metabolic syndrome X

Transcription: Role of AP-1 in regulation of cellular metabolism

Protein folding and maturation: Posttranslational processing of neuroendocrine peptides

Glutathione metabolism

INFLAMMATION AND EXTRACELLULAR MATRIX (ECM)

Immune response_IL-5 signaling via JAK/STAT

TGF-beta-induced fibroblast/ myofibroblast migration and ECM production

IL-17 and IL-17F-induced inflammatory signaling in normal and asthmatic airway epithelium

TNF-alpha-induced inflammatory signaling in normal and asthmatic airway epithelium

IL-1 beta- and Endothelin-1-induced fibroblast/ myofibroblast migration and ECM production

CANCER

IGF-1 receptor/EGFR cooperation in lung cancer

IGF family, invasion and metastasis in colorectal cancer

SAMPLE OF GENE EXPRESSION CHANGES IN HUMAN NASH and BY CRV431 IN PRECLINICAL MODELS

		NASH	CRV431
Apolipoprotein D	Promotes steatosis	↑	↓
Cadherin 11	Promotes fibrosis	↑	↓
Collagen 4A6	ECM/fibrosis	↑	↓
Glypican	ECM/fibrosis	↑	↓
Laminin	ECM/fibrosis	↑	↓
Nephronectin	ECM/cancer/inflammation	↑	↓
Platelet derived growth factor D	Promotes fibrosis	↑	↓
SOX4 and SOX9	Promotes fibrosis/cancer	↑	↓
Transforming growth factor beta	Promotes fibrosis	↑	↓
Apolipoprotein F	Improves HDL/LDL ratio	↓	↑
Insulin-like growth factor	Regulates metabolism	↓	↑

75% of overlapping CRV431 DEGs reverse NASH DEGs

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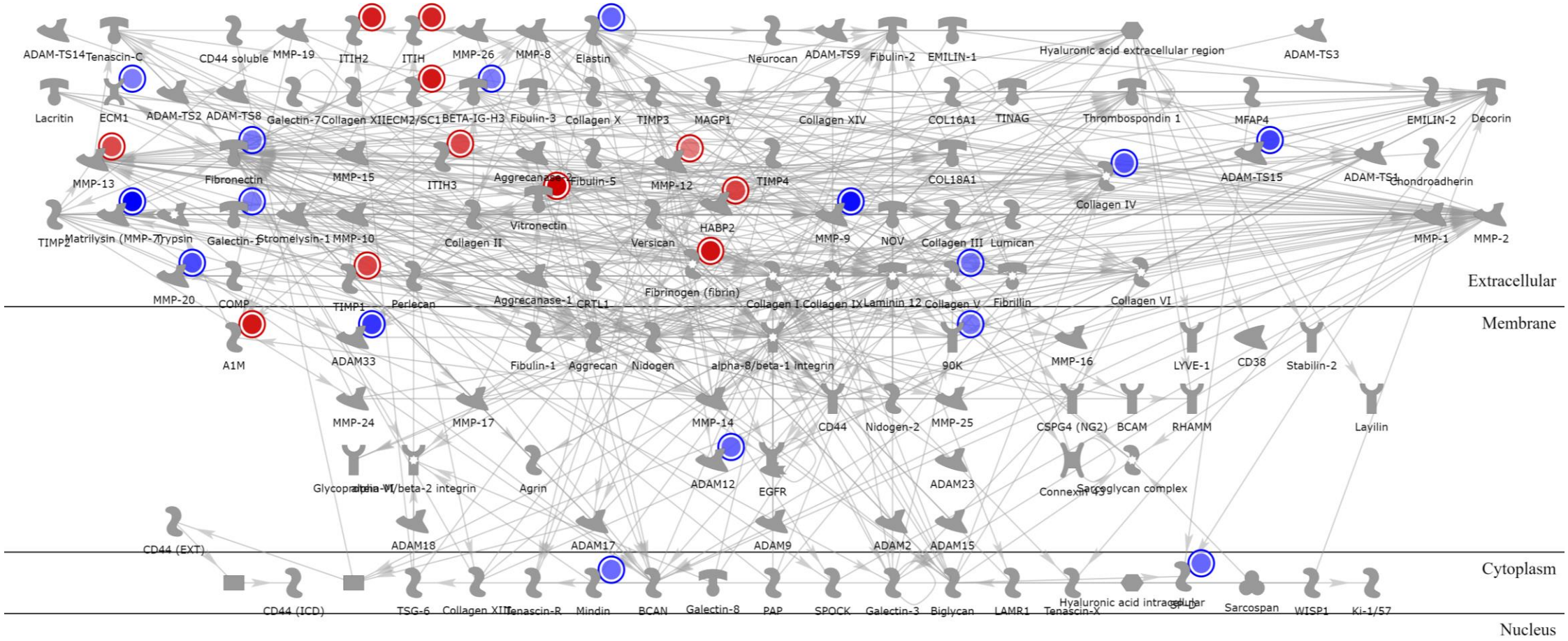
CRV431 Effects on Liver Gene Expression in Preclinical Models

