Our Expertise

Physiogenex NASH preclinical models

Your success
Physiogenex NASH/fibrosis models

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Ultra-fast 3-week NASH mouse:
Select your best drug candidate or combination in only 3 weeks

- Our original high fat/cholesterol/cholic acid diet with cyclodextrin in drinking water expedites NASH and liver fibrosis in C57BL6/J mice within 3 weeks.

- The cyclodextrin/cholesterol combination promotes hepatocyte cholesterol uptake, so that microvesicular steatosis and liver inflammation are already observed after 1 week of diet, while fibrosis can be observed after 3 weeks of diet.

Circles indicate microvesicular steatosis and inflammatory foci already observed after 1 week of diet.

Blue arrows indicate perisinusoidal and portal fibrosis observed after 3 weeks of diet.

Duparc et al. *Am J Physiol Gastrointest Liver Physiol* 2019
Briand et al. *Clin Transl Sci* 2020
Ultra-fast 3-week NASH mouse:
Major clinical benchmarks improve NASH within a 2-week treatment period

H&E and Sirius Red pictures at the end of 2-week treatment period in mice treated with vehicle, elafibranor, semaglutide, obeticholic acid or firoscostat. Circles indicate microvesicular steatosis and inflammatory foci – blue arrows indicate fibrosis
Ultra-fast 3-week NASH mouse:
Major clinical benchmarks improve steatosis, inflammation and fibrosis scoring

Steatosis, inflammation and fibrosis scores at the end of 2-week treatment period in mice treated with vehicle, elafibranor, semaglutide, obeticholic acid or firoscostat. Data are shown as median. *p<0.05, **p<0.01 and ***p<0.001 vs. vehicle
Note: unlike other DIO-NASH mouse model, Physiogenex administrates fructose in drinking water to increase daily fructose intake and favor metabolic disorders and liver lesions (mice on high fat diet eat limited amount of food). This expedites NASH and ensure a score 2 fibrosis after 25 weeks of diet.
Free-choice diet induced NASH hamster model:

Evaluate your drug or combination on both NASH and HFpEF in a more human-like context in 5 weeks

- Unlike mice (having HDL-c only and muricholic acids), hamsters have a similar lipoprotein cholesterol metabolism and bile acids profile (CA and CDCA) as compared with humans.
- Under a 15-week free-choice diet, hamsters develops human-like NASH, including hepatocyte ballooning and bridging fibrosis.

4-week old, male, Golden Syrian hamsters

15-week free choice diet induction (hamsters already on diet)

5-week treatment

screening procedure:
- blood/organs collection
- plasma ALT/AST, TC, body weight
- histology analysis and NAFLD activity scoring at baseline:
- hepatic gene expression
- % Sirius Red labelling and NAFLD activity score (NAS)

Identification of hepatocyte ballooning (square) is seen as adipocyte-like cells in mice and ballooning scoring is thus compromised. In contrast, hamsters develop similar histopathological features seen in humans which facilitates scoring.

Briand et al. Eur J Pharmacol 2018
Free-choice diet induced NASH hamster model:
Induction of both NASH/fibrosis and HFpEF in 10 to 20 weeks of free-choice diet

Free choice diet induces steatosis, inflammation (white squares) and clusters of ballooned hepatocytes (dashed black squares) as confirmed by CK18 and SHH immunostaining. Ballooned hepatocytes are surrounded by collagen III and alpha-SMA immunostaining. Free choice diet also results in portal and bridging fibrosis (Sirius Red staining - black arrows)

Free choice diet gradually increases:
1) NASH and fibrosis
2) heart failure (increased E/A and E/E' ratios) with preserved ejection fraction (HFpEF).
3) cardiac fibrosis also tends to increase with free choice diet
Elafibranor improves both NASH/fibrosis and HFpEF in free-choice fed hamsters.

Elafibranor improves:

1) NASH and fibrosis

2) heart failure (increased E/A and E/E' ratios) with preserved ejection fraction (HFpEF).
MERCI POUR VOTRE ATTENTION