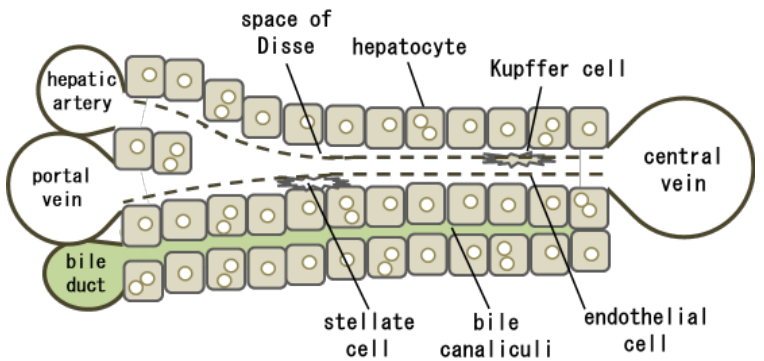
27th NIH Tissue Chip Consortium Meeting
+ CIVM Qualification Framework Public Workshop

NAMs Regulatory Needs in Japan

2026. Mar. 5-6

Sojo University
National Institute of Health Sciences
Seiichi ISHIDA



Hepatic Sinusoid

Liver MPS
DILI
Bile excretion
MASH

Self-Introduction

iMPSS Asia-Pacific Regional Chapter

Seiich Ishida
Chair

Zhonge Gu
Co-Chair

Regional Societies Representation

Dr. Alastair Stewart
Representing Australia

Dr. Jan Powell
Representing New Zealand

Dr. Kasturi Mahadik
Representing India

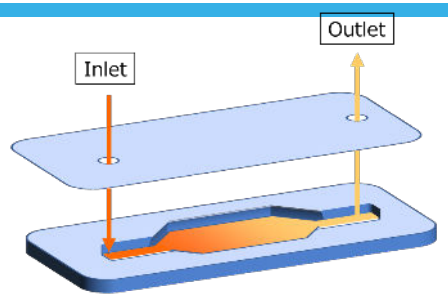
Dr. Noo Li Jeon
Representing South Korea

Dr. Seiichi Ishida
Representing Japan

Dr. Zaozao Chen
Representing China

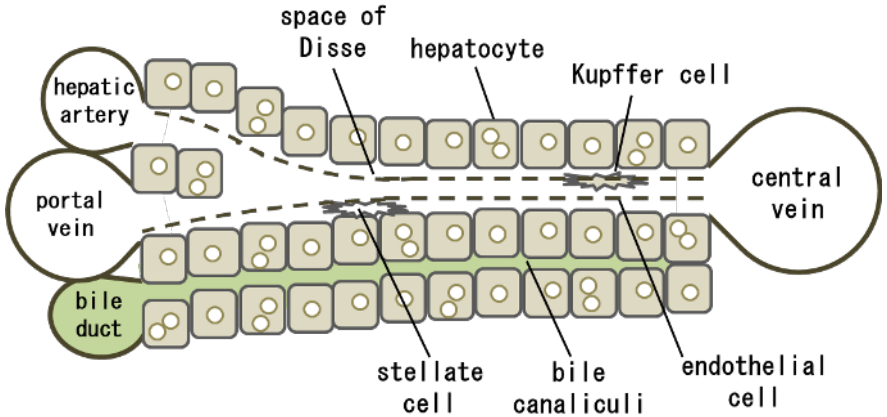
Research Background

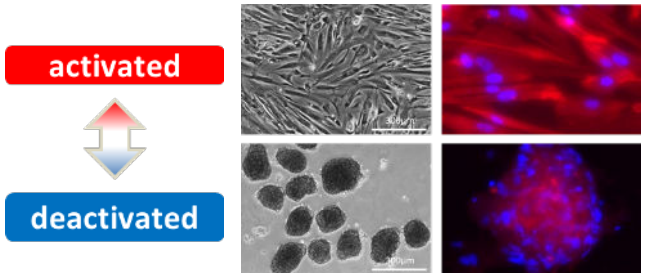
Basic research to reconstitute liver *in vitro* and development of drug efficacy and safety evaluation systems

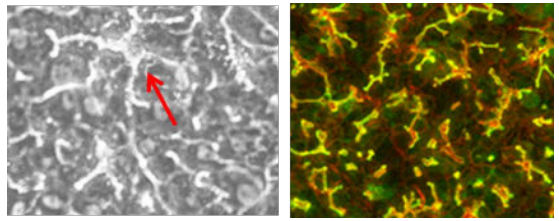


Utilize MPS to recreate the liver environment.

Hepatic Sinusoid







Develop a culture system for hepatic stellate cells and establish a pathological model of hepatitis and liver fibrosis.

Establish a culture system capable of evaluating bile excretion.

Today's Agenda

1. Background of MPS development in Japan
2. Importance of "in-line monitoring"
3. Utilization of "artificial scaffolds (biomaterials)"

