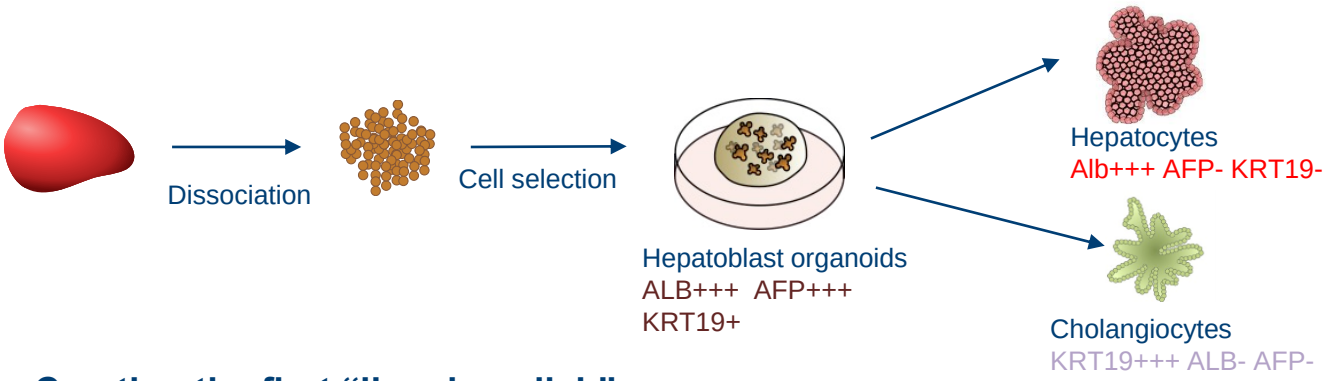
UNIVERSITY OF CAMBRIDGE
enterprise

Hepatoblast Organoids

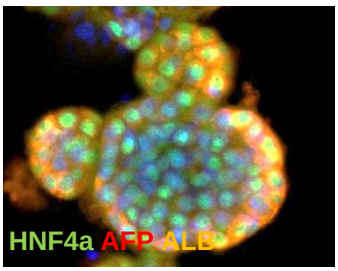
A novel three dimensional primary cellular model for drug screening and cell based therapy in liver



Creating the first "liver in a dish"

- ✓ Bipotential human hepatoblast cells can be expanded exponentially for more than a year in 3-D
- ✓ Hepatoblasts can uniquely generate both liver parenchyma cell types in one system (hepatocytes & cholangiocytes)
- ✓ Transplanted hepatoblast constructs differentiate to functional differentiated organoids in vivo

A



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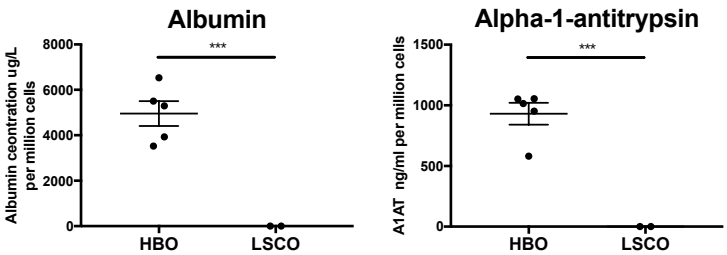

Figure 1: A) Immunofluorescent staining of a hepatoblast organoid. B) Protein production per litre of medium per million cells for albumin (left) and alpha-1-antitrypsin (right), for HBO (hepatoblast organoid) and LSCO (Liver stem cell organoids)

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Background

A source of liver cells that could be expanded and maintained long term *ex vivo* has long been sought after. Such a system offers potential solutions to two key problems. Firstly, an opportunity for large screening of the drugs both for their basic toxicity but also for their variability in metabolism between individuals. Secondly, such a system could be used to treat liver disease. Liver disease presents an increasing cause of morbidity worldwide and the only definitive treatment for liver failure is a liver transplant. Having a complex functional liver system that could be expanded and transplanted contribute to solving this issue.

Primary hepatocytes can be removed from donors and cultured briefly *in vitro,* however such systems cannot be expanded nor maintained long term. Biliary organoid systems do exist, however they are only able to generate cholangiocytes.

Technology

We have generated a unique human hepatoblast organoid (HBO, Fig. 1A) system that can be maintained for more than a year in each line. The lines expand exponentially, demonstrate transcriptional and genomic stability, express key functional hepatic proteins (Fig. 1B) and can be frozen down for long term storage. The HBO can be treated *in vitro* to differentiate towards cholangiocyte or hepatocyte lineages on demand. Furthermore, when transplanted in constructs, the HBO develop a blood supply and differentiate to complex structures containing interacting cholangiocytes and hepatocytes with a blood supply. These systems are able to generate albumin into the serum of the model organism.

Application

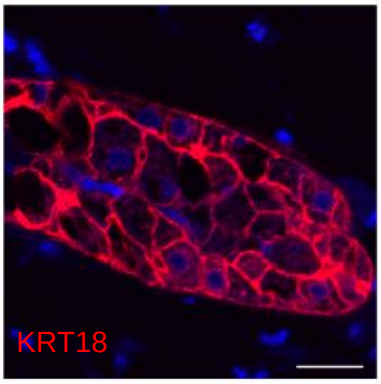
The HBO system offers two exciting areas of commercialisation.

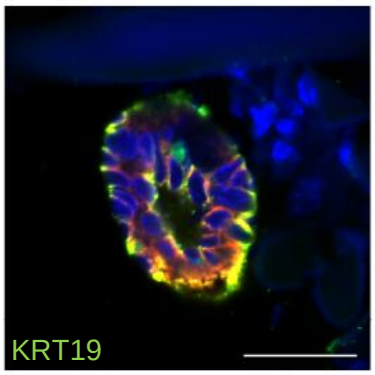
1) Drug screening

A large biobank of organoids could be rapidly generated. Such a biobank could be genetically sequenced and represent the variability seen in the population. Drug metabolism could then be assessed using the HBO system, and correlation between drug clearance and genetic variance could be rapidly assessed.

2) Cell based therapy

Our experiments in mice have demonstrated the first demonstration that a complex system containing hepatocytes and cholangiocytes can be generated and survive transplantation to become vascularised functional units (Fig. 2). Such a system presents an exciting prospect as a treatment for liver failure. Furthermore, given the large scale expansion potential and biobank generation, constructs could be specifically matched to potential recipients and surgery arranged as a scheduled procedure rather than the emergency.





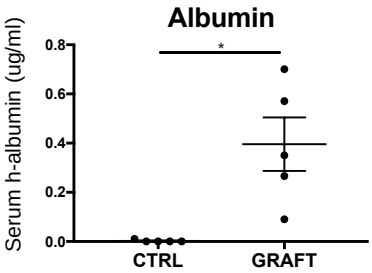


Figure 2: A) Immunofluorescent staining of human hepatoblast organoids after transplantation into mice. B) levels of human albumin detected in the serum of mice transplanted with human hepatoblast organoid constructs after one week

Commercialisation

We are seeking a commercial partner for collaboration and development of this technology, which is protected by GB patent application number: 1813127.6 and 1813128.4