NLRP3 inhibitor, NT-0796 reduces MASH in preclinical models

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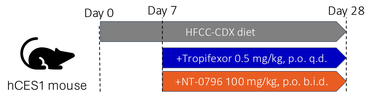
Background

Our clinical-stage NLRP3 inhibitor, NT-0796 has shown rapid, sustained and reversible reductions in multiple markers of inflammation in healthy volunteers, in patients living with high cardiovascular risk and obesity, and Parkinson's disease (1,2). We have also demonstrated a key role for NLRP3-dependent mechanisms in driving both peripheral and hypothalamic inflammation in preclinical models of obesity (3,4). Beyond this, NLRP3 inflammasome activation has been implicated in the pathogenesis of MASH (5), and here we test the hypothesis that NT-0796 can also reduce hepatic steatosis, inflammation and fibrosis.

Methods

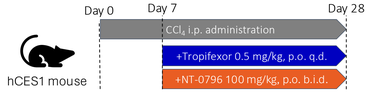
hCES1 mice were used for all studies. In hCES1 mouse line murine plasma Ces1c has been replaced with human CES1 to myeloid cells to achieve human-like traits of carboxylesterase biology (6). Mice were either challenged with **HFCC/CDX diet** (60% high-fat, 1.25% cholesterol, and 0.5% cholic acid diet with 2% cyclodextrin in drinking water (7)), or with **CCl_4 diet** (carbon tetrachloride solution 1:4 in olive oil) i.p. dosed at 3 µL/g body weight, twice a week, for 4 weeks to model steatosis and fibrosis, respectively. NT-0796 (100 mg/kg, p.o. b.i.d.) was dosed for the final 3 weeks of each study. The Farnesoid X receptor agonist, Tropifexor, (0.5 mg/kg, p.o. q.d.) was evaluated alongside. Statistical analysis was performed in GraphPad Prism 10.2.2 (GraphPad Software, USA) using one-way ANOVA followed by Dunnett's post-hoc.

HFCC-CDX model of fatty liver



Clinical hallmarks modelled:
- Hepatic steatosis
- Liver inflammation
- Elevated liver enzymes

CCl_4 model of liver fibrosis

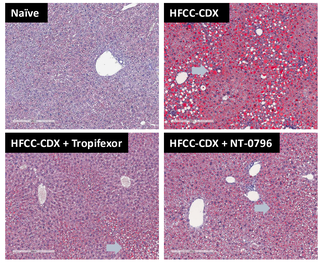


Clinical hallmarks modelled:
- Elevated liver enzymes
- Liver inflammation
- Liver fibrosis and cirrhosis
- Hepatotoxicity

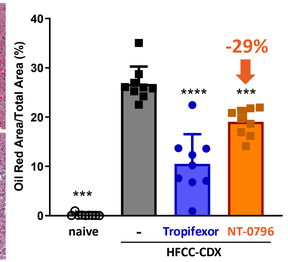
Results – liver steatosis

HFCC/CDX-driven steatosis (assessed by Oil Red O stain) was significantly reduced by NT-0796 (-29%, p=0.0004).
The efficacy of Tropifexor (FXR agonist) was also confirmed.

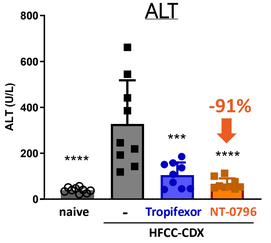
Hepatic Oil Red Staining



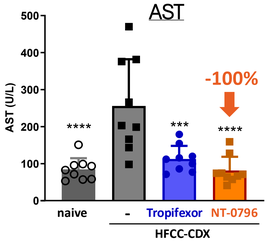
Oil Red Area



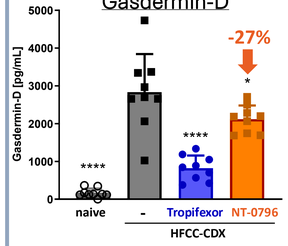
ALT



AST



Gasdermin-D

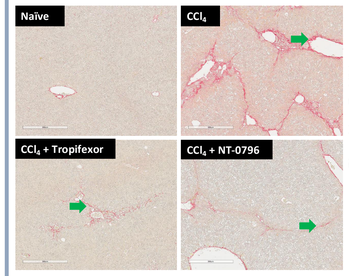


NT-0796 drove significant reductions in plasma ALT (-91%, p<0.0001) AST, (-100%, p<0.0001) and NLRP3 activation marker, Gasdermin-D (-27%, p=0.0296), consistent with NLRP3 inhibition.

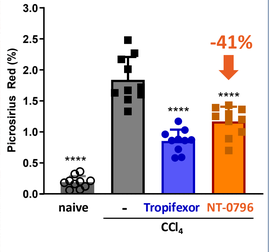
Results – liver fibrosis

CCl_4-driven fibrosis (assessed by Picrosirius Red stain) was significantly reduced by NT-0796 (-41%, p<0.0001).
The efficacy of Tropifexor (FXR agonist) was also confirmed.

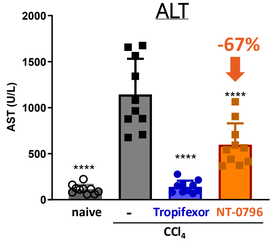
Hepatic Picrosirius Red Staining



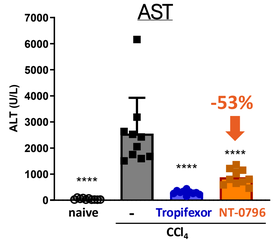
Picrosirius Red Area



ALT

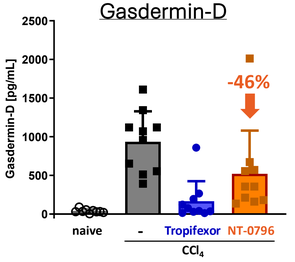


AST

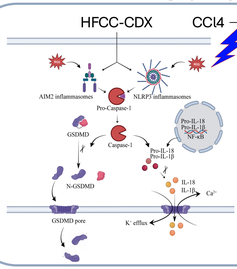


NT-0796 reduced elevations in plasma ALT (-67%, p<0.0001), AST (-53%, p<0.0001) and NLRP3 activation marker, Gasdermin-D (-46%, p<0.05).

Gasdermin-D

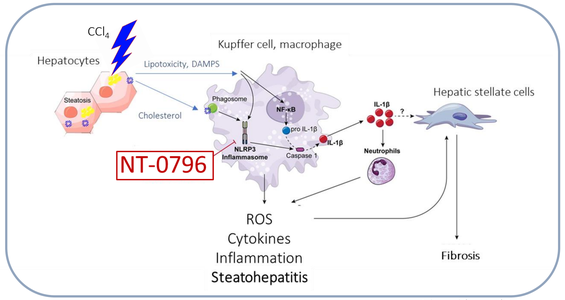


Conclusions



Adapted from ref 8.

- HFCC-CDX diet or CCl_4 challenge both drive NLRP3 activation as evidenced by release of plasma Gasdermin-D
- NLRP3 inhibition with NT-0796 reduces key MASH-associated pathologies, including hepatic steatosis, inflammation and fibrosis.
- Targeting hepatic NLRP3 may offer added therapeutic benefit for individuals at risk of MASH.
- Further translational studies are needed to explore the extent to which these mechanisms may contribute to liver disease in patient cohorts.



Adapted from ref 5.

References

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(3) Thornton et al. J Pharmacol Exp Ther 2024;388:813–826.
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