charles river

Overview

Charles River maintains a colony of pre-conditioned mice with diet-induced, biopsy-confirmed nonalcoholic steatohepatitis (NASH) for rapid study starts.

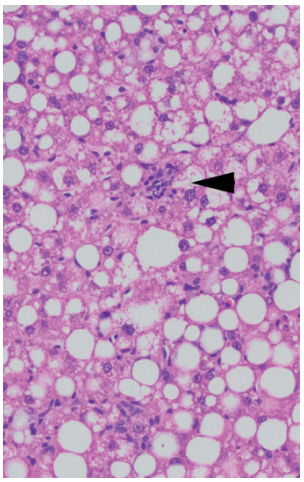
DISCOVERY

Animal Models of NASH

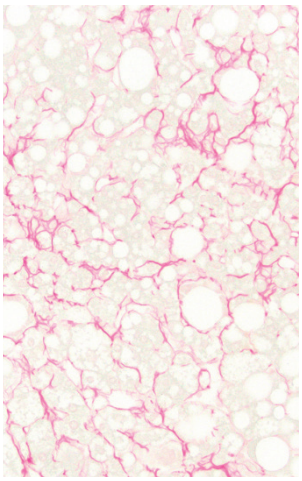
Intensive interest in discovering and developing safe and effective treatments for nonalcoholic steatohepatitis (NASH) has prompted the development of translatable animal models of the disease. Numerous approaches to this problem are cited in the literature, yet there is no clear consensus on a gold standard. The application of diets rich in fat and refined sugar are frequently used because they retain some of the metabolic context and recapitulate the histopathology found in human disease. Despite the use of inbred animal strains, considerable variability exists within studies; it is estimated between 20% - 50% of animals on a “NASH” diet fail to develop disease within a given study, and there is considerable variability with respect to disease severity among those animals that do. This variability can lead to false conclusions regarding efficacy of the candidate test article under examination. For example, if, by luck of the draw, most of the animals in the vehicle treated control group presented with minimal/no disease at the outset of treatment, and those assigned to a test article group had severe disease, a potentially effective therapy might be missed due to lack of significant disease in the untreated controls. Liver biopsies taken prior to initiation of treatment helps to reduce variability in the study. Tissue sections scored for steatosis, inflammation, hepatocyte degeneration, and fibrosis can be used to eliminate animals that failed to develop disease and to rationally distribute subjects to the various treatment groups based on NAS disease activity scores. In addition, each animal can serve as its own control and response to treatment rates can be calculated.

Of the myriad published NASH models, ob/ob (i.e., obese) mice fed a high fructose, high fat, cholesterol diet demonstrates excellent correlation with clinical trials across 3 mechanistically distinct candidate therapies for human NASH. Treatment of ob/ob mice on a NASH diet with obeticholic acid (FXR agonist), liraglutide (GLP-1 agonist), and Elafibranor (PPAR agonist) all produced data that are concordant with their respective clinical studies.

Representative Images – ob/ob Mice Fed High Fat, High Fructose, Cholesterol Diet



H&E staining demonstrating extensive steatosis and lobular inflammation.



Picrosirius red decoration of fibrosis (126 days).

Support from Our Center of Excellence

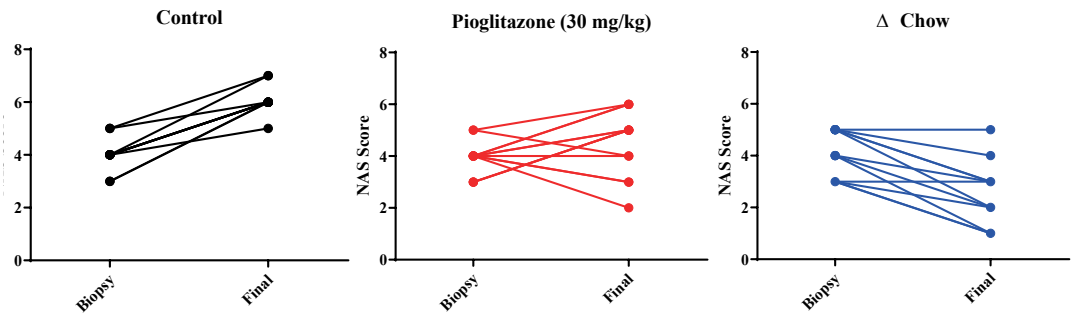
Scientists at our Center of Excellence for Metabolic Diseases in Shrewsbury, MA have extensive experience with multiple animal models of metabolic dysfunction, including diabetes (Type 1 and Type 2), metabolic syndrome, diet-induced obesity and liver diseases including NASH. Our veterinary surgical team performs liver biopsies, and the histopathologic assessment of target tissues is conducted by board-certified veterinary pathologists. We work in a variety of species including rodents, canines, and swine. We also have access to a large cohort of NHPs with various forms of naturally occurring metabolic dysfunction including obesity, metabolic syndrome, type 2 diabetes and hypertension.

Assessment of Candidate Therapies for NASH

We maintain a colony of ob/ob mice on high fat, high fructose, cholesterol diet with biopsy-confirmed NASH. Confirmation of disease stage reduces study variability by eliminating non-responding animals, establishing treatment groups at the same baseline level, and using each animal as its own control. Studies also include routine estimates of body weight and food intake, full clinical chemistry profiles, assessments of glycemic control (OGTT, PTT) and insulin resistance (ITT and calculation of HOMA score), and bioanalysis of test article for both trough and peak blood levels, and quantitation of serum and liver lipids. Other biomarkers (e.g., serum cytokines, liver OH-Pro, etc.), pharmacodynamic endpoints, transcriptomic profiling, and pathway analysis are also available. We have also qualified a model of biopsy-confirmed NASH in C57BL/6 mice fed a choline-deficient, defined amino acid (CDAA) diet.

Trial/Model	Vehicle/PBO	Test Article	Reference
LEAN Clinical Trial	9% (2/23)	39% (9/23) (Liraglutide)	Armstrong, et al. Lancet 387: 679, 2016
ob/ob – AMLN Diet	8% (1/12) – Improvement 0% (0/12) – Resolution	20% (2/10) – Improvement 0% (0/10) – Resolution (Liraglutide)	Tolbol, K. S., et al. World J Gastroenterol 2: 179, 2018
Golden Clinical Trial	21% (8/39)	48% (15/31) (Elafibranor)	Ratzui et al., Gastroenterol. 150: 1147, 2016
ob/ob – AMLN Diet	8% (1/12) – Improvement 0% (0/12) – Resolution	100% (11/11) – Improvement 90% (9/10) – Resolution (Elafibranor)	Tolbol, K. S., et al. World J Gastroenterol 2: 179, 2018
FLINT Clinical Trial	12% (13/109)	20% (22/110) (Obeticholic Acid)	Neuschwander-Tetri et al., Lancet 387: 956, 2015
ob/ob – AMLN Diet	8% (1/12) – Improvement 0% (0/12) – Resolution	100% (11/11) – Improvement 100% (11/11) – Resolution (Obeticholic Acid)	Tolbol, K. S., et al. World J Gastroenterol 2: 179, 2018

NAS Score – Biopsy vs. Terminal



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