

Physiogenex NASH preclinical models



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Physiogenex NASH/fibrosis models



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.



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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

Physiogenex DIO-NASH mouse model: Evaluate your drug candidate or combination in 6 weeks



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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

sidenex

- 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



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



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





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