Cell-matrix interactions

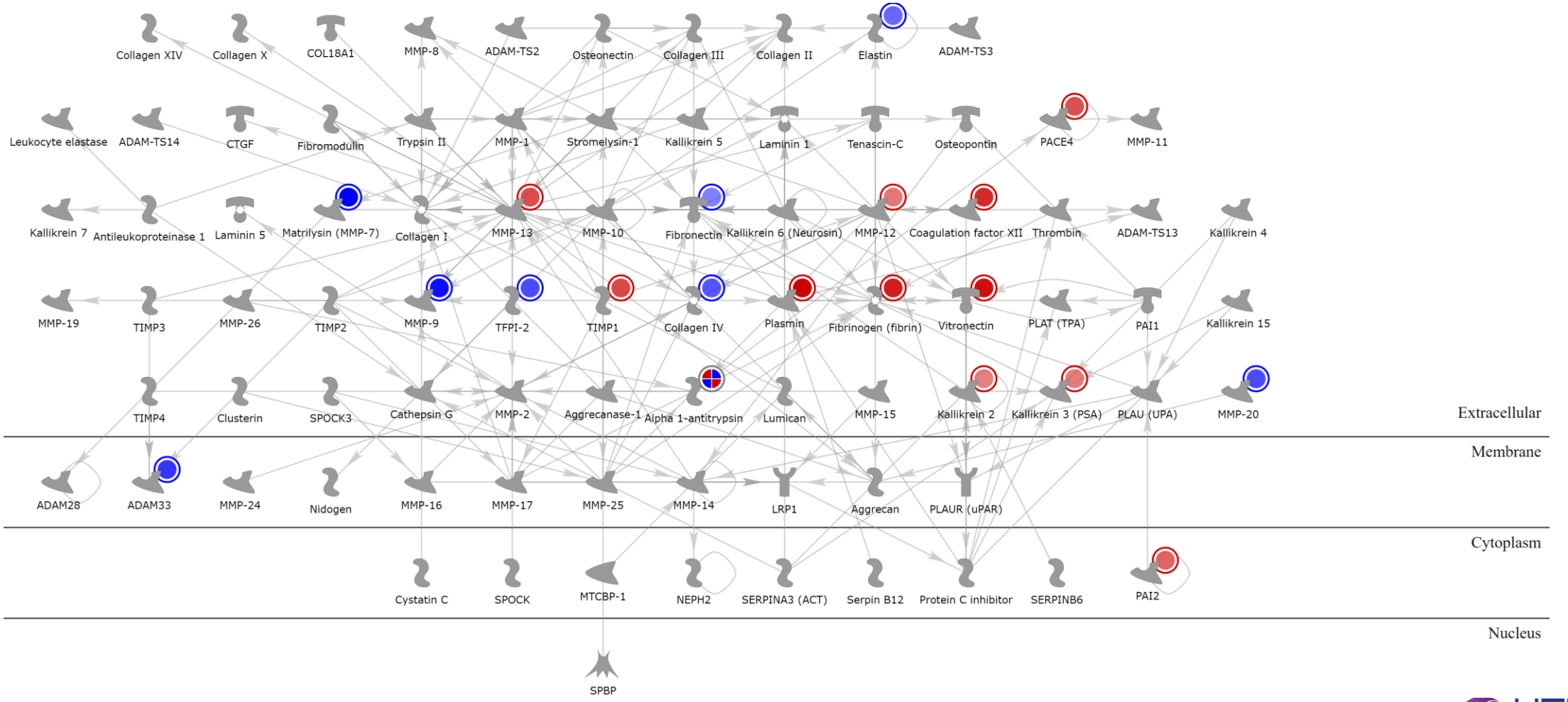
Gene downregulation Gene upregulation



CRV431 Effects on Liver Gene Expression in Preclinical Models

ECM remodeling