Background of MPS Development in Japan

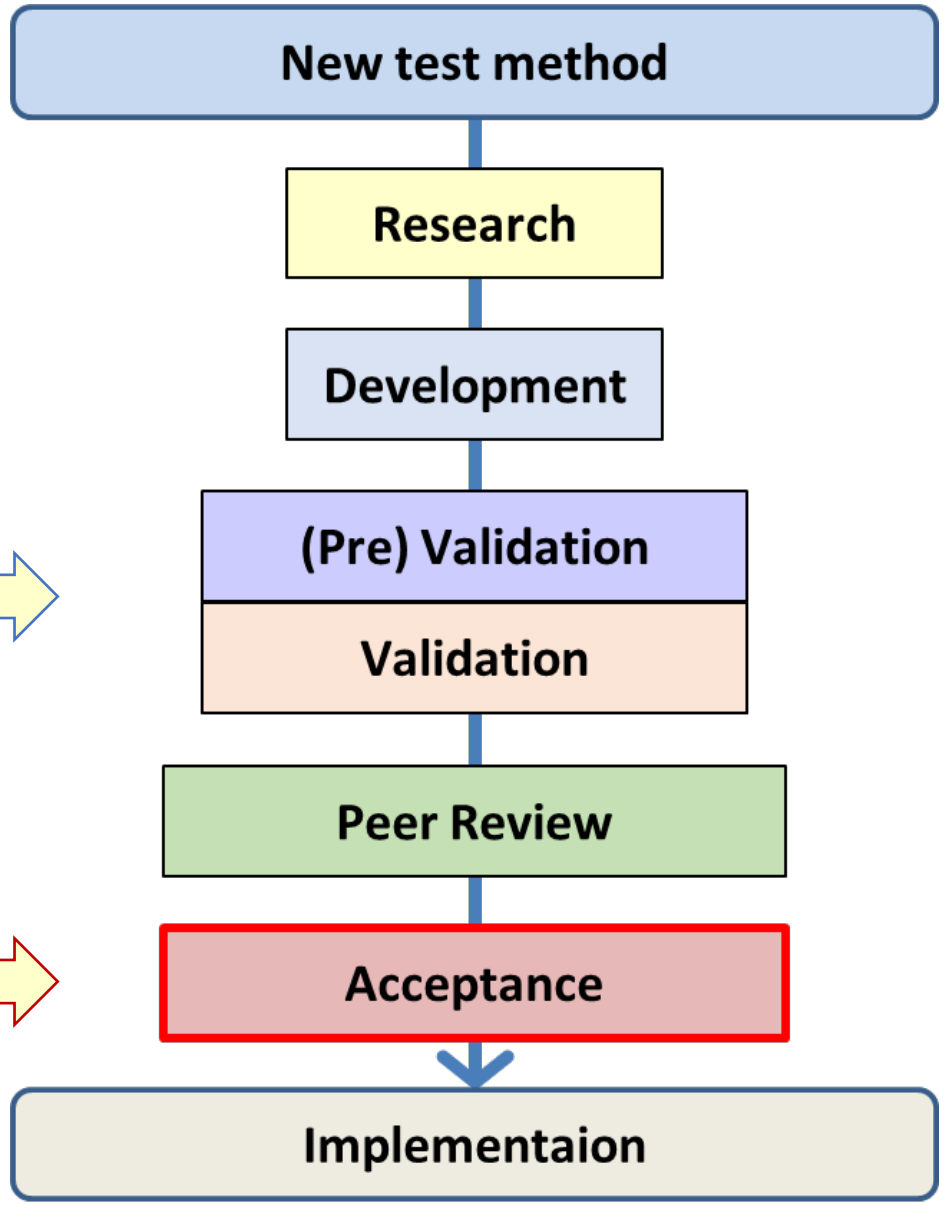
Today's Agenda 1

Toward Industrial Implementation and Regulatory Acceptance of MPS

Test Definition

Industrial Implementation

Regulatory Acceptance



OECD modified

AMED-MPS 1
by METI

AMED-MPS 2
by METI
⇒ ISO
→ ICH

bridging

MPS-RS*
by MHLW
⇒ OECD
→ ICH

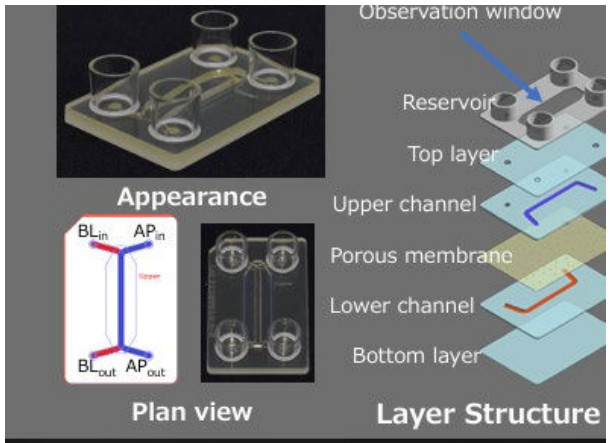
*RS: Regulatory Science

Commercially Available MPS Platforms in Japan

tok

Micro physiological system(MPS)

Fluid3D-X®

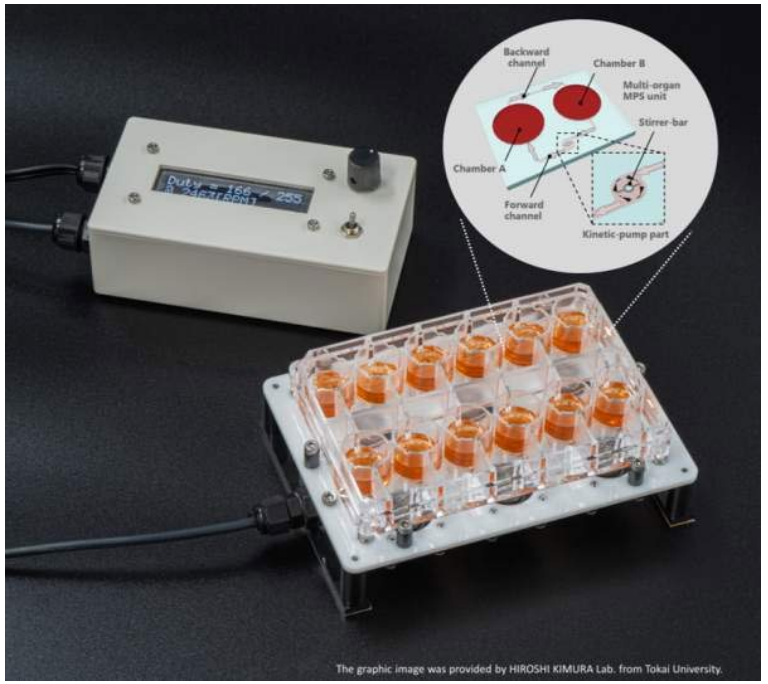


Sbio®

Sumilon™ MPS Series

BioStellar™ Plate

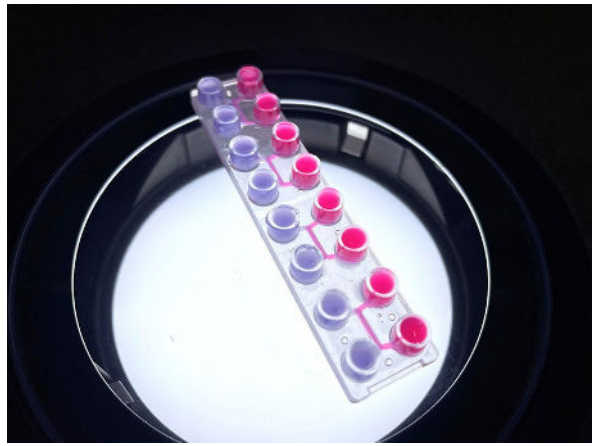
Multi-Organ Microphysiological System



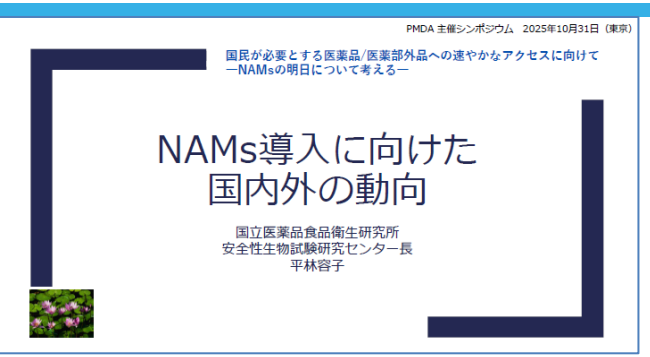
Physios Biotech

Boncyte™

Chip –Double Flow–



PMDA's Initiatives



■ Publication of Early Consideration

- Regarding the Policy on the Use of New Approach Methodologies (NAMs) in Applications for Quasi-Drugs (https://www.pmda.go.jp/files/000277384.pdf)

■ Establishment of the NAMs Review Working Group

- Composed of cross-sectional members from within the agency.
- it proceeds with discussions on various issues related to NAMs.

