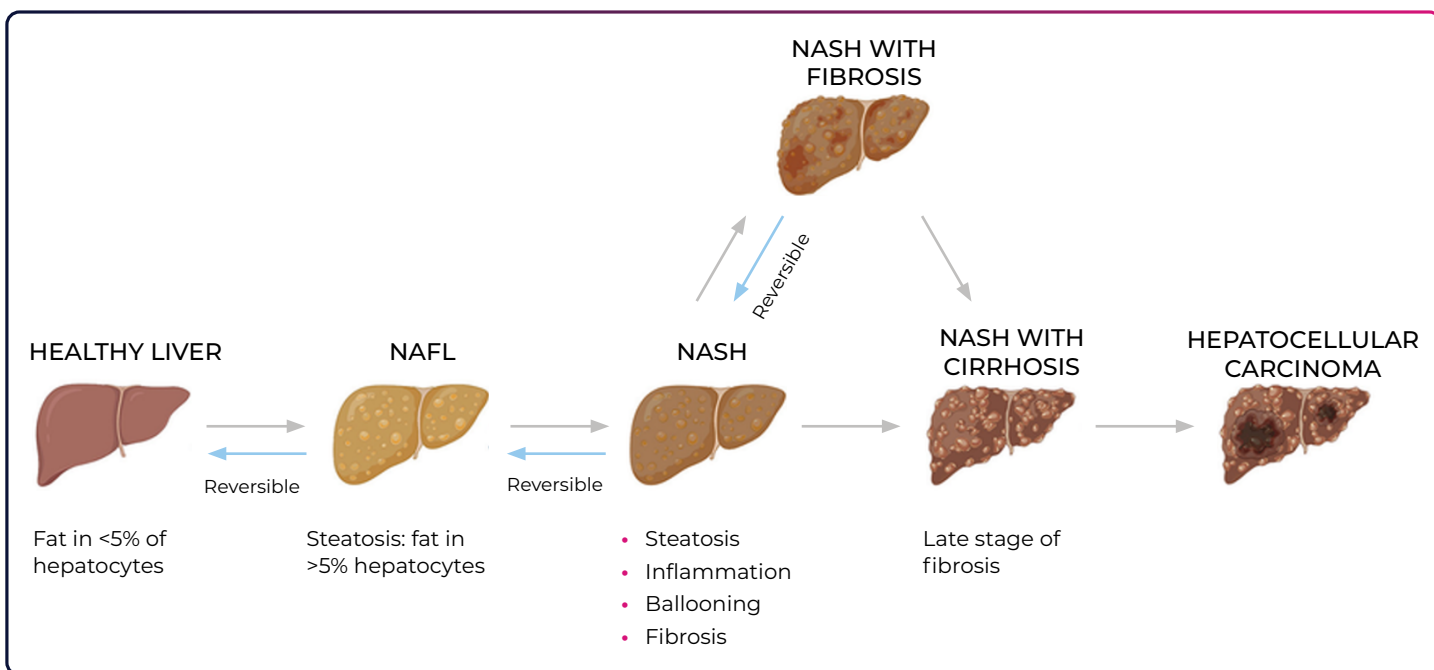


CHOLINE-DEFICIENT, L-AMINO ACID-DEFINED – HIGH FAT DIET-INDUCED (CDA-HFD) NASH MOUSE MODEL

- The global prevalence of NAFLD sits at ~25%, making it the most common cause of chronic liver disease
 - Manifestation of several conditions associated with metabolic dysfunction
 - Development and progression is complex and multifactorial; poor dietary habits, sedentary lifestyle, environmental factors, genetic factors
- Estimates suggest that the global NASH prevalence is ~5%
 - NAFLD may progress to NASH, which is characterized by steatosis, inflammation with ballooned hepatocytes and fibrosis
 - Greatest risk factor for NAFLD/NASH pathogenesis is fatty liver
- CDA-HFD is a classic model for NASH induction:
 - L-amino acid diet with 60 kcal% fat, 0.1% methionine, no added choline
 - Methionine deficiency decreases glutathione biosynthesis, leading to oxidative stress and contributing to liver damage
 - Choline deficiency inhibits the synthesis of phosphatidylcholine, leading to lipid accumulation in the liver

