PXL770, a New Direct AMP Kinase Activator, Acting on the Adipose Tissue and the Liver, Demonstrates Promising Effects for Treatment of Non-Alcoholic Steatohepatitis

Pascale Gluais-Dagorn[1], Pia Steen Petersen[2], Sanne S. Veidal[2], Michael Feigh[2], Pascale Fouqueray[1], Sébastien Bolze[1] and Sophie Hallakou-Bozec[1], [1]Poxel, Lyon, France, [2] Gubra, Hørsholm, Denmark

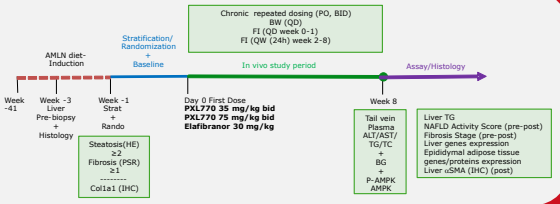
BACKGROUND and OBJECTIVES

Non-alcoholic fatty liver diseases (NAFLD) is characterized by hepatic lipid accumulation coming mainly from adipose tissue (AT) lipolysis (70%) and hepatic de novo lipogenesis (20%), pointing out the key role of AT in the development of NAFLD. Adenosine monophosphate-activated protein kinase (AMPK) is a key target acting on the 3 components: steatosis, inflammation and hepatic fibrogenesis. PXL770 is a first-in-class direct AMPK activator, demonstrating a good safety profile in healthy subjects during phase 1 studies. PXL770 has been shown to decrease de novo lipogenesis and to broadly improve metabolic profile in various rodent models suggesting that it could play an important role in the management of patients with NAFLD/NASH

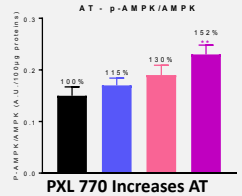
OBJECTIVES : to assess the PXL770 effects on liver and adipose tissue in a diet induced obesity biopsy proven-NASH mouse model

METHODS

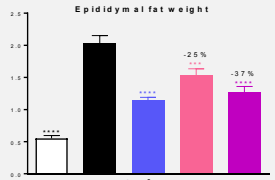
Male C57BL/6J were fed a diet high in trans fat (40%), fructose (20%) and cholesterol (2%) for a total of 41 weeks. After the diet induction period, a liver biopsy was collected to confirm steatosis and fibrosis status and to stratify the mice into diet induced obesity (DIO)-NASH groups treated per os for 8 weeks (n=12/group) with vehicle, PXL770 35 or 75 mg/kg twice daily or elafibranor (30 mg/kg daily).



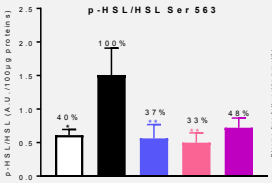
Benefits of PXL770 in the Adipose Tissue (AT)

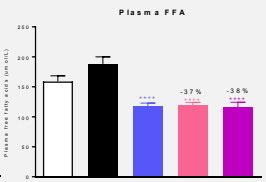


PXL 770 Increases AT AMPK activity

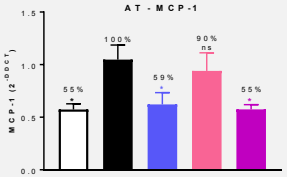


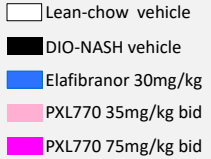
PXLP770 decreases epididymal fat weight



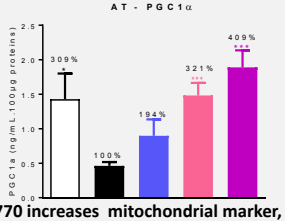


PXL 770 decreases epididymal AT hormone sensitive lipase (HSL) activity and decreases plasma free fatty acid (FFA)