■ Collaboration with Domestic Related Organizations

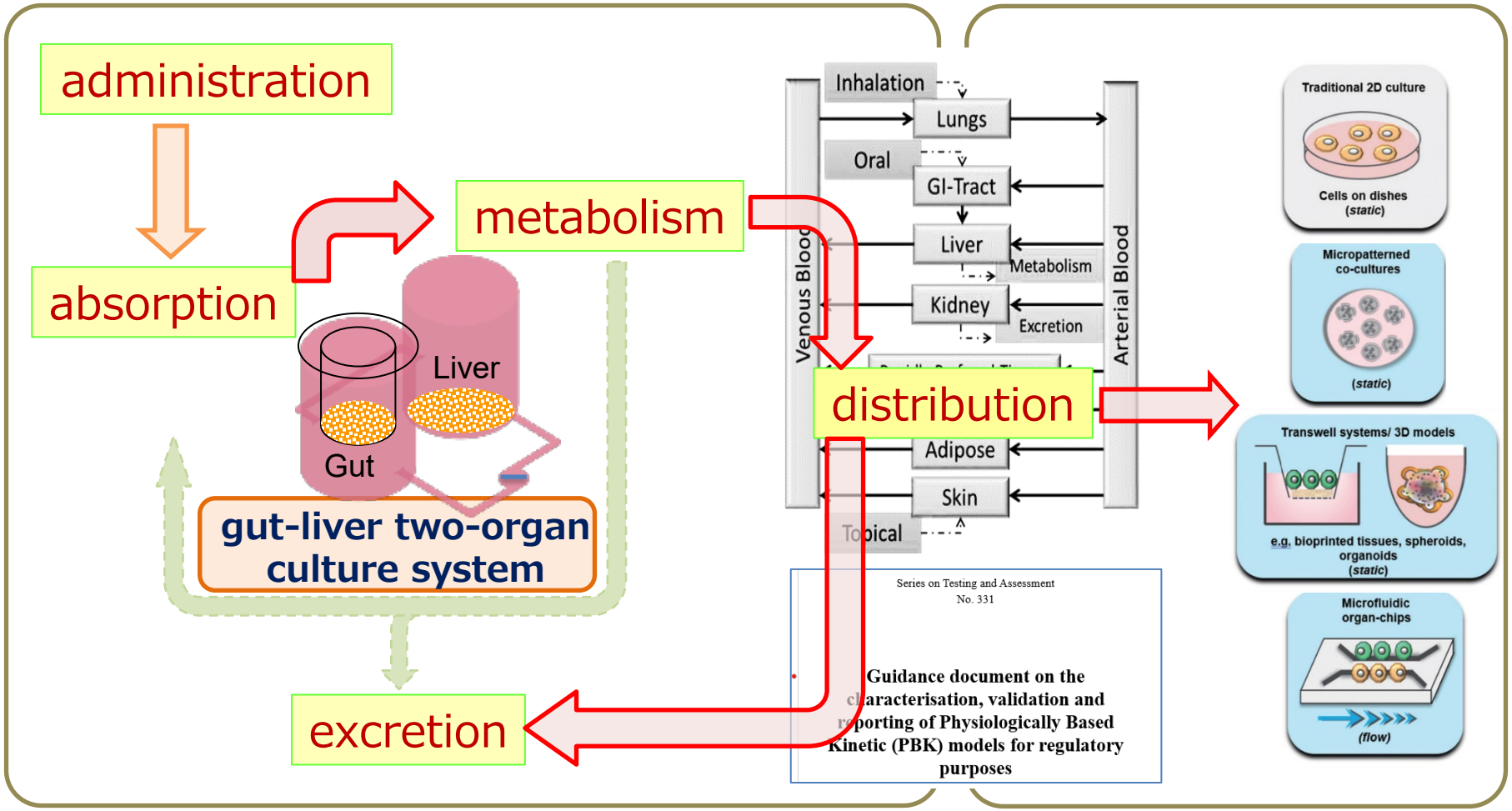
- In collaboration with the National Institute of Health Sciences / Japanese Center for the Validation of Alternative Methods (JaCVAM), industry, academia, etc., it proceeds with examining the potential applications of NAMs.

■ Collaboration with Foreign Regulatory Authorities such as FDA and EMA

https://www.pmda.go.jp/review-services/0071.html

New Concept of *in vitro* Toxicokinetics

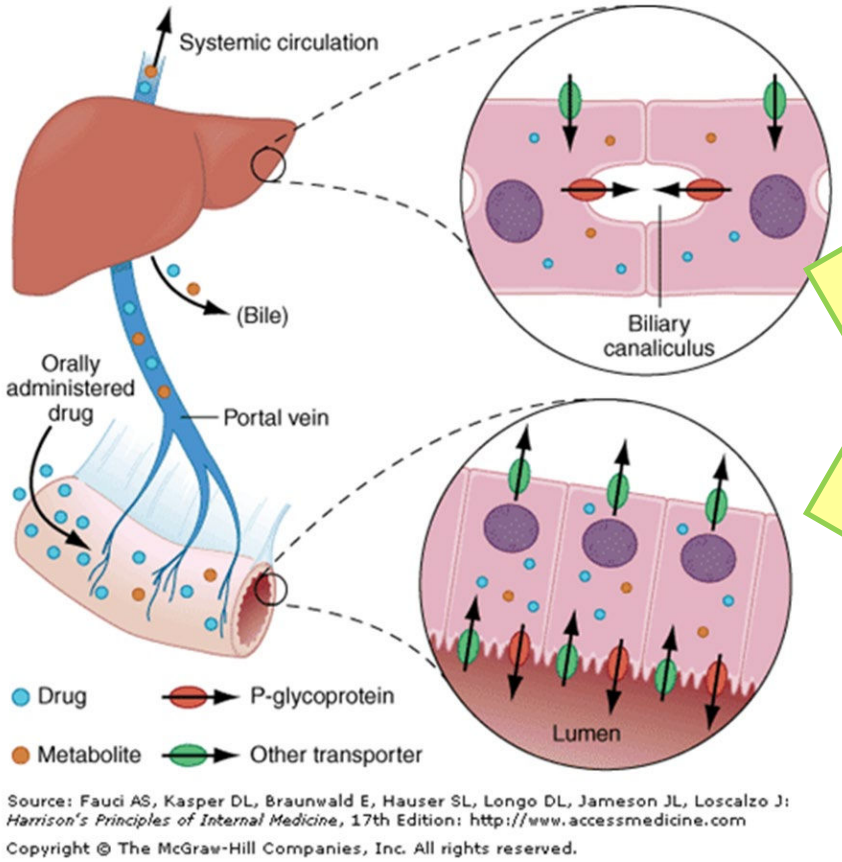
Risk Evaluation by Integration of Hazard Assessment by NAMs with Toxicokinetic under IATA



