Characterization of disease progression and pharmacological intervention in the GAN diet-induced obese mouse model of NASH with advanced fibrosis and hepatocellular carcinoma

Authors: Michael Feigh, Mathias B Møllerhøj, Sanne S. Veidal, Martin Rahn Madsen, Henrik H. Hansen

Corresponding author: Michael Feigh - mfe@gubra.dk - Gubra Aps - Harsholm, Denmark

Background & Aim

Pharmacological intervention targeting metabolic-associated NASH and hepatic fibrosis might also affect hepatocellular carcinoma (HCC). The GAN (Gubra-Amylin NASH) diet-induced obese (DIO) mouse model presents with key parameters of metabolic-associated NASH including moderate hepatic fibrosis. The present study aimed to characterize disease progression in the extended GAN DIO-NASH mouse model and evaluate treatment response for the late-stage clinical drug candidate elafibranor (PPAR-α/δ agonist).

Study outline

Disease progression – Histopathology and tumor assessment

Histopathological NAFLD Activity Score and Fibrosis Stage

Histomorphometric steatosis, inflammation, fibrosis and tumor assessment

Hepatic transcriptomic profile for HCC

CONCLUSION

+ DIO-NASH mice demonstrated advanced NAFLD Activity Score (>4) after 28 weeks on GAN diet.
+ DIO-NASH mice progressed to bridging fibrosis (stage F3) after 24 weeks on GAN diet.
+ DIO-NASH mice developed tumors including HCC after 28 weeks on GAN diet.
+ DIO-NASH mice demonstrated HCC-associated transcriptomic signature.
+ Elafibranor significantly improved NAFLD Activity Score and Fibrosis Stage in DIO-NASH-HCC mice.
+ Elafibranor reduced histological markers of steatosis, inflammation, and fibrosis in DIO-NASH-HCC mice.
+ Elafibranor improved HCC-associated transcriptomic signatures in DIO-NASH-HCC mice.
+ The GAN DIO-NASH-HCC mouse model is suitable for profiling novel drug therapies for advanced fibrosis and HCC.