Animal models of non-alcoholic steatohepatitis: comparison of the MCD, CD, H-FFC and ob/ob H-FFC mouse

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Introduction and Aim
Many animal models of non-alcoholic steatohepatitis (NASH) have been developed which mirror various aspects of the disease and choosing the most appropriate is a key question faced by the pharmaceutical industry. The aim of this present study was to characterise RenaSci’s four dietary-induced NASH mouse models, specifically the methionine/choline deficient (MCD) diet mouse, choline deficient (CD) diet mouse, high-fat/fructose/cholesterol (H-FFC) diet mouse and the genetically-obese (ob/ob) H-FFC diet mouse. The efficacy of the clinically effective agents pioglitazone and/or elafibranor on histological end-points, plasma parameters and liver biochemistry were also assessed.

Methods
Male C57BL/6J mice were maintained on standard chow, an MCD diet or a CD diet for 6 weeks. Alternatively male C57BL/6J and ob/ob mice were maintained on standard chow or a H-FFC diet for 12 weeks. Mice were randomised into treatment groups and received either vehicle (po), pioglitazone (15 mg/kg po qd) or elafibranor (30 mg/kg po qd, reduced to 20 mg/kg in the CD study) from the first day of the diet-induction. A blinded histopathological assessment of the individual and combined components of the NAFLD activity score (NAS: steatosis, hepatocellular ballooning and lobular inflammation) and fibrosis was performed. Additionally, plasma parameters and liver biochemistry were also assessed.

Study Design
Randomisation
Vehicle
Pioglitazone
Elafibranor

Results

Figure 1
Body weight in MCD, CD, H-FFC and ob/ob H-FFC mice. Data are presented as means ± SEM. Significant differences from the Chow group are denoted by *p<0.05, †p<0.01 and ††p<0.001. Representative images of H&E stained liver at 10x magnification are shown.

Table 1: Plasma parameters and liver biochemistry in MCD, CD, H-FFC and ob/ob H-FFC mice. Data are presented as means ± SEM. Significant differences from the Chow group are denoted by *p<0.05, †p<0.01 and ††p<0.001. ESLUS (formerly DRI-DIG) is a network of investigators who are involved in the acquisition of the data.

Conclusions
• RenaSci’s MCD, CD, H-FFC and ob/ob H-FFC mouse models each exhibit NASH and fibrosis.
• The clinically effective agents pioglitazone and/or elafibranor reduce NASH and fibrosis in each of these models.
• Plasma ALT and liver triglycerides were significantly increased in the MCD, CD, H-FFC and ob/ob H-FFC mouse and this increase was blunted by treatment with either pioglitazone or elafibranor.
• The MCD, CD, H-FFC and ob/ob H-FFC mouse each present a useful tool for assessing potential new therapies for NASH and fibrosis when their individual limitations are considered. The H-FFC mouse appears to be the model most closely aligned with the histopathology and pathogenesis of the disease. Which model will be the most predictive of treatment outcomes in the clinic is still unclear.