ARIA PHARMACEUTICALS

Nonalcoholic Steatohepatitis (NASH)

August 2022

SOUND SCIENCE

ARIA IDENTIFIES THE THERAPEUTICS MOST LIKELY TO SUCCEED

Success Rates	Industry	ARIA PHARMACEUTICALS
in vivo	1-2%	**30%**[1]
Phase II	30%	**80%**[2]

Cumulative likelihood of success *in vivo* through Phase 2

50x Higher

1 – Significantly disease-modifying hits in preclinical animal models identified by Symphony; N=18 diseases, on average 10 molecules per disease
2 – Retrospective efficacy success rate of clinical trials of molecules identified by Symphony; N=18 diseases, 283 Ph2 CTs

ARIA'S STRATEGIC ADVANTAGE IN NASH

MAXIMIZED LIKELIHOOD OF CLINICAL SAFETY – HUMAN SAFETY AT PHASE I

ESTABLISHED TOLERABILITY
MAGL inhibitor has safely completed Phase I

MAXIMIZED LIKELIHOOD OF CLINICAL EFFICACY – HUMAN EFFICACY AT PHASE II

HIGH CLINICAL PREDICTABILITY IN NASH
Symphony predicted 66.7% of Phase II successes in NASH

NON-ALCOHOLIC STEATOHEPATITIS (NASH)

MARKET

- **100+ MILLION** cases worldwide
- **15%** chance of Cirrhosis
- **0** FDA approved medications

$10B

2024 Market
($/Year)[1]

SPEED AND SUCCESS

- **5 OF 10 MOLECULES ADVANCED** from *in vitro* to *in vivo*
- **15 WEEKS** from program start to *in vitro* and *in vivo* results

LEAD MOLECULE TXR-612 IN VIVO HIGHLIGHTS:

- **NOVEL MOA** in NASH
- Significant **DECREASE** in steatosis, ballooning and inflammation score
  Significant **DECREASE** in fibrosis
- **GOOD TOLERABILITY** – clinically investigated mechanism

[1] *Pharmaceutical Intelligence Services, GlobalData LLC*

HIGH UNMET MEDICAL NEED FOR NASH

100+ MILLION CASES WORLDWIDE

25% and 5% of US population affected by NAFLD and NASH respectively

FATTY LIVER is the most common global liver disease

15% CHANCE OF CIRRHOSIS

METABOLIC DISEASE WITH HISTOLOGICAL DIAGNOSIS – fat accumulation (steatosis), hepatocyte injury, inflammation, fibrosis

0 FDA APPROVED MEDICATIONS

VITAMIN E, PIOGLITAZONE, LIFESTYLE CHANGE is current first-line therapy

NO DRUGS with FDA approval for NASH therapy

ACTIVE PH 2 & 3 clinical development

INVESTIGATIONAL DRUGS

SELECTED AGENTS - RECENTLY APPROVED, FAILED, OR IN ACTIVE PHASE II/III NASH CLINICAL TRIALS

Agent	Developer	Target(s)	Phase	Primary Endpoint (EP)	Status	Response
Obeticholic acid	Intercept	FXR	III	≥1 stage fibrosis improvement, 18 weeks	Rejected	23.1% vs 11.9% p=0.0002
MGL-3196	Madrigal	THRB	III	2-point NAS histology reduction, 52 weeks	Ongoing	Significant hepatic fat reduction
Dapagliflozin	S. Medical University	SGLT2	III	Histological treatment effect, 52 weeks	Ongoing	Hepatic biomarker improvement
Semaglutide	Novo Nordisk	GLP1R	III	NASH resolution, no worsening fibrosis, 72 weeks	Ongoing	Not available
Saroglitazar	Zydus	PPAR-a/g	III	NAS histology, 52 weeks, no worsening fibrosis	Ongoing	Not available
Emricasan	Conatus, Novartis	Caspase	IIb	≥1 stage fibrosis improvement, 72 weeks	Failed EP	No significant difference
NGM282	NGM, Merck	FGFR4	IIb	Histological treatment effect, 24 weeks	Failed EP	No significant difference
BMS-986036	Bristol-Myers Squibb	FGFR1/2	IIb	≥1 stage fibrosis improvement, 24 weeks[2,3]	Ongoing	Significant hepatic fat reduction
GS-0976	Gilead Sciences	ACC[1]	II	≥1 stage fibrosis improvement, 48 weeks	Ongoing	Significant hepatic fat, fibrosis reduction
TVB-2640	3-V Biosciences	FASN	II	Effect on hepatic fat fraction vs placebo	Ongoing	Not available

1. Selonsertib (ASK1), Cilofexor (FXR) combination Phase II trial
2. NASH Clinical Research Network (CRN) Fibrosis Score [Fibrosis measured on a 0-4 scale: 0 (none); 1 (perisinusoidal or periportal); 2 (perisinusoidal and portal/periportal); 3 (bridging fibrosis); 4 (cirrhosis)]
3. NAFLD Activity Score (NAS) [NASH disease activity in the liver measured on a 0-8 scale: unweighted sum of steatosis, or fat (scale: 0-3), lobular inflammation (scale: 0-3), and hepatocellular ballooning (scale: 0-2)]

DISCOVERY PROCESS IDENTIFIES TXR-612 IN 12 WEEKS

AI-Driven Discovery

Diverse Data, Methods:

- 25 data sources
- 50 methods
- 2M+ molecule chemistry library

50K Molecules

AI-Assisted Review

Novelty and Safety:

- Novel MOA
- Safety profile
- ADME properties

500 Molecules

Hit Diligence

PhD-led Deep Dive:

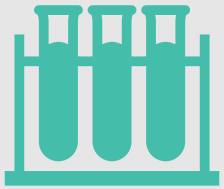
- MOA relevance
- MOA safety
- IP development path

50 Molecules

Preclinical

Optimal Disease Models:

