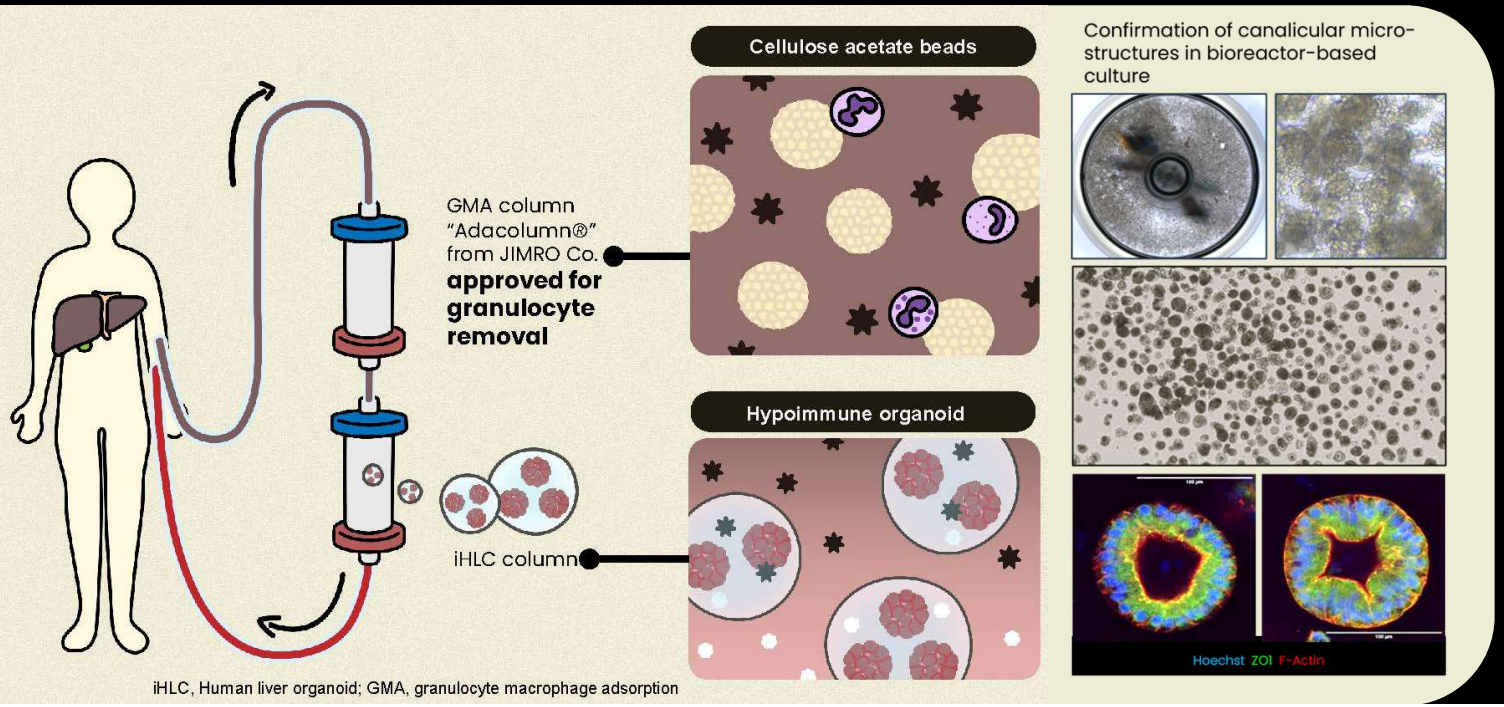
再生医療

Kanzo Biomedicines, Inc.

Kanzō Biomedicines

低免疫原性肝細胞体外循環回路(UTOpiA)を用いたBest-in-Classの慢性肝不全治療法



器官システム創生学　武部 貴則

B-163

Bioengineering human liver organoids

低免疫原性肝細胞システムを用いた肝機能補助療法の開発

The University of Osaka
Professor, Takanori TAKEBE

大阪大学
教授・武部 貴則

Bioengineering human liver organoids

Prof. Takebe is member of Kanzo leadership team

Jan 2025

肝臓 (Kanzō): Liver

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Executive Summary

Bioengineering liver to help patients suffering from severe liver failure

- High clinical unmet medical need: acute-on-chronic liver failure (ACLF) and prevention of liver failure in post liver resection; represent a total addressable market (TAM) $14 billion (￥2,000 billion) annually
- **Core value proposition: bioengineered allogenic hepatocytes for prevention of liver failure and extend life**
- Our differentiated capability is to create human liver organoids from clinical grade iPSCs that are superior in functionality and safety compared to conventional bioartificial liver therapy.
- **First program: proof-of-principle demonstrated**
  - Bioengineered, allogeneic hepatocytes incorporated into an ex vivo, extracorporeal circuit treat acute-on-chronic liver failure (ACLF)
  - The extracorporeal circuit, UTOpiA (**U**niversal **T**andem **Op**timized **i**nduced Hepatocyte-Like-Cells with **A**pheresis), addresses both severe liver synthetic dysfunction and systemic inflammatory response syndrome to reduce the high mortality rate
- **Second program: scientific research underway**
  - Multi-zonal allogeneic hepatocytes bioengineered solution with further improved functionality (Nature, 2025)
- Intellectual Property: wholly-owned unique method & process patents for generating therapeutic cells and composition of matter of UTOpiA; additional patent filings and enablement underway
- Rich near term milestones: in vivo efficacy in rabbit (2024), tech transfer and master cell bank generation at CRO in Japan (2025), submission grants to AMED (2026) and CIRM/SBIR NIAAA (2026)
- **Team:** Experienced clinician scientists and repeat entrepreneurs with track record of cross-border collaborations
- **Raising:** $6.0-7.0 MM to fund manufacturing development activities to **nominate development candidate**

