Modeling NAFLD Using 3D Bioprinted Human Liver Tissue
Dwayne E. Carterb, Deborah G. Nguyenb, David Brennerb, Sharon C. Presnellb, and Alice E. Chenb
aOrganovo, 6275 Nancy Ridge Drive, San Diego, CA 92121
bUniversity of California San Diego, School of Medicine, 9500 Gilman Drive, La Jolla, CA 92039

Background
Nonalcoholic fatty liver disease (NAFLD) is a chronic condition that originates as lipid accumulation within hepatocytes (steatosis) and progresses into nonalcoholic steatohepatitis (NASH), characterized by liver inflammation, fibrosis, collagen and fibrosis. NAFLD is now recognized as the most common cause of chronic liver disease, with a prevalence of 20% worldwide, and projected to become the leading indication for liver transplantation in 2030. Despite decades of research, the mechanisms of NAFLD progression, therapeutic approaches and non-invasive diagnostics are still insufficiently addressed. The study of NAFLD and NASH has traditionally utilized in vitro models, which are time consuming to generate and do not fully recapitulate the complex phenotypes associated with the human disease. Furthermore, current 2D cell culture models lack relevant liver epithelial and stromal cells, and have limited ability to recapitulate cell-cell and cell-matrix interactions. Thus, there is a significant need for a more predictive human multicellular 3D in vitro model to study the progression of steatosis into NASH.

Methods
EnVivo™ Human Liver Tissue, a bion® in vitro 3D bioprinted liver model comprising primary human hepatocytes, hepatic stellate cells, and resident cells, enables a multi-dimensional architecture similar to that of native liver and exhibits metabolic, cellular and specific functions for at least 6 weeks in culture. To mimic the proposed pathogenesis of NASH, human hepatocytes were co-printed with “fibroblast”-like cells to generate a more realistic tissue microenvironment that can elicit a mature fibrotic phenotype. In this study, we utilized the EnVivo™ human liver model to study the development and progression of NAFLD.

Technology Overview

Steatosis Induction in 3D Bioprinted Liver Tissue

NASH Induction in 3D Bioprinted Liver Tissue

Summary and Conclusion

Future Directions

NASH-induced 3D bioprinted liver tissues demonstrate increased triglyceride (TG) accumulation compared to controls. The fold changes in lipodystrophic tissues correlate with fold changes seen in native NAFLD tissues.

Future research on this platform can be explored to achieve additional studies and elucidation of chronic inflammation regulation of native development.

References

By the term "biofabrication" we mean the process of forming tissues or organs using the techniques, methodologies and equipment in the field of tissue engineering. This includes, but is not limited to, the use of biodegradable scaffolds, cell cultures, and 3D printing to create complex structures. The field of biofabrication has made significant strides in recent years, with advancements in techniques such as bioprinting and tissue engineering enabling the creation of more complex and functional tissues. However, there are still many challenges to overcome, including the integration of these tissues into the body and the long-term viability of the created tissues. This is an exciting area of research, and continued investment in this field is important for the future of regenerative medicine.

A schematic of the liver tissue model, showing the relationship between hepatocytes, stellate cells, and the extracellular matrix. The illustration includes a cross-sectional view of the liver tissue, highlighting the different cell types and matrix components. This model is designed to mimic the complex architecture and functions of the liver, allowing for the study of various liver-related diseases and conditions.

A representative of native disease onset. The figure shows the progression of steatosis-induced liver injury in a 3D bioprinted human liver tissue model.

An image of a rat liver biopsy, demonstrating the histological changes observed in NASH. The tissue sections are stained with hematoxylin and eosin (H&E) to highlight the lipid accumulation and inflammation.

A schematic of a liver tissue model showing the relationship between hepatocytes, stellate cells, and the extracellular matrix. The illustration includes a cross-sectional view of the liver tissue, highlighting the different cell types and matrix components. This model is designed to mimic the complex architecture and functions of the liver, allowing for the study of various liver-related diseases and conditions.

A representative of native disease onset. The figure shows the progression of steatosis-induced liver injury in a 3D bioprinted human liver tissue model.

An image of a rat liver biopsy, demonstrating the histological changes observed in NASH. The tissue sections are stained with hematoxylin and eosin (H&E) to highlight the lipid accumulation and inflammation.