Toxicokinetics × **Hazard**

Risk

Construction of Assay System: Cells & MPS



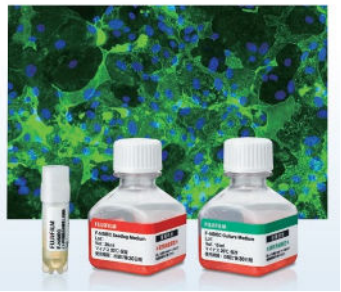
Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

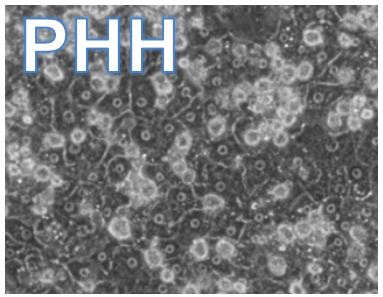
in vitro model

Cell

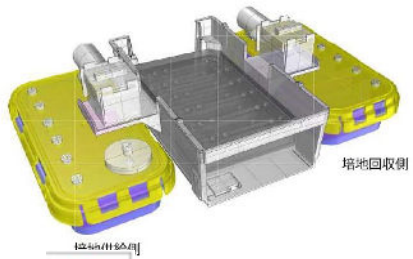
FUJIFILM
Value from Innovation

ヒトiPS細胞由来腸管上皮細胞
F-hiSIEC™
アプリケーションのご紹介

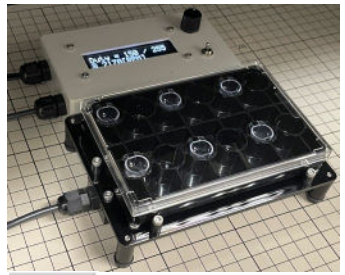




MPS



MS-plate



BioStellar™

PhysioMimix

ICCP

PD-MPS

HUMIMIC

Road-map to the OECD Test Guideline Proposal

Work plan for the OECD Test Guidelines Programme (TGP)
Project 4.188: Detailed Review Paper for in vitro Toxicokinetics

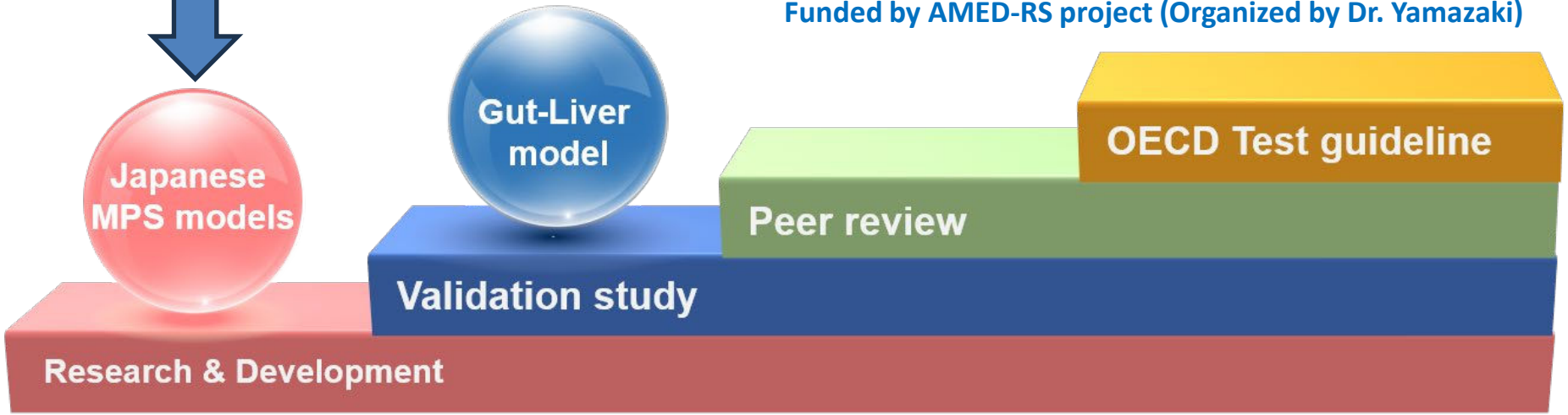
BioStellar™ Plate

Pre-validation test

Test lab. NIHS, TOKAI UNIVERSITY, AXCELEAD

Support lab. JaCVAM, SOJO UNIVERSITY, Sbio

Funded by AMED-RS project (Organized by Dr. Yamazaki)

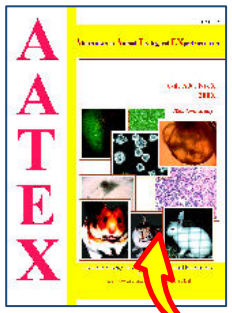


Please contact to Daiju Yamazaki (daiju-y@nihs.go.jp), Seiichi Ishida (ishida-s@bio.sojo-u.ac.jp)

Process of Establishing Specifications for Regulatory Acceptance of MPS

Establishment of Context of Use by User

Extraction and verification of “Consideration Points" necessary for the regulatory acceptance of MPS



User unmet needs

MPS performance standard

Consideration Points

- **Good functionality fit for CoU on the MPS**
- **Differentiation and maturation on MPS**
- **Good cell adhesion to MPS**
- Variation in cellular function

Criteria for Cell

Selection of Model Cell

Standard for Device

Development of Device

Consideration Points

- **Good supply of oxygen**
- Evaluation of sorption of compounds
- Evaluation of effects of plasticizer
- Cell Observability
- Long-term sterility
- Sufficient sampling volume
- Simultaneous execution of multiple experiments

Test Procedures
· Cell
· Reference Compounds
· Function Analysis
· MPS handling

Test by Users

Consideration Points

- Repeatability
- Reproducibility
- Robustness
- Ruggedness
- Stability
- Proficiency test

- Test Compounds
- *In vitro* to *in vivo* extrapolation

“Context” of Use does not merely mean the intended use but “the situation, events, or information that are related to something and that help you to understand it,”

Importance of "in-line monitoring"

