

# Rodent Models of Obesity

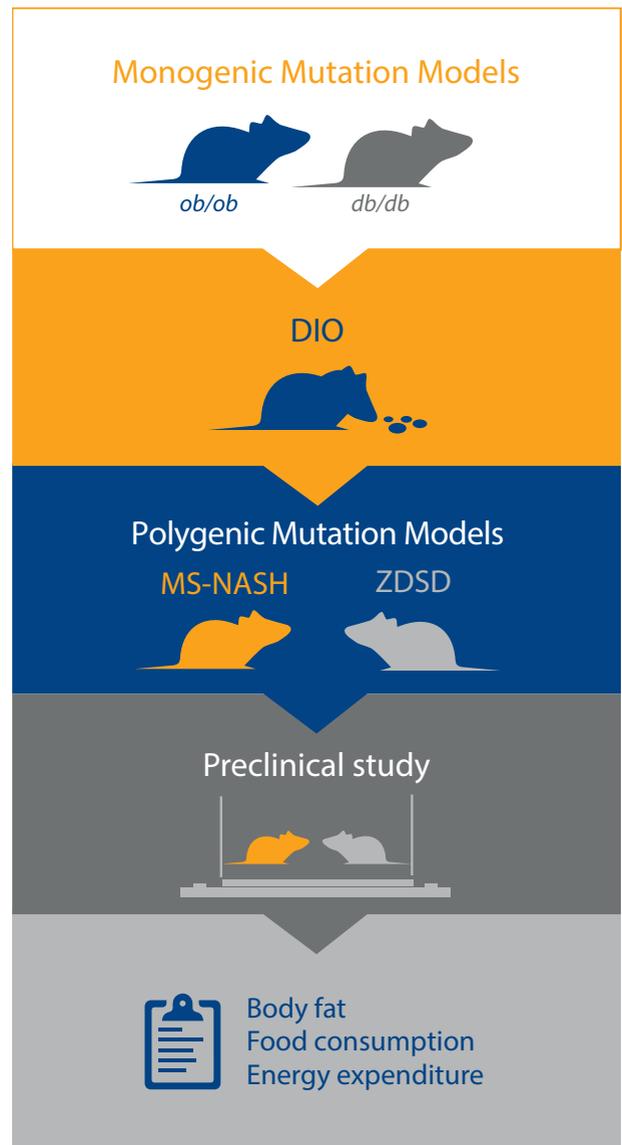
Discover CrownBio's complete collection of conventional and translatable rodent obesity models

Discover how our comprehensive collection of models, combined with key obesity research endpoints, can drive forward your anti-obesity drug development programs.

Rodent models are the first step in an *in vivo* preclinical translational program, providing key data on disease mechanisms, efficacy, and safety to make early stage go/no-go decisions on progressing agents to further study. For obesity research, appropriate preclinical rodent models are needed to elucidate the full molecular mechanisms of obesity, and evaluate novel agents to target the disease.

CrownBio provides a wide ranging rodent obesity research platform, including:

- Any commercially available rat or mouse model, as well as models naturally prone to obesity or diet induced obesity (DIO) models.
- Highly translational models of obesity - the polygenic MS-NASH (formerly called FATZO) mouse and ZDSD rat, which become spontaneously obese on standard chow.
- Key obesity endpoint monitoring and analyses, including body fat, food consumption, and energy expenditure.
- Customizable study design including monitoring all endpoints within the same study, to rapidly progress preclinical obesity studies.





# Rodent Models of Obesity Key Facts

## Our comprehensive rodent obesity research platform is used for preclinical evaluation of anti-obesity agents:

- With monitoring of three key endpoints in obesity research, which can be combined in customizable studies:
  - Percent body fat as determined by qNMR, with associated percent lean mass and water data provided.
  - Food consumption through weighing provided food.
  - Energy expenditure measured via indirect calorimetry by the OxyMax system.
- In highly translatable polygenic models of obesity – the MS-NASH mouse and ZDSD rat which closely mimic the human condition – developing spontaneous obesity on a normal chow diet without leptin/leptin receptor mutations.
- As well as conventional and induced diabetes models for consistency with historical research:
  - Any commercially available model.
  - Rodents naturally prone to obesity e.g. Zucker *fa/fa* and obese prone SD rat, and *ob/ob* mouse.
  - High fat DIO rat and mouse models.