Kanzo leadership Team

Takanori Takebe, MD PhD

Institute of SCIENCE TOKYO
大阪大学 OSAKA UNIVERSITY
Cincinnati Children's changing the outcome together

Mani Subramanian, MD PhD

GILEAD Creating Possible
HGS
CELERA

Ravi Rao, PhD

booz&co.
Vtesse
AstraZeneca
MedImmune
Complexa
genocea BIOSCIENCES
REXBIO

Rob Myers, MD

GILEAD Creating Possible
UNIVERSITY OF CALGARY
HÔPITAUX UNIVERSITAIRES PITIÉ SALPÊTRIÈRE CHARLES FOIX

Maki Kumagai

大阪大学 OSAKA UNIVERSITY
Healios

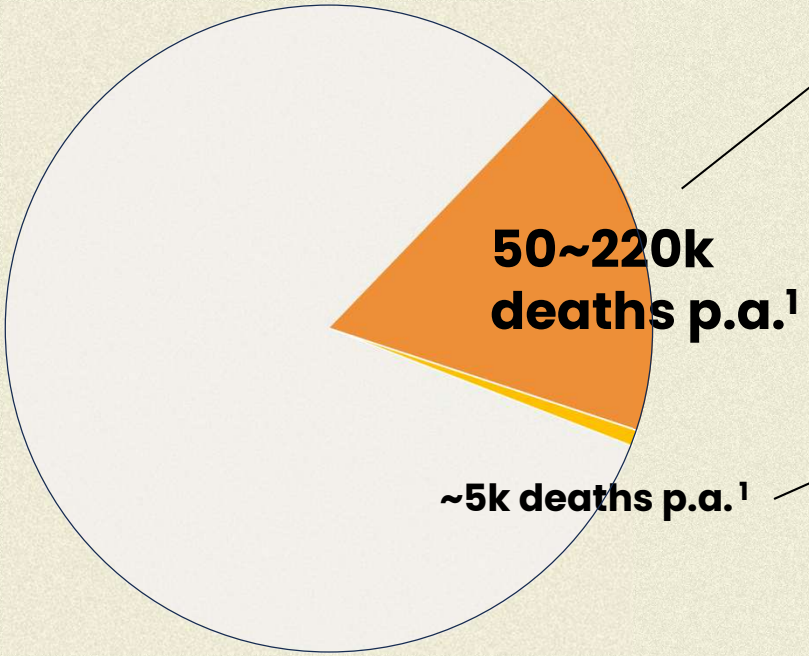
Our team has led and supported the research, clinical and strategic journeys of multiple approved drugs

SOVALDI
HARVONI
Vemlidy
EPCLUSA
VOSEVI
Fasenra
LUMOXITI moxetumomab pasudotox-tdfk

The issue

Liver failure is a leading health problem worldwide

"2 million deaths caused by Liver diseases worldwide"



1: estimated total number from US, EU and Japan

ACLF (acute-on-chronic liver failure)

- Occurs in patients with pre-established liver exposed to acute insults (e.g. alcohol, new infection)
- Rapid deterioration of liver function accompanied with systemic inflammation leading to multi-organ failure
- **20-80%** mortality rate

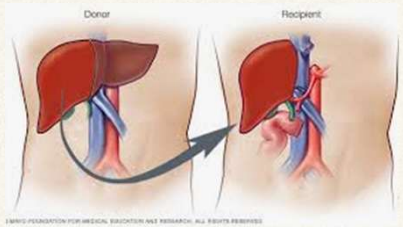
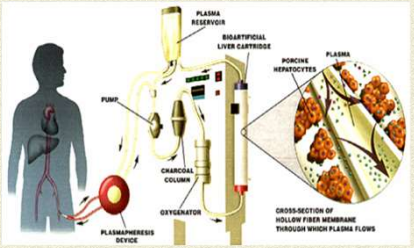
Liver failure post-hepatic resection

- Occurs in patients going through extended hepatic resections for hepatocellular carcinoma or hepatic metastases
- Remaining liver tissue cannot sustain normal functions
- **2-5%** mortality rate for all patients undergoing hepatectomy

Devarbhavi et al., 2024

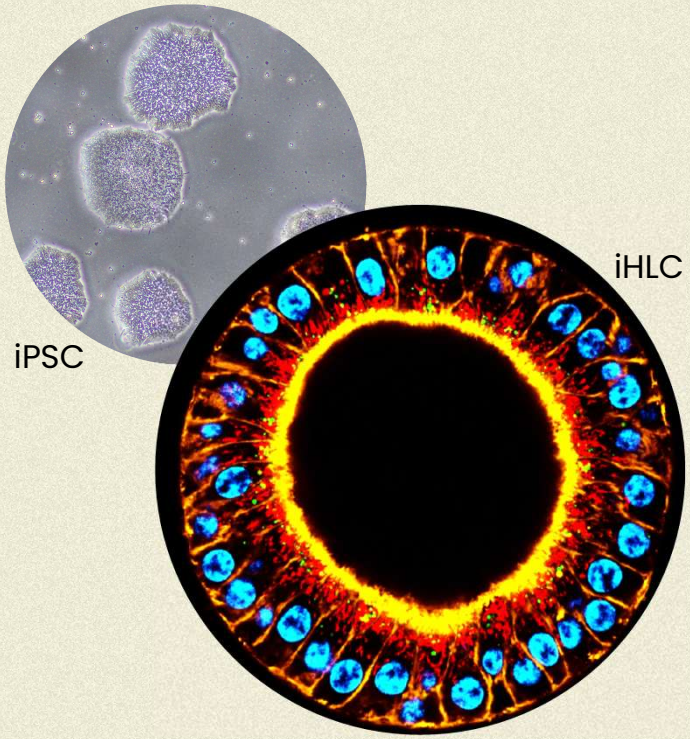
The issue Liver transplantation is curative but availability limited

