NAFLD/NASH

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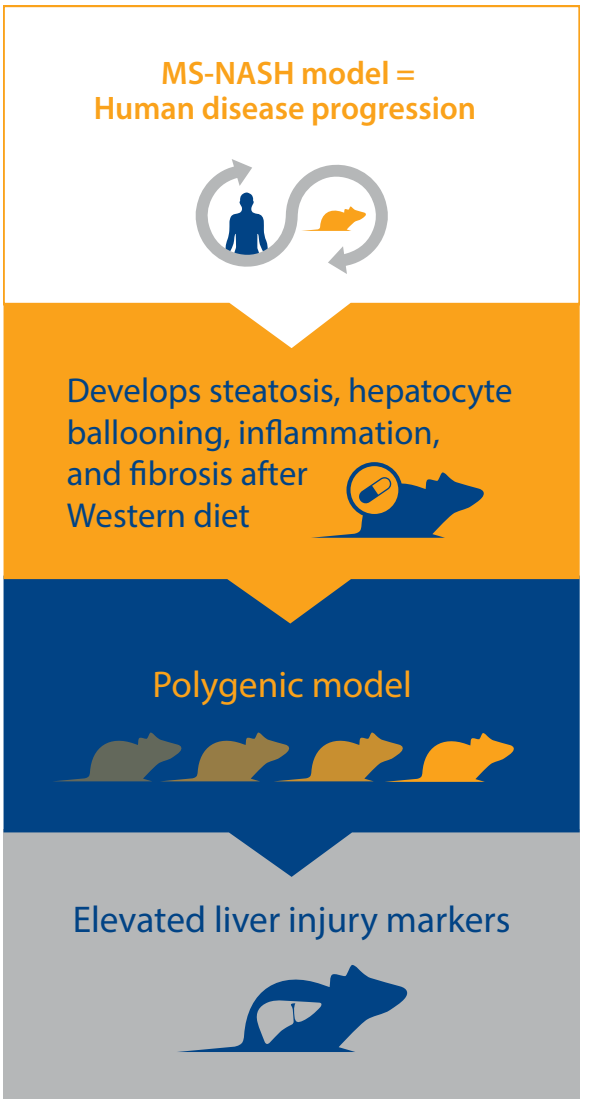
MS-NASH: A more translatable polygenic model for drug development

Advance your preclinical liver disease studies with a rodent model that more closely mimics human NAFLD/NASH disease progression.

The MS-NASH mouse (formerly FATZO) provides a more translatable choice for the evaluation of NAFLD/NASH therapeutics. Featuring an intact leptin pathway, the model closely mimics human metabolic disease progression, providing an inherently dysmetabolic, obese, and diabetic preclinical mouse model for NAFLD/NASH therapeutic development.

Through the administration of a "Western diet", the MS-NASH mouse develops liver steatosis leading to NAFLD/NASH.

- With metabolic stress on the liver indicated by elevated liver injury markers (ALT, AST) and liver triglycerides.
- Steatosis observed by 4-8 weeks, consistent with lobular inflammation.
- Hepatocyte ballooning observed by 16 weeks.
- Fibrosis observed by 20 weeks.
- Progressive worsening and histological changes from NAFLD observed over time.
- Accelerated NAFLD/NASH progression and exacerbated pathology following CCl_4 administration, with fibrosis observed in only 12 weeks.
- Improved NAS score and lipid profile with OCA treatment.



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MS-NASH Mouse Key Facts

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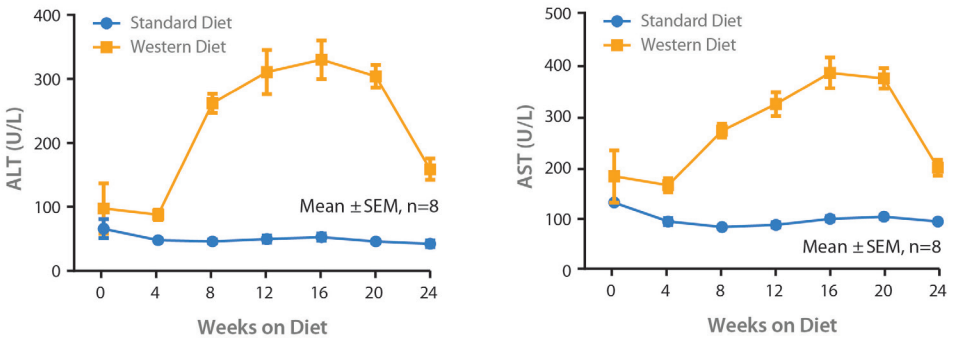
Utilize a unique, human disease-relevant NAFLD/NASH mouse model to progress preclinical research:

