MS-NASH Mouse Factsheet

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Use the MS-NASH mouse (formerly called FATZO), a more translatable polygenic mouse model of metabolic syndrome and NASH, for preclinical research

Rapidly progress your preclinical studies with the MS-NASH mouse, which more closely mirrors human metabolic syndrome than currently available rodent models.

Conventional rodent models for metabolic syndrome research lack translatability to the human condition. For preclinical assessment of agents targeting metabolic syndrome components e.g. obesity and diabetes, more translational models better recapitulating human disease are needed.

CrownBio has developed the MS-NASH mouse, a more translatable rodent model for obesity, metabolic syndrome, and diabetes drug development.

Human-Like Disease Progression:

- Polygenic model with an intact leptin pathway as in human disease, but unlike conventional rodent models of metabolic syndrome.
- More closely resembling human disease with spontaneous obesity, dyslipidemia, and rapid insulin resistance.
- Also developing liver steatosis leading to NAFLD/NASH.
- Allowing the evaluation of pharmacological interventions for metabolic syndrome components.
- Responds to anti-diabetic standard of care treatments like humans.

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MS-NASH Mouse Key Facts

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CrownBio provides the MS-NASH mouse, a highly translatable rodent model for obesity, metabolic syndrome, and diabetes:

- Developed by crossing the *C57BL6/J* with *AKR/J* mice and selective breeding for obesity, insulin resistance, and hyperglycemia phenotype, followed by inbreeding for more than 30 generations.
- Polygenic model of obesity, metabolic syndrome, and diabetes with an intact leptin pathway.
- Progressively develops human-like features of metabolic syndrome while on a normal chow diet, including rapid weight gain to obesity, dyslipidemia, and rapid insulin resistance leading to diabetes; also develops liver steatosis leading to NAFLD/NASH on a western diet + fructose.
- Allows evaluation of novel agents targeting metabolic syndrome, including anti-diabetic agents, with response to SoC therapeutics rosiglitazone and semaglutide observed.
- Cohorts readily available in Europe and North America.

What is the MS-NASH mouse?

The MS-NASH mouse is an inbred polygenic animal model for obesity, metabolic syndrome, diabetes, and NAFLD/NASH. Unlike other rodent models of metabolic disease, the MS-NASH mouse has a functional leptin pathway, which more closely mimics the human condition, and results in a more translatable choice for testing the efficacy of anti-obesity and anti-diabetic compounds.

The MS-NASH mouse was developed by crossing *C57BL6/J* with *AKR/J* mice and was selectively bred for obesity, insulin resistance, and hyperglycemia phenotype, followed by inbreeding for more than 30 generations. The resulting MS-NASH mouse model has:

- rapid weight gain, comparable to *db/db* or *ob/ob* models.
- males which become hyperglycemic at 14 weeks of age.
- insulin resistance which develops at an early age.

The MS-NASH Mouse More Closely Mirrors the Human Metabolic Syndrome Phenotype than Conventional Rodent Models

Most rodent models of Type 2 diabetes have a monogenic mutation that is responsible for the initiation of obesity and insulin resistance; however, both leptin and leptin receptor mutations are rare in human disease. The two most common obesity causing mutations involve:

- the leptin receptor, observed in
  - Zucker Fatty (ZF) rat
  - Zucker Diabetic Fatty (ZDF) rat
  - *db/db* mouse
- the leptin molecule, observed in
  - *ob/ob* mouse

The MS-NASH mouse closely mirrors the human metabolic syndrome, with spontaneous development of obesity, dyslipidemia, and insulin resistance (**Figure 1**) all with a functional leptin pathway, and expressed using a standard chow diet. Liver steatosis leading to NAFLD/NASH develops on a western diet + fructose.

A comparison of the MS-NASH mouse with other less translatable, more conventional rodent models with leptin/leptin receptor mutations or diet induced obesity (DIO) is shown in **Table 1**, and in **Figure 1** with a DIO model in male *C57/BL6* mice.

Figure 1: Development of Obesity, Dyslipidemia, Hyperglycemia, and Insulin Resistance in MS-NASH and DIO Mouse Models