Standard of care ⟵ ⟶ Investigational

	Liver transplantation	MARS	ELAD	Xenotransplantation
				
MoA	Healthy liver from donor transplanted into liver failure patients.	Mechanical, extracorporeal circulation to supplement albumin, ion exchange and for dialysis removal of toxins.	Extracorporeal circulation incorporating HepG2 cells for its biogenesis & detoxification function	Humanized liver from pigs to be transplanted into human – in effect, work as human LTx
Challenges	**Limited donor availability**, and long wait list attributes to high mortality	Past clinical studies showed **minimal efficacy**, as poor functional substitution & inflammation management	Past clinical studies showed **minimal efficacy and Terminated**. Hep cells are not sufficiently efficacious.	Clinical study to start in 2025 but **Safety concern** – past use of pig hearts failed due to retroviral infection

Our solution

Bioengineering human liver organoids from iPSC



Bioengineering highly functional liver organoids:

superior liver functionality compared to hepatocyte cell lines or mechanical dialysis

Hypoimmune human iPSC as source:

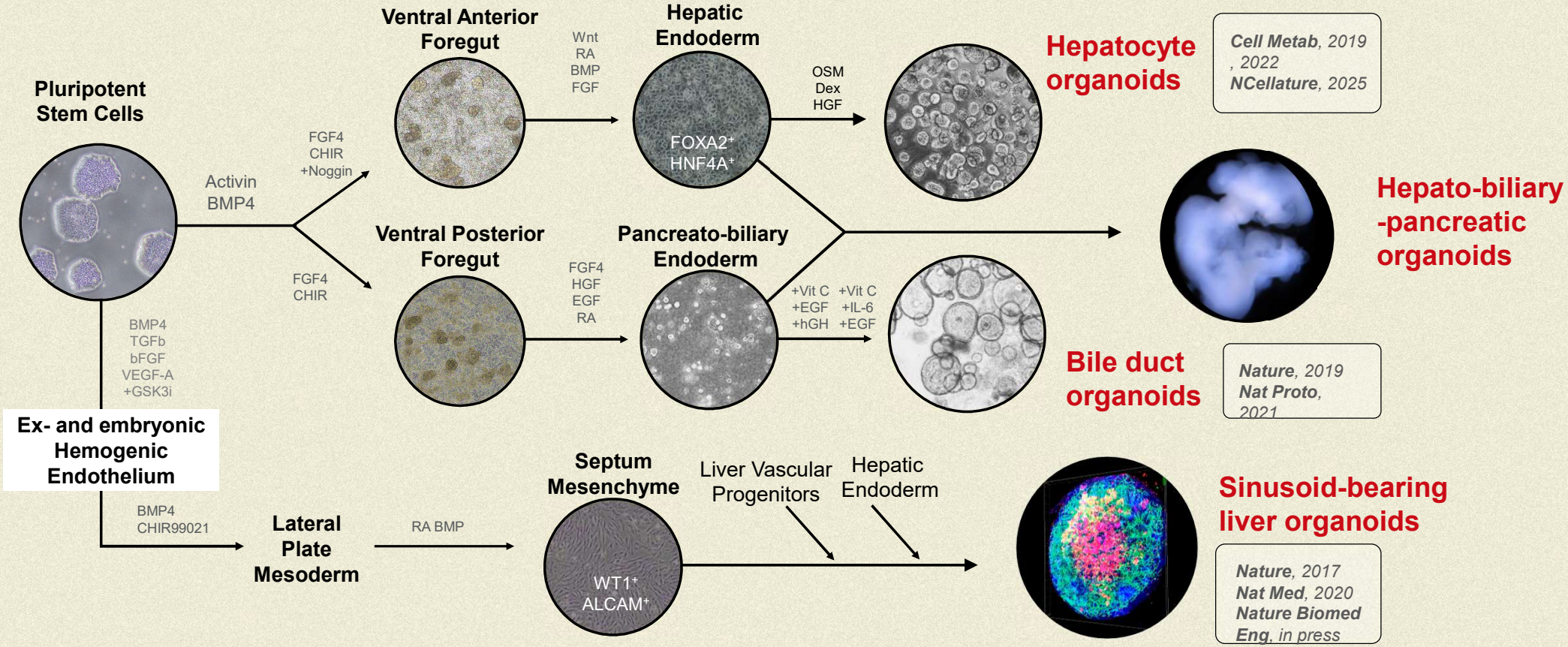
unlimited availability of source materials and manufacturing scale merit

Favorable risk-benefit profile:

patient survival, with minimized risk of complications from therapy (ex. inflammatory response to xenografts)