- Test diverse MOAs
- CRO availability
- Rapid *in vivo* efficacy



10 Molecules

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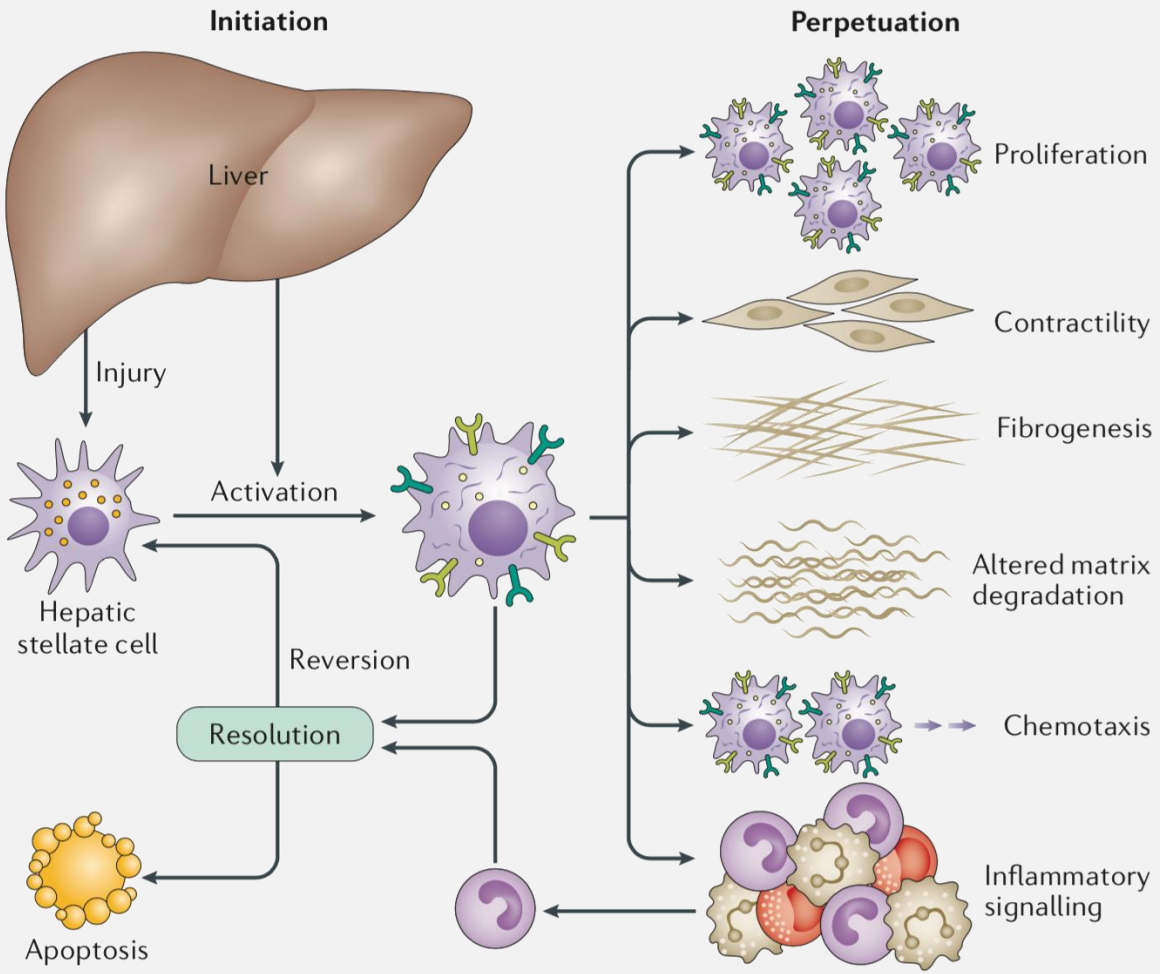
TXR-612 BACKGROUND

HEPATIC STELLATE CELLS PLAY A VITAL ROLE IN NASH PATHOLOGY



Hepatic Stellate Cells (HSCs) represent 10% of all liver cells

HSC Activation: A molecular and cellular program that leads to multiple phenotypic changes with the purpose of resolving liver and hepatocyte injury

NASH develops from sustained insult and injury or failure to resolve the injured state

Tsuchida and Freidman. 2017.
Nature Reviews Gastroenterology & Hepatology

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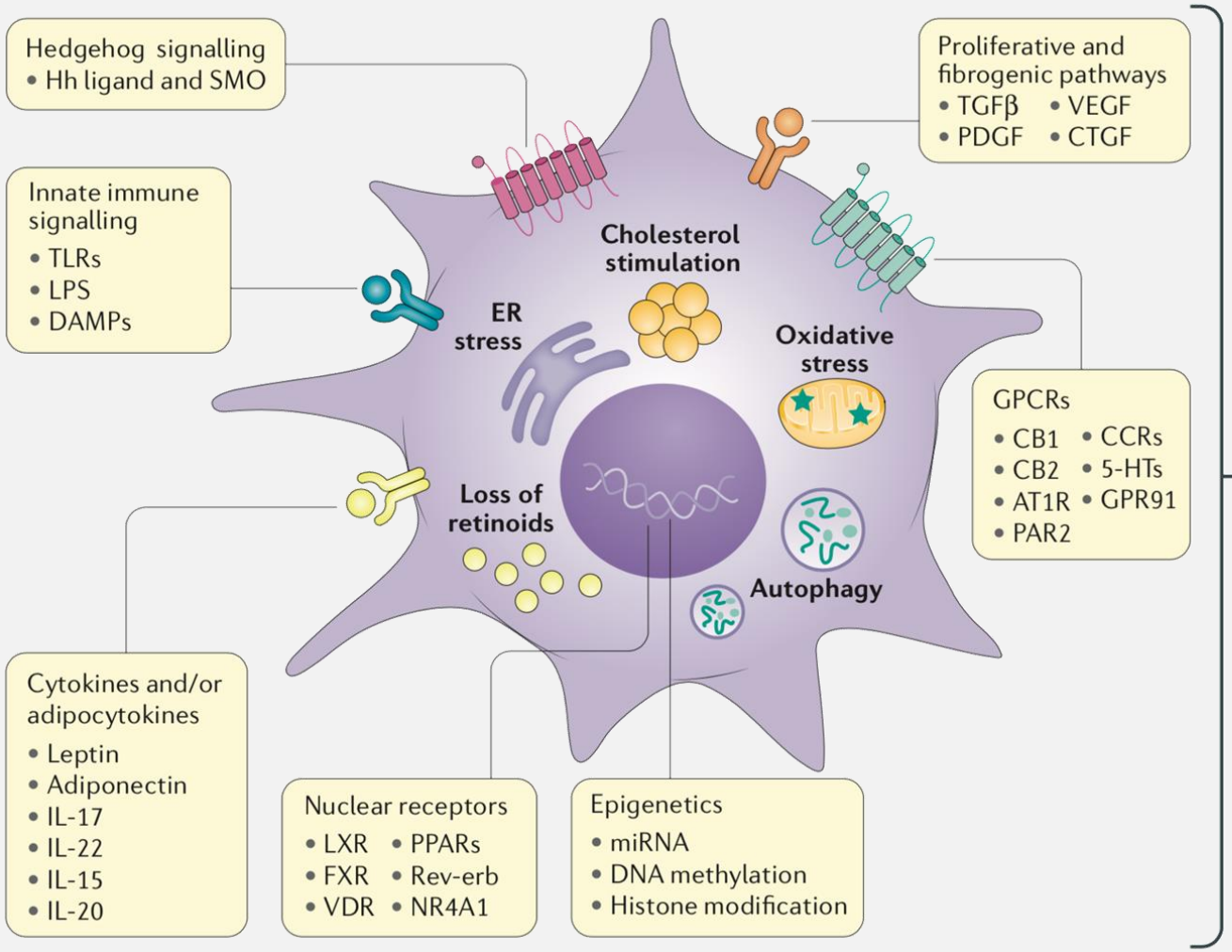
HEPATIC STELLATE CELL ACTIVATION IS A COMPLEX PROCESS

