PXL770, A NEW DIRECT AMP KINASE ACTIVATOR AND POTENTIAL NASH THERAPEUTIC, PRODUCES ANTI-INFLAMMATORY EFFECTS IN MOUSE LIVER AND ADIPOSE TISSUE AND IN HUMAN IMMUNE CELLS

Pascale Gluais-Dagorn[1], Pierre-Axel Monternier[1], Bruno Guigas[2], Sébastien Bolze[1], David E. Moller[1] and Sophie Hallakou-Bozec[1], [1]Poxel, Lyon, France, [2] Leiden University Medical Center

BACKGROUND and OBJECTIVES

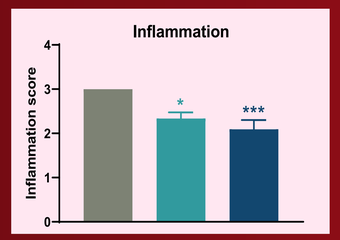
Adenosine monophosphate-activated protein kinase (AMPK) plays a key role in regulation of cellular energy metabolism. Recently, AMPK has been reported to have anti-inflammatory effects. PXL770 is a first-in-class direct AMPK activator which successfully completed a phase 2a clinical trial for treatment of nonalcoholic steatohepatitis (NASH). We assessed PXL770 effects (in vivo and in vitro) on inflammation by examining anti-inflammatory effects: (i) in liver from diet induced NASH mice; (ii) on ob/ob mouse adipose tissue; and (iii) on human immune cells.

METHODS

PXL770's effect (75 mg/kg, bid, per os, 8 weeks) was assessed histologically on liver steatosis and inflammation, in diet-induced obese (DIO) NASH mice. Liver inflammatory cells were assessed by flow cytometry. PXL770's effect (50µM) on cytokine release and nuclear NFkB activity were evaluated using ob/ob mouse-derived epididymal tissue explants in the presence of LPS or IL-1β, respectively. PXL770's effect on cytokine production from human M1 macrophages was assessed along with immature dendritic cells (DCs) after a challenge with LPS and on DC-mediated T cell skewing.

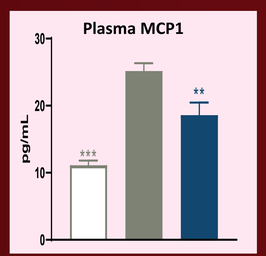
RESULTS - DIO NASH mice

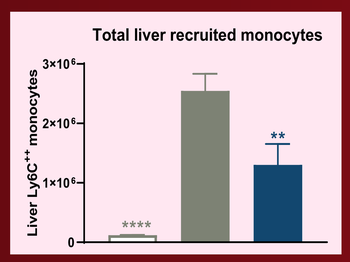
In DIO-NASH mice, PXL770 improved NAFLD score activity by decreasing liver steatosis, hepatic ballooning and liver inflammation.

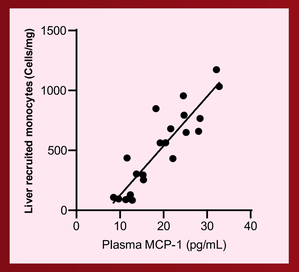


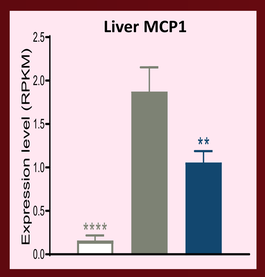
* p<0.05, *** p<0.001, compared to DIO-NASH vehicle, (n=11-12/group)

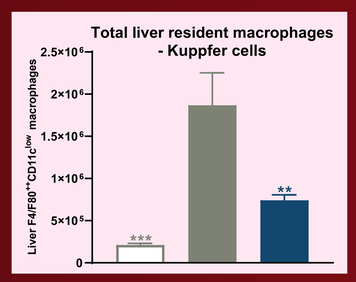
DIO-NASH Vehicle
PXL770 (35 mg/kg)
PXL770 (75 mg/kg)









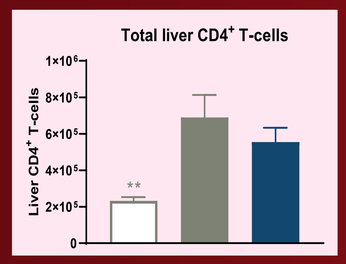


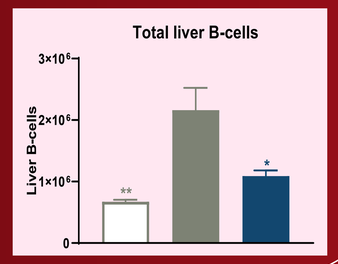
PXL770 reduced plasma and liver MCP1 levels; plasma MCP1 was also correlated with levels of total liver recruited monocytes. PXL770 decreased liver resident macrophages

* p<0.05, ** p<0.01, *** p<0.001, **** p<0.0001 compared to DIO-NASH vehicle, (n=8-13/group)

