Modelling liver diseases from acute and chronic injury to hepatocellular carcinoma for development of new treatments

#5638

Vector of innovation.

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1 INTRODUCTION

According to National statistics in the UK, liver diseases have been ranked as the fifth most common cause of death. Liver diseases are recognized as the second leading cause of mortality amongst all digestive diseases. For now, liver transplantation remains the only effective therapeutic option.

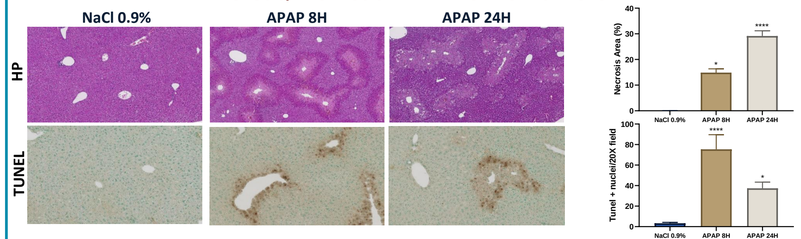
Acute liver injury is a syndrome of severe and abrupt hepatocyte injury and inflammation leading to liver failure. Many different etiologies have been identified, with acetaminophen (APAP) overdose and viral hepatitis being the most common causes worldwide. Chronic Liver Diseases (CLD), irrespective of the etiology, are characterized by parenchymal injury, increased reactive oxygen species and oxidative stress, activation of inflammatory response, angiogenesis, sustained activation of liver fibrogenesis and wound healing response. Liver cirrhosis represents an advanced stage of CLD characterized by the formation of fibrotic septa surrounding regenerative nodules, changes in vascular architecture, portal hypertension and complications such as liver failure and hepatocellular carcinoma (HCC). Of importance, Non-alcoholic steatohepatitis (NASH) has emerged as the most rapidly growing indication for liver transplantation in HCC patients.

Providing palliative and curative solutions is an urgent necessity. At Oncodesign, we offer and develop both complementary and integrated strategies to mimic the different steps of liver diseases and cancer progression in mouse models, in order to develop novel therapies and elucidate their mechanisms of action.

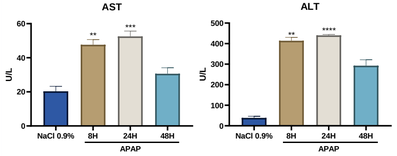
2 ACUTE LIVER INJURY MODELS

ACETAMINOPHEN (APAP) MODEL

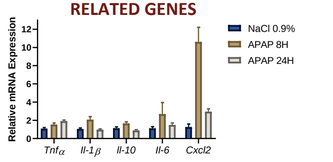
NECROSIS/APOPTOSIS AND IMMUNE CELLS RECRUITMENT