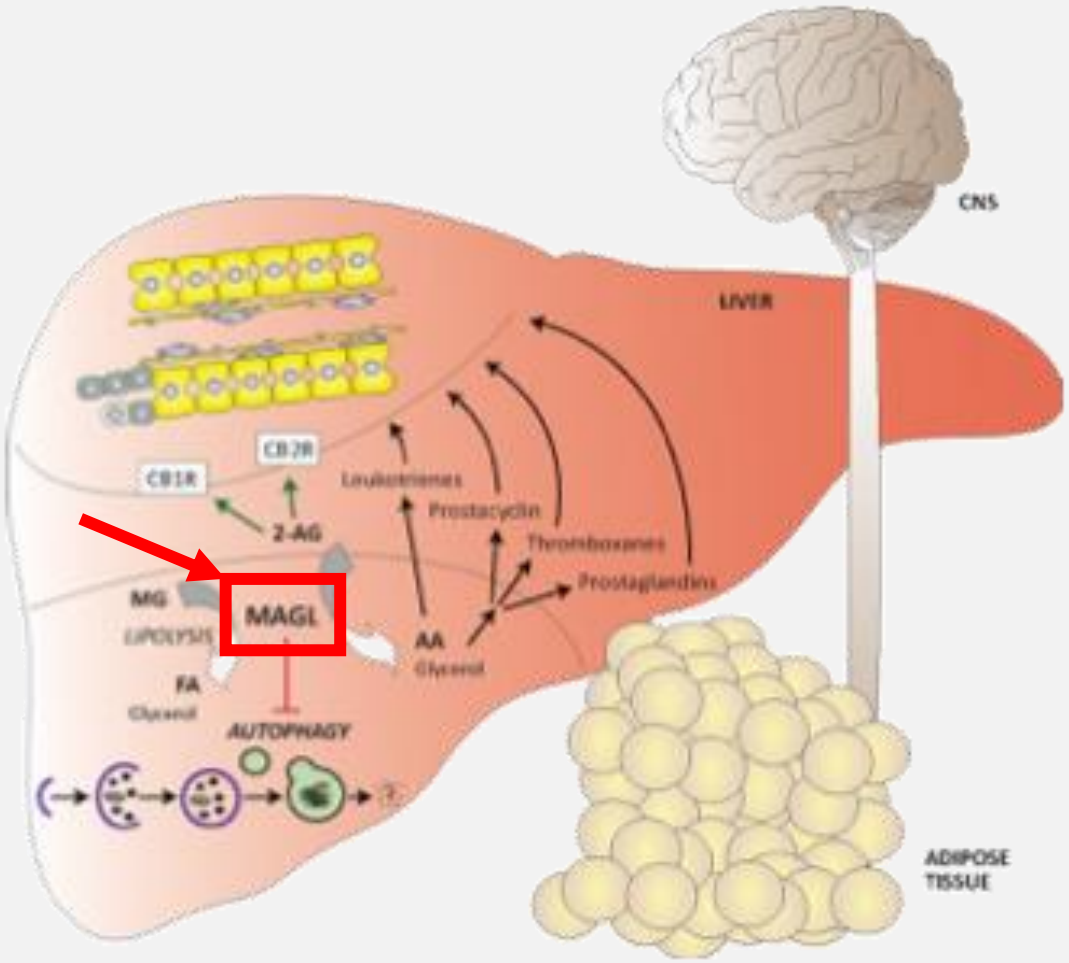


- Inflammation
- Vascular remodeling
- Fibrogenesis
- Apoptosis

Many possible therapeutic targets

Tsuchida and Freidman. 2017.
Nature Reviews Gastroenterology & Hepatology

TXR-612 IS A MAGL INHIBITOR



- Monoacylglycerol lipase (MAGL) is mainly expressed in the liver, the central nervous system (CNS), and adipose tissue.
- MAGL is the rate-limiting enzyme in the degradation of monoacylglyerides (MG) into glycerol and fatty acids (FA).
- MAGL catalyzes the hydrolysis of 2-arachidonoyl glycerol (2-AG) into glycerol and arachidonic acid (AA).
- 2-AG is an endogenous agonist of the cannabinoid 1 and 2 receptors (CB1R; CB2R), both expressed by different liver cells.
- Generally, CB1R acts profibrogenic while CB2R exhibit anti-inflammatory and antifibrogenic effects.
- AA is the precursor of different prostanoids (prostaglandins, prostacyclins, thromboxanes) and leukotrienes that act as intracellular and extracellular signaling molecules and herewith also affect different parenchymal and non-parenchymal liver cells as well as extrahepatic cells.
- Inhibitory effect of MAGL on autophagic flux and autophagosome biosynthesis in macrophages has been described.

Hellerbrand et al; . 2018. *Gut*

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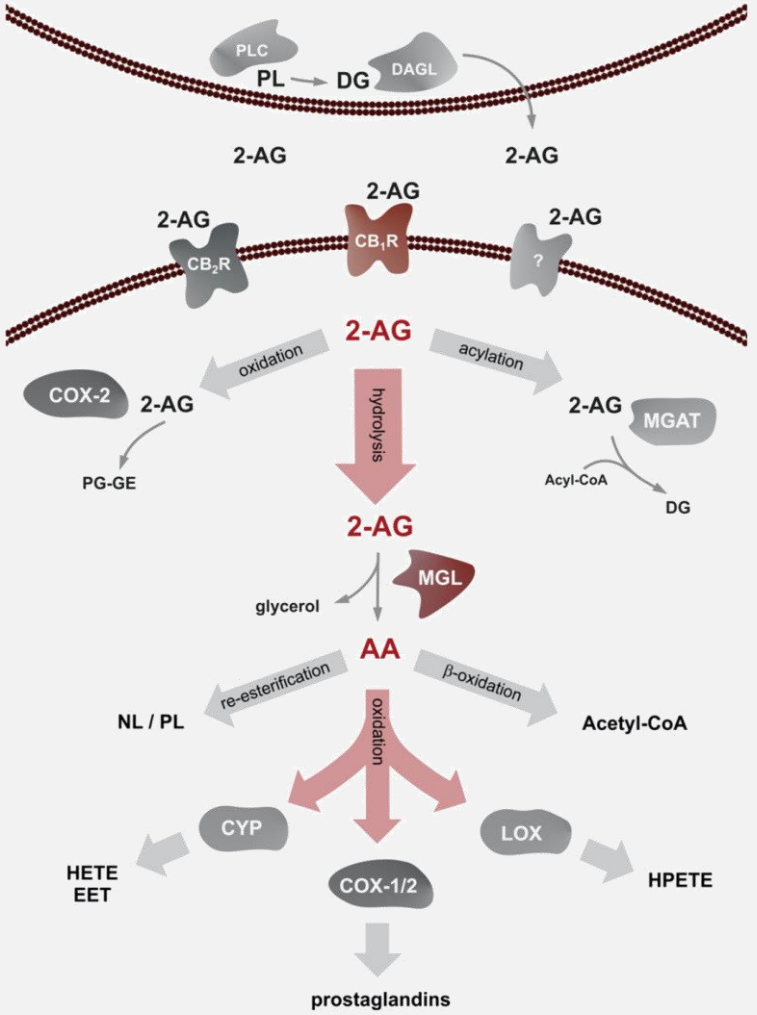
NASH: TXR-612 MOA AFFECTS MULTIPLE BIOLOGICAL PATHWAYS AND PROCESSES

- **TXR-612: MAGL Inhibition**:
  - Lipid metabolism
  - Arachidonic acid metabolism
  - Endocannabinoid expression
  - Liver health and disease
  - Health and disease beyond liver function, e.g., obesity, cancer, inflammation, pain, cardiac, depression, and addiction

- **Few clinical trials with MAGL inhibitors**
  - Well tolerated in Phase 2 Tourette's study
    - Our plan is to avoid CNS exposure



