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Novel Pathways Implicated in the Seladelpar-mediated Reductions of Established Liver Fibrosis are Identified from RNAseq Data using Plex Search and Two Independent Mouse Pharmacology Datasets

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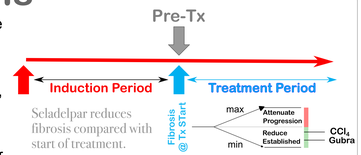
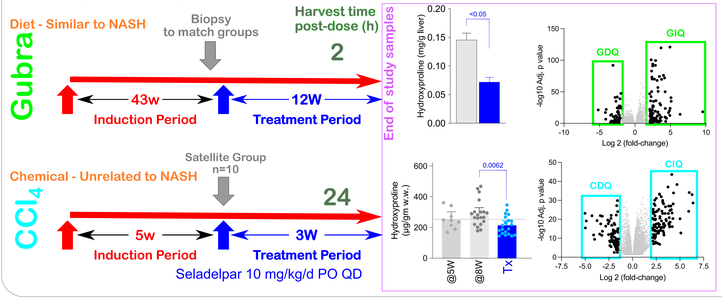
Background and Aims

Seladelpar reduces established liver fibrosis in multiple mouse models, despite differences in fibrotic stimuli.
Using previously existing unbiased RNAseq datasets from two different models, the top 100 changed genes from both studies were used as queries in Plex search, an AI based search engine.
The AIM was to identify seladelpar-regulated protein families common to both models.
Assumption: MOA for seladelpar-mediated reduction of fibrosis utilizes common pathway(s).

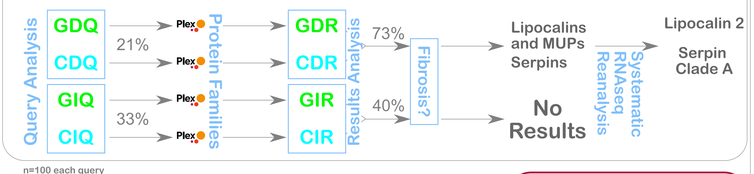


Seladelpar reduces hydroxyproline and collagen in two models with unrelated etiologies.

Introduction - Studies



Workflow and Graphical Results



n=100 each query
G = Gubra D = Decreased Q = Query
C = CCl_4 I = Increased R = Results

Knowledge graph based search engine that allows multiple query types, including chemical structure, genes, and perturbations. In this case lists of 100 RNA transcripts were used to ask:
Where has a similar gene signature been observed?
Do they represent a common protein family?
The Plex knowledge graph contains >500M data points and covers diverse experimental and curated data sources including multi-omics, pharmacology, clinical, and public domain databases.

New Hypothesis: Seladelpar reduces established liver fibrosis in mice via reduction of lipocalin 2 and/or serpin clade A.

Seladelpar Results

2018 AASLD
2019 Keystone
2019 EASL
2021 EASL
2022 EASL

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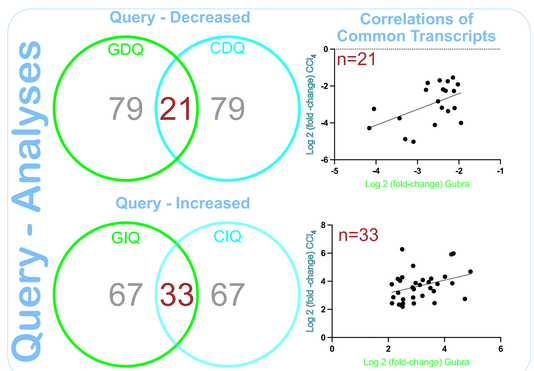
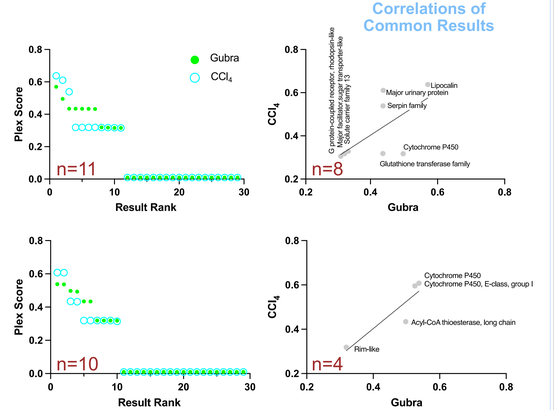
5 minute YouTube video
The video contains a high level overview of the poster contents.



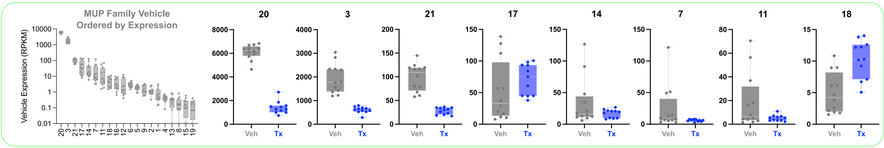
Results - Analysis

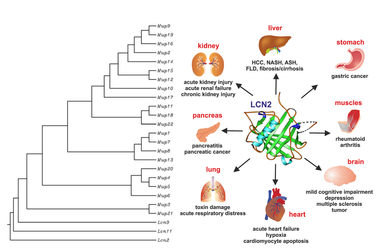


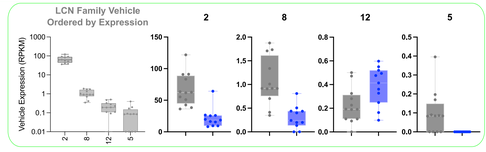
Despite the small overlap in the query sequences, the protein family results indicate congruent pharmacology as indicated by the similarity of decreased genes. Liver fibrosis is decreased in both models, in the presence of the fibrotic stimuli, we further analyzed the common protein families and assessed the known connections to fibrosis, if any.

