A human in vitro three-dimensional bioprinted liver tissue system can be used to model nutritional damage and protective effects of MSDC-0602K, a novel modulator of the mitochondrial pyruvate carrier (MPC).

INTRODUCTION

The growing global incidence of NASH mirrors the availability of nutrients. Overnutrition also results in insulin resistance and type-2 diabetes, which are often co-morbidities associated with NASH and are known to drive more adverse outcomes.

MSDC-0602K, a modulator of the mitochondrial pyruvate carrier (MPC), is in clinical trials as a potential treatment for NASH. Preclinical studies have shown that the mitochondrial pyruvate carrier is increased in expression in animals fed a high fat diet. Moreover, selective knockouts of each of the mitochondrial proteins that make up the carrier have shown that the MPC is a key driver of both NASH pathology and pharmacology of MSDC-0602K.

Nutrient-induced disease using a three-dimensional multicellular human tissue model provides the potential to reconstruct the effects of overnutrition in vitro and to potentially model the actions of an agent like MSDC-0602K.

AIM

To determine whether bioprinted human liver tissue can be used to model the pathology produced by over nutrition.

To characterize the ability of MSDC-0602K to modulate disease phenotype in a human relevant model of NASH.

To further the understanding of the pharmacology of MSDC-0602K and provide evidence for non-invasive biomarkers that might predict clinical response.

METHODS

ExVive Human Liver Tissue (Organovo, San Diego) was fabricated by bioprinting primary human hepatocytes, hepatic stellate cells, Kuffer cells, and endothelial cells into a 3D tissue architecture. Tissues matured in vitro for three days and then were challenged with various concentrations of simple sugars and fatty acids.

To determine whether bioprinted human liver tissue can be used to model the pathology produced by over nutrition.

RESULTS

Two human in vitro three-dimensional liver tissue systems can be used to model nutritional damage and protective effects of MSDC-0602K, a novel modulator of the mitochondrial pyruvate carrier (MPC).

CONCLUSIONS

These data show that human 3D bioprinted liver tissue can be adapted for demonstrating NASH-type liver pathology and the pharmacology of a novel MPC modulator can be modeled in this system.

- Addition of sugars and fatty acids are sufficient to induce steatosis and tissue damage including putative hepatocyte ballooning, stellate cell activation, and fibrosis.
- The addition of 10 µM MSDC-0602 either before or after initiation of the nutrient-stimulated damage showed protective effects against disease progression.
- Stimulating the bioprinted liver tissue with fructose alone was also associated with the induction of NASH-like pathology.

REFERENCES


PHASE 2B CLINICAL TRIAL: EMINENCE™ (ID: NCT02784444)

- 52-week evaluation of 3 exposures of MSDC-0602K versus blinded placebo in subjects with biopsy confirmed NASH
- Once-daily oral dosing
- 45 US sites
- At least 380 subjects to be enrolled