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HepatiCan, a cryopreservable cell therapy and medical device to rescue patients with liver failure

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INTRODUCTION

- Liver disease is increasing worldwide.
- Transplantation is curative, but donor organ shortages are well-known
- Best use of available organs is vital.
- The liver can regenerate, **given time**
- Solutions that **"buy" that time** are needed, so the liver has **time to regenerate**.

AIM

To design, build and test a cryopreservable bioartificial liver.

To provide, temporarily, normal liver functions to patients in liver failure, so their own liver has time to regenerate.

METHOD

- Prepared a cryopreserved and reconstituted clinical-scale biomass (70 billion cells as organoids) in single-use bioreactor (ATMP)[1-2]
- The HepatiCan device for ICU/HDU bedside was designed to contain a biocartridge (Chamber + ATMP), two circuits to mimic portal and peripheral venous blood flow, with safety features
- Device tested for Electrical & Mechanical Safety (IEC 60601-1)
- Tested the cryo-recovered biomass *in-vitro* in prototype device with human plasma (FFP) continuously for >72h. Plasma samples analysed in routine Chem. Path lab
- Per cell performance: metabolic viability (fluorescence) and cell number (Nucleocounter)

RESULTS

- *The cell therapy (ATMP, Fig 1), recovered to pre-freeze (PF) viable cell yields (Fig 2)*
- *Single use consumables: chamber holding clinical-scale ATMP; safety & functional filters, & 3-circuit tubing set all in workstation (Fig 3).*
- *HepatiCan device meets electrical & mechanical safety requirements (IEC 60601-1) for use in ICU/HDU. It interfaces with apheresis machines (eg Spectra Optia) as a secondary process device.*
- *HepatiCan delivers plasma at 300-500ml/min (fast circuit) and 35-50ml/min (slow circuit) for >72h. These are typical flow rates used in plasma exchange*
- *Metabolic Cell viability maintained at >95% (Fig 4 a); Viable cell number >78% of starting value by 72h (Fig 4b), Functional performance (glucose & oxygen, protein synthesis (Fig 5a,b,c)*

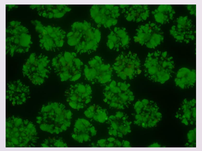

Fig 1. *A fluorescent image of viable cell organoids within alginate beads that comprise the ATMP biomass.* ***Fluorescein diacetate (green) measures metabolic viability.***

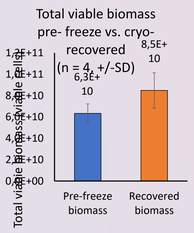

Fig 2. *Comparison of pre-freeze total viable cell yield biomass with recovered viable cell yield >48h after cryopreservation.*
This indicates cryopreservation and thawing is not detrimental to biomass yield for use in patient treatment



Fig 3 HepatiCan™ System: *comprising workstation with single-use disposables for patient treatment.*

- ***The biocartridge*** *comprises the* ***ATMP biomass in a disposable chamber.***
- *The chamber design leads to* ***excellent mass transfer***
- *HepatiCan connects to a patient via an apheresis machine as a* ***secondary process device****. This provides* ***added safety*** *for the new device when in clinical trial*
- *The intended treatment time is* ***up to 5 days of continuous treatment***

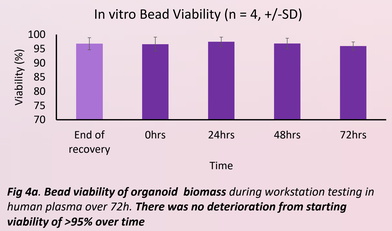

Fig 4a. Bead viability of organoid biomass *during workstation testing in human plasma over 72h.* ***There was no deterioration from starting viability of >95% over time***

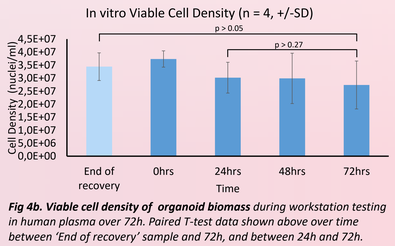

Fig 4b. Viable cell density of organoid biomass *during workstation testing in human plasma over 72h. Paired T-test data shown above over time between 'End of recovery' sample and 72h, and between 24h and 72h.*

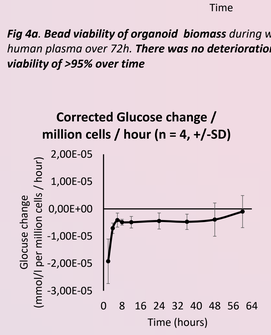

Fig 5a. Functional Performance *Evidence of* ***maintained metabolic activity (glucose consumption)*** *during plasma perfusion of ATMP in HepatiCan system over time.*

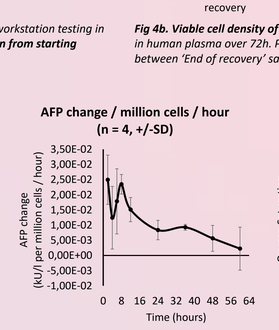

Fig 5b. Functional performance *Evidence of* ***protein synthesis and secretion*** *during plasma perfusion of ATMP in HepatiCan system over time. Alpha-foetoprotein (AFP) is used as a surrogate protein showing biomass specific synthetic function, against a background protein mix of human plasma*

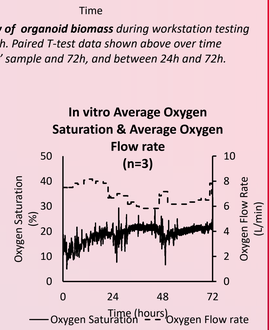

Fig 5c. Functional performance Oxygen consumption
Oxygen inflow ***(upper curve)*** *into the biocartridge was adjusted* ***regularly*** *to ensure a level of approximately 21% O_2 saturation* ***(lower curve)*** *was maintained throughout.*

CONCLUSION

HepatiCan delivers a cell therapy (ATMP) at clinical scale.[3-4]

It maintains cell function, interfaces with apheresis machines as secondary process device, for several days

HepatiCan can temporarily provide liver function to patients in liver failure whilst their own liver repairs itself, and be delivered 'off the shelf' after cryopreservation. It can also prevent patient deterioration whilst awaiting transplant.

HepatiCan will offer patients, with acute or decompensated liver failure, an alternative to whole organ transplantation, allowing better use of donor organs.

With new therapies for reducing cirrhosis/fibrosis, and targeted therapy for liver tumours, HepatiCan will offer support and confidence for these to be used effectively.

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In 2023, Hepatican Ltd (company number 15014627), an SME was formed to deliver this new therapy approach to patients. In Nov 2024 it was awarded an NIHR Connect 8 grant, ongoing, to deliver new work.

Conflict of Interest: C SELDEN is the Founder of Hepatican Ltd (currently pro bono) but also works at 0.8FTE for UCL.

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