Our solution

Mastery of generating endodermal tissues from iPSCs



Cell Metab, 2019 , 2022
NCellature, 2025

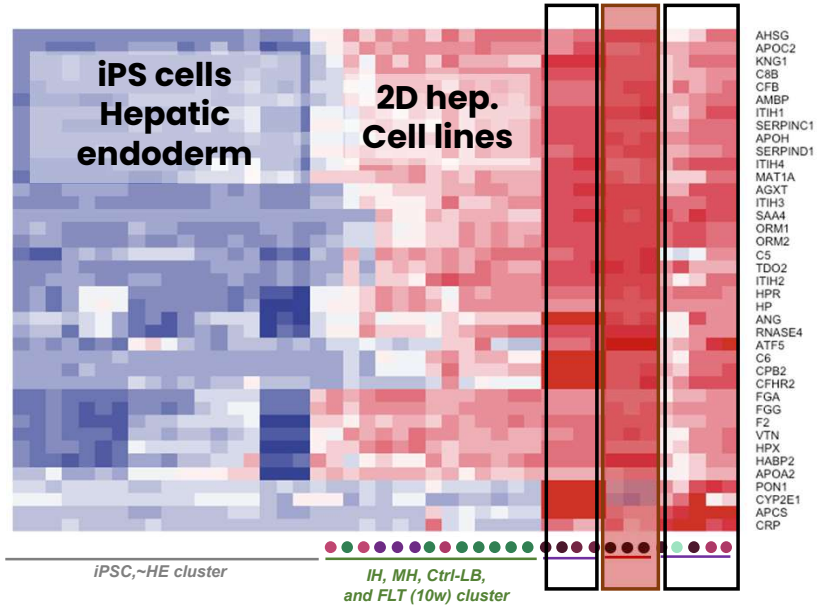
Nature, 2019
Nat Proto, 2021

Nature, 2017
Nat Med, 2020
Nature Biomed Eng, in press

Our solution

iHLCs are transcriptomically and functionally akin to *in vivo* liver

Hierarchical clustering of transcriptome shows similarity of iHLC to *in vivo* liver tissues



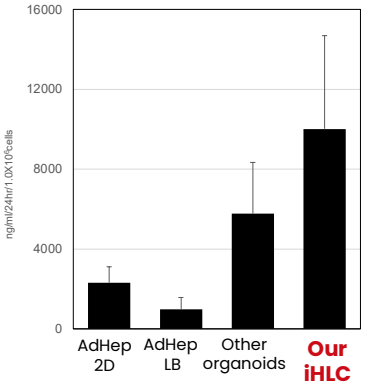
Adult liver tissues
Infant liver tissues

iHLC

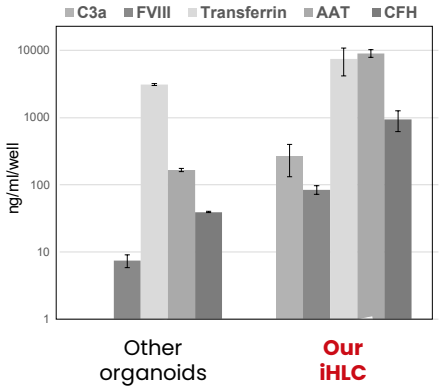
Fetal liver tissue

iPS-derived iHLC demonstrate functionality *in vitro*

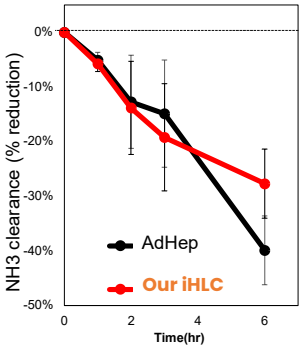
Albumin production



Biogenesis of key hepatic proteins



Ammonium clearance



Our iHLC: all *iPSC-derived, mass-produced liver organoids (hep, mesenchimal & endothelial cells)*
Other organoids: *iPSC-hepatocytes mixed with immortalized mesenchymal & endothelial cells*
AdHep: *Adult primary hepatocyte explant*
AdHep LB: *AdHep co-cultured with mesenchymal & endothelial cell lines*

Takebe et al., 2013, Nature; Takebe et al., 2017, Cell Reports

Our solution

Our iHLC is best-in-class simulating organogenesis process

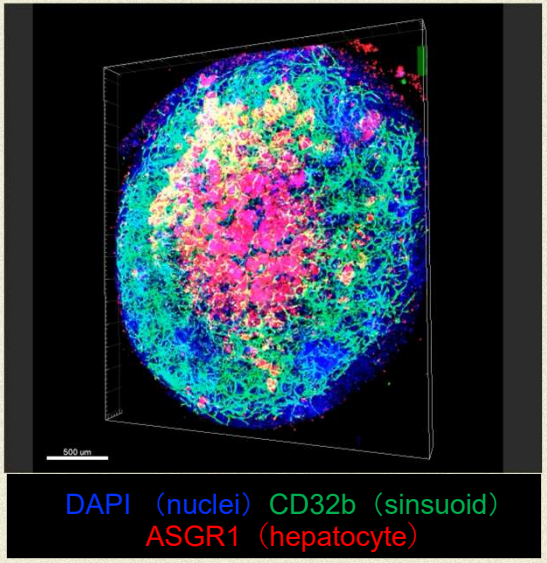
Self-organization

iPS-derived hepatocytes mixed with endothelial & mesenchymal cells self-organize into tissue simulating organogenesis, ascertaining hepatic identity and function (video 1).

*Takebe et al., **Nature,** 2013*
*Takebe et al., **Cell Stem Cell**, 2015*

Cellular Topology

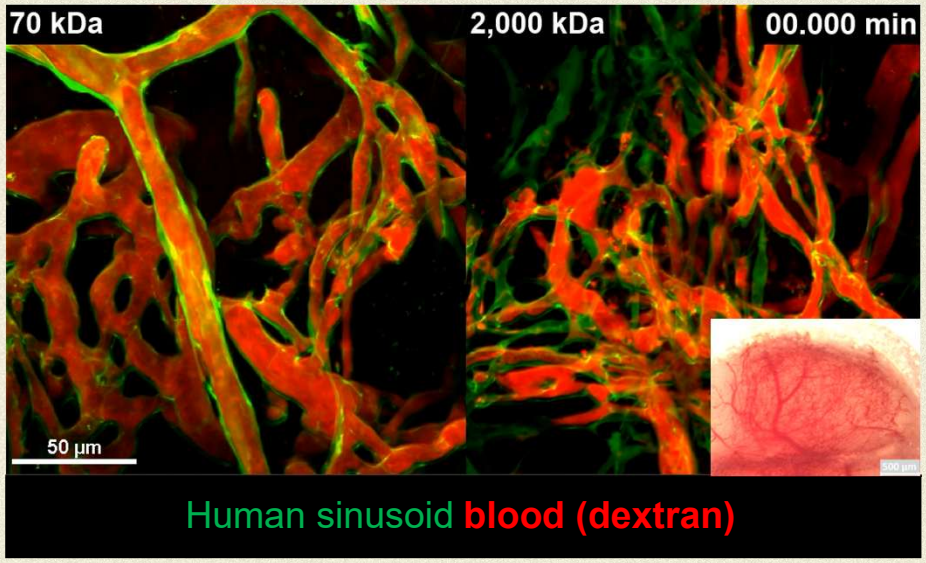
Development of spatially organized multicellular systems with cellular polarity emulated in vivo development and enables maturation of hepatocytes (video 2).