Gene downregulation Gene upregulation



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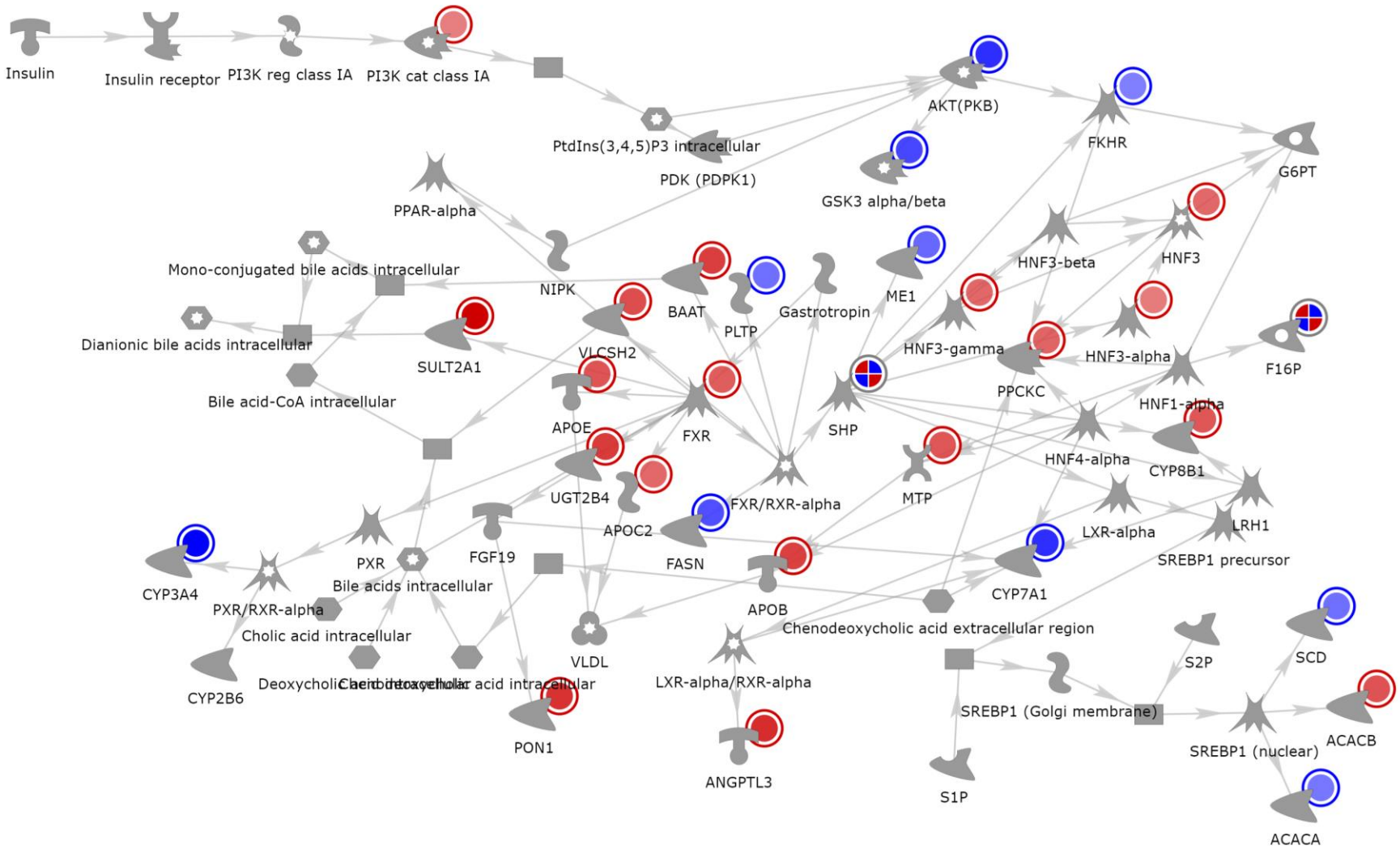
CRV431 Effects on Liver Gene Expression in Preclinical Models