LEAN- Chow vehicle
DIO-NASH vehicle
DIO-NASH PXL770 75mg/kg

PXL770 reduced total liver CD4⁺ T-cells and Significantly reduced total liver B-cells

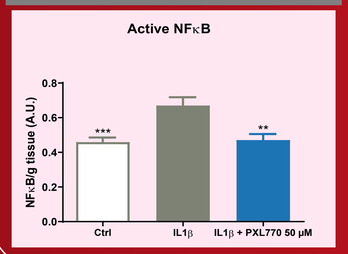




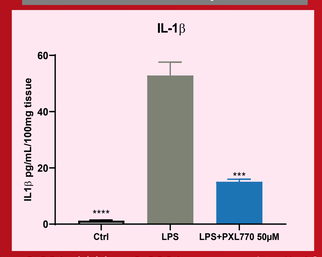
RESULTS - Mouse epididymal tissue explants

In ob/ob mouse epididymal adipose tissue explants, PXL770 totally prevented the nuclear activation of NF-kB and concomitantly reduced secretion of several inflammatory cytokines.

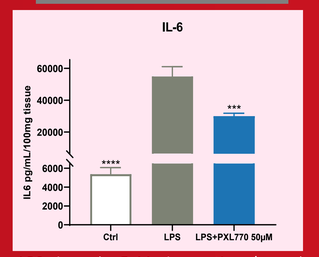
PXL770 reduced Nucleus NFKB level



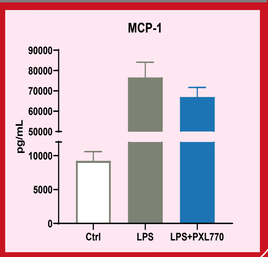
PXL770 reduced IL-1β release



PXL770 reduced IL-6 release



PXL770 reduced MCP1 release

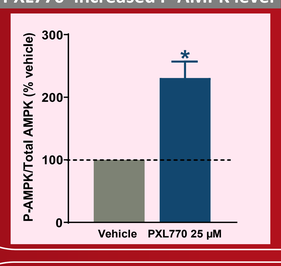


** p<0.01, *** p<0.001, **** p<0.0001 compared to IL-1β or LPS alone (n=5-11 observations/group)

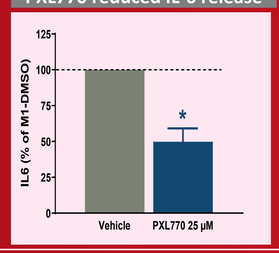
RESULTS - Human macrophages

PXL770 by increasing P-AMPK, reduced IL-6, MCP1 and TNFα release in human macrophages.

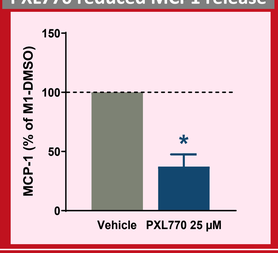
PXL770 increased P-AMPK level



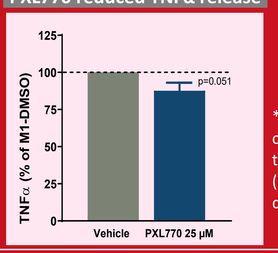
PXL770 reduced IL-6 release



PXL770 reduced MCP1 release



PXL770 reduced TNFα release

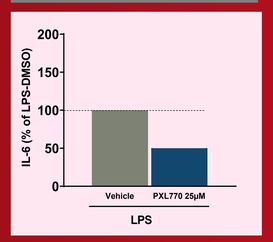


*p<0.05 compared to vehicle, (n=5 donors)

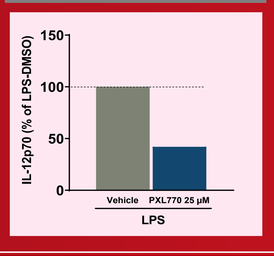
RESULTS - Human dendritic cells (preliminary results, n=2 donors)

PXL770 reduced IL-6, IL-12, TNFα release in human DCs and promoted an increase in T_{regs} cells

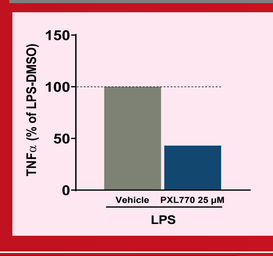
PXL770 reduced IL-6 release



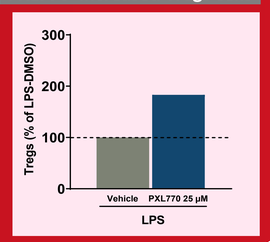
PXL770 reduced IL-12 release



PXL770 reduced TNFα release



PXL770 increased Tregs cells



CONCLUSION

By directly activating AMPK, PXL770 reduced liver and adipose tissue inflammation in mice. PXL770 exerted direct anti-inflammatory effects on human immune cells and on adipose tissue in mice. These direct benefits demonstrate effects of AMPK activation that extend beyond metabolic modulation. PXL770 appears promising for the treatment of NASH and may also be considered for treatment of other inflammatory diseases.

Acknowledgements

- Gubra – Danemark
- Metabrain Research- France