*Koido et al., **Nature Medicine**, 2020*
*Kimura et al. **Cell**, 2022;*
*Al Reza et al. **Nature** 2025*

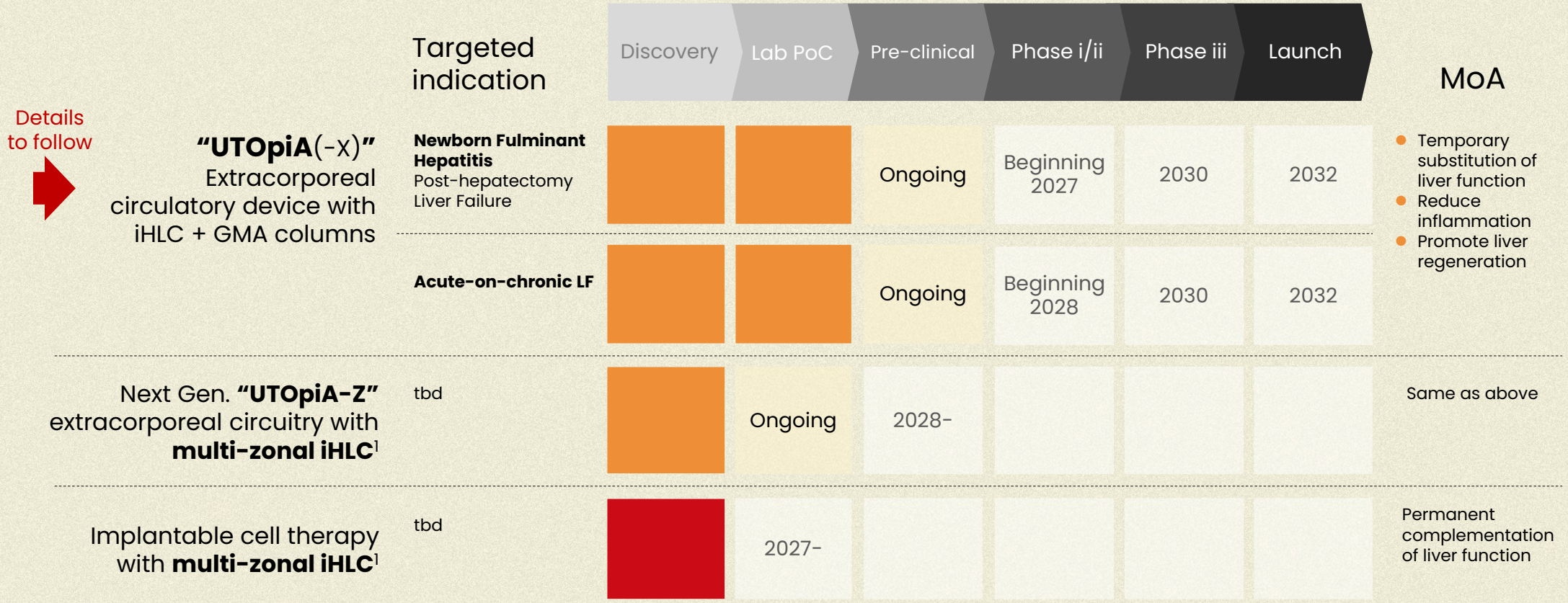
Functional Emergence

In vivo transplantation of our iHLCs leads to development of in vivo-like vein-to-sinusoid circulatory networks essential for secretory, electric and metabolic activities of hepatocytes – developed sinusoids show in vivo-like permeability passing 70kDa dextran for clearance but not 2000kDa (video 3)



*Kawakami et al. **Cell Stem Cell**, 2023*
*Saiki et al. **Nature Biomed Eng**, 2025;*
*Rezvani et al, **Nature**, 2025*

The Product First to develop extracorporeal support, with ultimate goal for implants



1: precise definition tbd: bioengineering hepatic zonation to mimic native liver physiology and superior functionality