Lipocalins and Major Urinary Proteins (MUPs)

Gubra

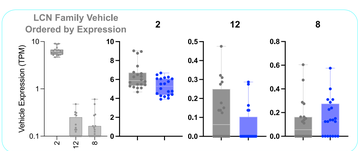




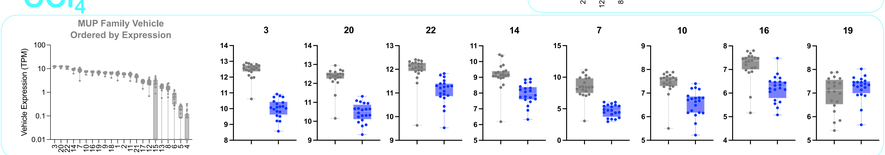


Conserved family of proteins with 8-β barrels
The MUP cluster evolved from the LCN family via evolutionary bloom (1)
LCN_2 represses IL-10 expression in macrophages (2)
$LCN_2^{-/-}$ mice are protected from CCl_4 fibrosis (2)
In vitro LCN_2 induces *Col1A1* in human hepatic stellate cells (2)

All expressed family members shown in graph with grey bars.
Sorted by expression in Veh group.
Top 8, Veh vs Tx shown in individual graphs.
All MUPs stat. sig. *except* 17, 18 (Gubra) and 19 (CCl_4)
LCN2 is the dominant isoform and reduced in both experiments.

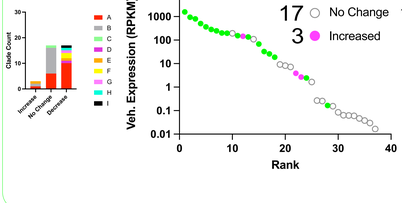


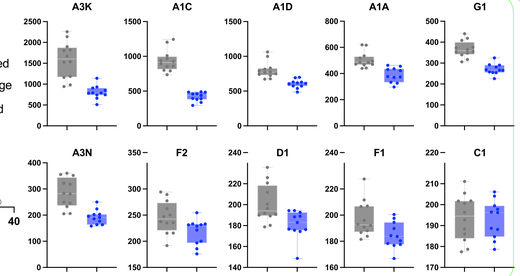
CCl_4



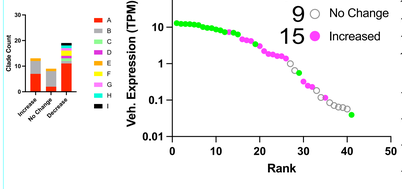
SERPINS

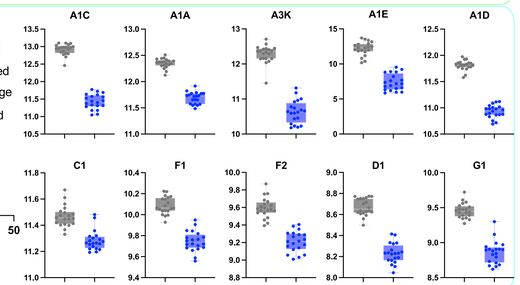
Gubra



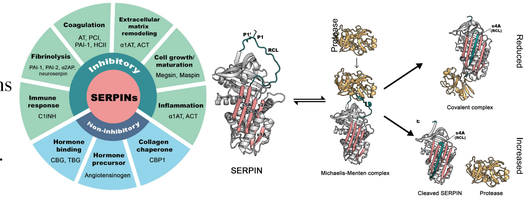


CCl_4





Conserved family of serine (or cysteine) peptidase inhibitors (3).
May also play important signaling functions within cells.
Biological roles of serpins and selected serpin isoforms are not well characterized.



All expressed family members shown in the graphs, ranked by expression in the vehicle group.
Color coding indicates decreased, no change, or increased
Top 10, Veh vs Tx shown in individual graphs for each experiment
Clade A serpins are the highest expressing serpins and the majority are decreased by seladelpar.
Clade B are the next most numerous and generally unaffected by seladelpar.
The role(s) serpins in liver fibrosis is generally unknown.

Conclusions

Assuming a common MOA for seladelpar-mediated reductions of established liver fibrosis in disparate murine models:
Counterintuitively*, the two protein families with established literature connections to fibrosis were *reduced* by seladepar.
Lipocalin 2 and SERPIN clade A.
LCN2 is positively correlated and mechanistically linked with fibrosis (2).
SERPINS are proteins that inhibit proteases (under certain conditions).
Further experiments are required to elucidate the mechanism(s) by which LCN2 and SERPINS are related to seladelpar-mediated reduction of established liver fibrosis in murine models.

*Counterintuitively for two reasons, First, nuclear receptors induce gene transcription due recruitment of coactivators, therefore increases in expression are associated with agonism, Second, neither LCN2 nor SERPINS have been described as PPAR-responsive genes.

Note of Interest

LCN2 has been implicated in the profibrotic phenotype in cholestatic liver diease (4).
A recent review (5)

References and QR code

1. Charkoftaki (2019) 30782214
2. Chen (2020) 32968110
3. Bouton (2023) 37158379
4. O'Brien (2022) fasebj.2022.36.S1.R5479.
5. Sanrattana (2019) 30809526

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