Grabner et al 2017 Pharmacology & Therapeutics

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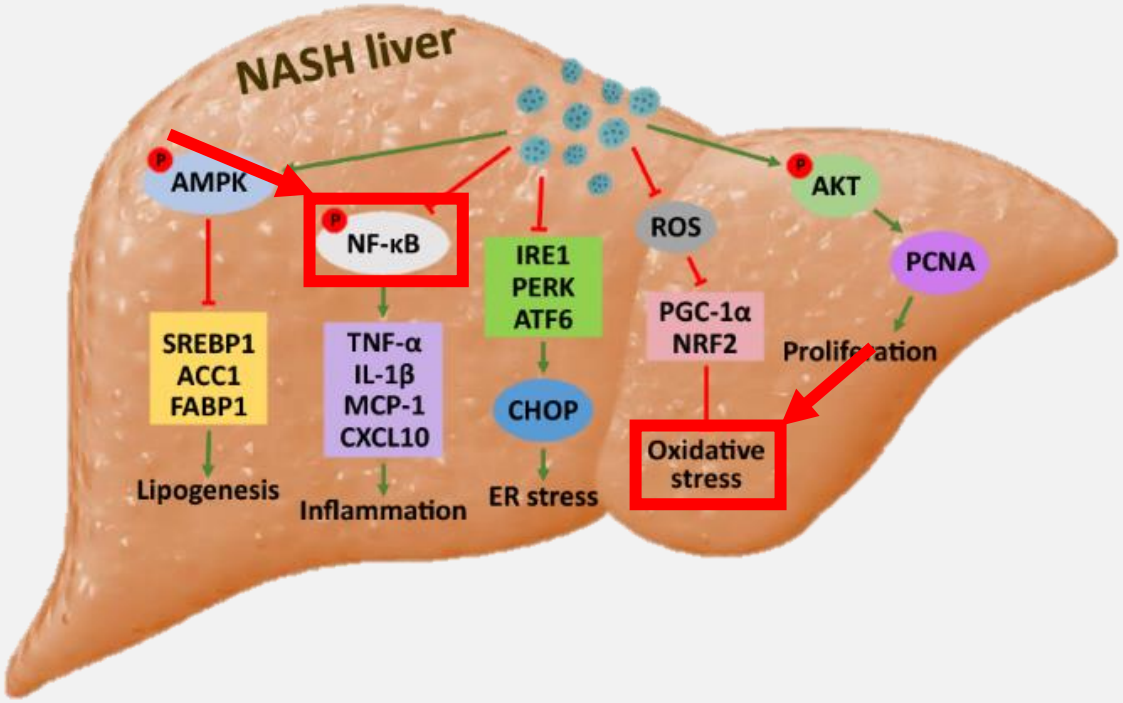
TXR-611 BACKGROUND

TXR-611 INHIBITS THIOREDOXIN REDUCTASE (TXNR)

- **Thioredoxin reductase inhibition acts on NASH in at least two distinct ways**
  - Regulation of NF-κB[1]
  - Regulation of oxidative stress

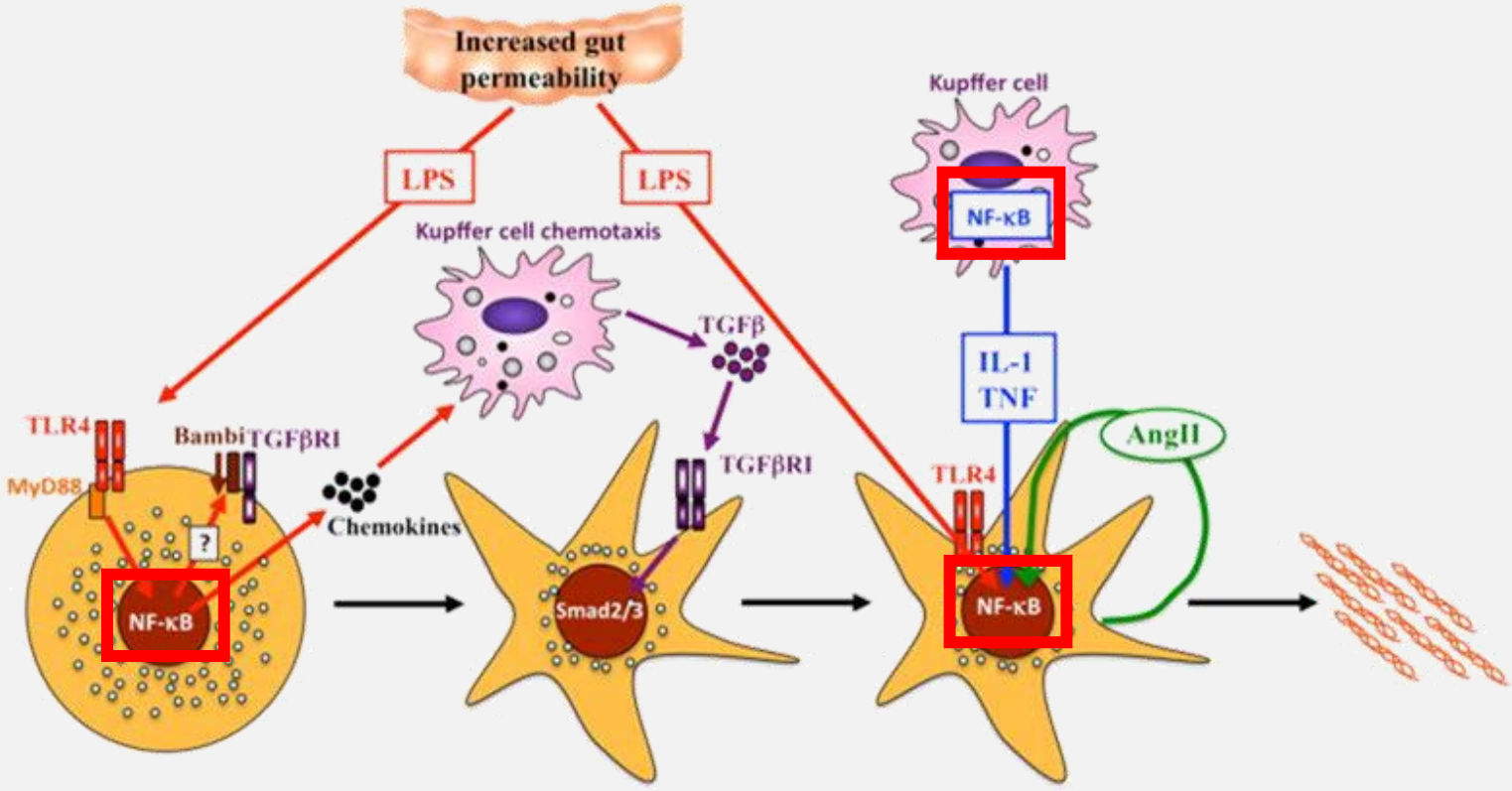


Modified from Kim, *et al.*; 2021. J Nanobiotech

1. Heilman, *et al.*; 2011. Free Radic Biol Med.

NF-KB IS EXTENSIVELY ASSOCIATED WITH NASH

- NF-κB promotes persistent HSC activity[1].
- Blocking of NF-κB protects against diet-induced hepatic steatosis[2].
- Chronic activation of the NF-κB pathway promotes lipogenesis in hepatocytes[3].
- Activation of NF-κB signaling in the liver induces fibrosis via chronic inflammation[4].