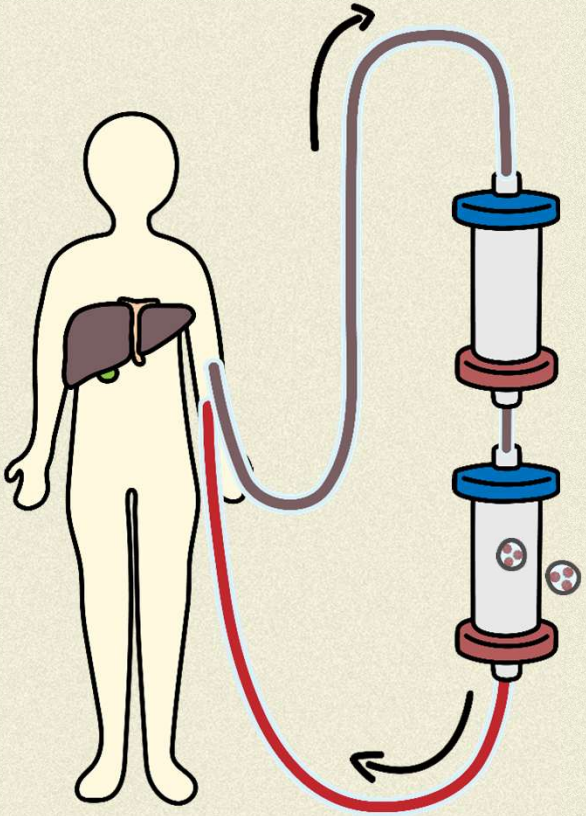
The Product

Our 1st product: extracorporeal UTOpiA system

UTOpiA® SYSTEM

Universal Tandem
Optimized iHepatocyte
with Apheresis

- Temporary substitute impaired **metabolic function** of liver – biogenesis & detoxification
- **Immune suppression** to overcome systemic inflammation associated with LF
- **Promote regeneration** of patient liver

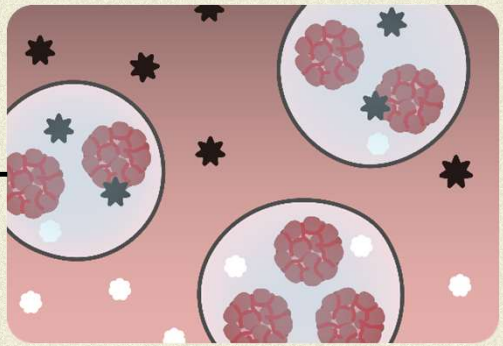


GMA column
"Adacolumn®"
from JIMRO Co.
approved for granulocyte removal

iHLC column

Cellulose acetate beads

Hypoimmune organoid

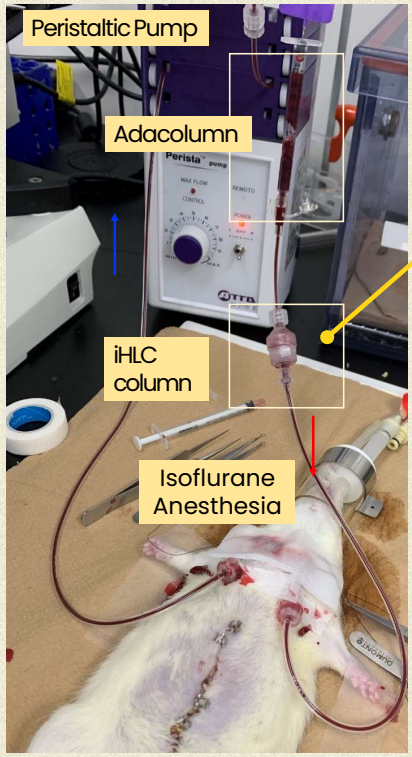


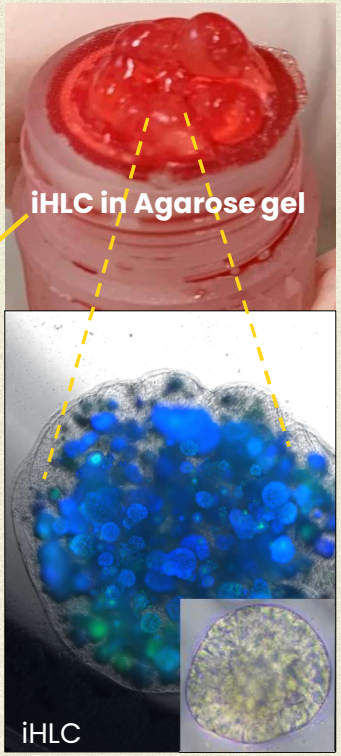
iHLC, Human liver organoid; GMA, granulocyte macrophage adsorption

The Product

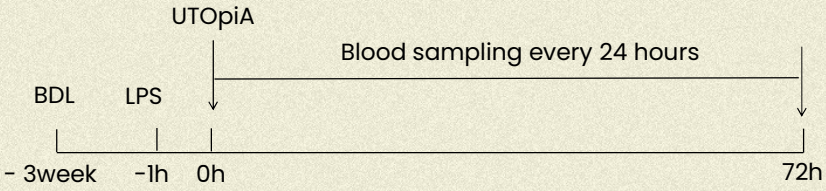
Demonstration of in vivo efficacy with UTOpiA