LIVER INJURY MARKERS

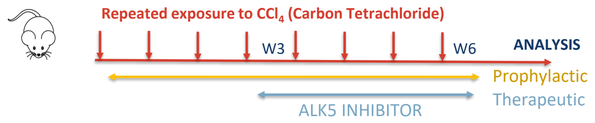


UP-REGULATION OF CYTOKINES/CHEMOKINES-RELATED GENES

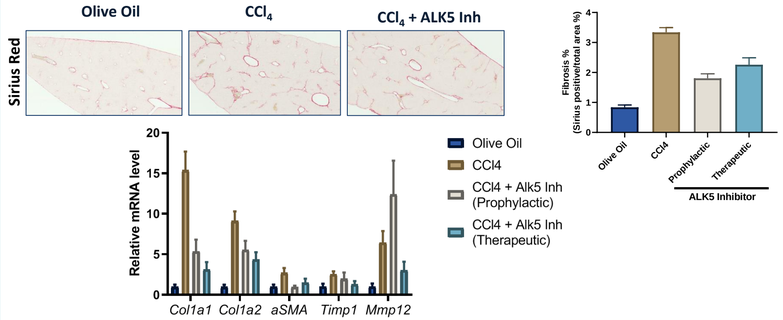


3 CHRONIC LIVER INJURY MODELS

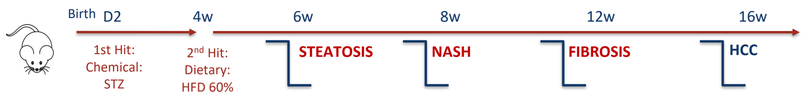
CLASSICAL CCl_4 FIBROSIS MODEL



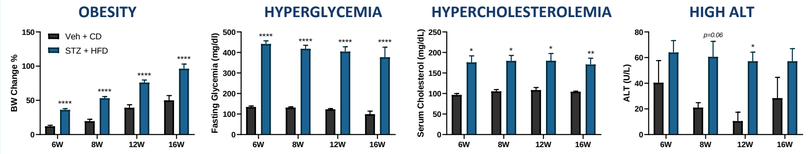
PHARMACOLOGICAL VALIDATION USING ALK5 INHIBITOR (TGFβ signalling)



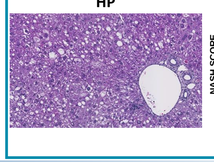
NASH-HCC MODEL: STZ + HFD



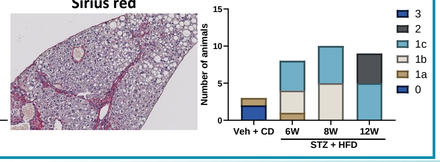
IMPAIRED METABOLIC AND LIVER FUNCTION PARAMETERS



NASH SCORE

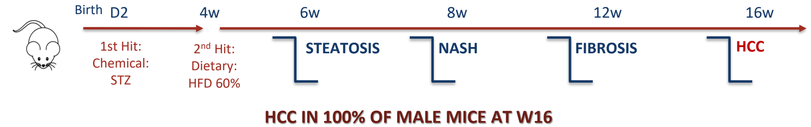


FIBROSIS SCORE



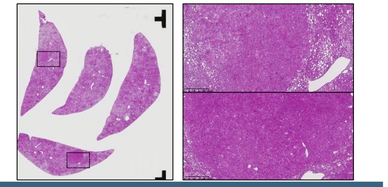
4 LIVER CANCER MODELS

NASH-HCC MODEL: STZ + HFD



HCC IN 100% OF MALE MICE AT W16

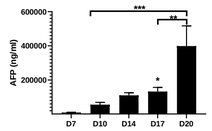
- Reproduce histolological and molecular heterogeneity observed in humans
- Therapeutic window from 12 to 16-20 weeks
- Longitudinal study using MRI from 13 weeks to 16-20 weeks



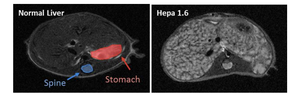
ORTHOTOPIC HEPA1.6-DERIVED LIVER TUMORS

HEPA1.6 TUMOR CELLS ENGRAFTMENT IN 80-90% OF TOTAL LIVER MASS

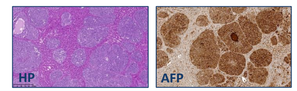
SERUM AFP



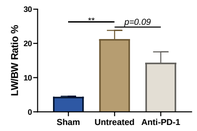
MRI on D10



HISTOLOGY ANALYSIS on D20

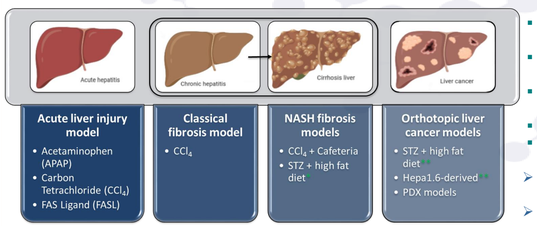


RESPONSE TO ANTI-PD-1



- 42% of mice responded to anti-PD-1

5 CONCLUSION



ENDPOINTS

- Biochemistry parameters (AST/ALT, LDH, Cytokines)
- Metabolic parameters (Glycemia, Serum TG, NEFAs, Cholesterol)
- Histology (Necrosis/Apoptosis, Fibrosis score, NASH score, IHC)
- Biomarkers (Gene expression, IHC, Multiplex)
- MRI Imaging

PERSPECTIVES

- *Pharmacological validation with Elafibranor and OCA
- **Pharmacological validation with Lenvatinib and anti PD-1
- Characterization of immune cell populations
- Model of Humanized liver and immune system