- Spontaneously obese and dysmetabolic polygenic model with an intact leptin pathway.
- On a Western diet (21% fat, 0.2% cholesterol, 5% fructose in drinking water), the MS-NASH mouse develops:
  - Elevated body weight, body fat, and liver weight.
  - Elevated liver injury markers (ALT, AST) and liver triglycerides.
- Progressively develops key disease indicators similar to human NAFLD/NASH on a Western diet:
  - Steatosis by 4-8 weeks.
  - Hepatocyte ballooning and inflammation by 16 weeks.
  - Fibrosis by 20 weeks.
- CCl_4 administration accelerates NAFLD/NASH progression and exacerbates disease pathology:
  - Steatosis by 4 weeks.
  - Hepatocyte ballooning by 4-8 weeks.
  - Inflammation by 8-16 weeks.
  - Fibrosis observed in as little as 12 weeks, exacerbated from mild/moderate to severe fibrosis.
- Robust study designs and comprehensive endpoint panels already validated, ready to rapidly initiate and progress preclinical NAFLD/NASH studies.

The MS-NASH mouse is an inbred polygenic model for metabolic syndrome, spontaneously developing obesity, dyslipidemia, and insulin resistance on a standard chow diet. Unlike other rodent models of metabolic disease, the MS-NASH mouse has a functional leptin pathway, more closely mimicking human disease progression. This provides a more translatable preclinical model for the evaluation of therapeutic agents.

With the addition of a Western diet and fructose in the drinking water, the MS-NASH mouse develops liver steatosis leading to NAFLD/NASH. Following 24 weeks on Western diet, the model demonstrates significant liver enzyme increases, indicating metabolic stress on the liver (**Figure 1**, compared with animals fed standard chow).

Figure 1: Elevated Injury Markers in MS-NASH Mouse Model



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MS-NASH Mouse Factsheet

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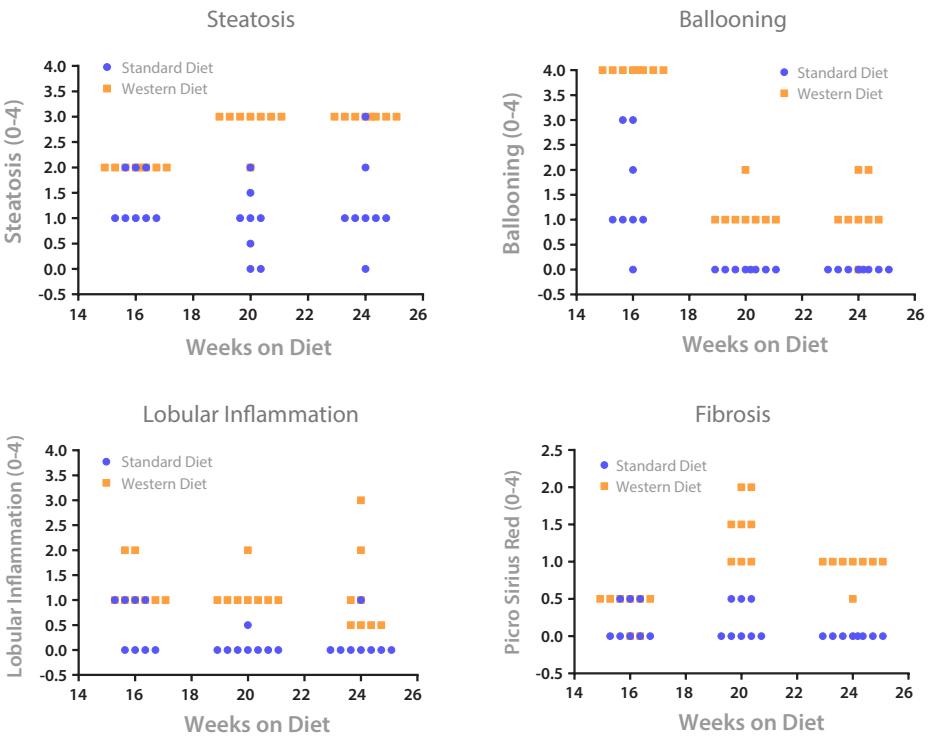
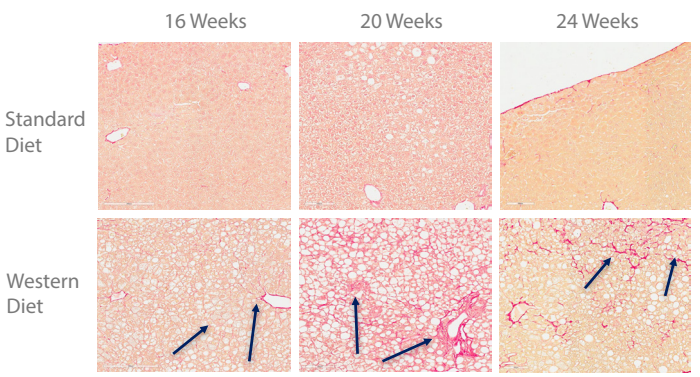
Key NAFLD/NASH liver pathologies are observed in MS-NASH models on Western diet plus fructose, evaluated using the NASH Clinical Research Network histological scoring method. Significantly elevated scores for steatosis, lobular inflammation, and hepatocyte ballooning were observed after 16 to 24 weeks on diet, compared with models on standard chow (**Figure 2**). For the Western diet fed animals, steatosis was observed at all assessed-time points, as was significant and consistent lobular inflammation.