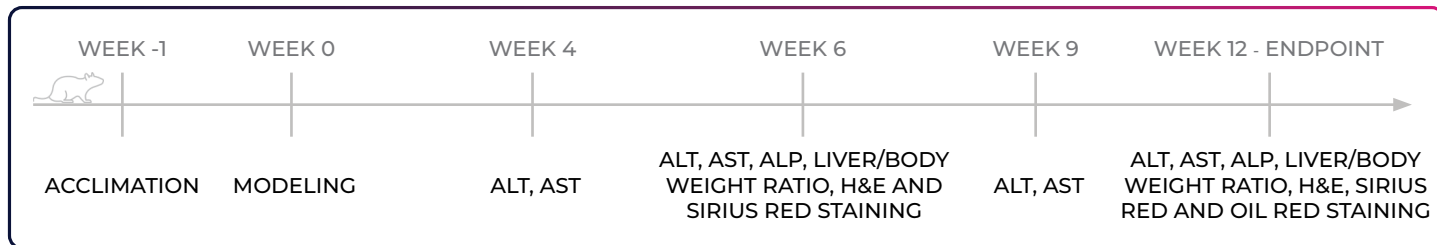


ChemPartner has developed and validated a CDA-HFD mouse model, which exhibits non-metabolic associated NASH with progressive fibrosis:

- ✓ Ready to use
- ✓ Non-obese mice
- ✓ Rapid disease progression
- ✓ Cost-effective
- ✓ Early onset of hepatic steatosis and fibrosis
- ✓ Validated endpoints

STUDY OUTLINE

CDA-HFD-INDUCED NASH PRECLINICAL IN VIVO MOUSE MODEL



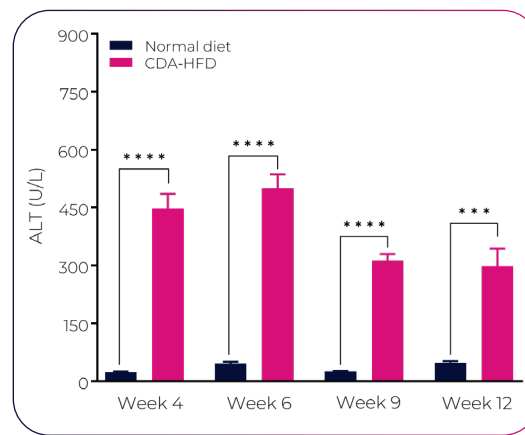
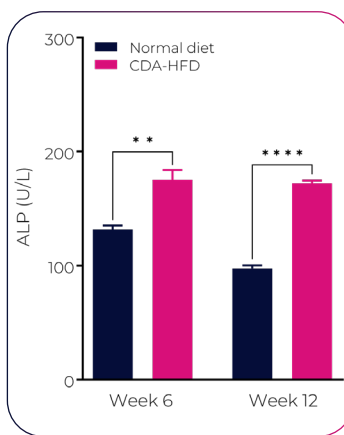
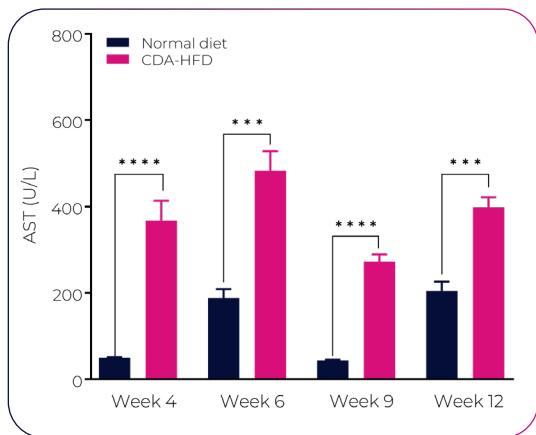
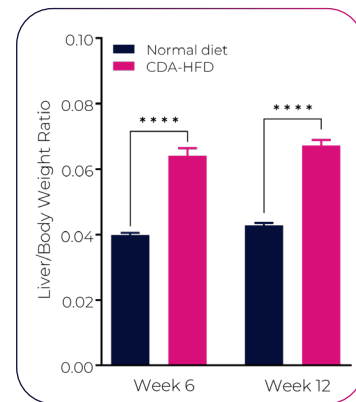
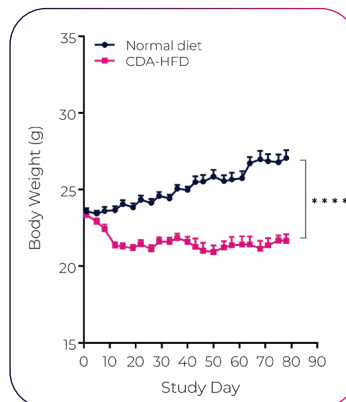
- Strain
 - Male C57BL/6 mice, 7 weeks on arrival
- Model
 - CDA-HFD (L-amino acid diet with 60 kcal% fat, 0.1% methionine, no added choline; Research Diets Inc #A06071302) – diet fed weeks 0-12
 - Control diet – standard rodent chow (PMI Nutrition International; product number 5C02C)