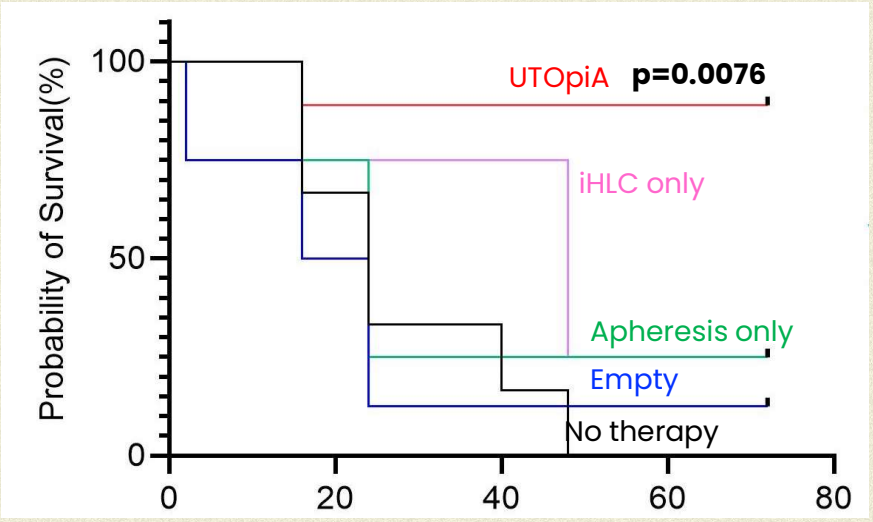
UTOpiA setup





Combination of iHLC & adacolumn significantly improved survival in ACLF model

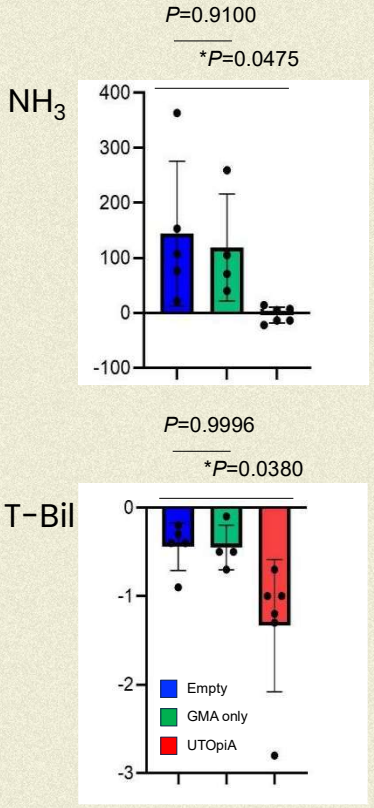




MOA

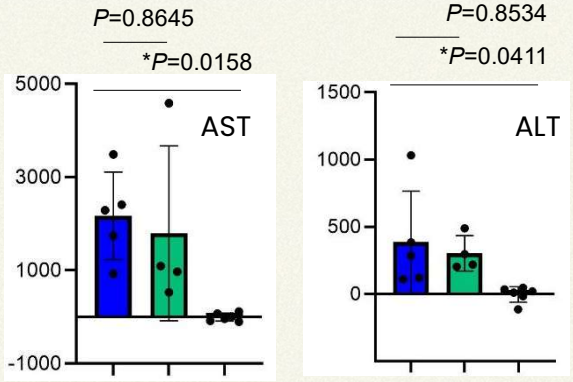
ACLF survival as UTOpiA substitute liver function & promote regeneration

Detoxification of plasma

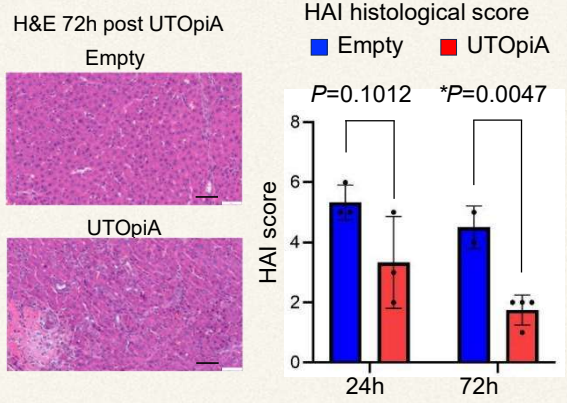


Reduced liver damage

Plasma conc. of liver enzyme: Indicate of liver cell death

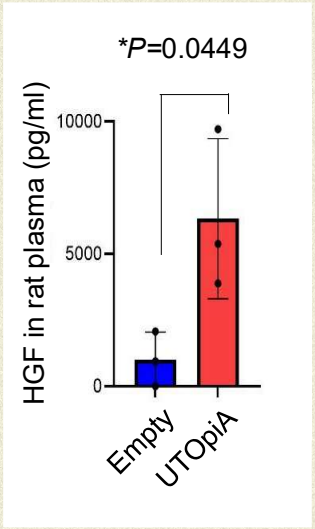


Histological score of liver damage, fibroasis and Inflammation (lower score =healthy)

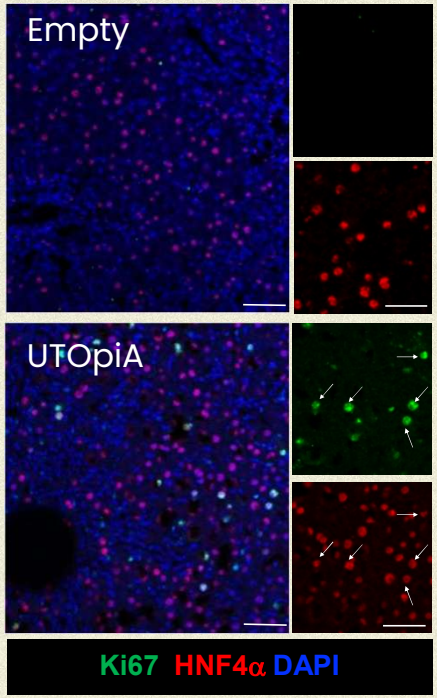


Liver regeneration promoted

HGF secreted from liver promotes regeneration



HNF4α+ hepatocytes are proliferating (KI67+)