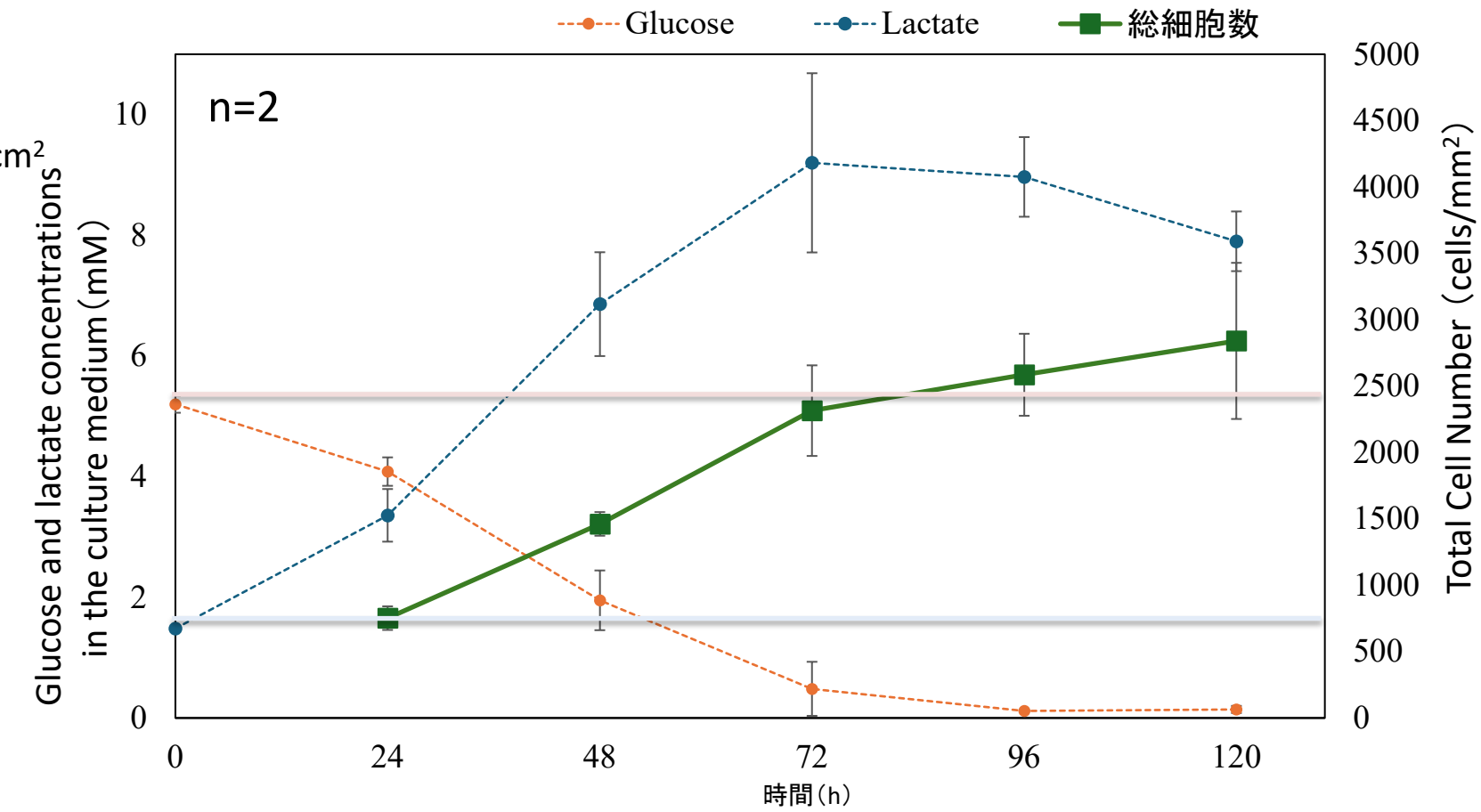
Utilization of "artificial scaffolds (biomaterials

Today's Agenda 2

Conventional Dish Culture

Changes in Glucose and Lactate Concentrations in Culture Medium

使用細胞：HepG2(J)
使用培地：MEM+10%FBS
培養時間：120h（5日間）
播種密度：5.0 × 10^4 cells/cm^2
培養器材： 48well plate
培地量：250 µL/well



Glucose conc. In fresh culture medium

Lactate conc. in fresh culture medium

Changes in Glucose and Lactate Concentrations in Culture Medium

使用細胞：HepG2(J)
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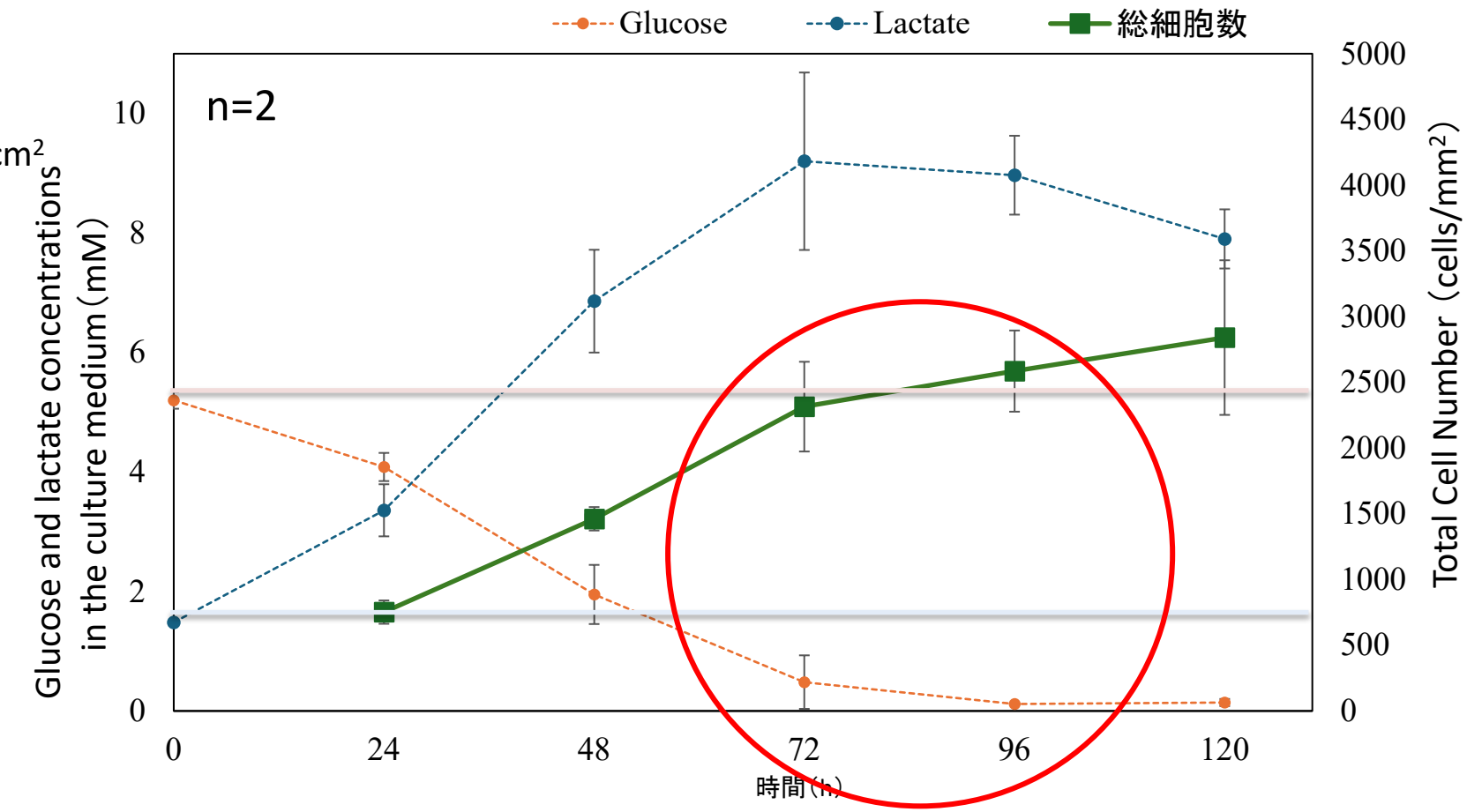
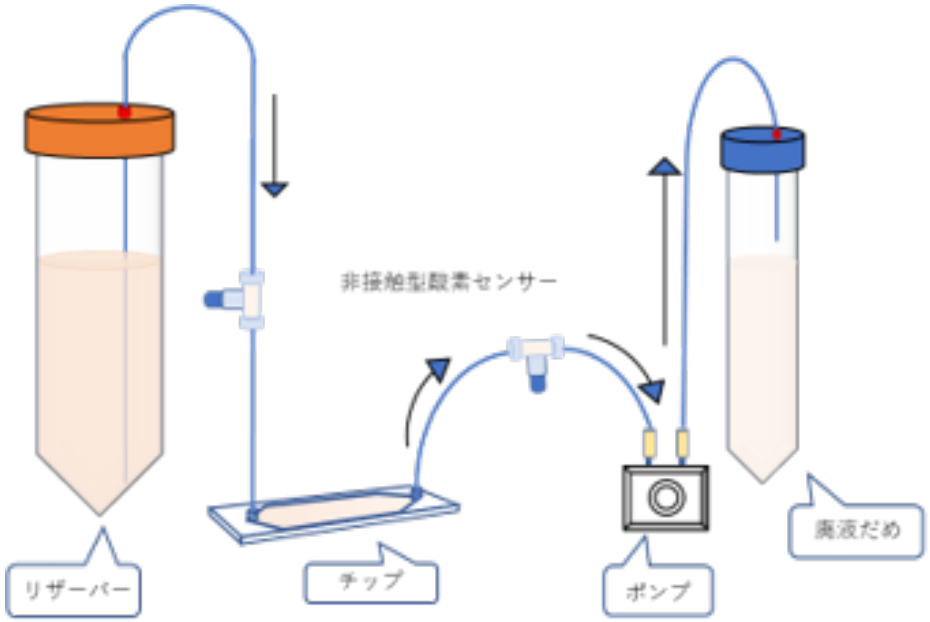