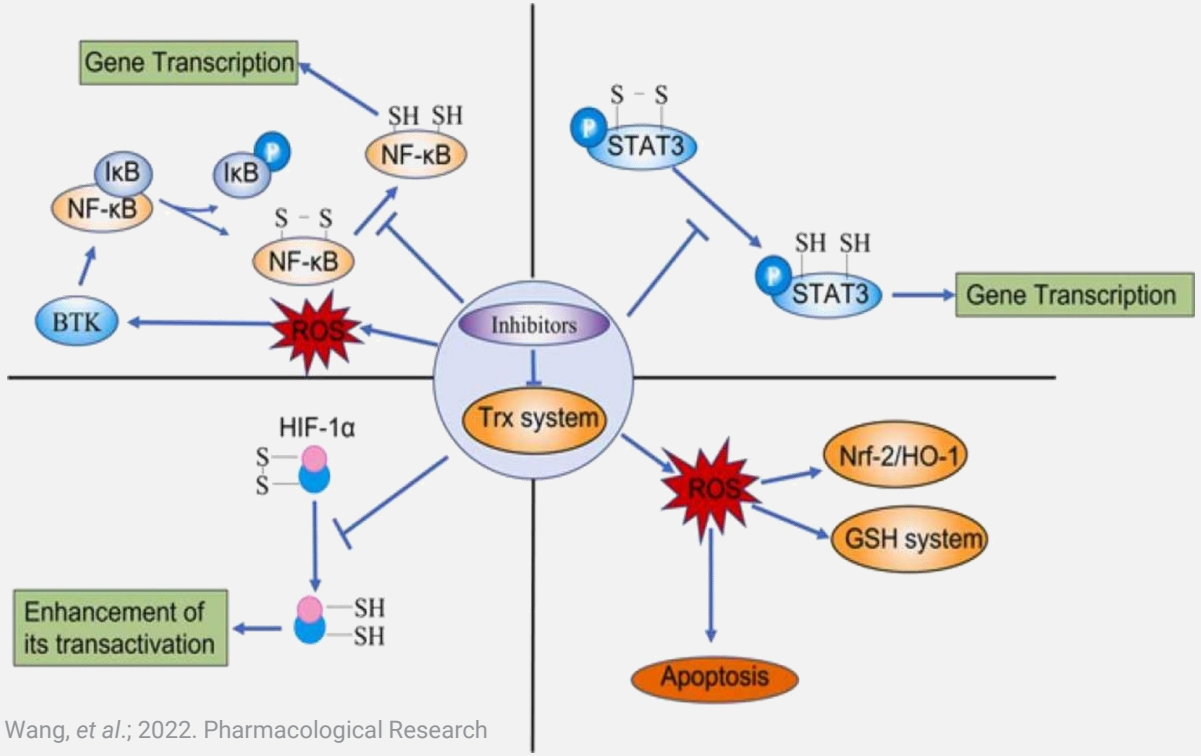


HSC activation. Modified from Luedde & Schawbe, 2010. Nat Rev Gastroenterol Hepatol.

1. Mann & Smart, 2002. Gut
2. Zeng, *et al*.; 2016. PLoS One
3. Heida, *et al*.; 2021. Molec. Metab.
4. Sunami, *et al*.; 2012. Hepatology

OXIDATIVE STRESS REGULATION IN NASH

- Increased oxidative stress (OS) is hypothesized to be a key part of the “multiple parallel-hit” model of NASH[1].
- The thioredoxin and glutathione systems are responsible for the detoxification of OS, however:
  - A thioredoxin reductase (TXNR) inhibitor therapeutically improves liver fibrosis while decreasing TGF-β expression and activity[2].
  - Glutathione-deficient mice demonstrate attenuated progression of diet-induced steatohepatitis and increased heme oxygenase (HO-1) expression. HO-1 protects against steatohepatitis and liver fibrosis[3].
    - In lung epithelial cells, TXNR inhibition increases HO-1 expression via an Nrf2-dependent mechanism[4].



Wang, *et al.*; 2022. Pharmacological Research

1. Masarone, *et al.*; 2018. Oxid Med Cell Longev
2. Jiao et al;. 2021. *Font. Mol. Biosci.*
3. *Haque* et al;. 2010. *Lab. Invest.*
4. Dunigan, *et* al.; 2018. Am J Physiol Lung Cell Mol Physiol.

IN VITRO STUDY DESIGN

NASH HSCs

- Fibrosis associated gene expression
- αSMA and COL1 protein immunostaining

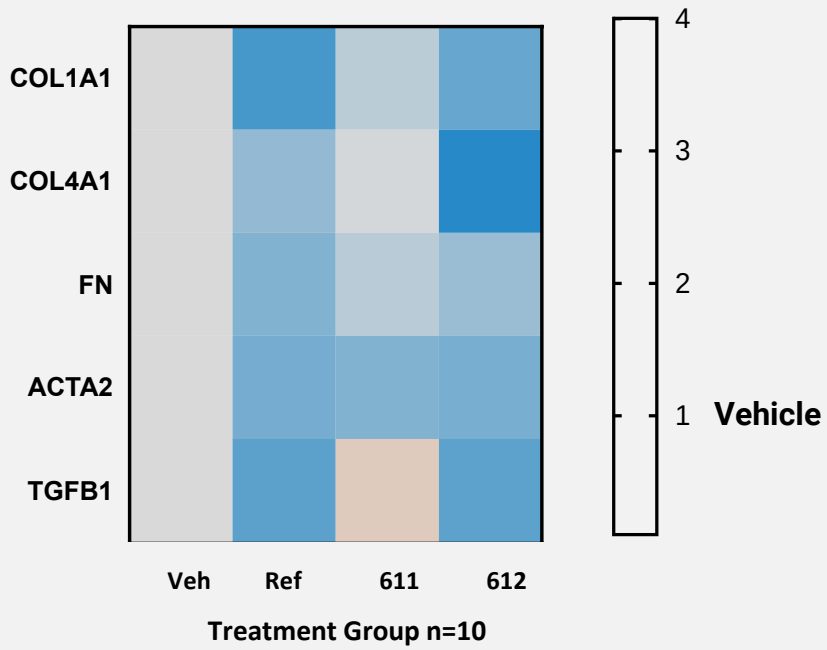
REFERENCE THERAPY

- Galunisertib (LY2157299): TGF-β type 1 kinase inhibitor, substrates include SMAD2

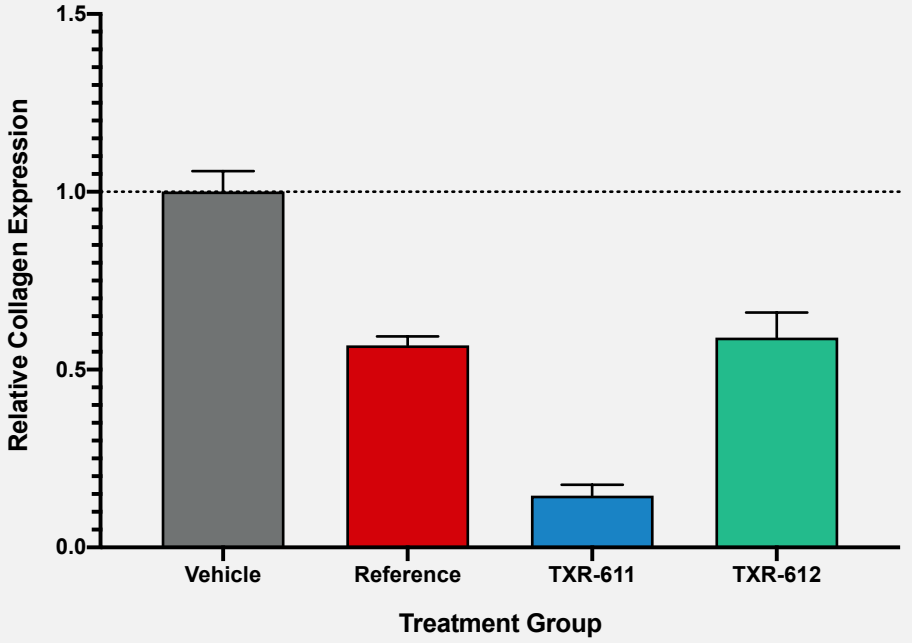
IN VITRO RESULTS SUPPORT HYPOTHESIS

- TXR-611 & TXR-612 modulate *in vitro* mRNA and protein expression in HSCs
- Expression changes in HSCs similar to the reference, Galunisertib

mRNA Expression



COL1A1 Protein Expression



qRT-PCR Analysis: The expression of 6 fibrogenic genes (COL1a1, COL4a1, Fibronectin/FN , COMP, ACTA2, TGFb) was normalized to the internal control gene HPRT. And then the relative expression was calculated by normalizing the compound-treated samples to DMSO-treated sample on the same plate . Quantification of relative signal intensities for COL1a1 following immunofluorescence staining