Bile acid regulation of lipid metabolism

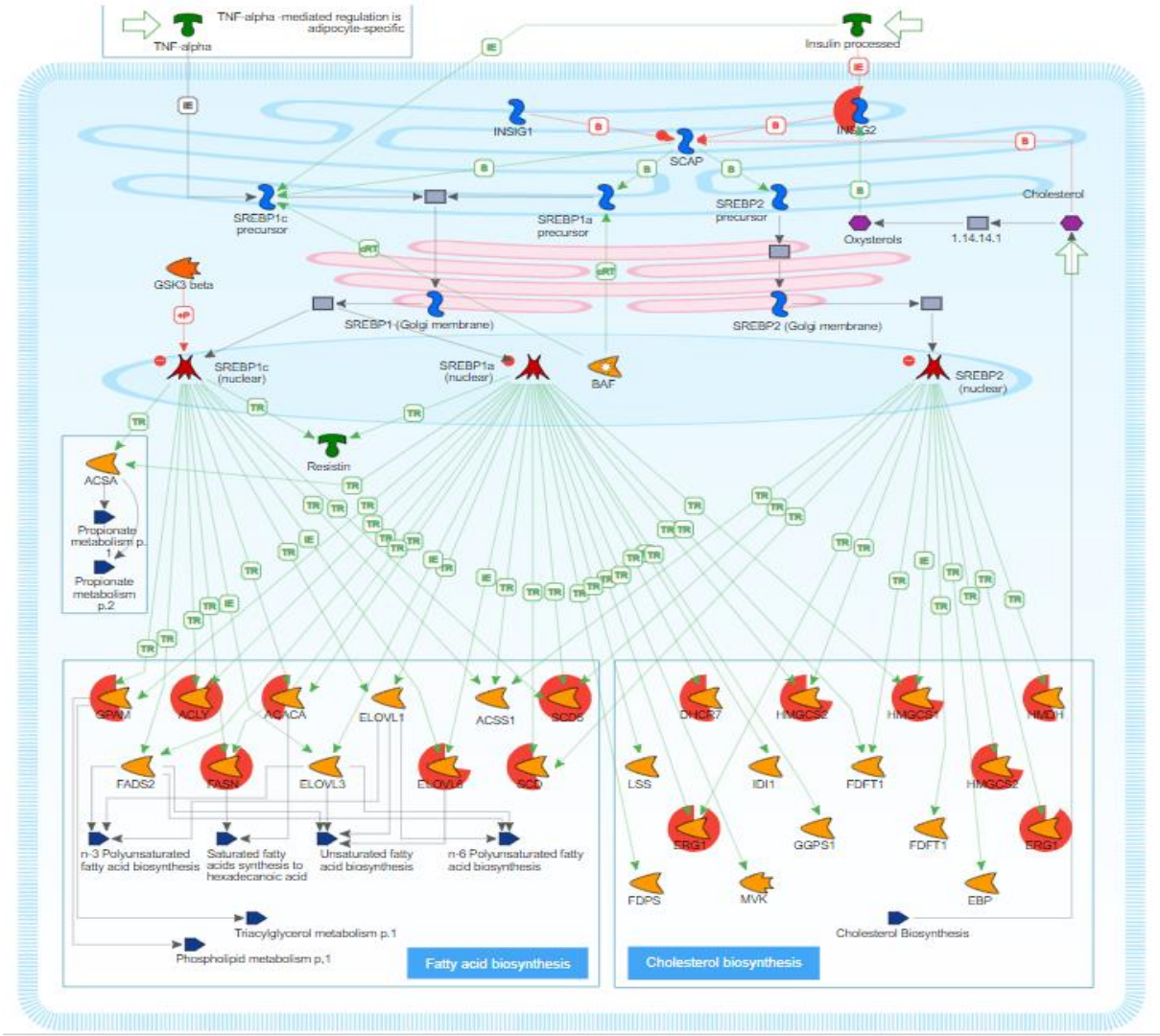
Gene downregulation Gene upregulation



Causal Analysis of CRV431 Effects in Western Diet/CCl_4 Model

SREBP Transcriptional Control of Cholesterol and Fatty Acid Biosynthesis

CRV431 downregulated several enzymes involved in fatty acid biosynthesis and cholesterol biosynthesis