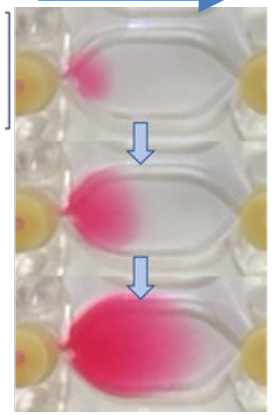
Glucose conc. In fresh culture medium

Lactate conc. in fresh culture medium

What about MPS culture?

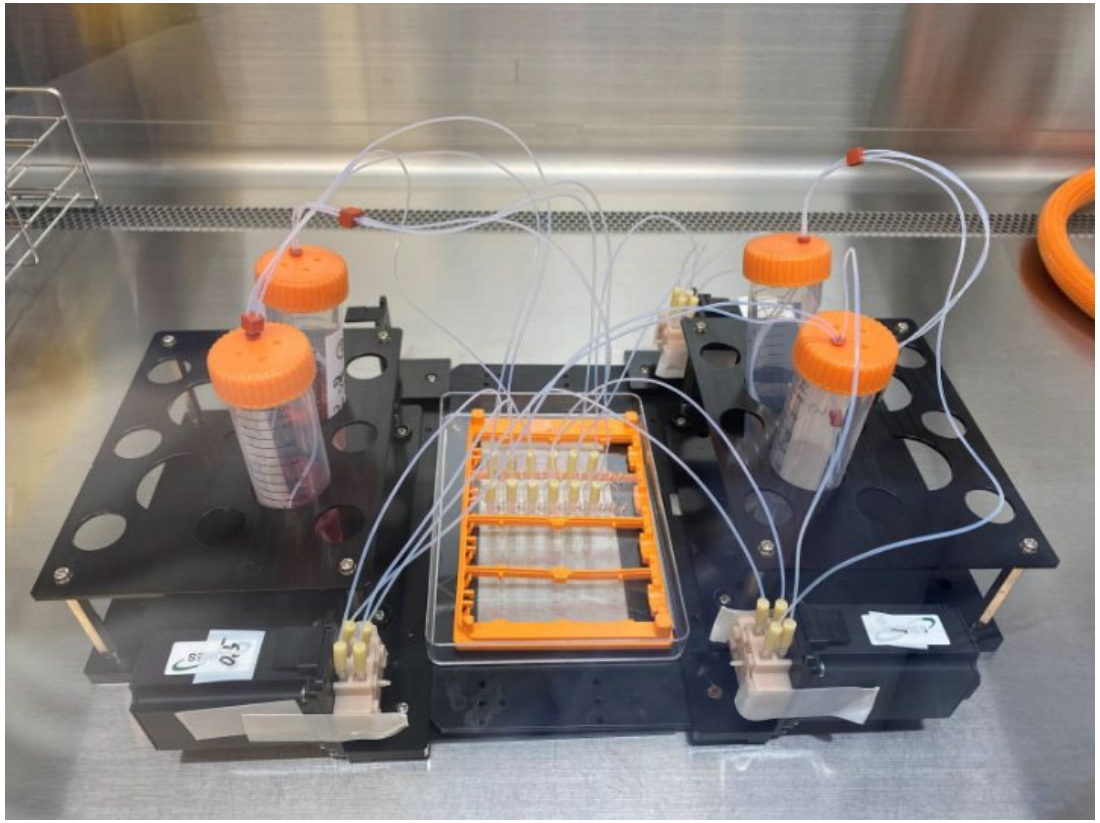


flow



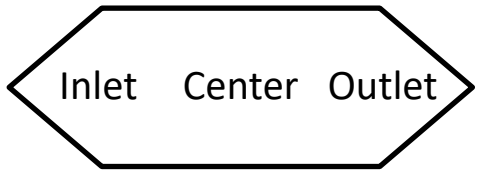
inlet

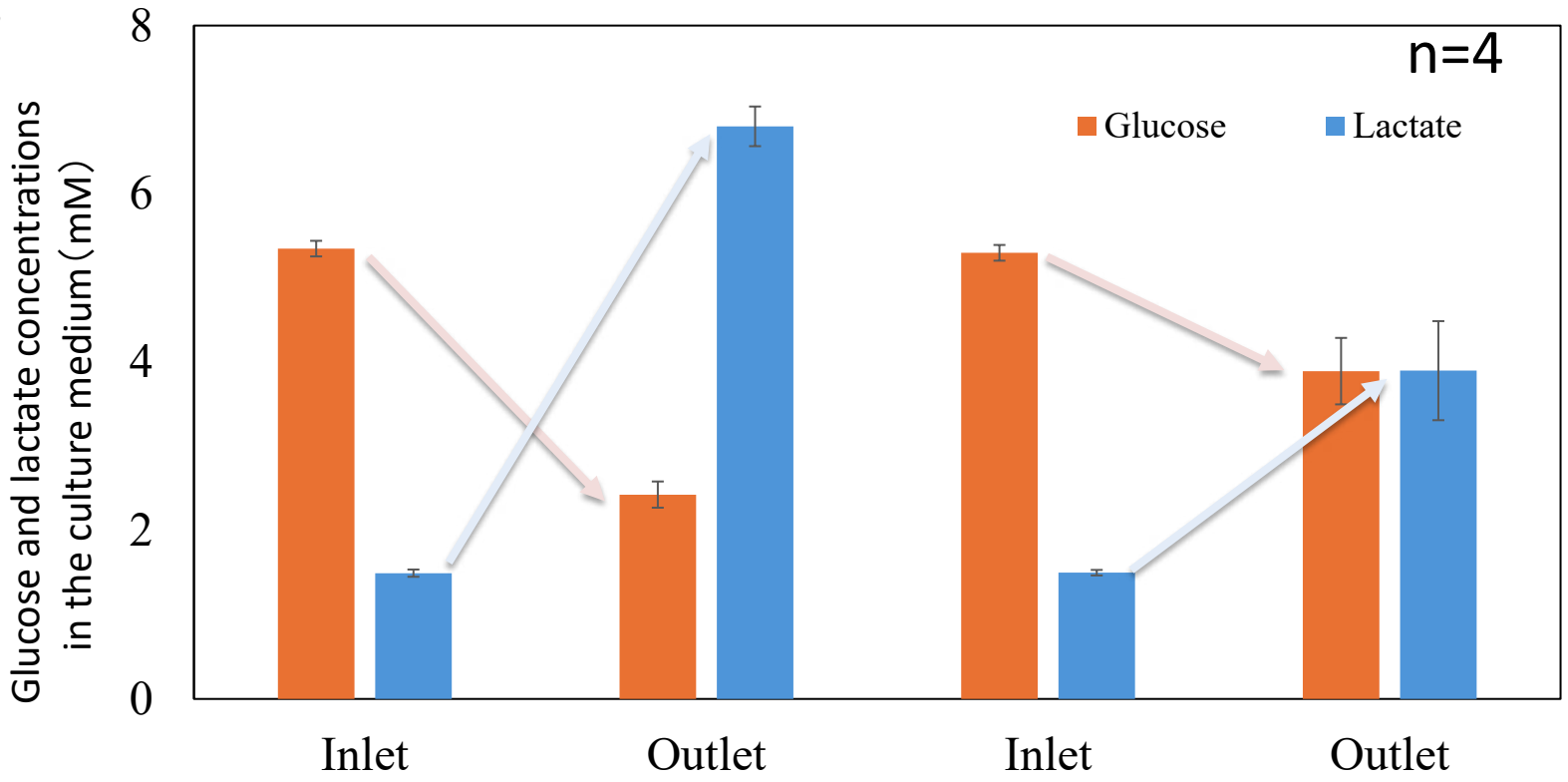
outlet



Comparison of Glucose and Lactate Concentrations by Medium Flow Rate

細胞：HepG2(J)
培養時間：72h
播種密度：5.0×10^4 cells/cm^2
デバイス：反応チャンバチップ





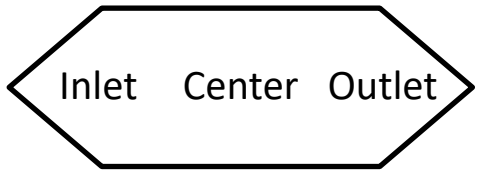
Glucose conc. In fresh culture medium