CMC

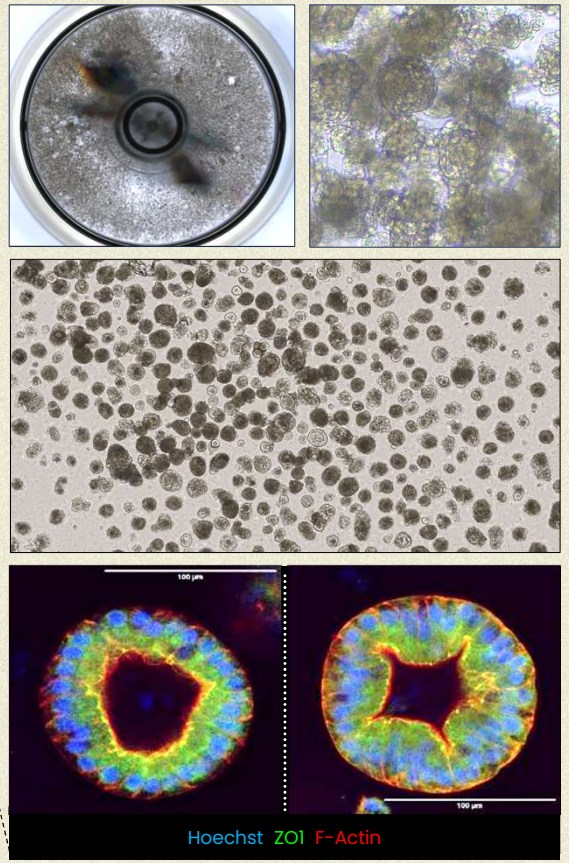
Scaling up organoid manufacturing in collaboration with CDMO

CMC process development and scale-up underway: ~30-day manufacturing process using stir bioreactor

Ambr bioreactors for
Quality-By-Design based manufacturing
(funded by AMED grant)

Currently using 5ml reactor, now scaling-up

Confirmation of canalicular micro-structures in bioreactor-based culture



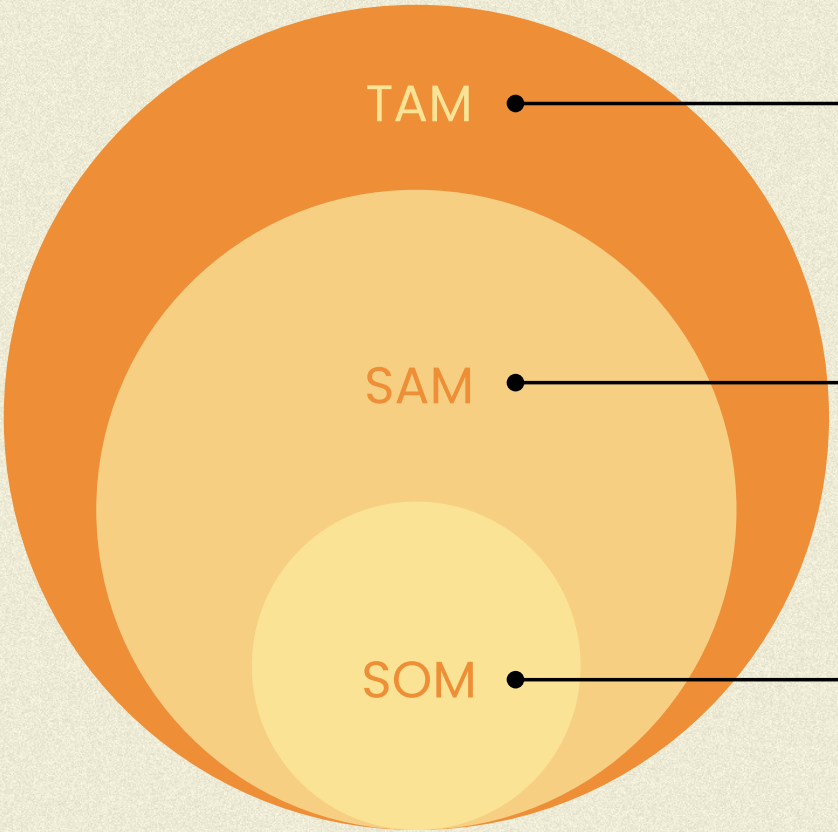
MCB, master cell bank; WCB, working cell bank

Competition Superiority as UTOpiA manage inflammation & supplement liver function

	miromatrix.	HEXAELL biotech	Satellite BIO	MORPHOCELL technologies	Kanzō Biomedicines
Product	Extracorporeal circulation with porcine ECM repopulated with **human primary hepatocytes**	Extracorporeal circulation with hepatocyte-like cell aggregate **derived from fibroblast via direct reprogramming**	**Primary expanded hepatocytes** bioprinted with HUVECs and hydrogel	**iPSC-derived** liver organoids encapsulated into non-degradable materials, transplanted into body	Extracorporeal circulation with **iHLC in tandem with adacolumn** to remove granulocytes
Liver functionality	✗ Limited biogenic ability of primary Hep once extracted	✗ Limited functionality as only hepatocyte-like cells with limited structural organization in 3D	✗ • Limited biogenic ability of primary Hep once extracted • Suboptimal survival data	? Little in vitro / in vivo data accessible	✓✓ Superior as organoid with canalicular organization and function similar to in vivo tissue
Immune-suppression	✗ No considerations to managing inflammatory reaction in LF	✗ No considerations to managing inflammatory reaction in LF	✗ No considerations to managing inflammatory reaction in LF	✗ No considerations to managing inflammatory reaction in LF	✓✓ Use of adacolumn to suppress harmful systemic inflammation
Safety	✓ Extracorporeal approach ensures no cellular components of device migrate into patients	✓ Extracorporeal approach ensures no cellular components of device migrate into patients	✗ Transplanted in vivo with concern of tumourigenesis	Require in vivo transplantation, concern for use of “non-degradable materials”	✓✓ ✓ Extracorporeal approach ensures no cellular contact ✓ Gene-editing to minimize immune reaction against cellular components

The Business

We expect UTOpiA to address $14 billion market



$14 billion

Treating US/EU/JP patients with acute-on-chronic liver failure (CLIF-SOFA grade 2/3) and post-hepatectomy liver failure

$6 billion

Treating patients with post-hepatectomy liver failure, whom become newly operatable thanks to the usage of UTOpiA (CP-AB, currently no resection patients)

$600 million

Assuming market share of 10%, only those who get LF post-operation

Our Operation Our 1st pipeline to enter clinics in 2027