CHIEF SCIENTIST OFFICE

CODE: TCS/16/37

RESEARCH PROJECT BRIEFING

Exploiting liver and blood vessel cell interactions to build scalable liver tissue for human biomedicine

AIMS

The aim of the funded CSO project was to understand the liver cell (hepatocyte) and blood vessel cell (endothelial cell) interactions required for efficient tissue formation, and to exploit this relationship to deliver human liver tissue at scale for human biomedicine

KEY FINDINGS

- It is possible to efficiently drive cellular differentiation of hepatocyte and endothelial cells from the same genetic background.
- Building human liver tissue from stem cell derived somatic cells was possible using agarose microwell technology.
- Lab engineered human liver tissue could be used to study human liver injury and disease.
- The identification of the minimal requirements for cost effective manufacture, process automation and liver tissue scale-up

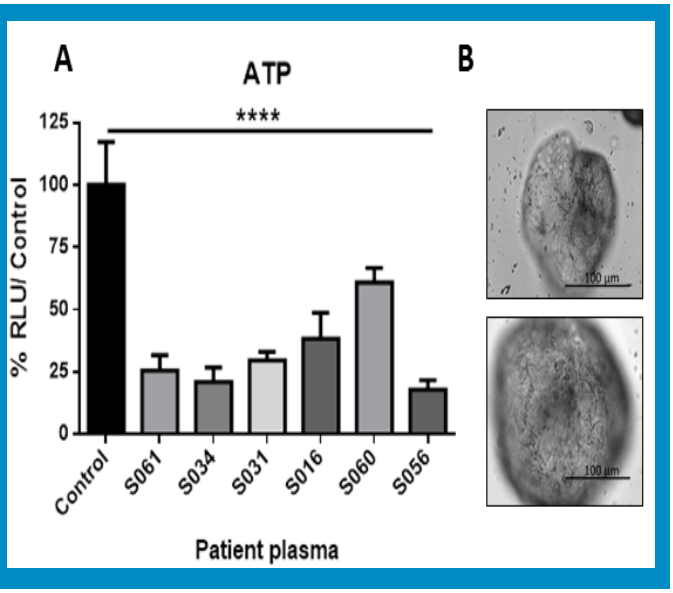
WHAT DID THE STUDY INVOLVE?

The aim of our study was to generate functional and stable human liver tissue from pluripotent stem cells. Following somatic cell generation from the stem cell lines, liver tissue engineering commenced and was driven by cell self-assembly in microwells. Following successful sphere formation the technology was scaled up using an automated system developed in the lab. The final product was then assessed for long-term stability and performance in clinically relevant situations, for example the exposure to plasma from liver failure patients and to drugs which are known to cause drug induced liver injury.

WHAT WERE THE RESULTS AND WHAT DO THEY MEAN?

Stem cell derived liver spheres were produced using our novel system, and subsequently exposed to plasma isolated from patients with acute liver failure after paracetamol intoxication. The goal of these studies were to test how robust the liver spheres were in a hostile environment, with the rationale that they could be useful to treat failing human liver function in the clinic in the future. Stem cell derived liver spheres did respond favourably to liver failure plasma. Although we observed a reduction in cell viability (measured by ATP production, Figure 1A), which was relatable to the severity of patient liver damage and clinical outcome, we did not observe gross changes in liver sphere structure (Figure 1B). We believe that this study provides important information for the field and delivers a renewable source of human liver tissue that could be used to treat human disease in the clinic.

Figure 1: 3D spheres tolerate human liver failure plasma.
A. 3D hepatospheres were exposed to plasma for 48 hours. This was isolated from patients with liver failure. The depletion of a cell viability marker (ATP) was observed.
B. Although ATP depletion was observed, liver sphere integrity was not compromised.
Data was analysed using with a 1-way analysis of variance (ANOVA) (α=.05)



WHAT IMPACT COULD THE FINDINGS HAVE?

The development of scalable tissue engineering has the potential improve society's health and wealth within Scotland. The technology developed has two major impacts. The near term impact is the development of new drugs, or repurposing of existing drugs, for the clinic. The longer-term impact is to generate liver tissue for the clinic to treat failing liver function in humans.

HOW WILL THE OUTCOMES BE DISSEMINATED?

The project outcomes will be disseminated to the scientific community through publication in reputed journals. So far, project outputs have been presented at scientific meetings. In addition, I have presented our project on the BBC's Naked Scientist show and recently featured in a Financial Times article. Going forward we wish to develop a liver implant for the clinic and are currently preparing a funding application to move this work towards phase I clinical trials in humans.

CONCLUSION

In conclusion, we demonstrate that it is possible to build renewable sources of human liver tissue from pluripotent stem cells. Importantly, we are able to scale up and automate our prototype technologies to levels that are suitable for drug screening or repurposing studies. Additionally, were are able to generate stem cell derived liver tissue at levels that could have clinical impact in the future. Going forward, our aspirations are to build clinical grade human liver tissue to treat patients with failing liver function.

RESEARCH TEAM & CONTACT

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Additional Information

The project was completed in February 2020 and the total amount awarded was £372K