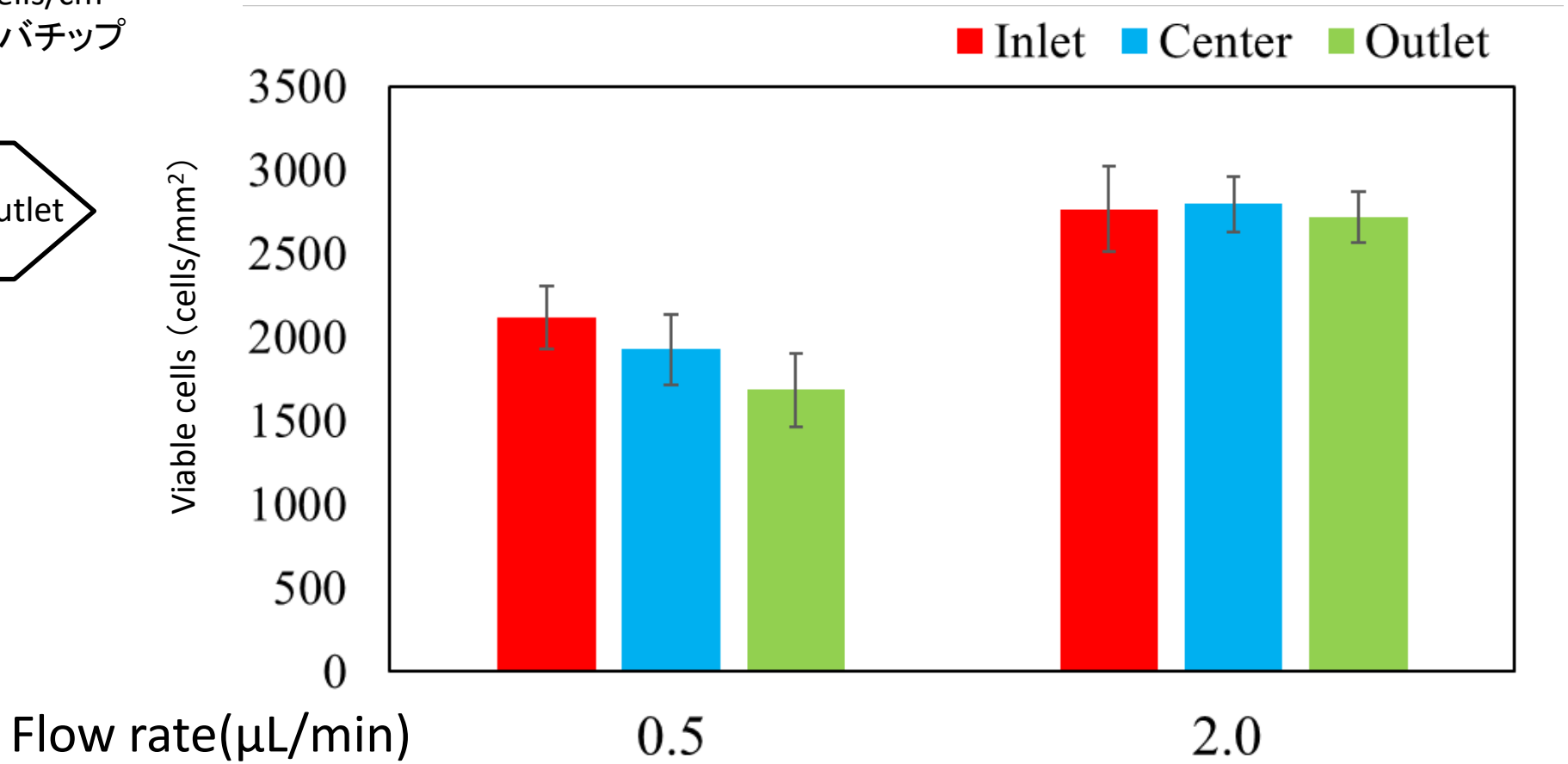
Lactate conc. in fresh culture medium

Flow rate(μL/min) 0.5 2.0

Comparison of Glucose and Lactate Concentrations by Medium Flow Rate (Viable cells)

細胞：HepG2(J)
培養時間：72h
播種密度：5.0×10^4 cells/cm^2
デバイス：反応チャンバチップ





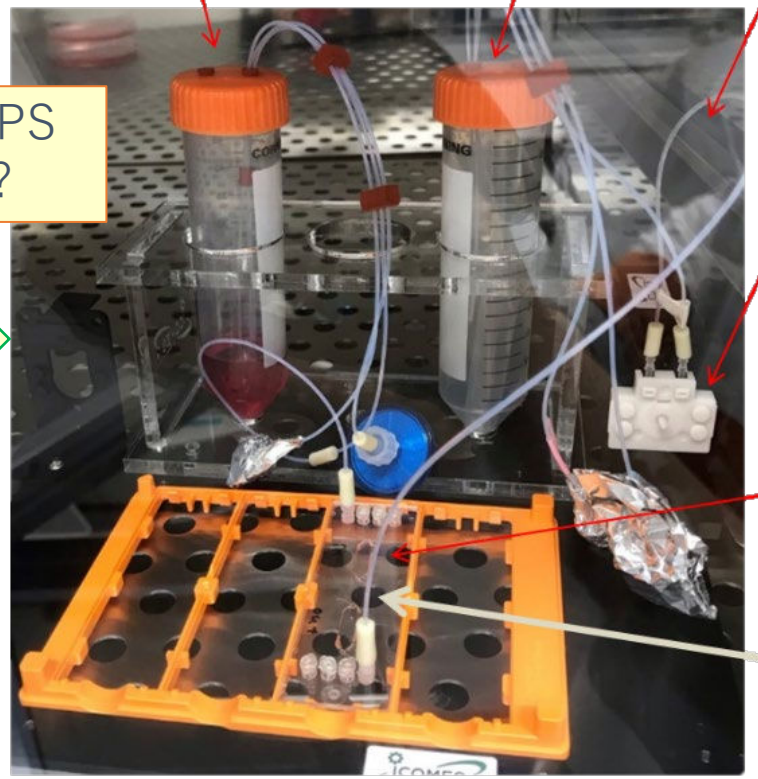
Animal Testing Facility vs How should MPS be Designed?

Animal Testing Facility

Good Laboratory Practice

How should MPS be designed?

MPS



日本クレアHPより
https://www.clea-japan.com/products/service/item_c0030

How should MPS be Designed?