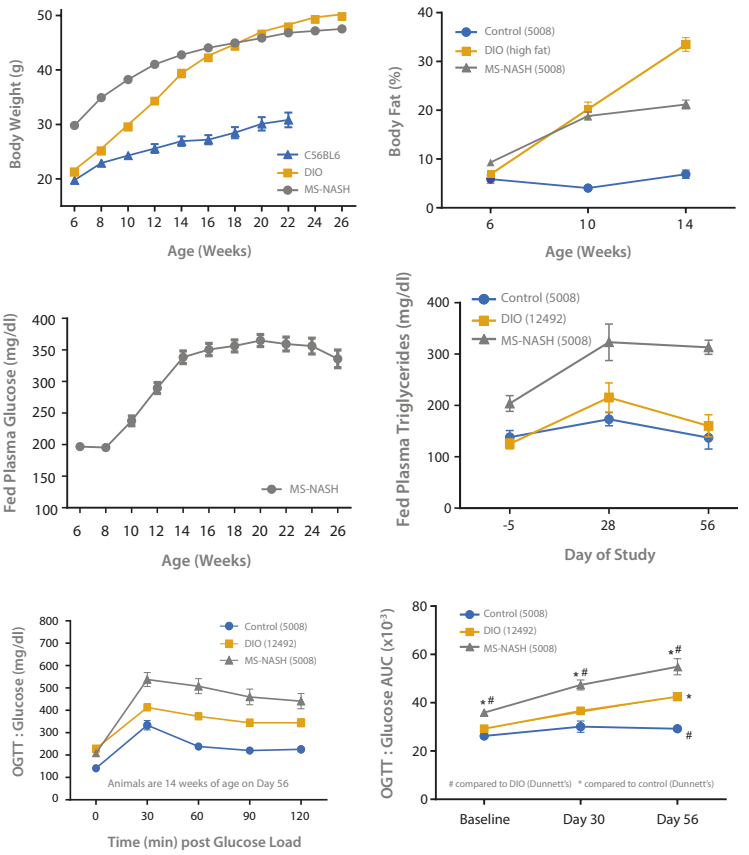

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Table 1: The MS-NASH Mouse vs Conventional Murine Models

	Human	MS-NASH Mouse	DIO	*ob/ob*
Polygenic Disease	Yes	Yes	Yes	No
Intact Leptin Pathway	Yes	Yes	Yes	No
Insulin Resistance	Yes	Yes	Diet Induced	Yes
Weight Gain	Yes	Yes	Diet Induced	Yes
Hyperglycemia	Yes	Yes	Minimal	Mild/ Variable

The MS-NASH Mouse Responds to Anti-Diabetic Agents

The MS-NASH mouse has been shown to respond to anti-diabetic therapies, providing a translatable model for evaluation of new agents. Glucose intolerance in the MS-NASH mouse is reduced with rosiglitazone treatment at 14 weeks of age (**Figure 2**), and semaglutide has been shown to reduce both food intake and body weight, as well as glycemia in this model (**Figure 3**).

Figure 2: Rosiglitazone Treatment Improves Glucose Tolerance in the MS-NASH Mouse

Animals are 18 weeks of age on Day 89.

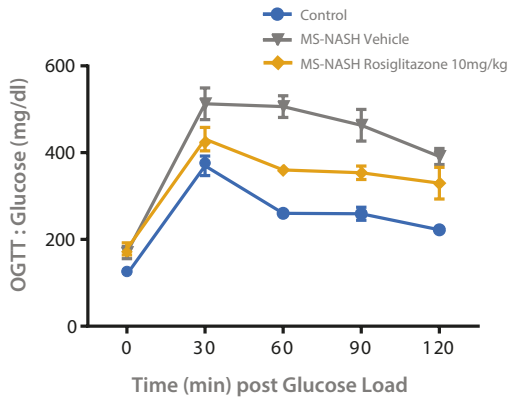
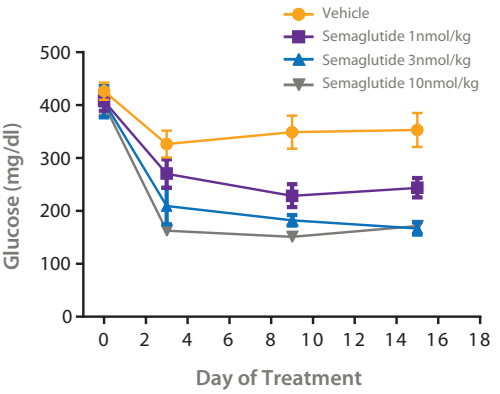


Figure 3: Semaglutide Treatment Reduces Glycemia in the MS-NASH Mouse



Summary

The MS-NASH mouse is a more translatable mouse model for obesity, metabolic syndrome, and diabetes drug development. The model develops characteristics of metabolic syndrome, progressing to diabetes, whilst maintaining an intact leptin pathway. The polygenic MS-NASH mouse provides an excellent model of obesity, hyperglycemia, and NAFLD/NASH, and is a replacement for currently used monogenic *ob/ob, db/db,* and polygenic (DIO) mouse models. Response to standard therapies such as rosiglitazone and semaglutide have been observed, showing the model to be highly translatable to the human condition.