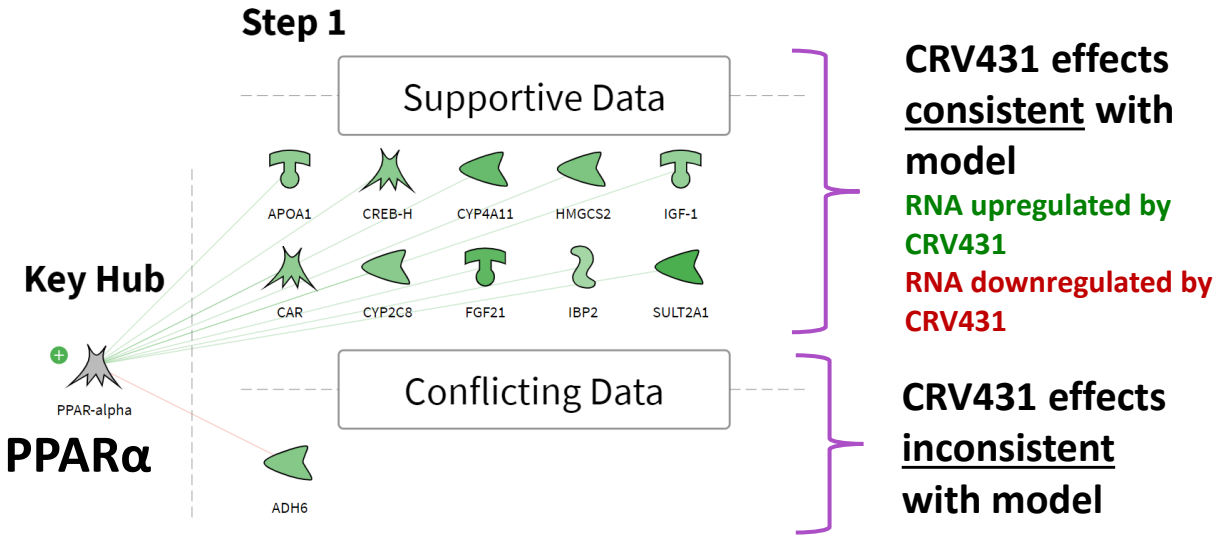


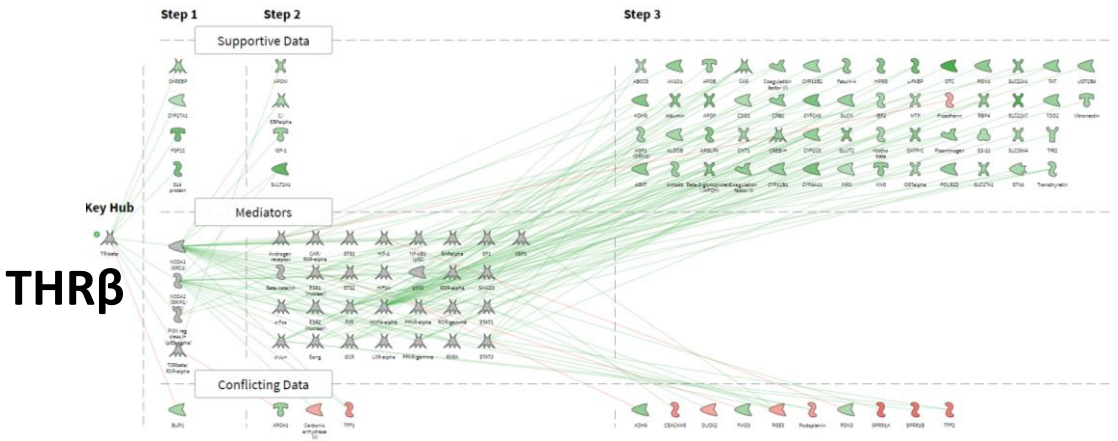
Gene upregulation

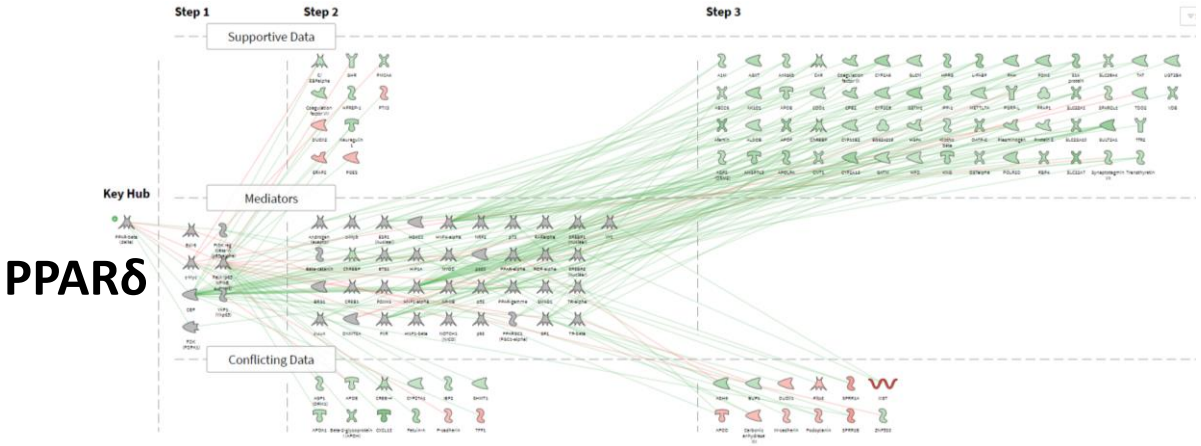
Gene downregulation

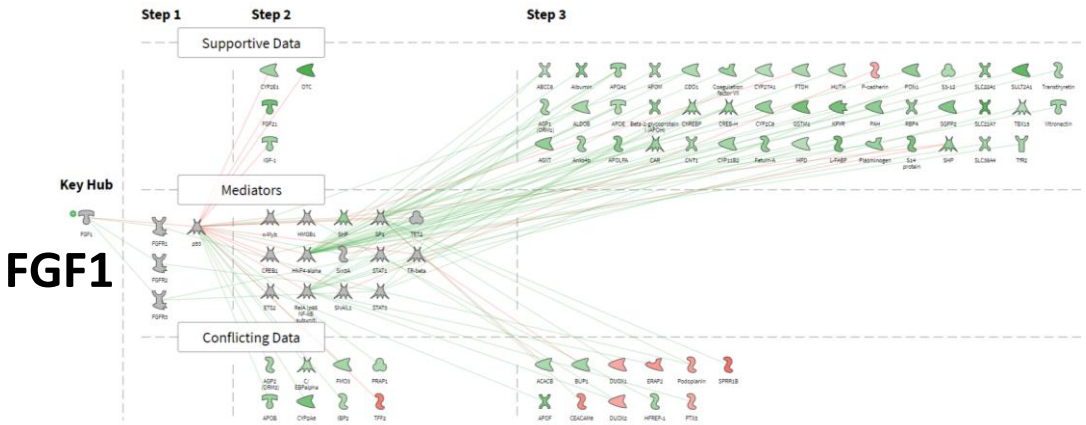
Human Liver Slices: CRV431 Effects on Transcriptome

Predicted key hub genes include multiple, familiar NASH drug targets









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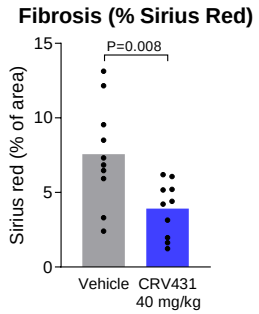
Bioinformatics Analyses - Metabolomics

OWL Metabolomics

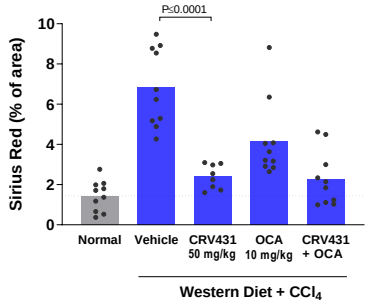
Thioacetamide Rats



CRV431 effects on *liver* metabolome:

- altered expression of 14% of metabolites
- majority of changes consistent with attenuation of thioacetamide effects
- phospholipids major class elevated by TAA and attenuated by CRV431

Western Diet/CCl_4 Mice



in progress

CRV431 effects on *plasma* metabolome:

- altered expression of 7% of metabolites
- modest attenuation of thioacetamide effects
- bile acids major class elevated by TAA and attenuated by CRV431