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IN VIVO STUDY DESIGN

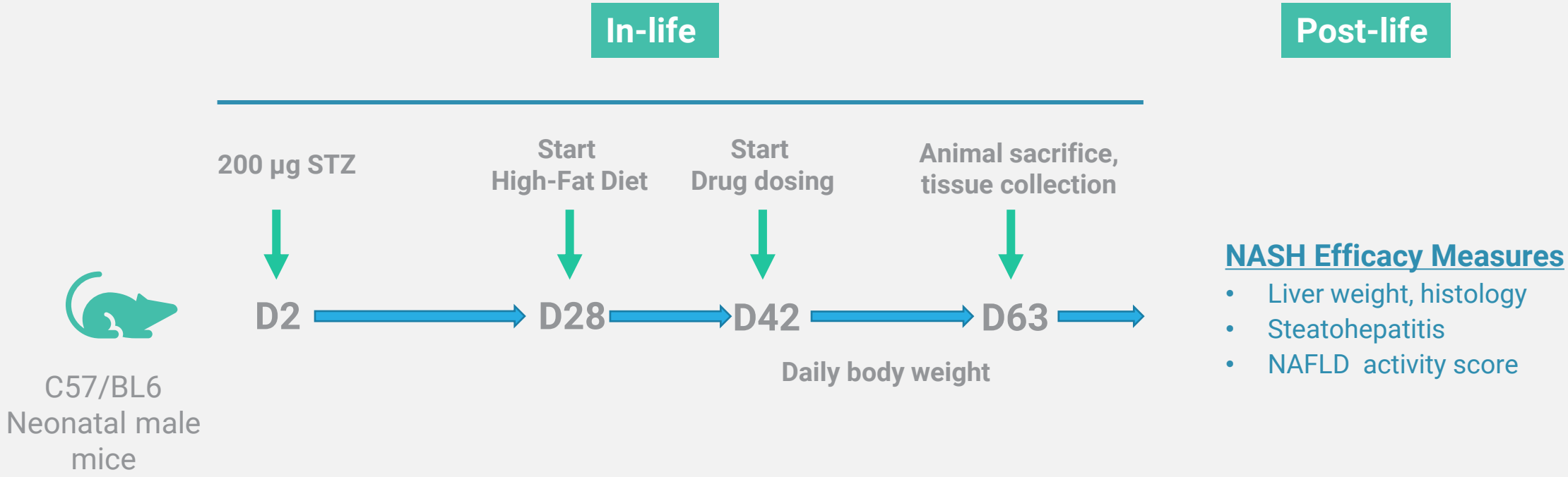
STAM MOUSE

- Steatohepatitis
- NAFLD activity score
- Liver histology data

REFERENCE THERAPY

- Telmisartan: Angiotensin receptor inhibitor; PPAR-γ agonist

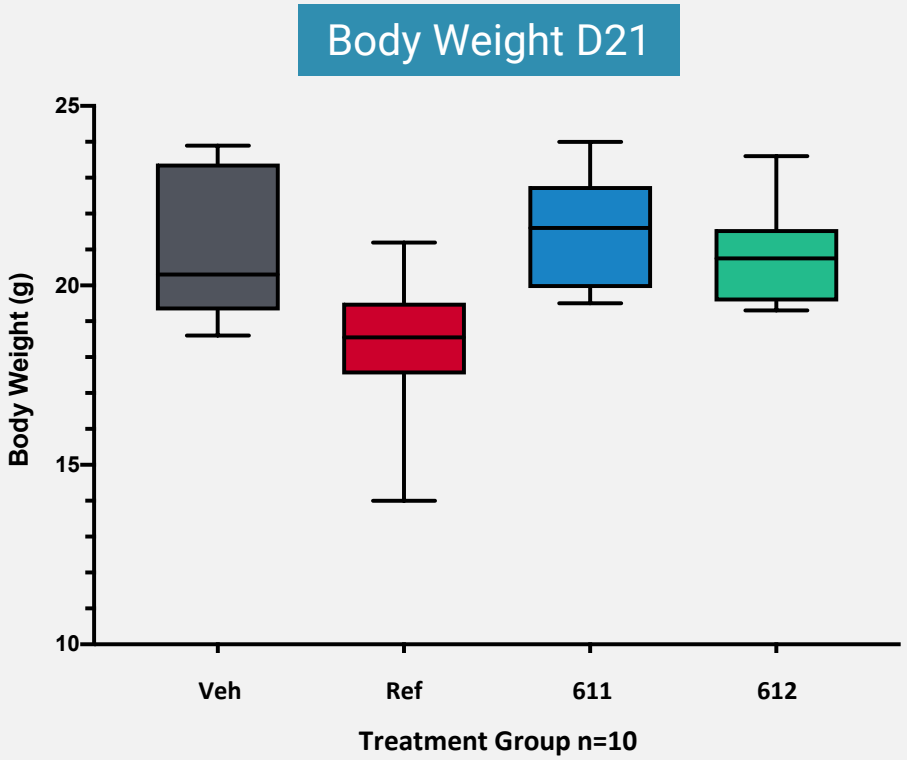
IN VIVO STUDY DESIGN



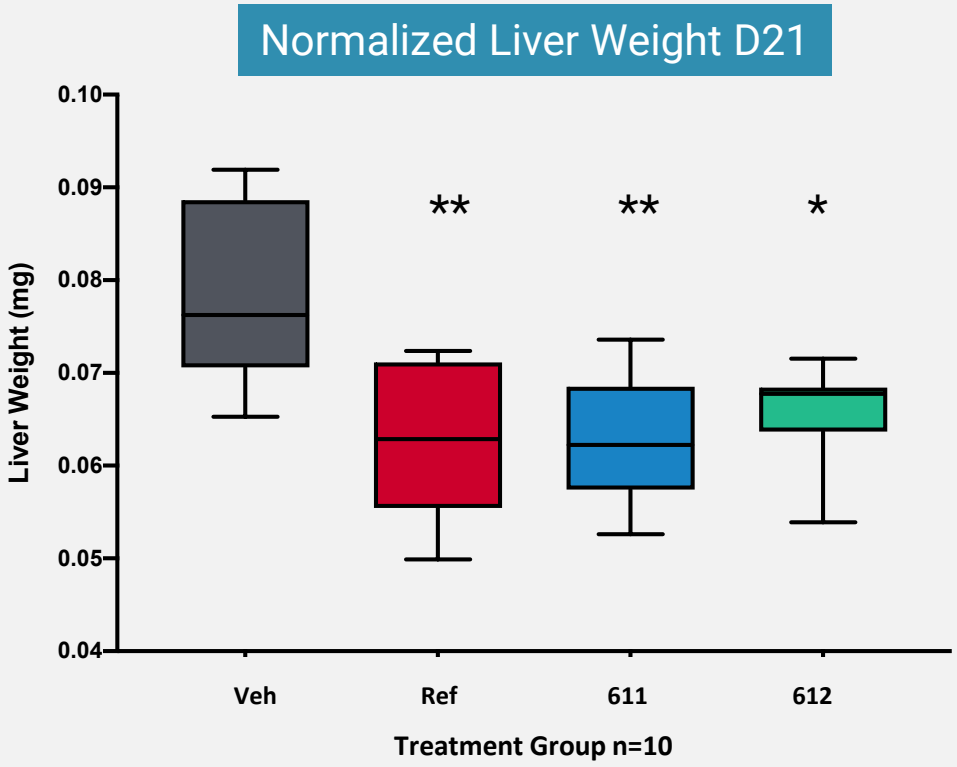
- STAM mouse NASH model
- Fibrosis-associated NASH in neonatal mice that progresses to HCC
- Proof-of-concept model for initial drug candidate evaluation
- Two candidates identified; TXR-612 MOA selected for development, TXR-611 MOA as backup
- Adult mouse NASH models available for further candidate investigation