## Body Fat Measurement via qNMR

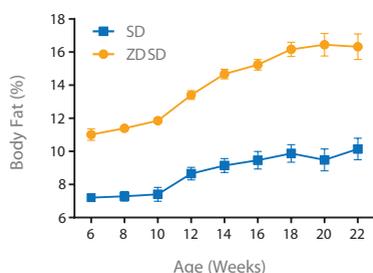
Percent body fat is measured in our obesity studies by qNMR (EchoMRI). This technique utilizes a low field electromagnet to measure conscious whole body composition in only three minutes, providing data on:

- Percent body fat
- Percent lean mass
- Percent water

Anti-obesity agents can then be evaluated to identify decreases in body fat and baseline body fat (via prefeeding) or to determine how much model body fat is converted into lean mass. Body weight is also recorded as standard in our assays.

Example body fat data is shown in **Figure 1** comparing a control SD rat with an obese, Type 2 diabetic ZDSD rat. The ZDSD rat has a higher proportion of body fat than control animals, both of which show increases in fat levels over time and while aging.

**Figure 1: The ZDSD Rat has a Greater Percent Body Fat than SD Control, which Increases with Age**

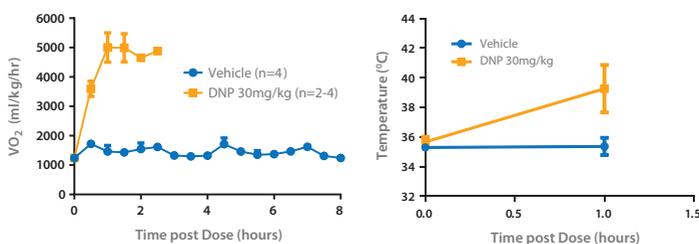


## Energy Expenditure Data

Energy expenditure is measured via indirect calorimetry (OxyMax system, Columbus Instruments). Animals are placed in a sealed unit, which has a known amount of oxygen delivered (allowing measurement of oxygen consumption,  $VO_2$ ) and the amount of oxygen that is converted to  $CO_2$  is recorded as it leaves the unit ( $VCO_2$ ). Infra-red is used to measure animal movement and activity, and body temperature can also be monitored as required.

**Figure 2** shows the validated energy expenditure data that can be provided by the OxyMax system (specifically oxygen consumption and body temperature data). The mitochondrial uncoupler DNP is orally administered to the research animal of choice, and interrupts mitochondrial respiration, which results in a lack of ATP production. This causes an increase in metabolic rate and a rapid rise in oxygen consumption, as well as a heat buildup which results in an acutely increased body temperature (which can be monitored remotely via subcutaneous radio chip implants). Models expire approximately 2 to 2.5 hours post-dosing, which mimics the effects of DNP overdose in humans. This system can be used to evaluate novel anti-obesity agents and their effects on energy expenditure.

**Figure 2: DNP Causes an Increase in Energy Expenditure in SD Rats as Measured by the OxyMax System**





# Rodent Models of Obesity Factsheet

## Food Consumption Measurement

Monitoring food consumption in obesity studies is a standard endpoint, to confirm that weight loss/reduction in body fat is due to the agent under evaluation rather than a reduction in food intake. CrownBio can calculate the total food intake by weighing of provided food either daily or weekly.

## Summary

Obesity is becoming a serious epidemic issue in many countries, with more than 650 million adults classified as obese in 2016. The underlying cause of obesity is an energy imbalance between calories consumed and calories expended, with a worldwide increase in eating energy-dense, high-fat foods and a decrease in physical activity. The precise molecular and cellular mechanisms of obesity-associated health problems have not yet been fully elucidated and appropriate preclinical technologies and models are needed to further both obesity research and evaluation of anti-obesity agents.

CrownBio provides monitoring of three main study endpoints in obesity research: percent body fat via qNMR, food consumption, and energy expenditure via the OxyMax system. We work with clients to design the optimal study for their agents, which can monitor all three endpoints in one study if required. The techniques can be performed in any commercially available model for consistency with historical research, as well as in models with a tendency for obesity, and high fat diet induced obesity.

We also monitor these parameters in more human disease translatable models including the MS-NASH mouse and ZSD rat. These polygenic models of dysmetabolism naturally develop obesity on a normal diet and without leptin/leptin receptor mutations, closely mimicking human obesity and providing more translatable research models.



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