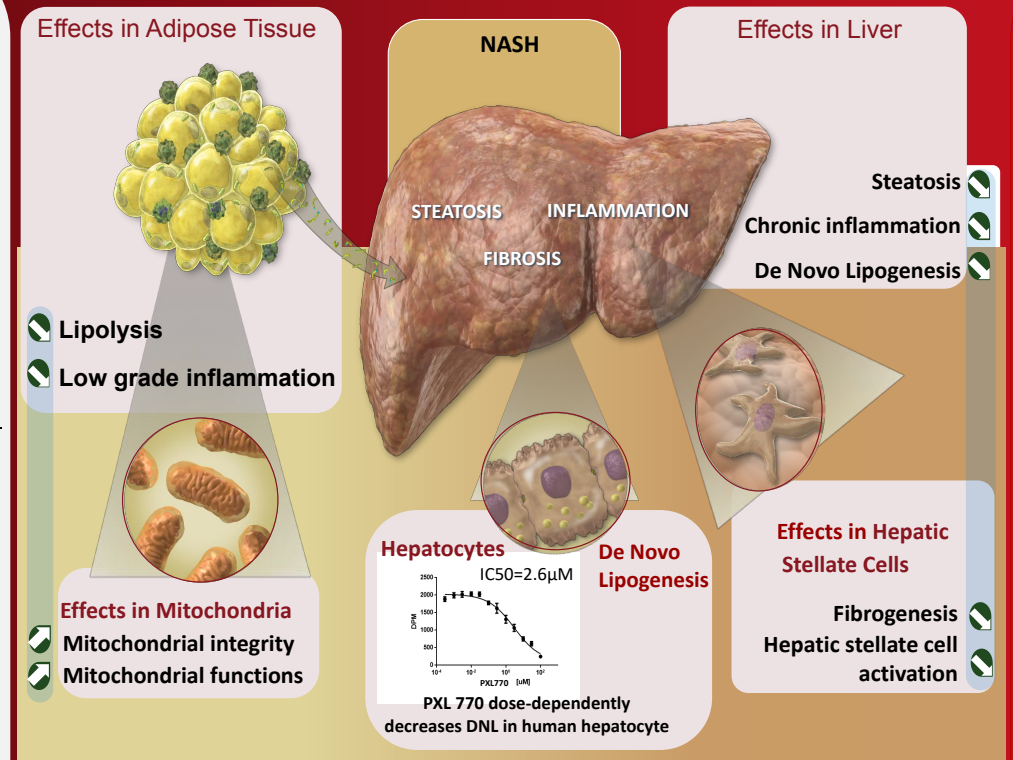


PXL 770 decreases inflammation marker, MCP-1, in epididymal AT



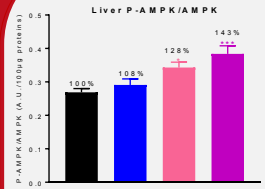
PXL 770 increases mitochondrial marker, PGC-1α, in epididymal AT

PXL770 Effects in physiopathology of NASH

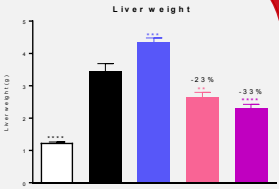


PXL 770 dose-dependently decreases DNL in human hepatocyte

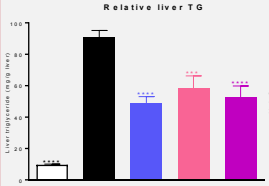
Benefits of PXL770 in the Liver

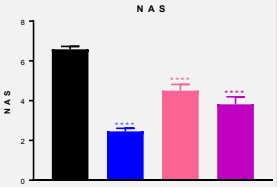


PXL 770 increases liver AMPK activity

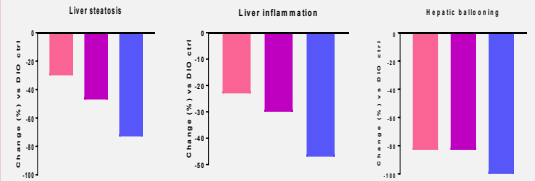


PXL770 decreases liver weight

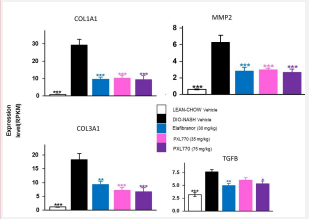




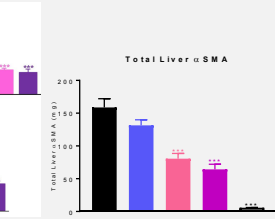
PXL 770 decreases Liver Steatosis and improves NAS



PXL 770 improves steatosis, Hepatocytes Ballooning and Inflammation scores



PXL 770 down-regulates genes expression involved in fibrosis



PXL 770 decreases Stellate cells activation

*p<0,05, **P<0.01, ***P<0.001, ****p<0.0001 vs. DIO-NASH Vehicle; One-way ANOVA with Dunnett's post-hoc test

CONCLUSION

In this DIO biopsy proven-NASH mouse model, PXL770 by directly activating AMPK demonstrates benefits on liver and adipose tissue, two main targets involved in NASH:

- PXL770 reduces liver steatosis, liver inflammation and liver fibrogenesis
- PXL770 inhibits lipolysis, reduces adipose tissue inflammation and improves mitochondria biogenesis

According to these results, PXL770 appears as a promising compound for the treatment of NASH