TXR-611 & TXR-612 WELL TOLERATED AND DECREASES LIVER WEIGHT

- Good tolerability demonstrated by no significant change in body weight
- Efficacy demonstrated by decreased liver weight (comparable to telmisartan)



* P<0.05
** P<0.01



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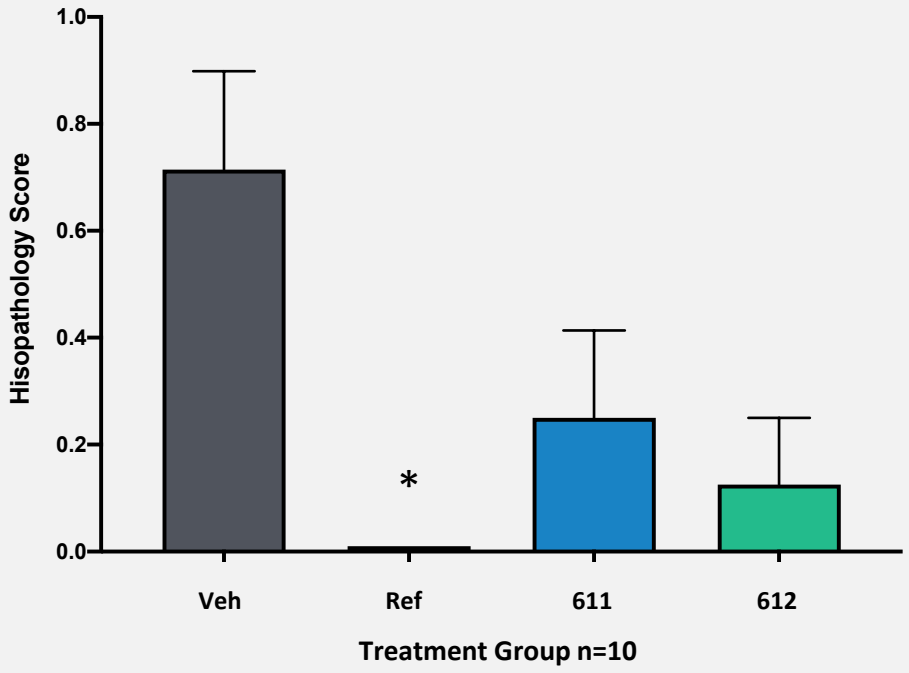
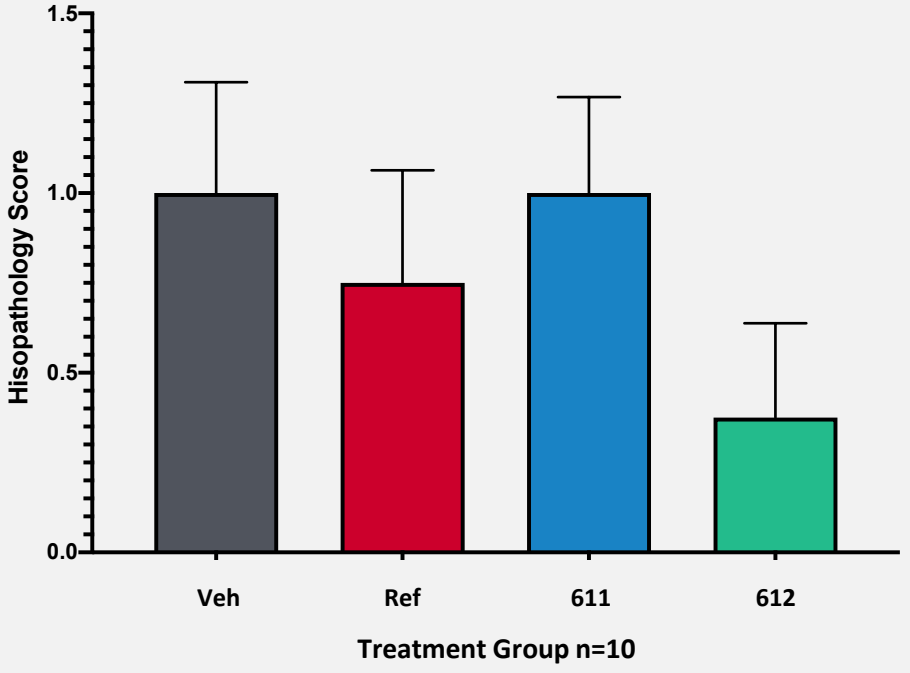
TXR-612 IMPROVES LIVER STEATOSIS AND HEPATOCYTE BALLOONING

- Decreased steatosis and ballooning
- Directional – more animals required to achieve statistical significance

Steatosis



Hepatocyte Ballooning



* P<0.05

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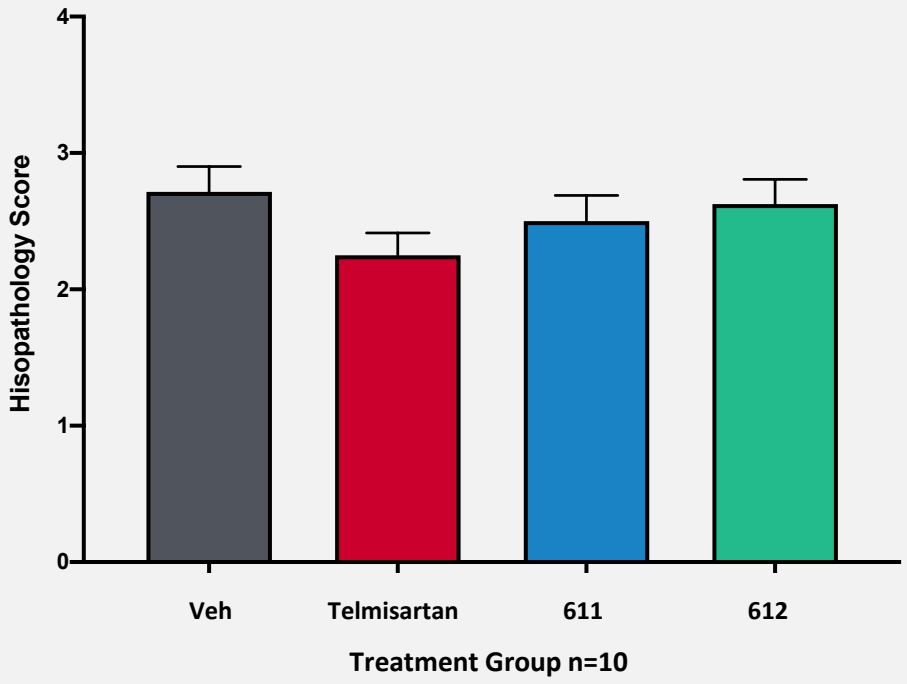
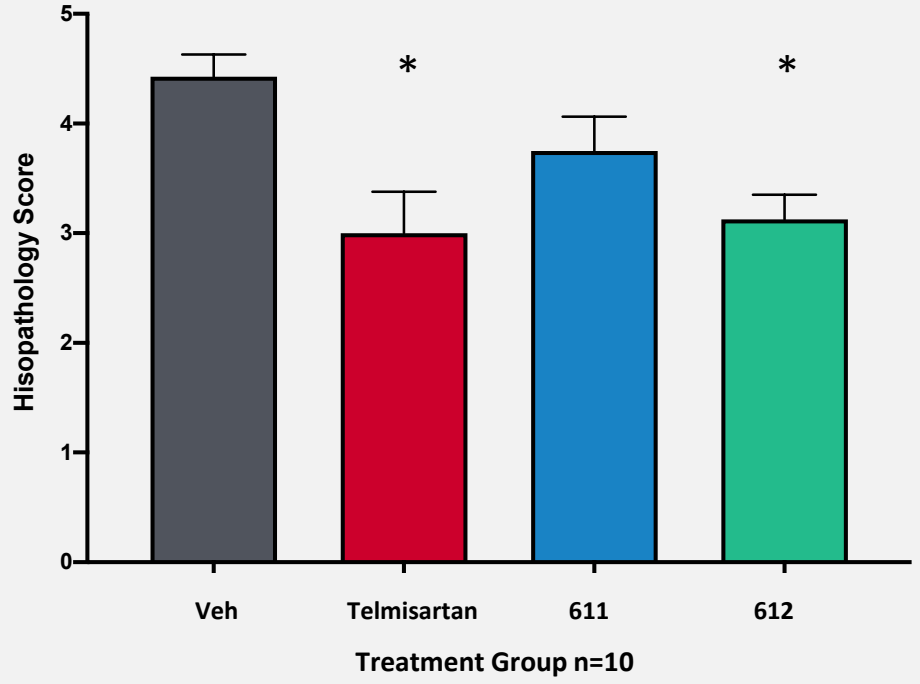
TXR-612 IMPROVES NAFLD ACTIVITY SCORE