MAJOR READOUTS

- Body weight
- Liver/body weight ratio
- Blood: AST, ALT and ALP
- Pathology: H&E, Sirius Red and Oil Red staining
- NAFLD activity score (NAS) and fibrosis score

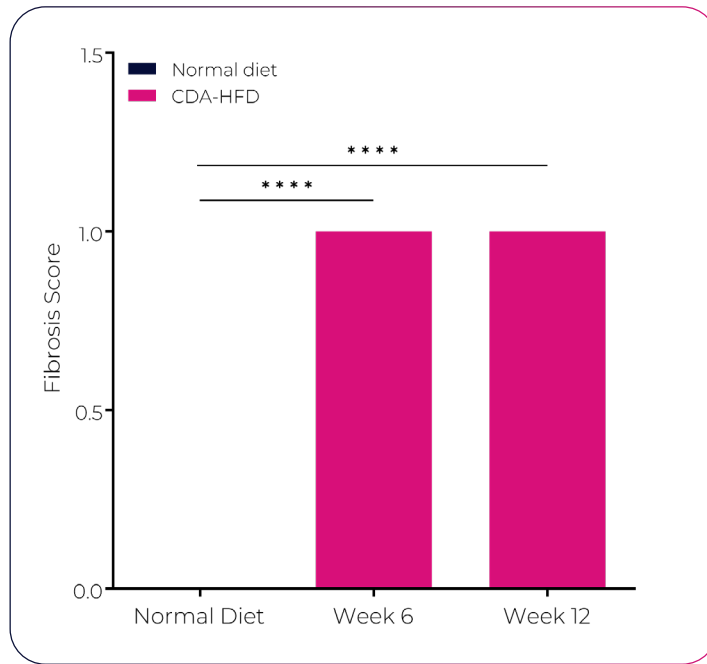
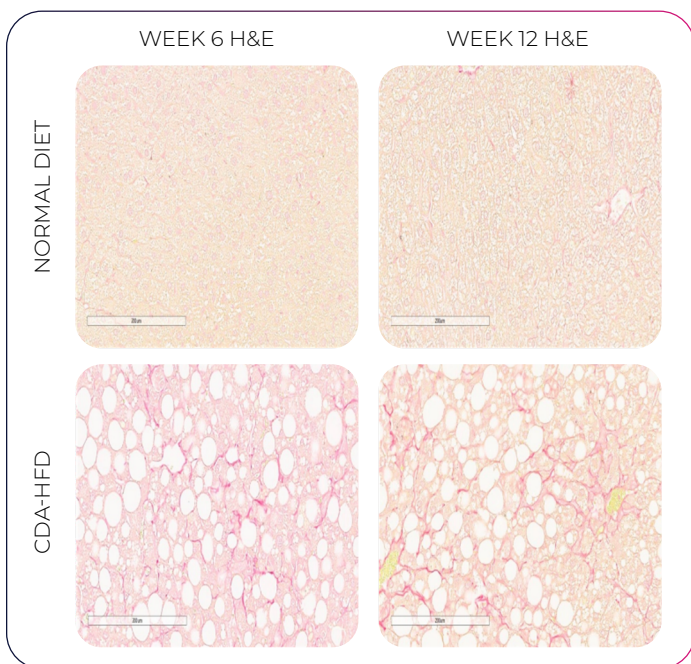
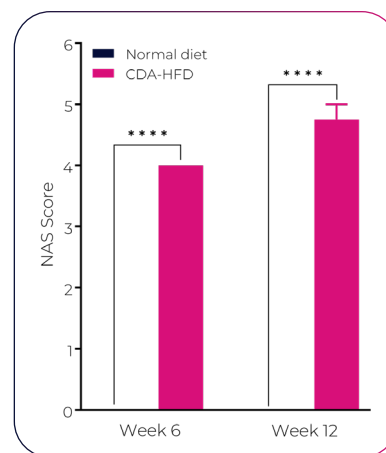
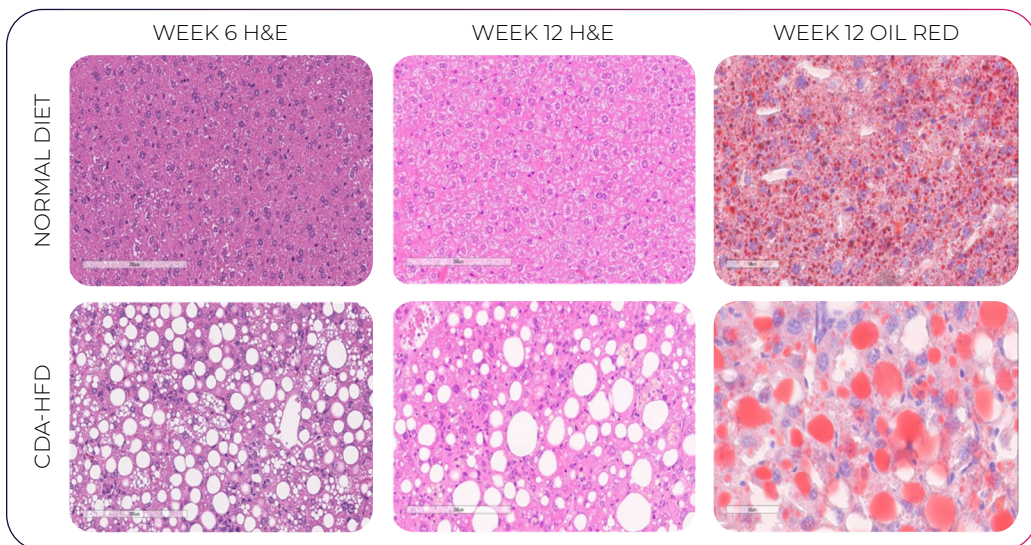
KEY MODEL CHARACTERISTICS:

- ✓ Mice fed continuously on CDA-HFD
- ✓ Diet-induced non-obese mouse model
- ✓ Increased liver/body weight ratio in week 6 and 12
- ✓ Elevated blood aspartate aminotransferase (AST) from week 4 to week 12
- ✓ Elevated blood alanine transaminase (ALT) from week 4 to week 12
- ✓ Elevated blood alkaline phosphatase (ALP) from week 6 to week 12
- ✓ Prophylactic and therapeutic drug efficacy



HISTOPATHOLOGICAL FEATURES

- ✓ Pale liver
- ✓ Hallmarks of NASH; increased hepatic steatosis, lobular inflammation
- ✓ Significantly increased NAS score from week 6
- ✓ Evidence of lipogenesis
- ✓ Observed fibrosis in the liver tissue of CDA-HFD fed mice



SUMMARY

The CDA-HFD-induced mouse model is a robust and well validated model, offering a non-obese, non-metabolic NASH phenotype, which is simple, reproducible, and technically undemanding.

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