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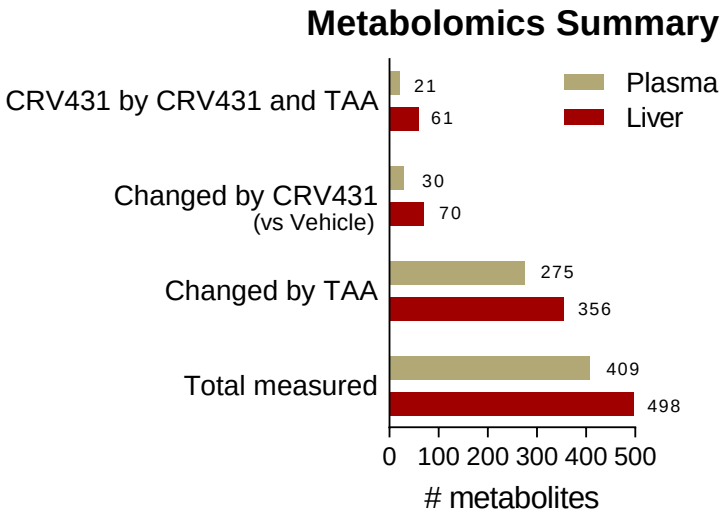
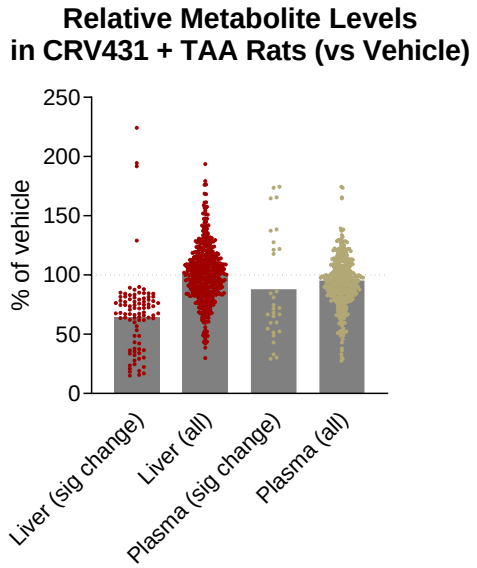
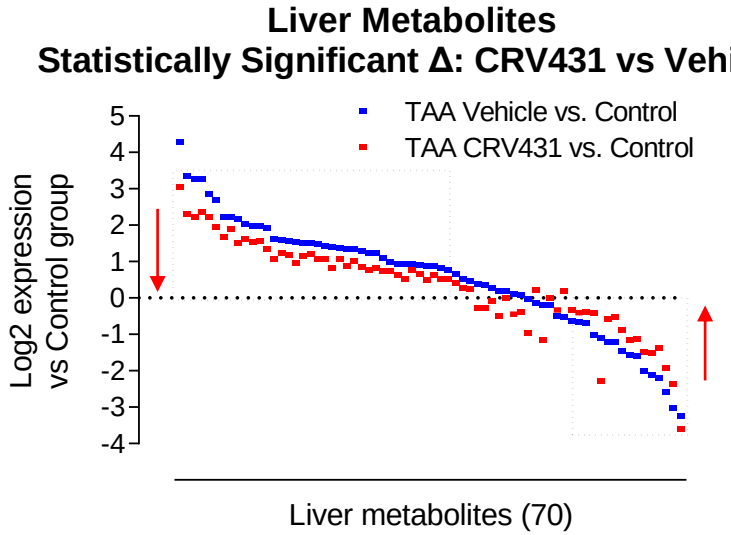
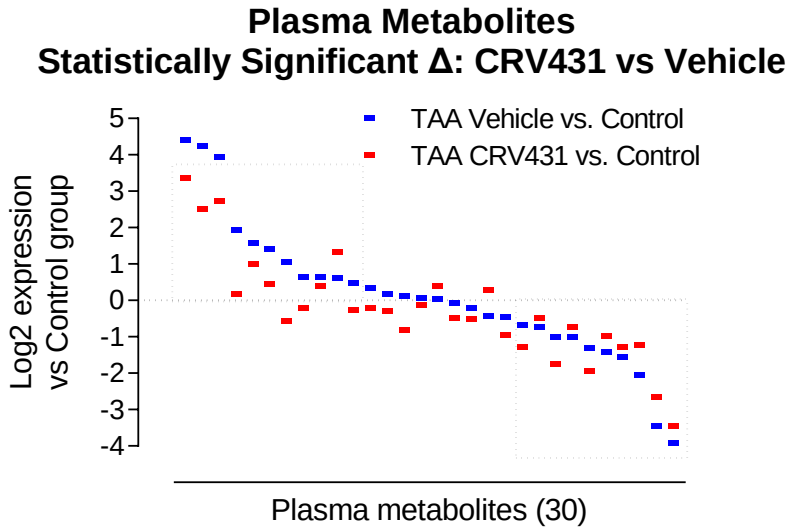
Metabolomics in Thioacetamide Rats

CRV431 attenuated many changes induced by 9 weeks thioacetamide









Changes induced by CRV431 in the *liver* mostly opposed the effects of TAA.

Less normalization by CRV431 was observed in the *plasma* metabolome.