Figure 2: MS-NASH Mouse Model Develops NAFLD Progressing into NASH by 20 Weeks on a Western Diet



Mild liver fibrosis occured at 16 weeks on diet in half of the models, with more significant fibrosis observed at 20 and 24 weeks on Western diet and fructose. Little to no fibrosis is observed for control models. The progressive worsening and histological changes from NAFLD in Western diet fed animals is shown in **Figure 3**.

Figure 3: Development of Fibrosis by 20 weeks in MS-NASH Model (Picro Sirius Red Staining)



MS-NASH Mouse Factsheet

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Accelerate NAFLD/NASH in the MS-NASH Model through CCl_4 Administration

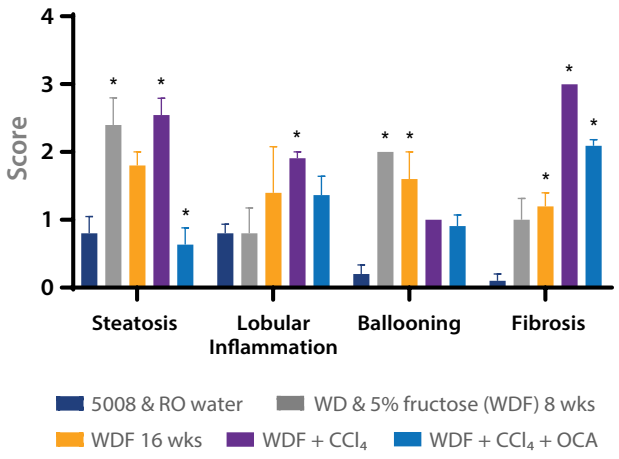
The addition of CCl_4 to the Western diet induces NASH in a shorter time frame (12-16 weeks) and also exacerbates fibrosis. The mild to moderate fibrosis (score ~1.5) usually observed at 20 weeks is worsened to severe fibrosis (score >2.5), and seen in only 12-16 weeks.

Table 1: MS-NASH Mouse NAFLD/NASH Progression on Western Diet and Accelerated Western Diet + CCl_4

	Western Diet	Western Diet + CCl_4
Steatosis	4-8 weeks	4 weeks
Ballooning	16 weeks	4-8 weeks
Inflammation	16 weeks	8-16 weeks
NASH/Fibrosis	16-20 weeks	12-16 weeks

NASH induced by both Western diet and Western diet + CCl_4 can be alleviated by OCA treatment, with reduced symptoms, improved lipid profile, and improved NAS score (**Figure 4**).

Figure 4: Liver NAS and Fibrosis Scoring of MS-NASH mice under Different Diets and Treatments



Summary

The MS-NASH mouse, a polygenic model of obesity and type 2 diabetes, is a unique translatable model that more closely resembles human NAFLD and NASH when fed a Western diet and fructose.

Disease progression and pathology are further exacerbated and accelerated through the addition of CCl_4, with faster and more severe fibrosis observed.

The MS-NASH mouse with relevant NAFLD/NASH disease pathology and progression provides an ideal model for preclinical evaluation of novel agents for the prevention or treatment of NAFLD/NASH.