- TXR-612 significantly decreases NAFLD Activity Score
- NAFLD activity score is composite score integrating steatosis, ballooning, and inflammation effects

Lobular Inflammation



NAFLD Activity Score



* P<0.05

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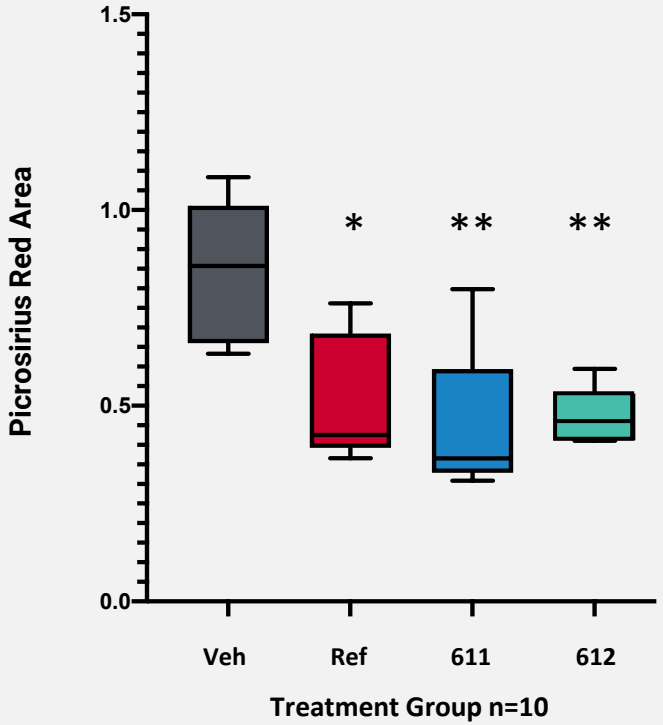
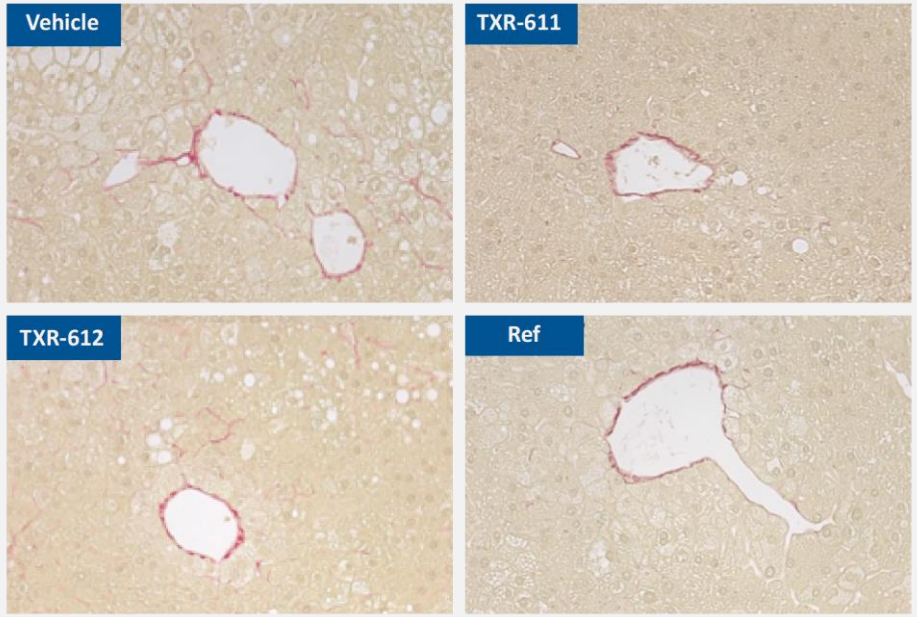
TXR-611 & TXR-612 DECREASE FIBRILLAR COLLAGEN DEPOSITION IN STAM MICE

- TXR-611 & TXR-612 significantly improve key measure of fibrosis

Picrosirius Red Staining (Collagen)



* P<0.05
** P<0.01



Picrosirius red was used to stain collagen in liver sections and quantified using histopathological scoring system

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TXR-612 SELECTED AS LEAD

- In two preclinical models, TXR-612 showed significant improvement in multiple readouts demonstrating more consistent efficacy than TXR-611
- Irreversible MAGL inhibitors provide extensive SAR data for various chemotypes
    - Recent advances have led to identifying reversible inhibitors as well
- Co-crystal structures with MAGL inhibitors are available for structure-based drug discovery and pharmacophore-based optimization
- Irreversible inhibitors have been extensively utilized to confirm the beneficial biological effects of MAGL inhibition on CNS disease pathologies and ABX-1431 has been evaluated in clinical trials

TXR-612 SUMMARY

TXR-612 DEMONSTRATES POSITIVE INITIAL EFFICACY WITH A NEW MECHANISM

GOOD TOLERABILITY – clinically investigated mechanism

LIVER WEIGHT– decreased weight; general efficacy measure

LIVER HISTOLOGY – decreased steatosis, ballooning, inflammation, fibrosis

NAFLD ACTIVITY SCORE – decreased NAS

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TXR-612 SUPPORTED BY NASH KOLs

Anna Mae Diehl
Duke University School of Medicine

Elizabeth Parks
Univ of Missouri Inst for Clinical Translational Science

STRENGTHS

- "Very intriguing data in the STAM model that captures epigenetic effect of NASH"
- "Fibrosis effects on primary human HSCs is good to see"

– Anna Mae Diehl

- "Amazing job culling compounds in an early study"
- "Very interesting, convincing data"

- Elizabeth Parks

CHALLENGES

- "Few animal models adequately address hepatocyte ballooning"

– Anna Mae Diehl

- "Difficult to find ballooned hepatocytes in mouse models of NASH. This contributes to data variability and is a challenge for achieving statistical significance"

- Elizabeth Parks

SUMMARY

- NASH is a major market with no approved drugs
  - Obeticholic acid: achieved its presumed pre-negotiated phase 3 primary endpoint, but FDA didn't approve it presumably for safety concerns
  - Multiple phase 2 & 3 failures
  - No approved drugs = no validated animal models, although candidates abound
- TXR-612
  - Retrospectively predictable MOA that is different than anything tried so far
  - Unsurprising safety profile in a different patient population
  - Positive preclinical data in first 2 studies
  - Additional pharmacology studies ongoing and planned

www.ariapharmaceuticals.com

SoftBank Ventures ANDREESSEN HOROWITZ OS Fund Stanford StartX Med MIT STARTUP EXCHANGE