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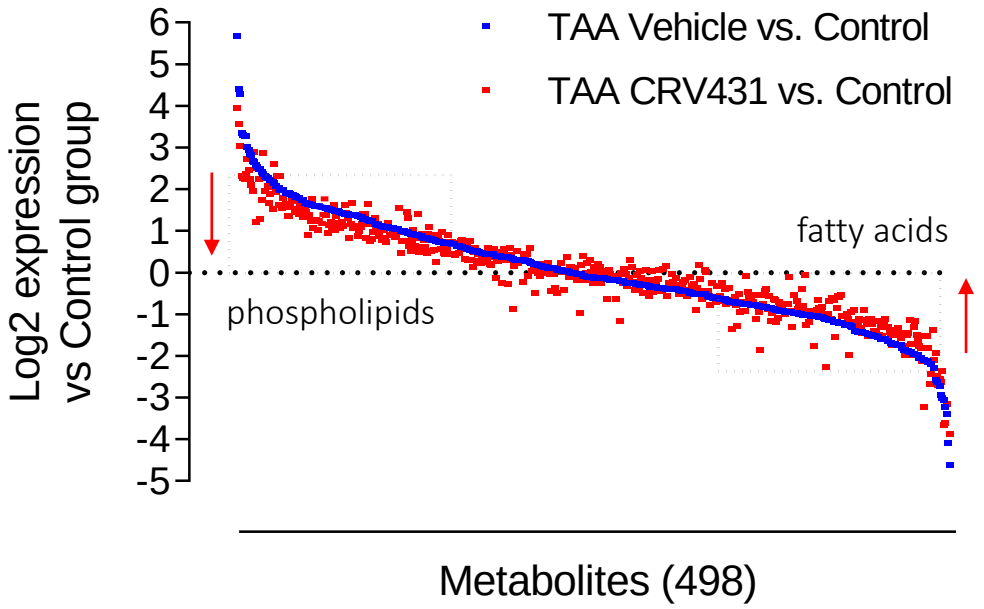
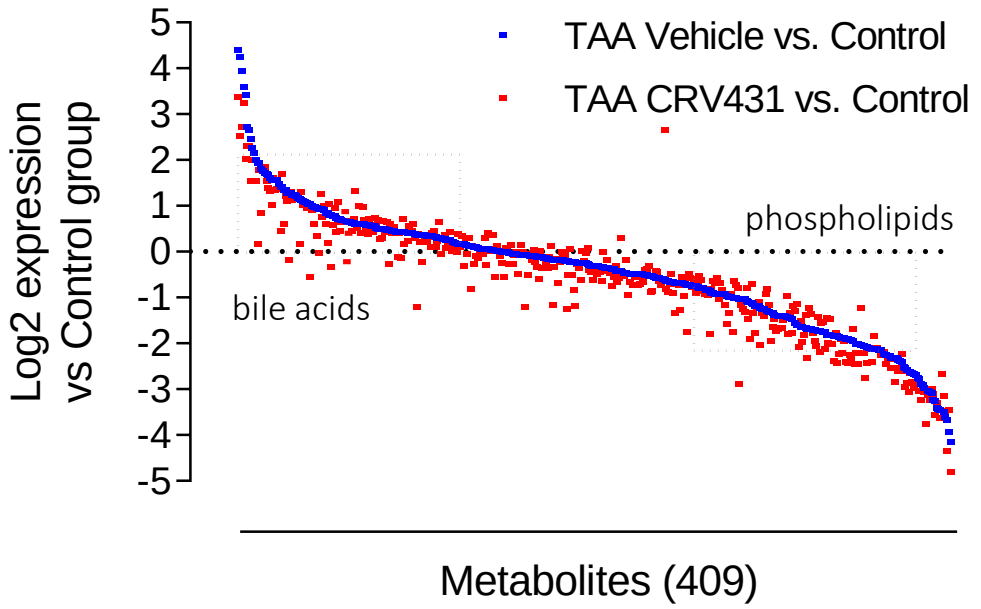
Metabolomics in Thioacetamide Rats

CRV431 attenuated many changes induced by 9 weeks thioacetamide

Liver Metabolites Log_2-fold change vs Control



Plasma Metabolites Log_2-fold change vs Control



CRV431 shifted the *liver* metabolome of TAA rats towards normal expression, but less for the *plasma* metabolome.

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SUMMARY

CRV431

- Multiple therapeutic actions in diverse liver injury models
- Therapeutic activities consistent across several analytical platforms
- Phase 2 clinical trials:
  - DATA-RICH: histopathology, multi-omics, biomarkers, clinical labs, imaging
  - AI-POWR™: in-house, AI/deep learning platform for biomarker selection, protocol optimization, and response predictions

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