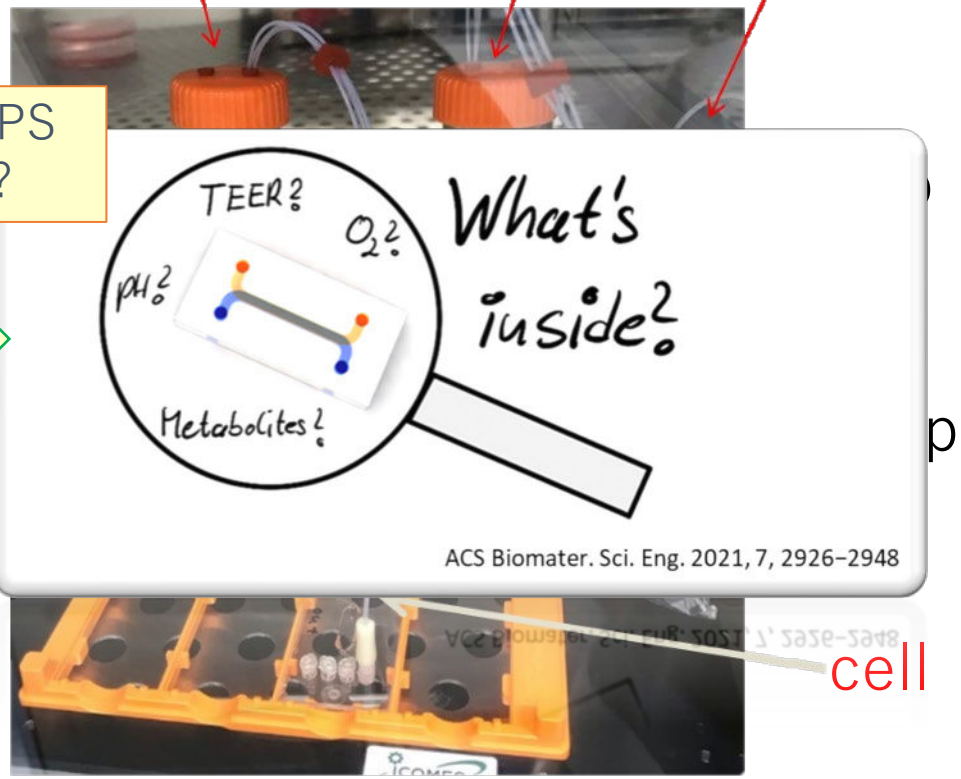
Animal Testing Facility

Good Laboratory Practice

How should MPS be designed?

M PS

reservoir waste tube



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日本クレアHPより
https://www.clea-japan.com/products/service/item_c0030

Key in-line Monitoring Points for Healthy MPS

In-Line Cell Vital Monitoring

Aspect	What should be monitored in-line	Positioning in the review	Implications for MPS culture
Culture environment	Continuous monitoring of oxygen, pH, and nutrient conditions	Fundamental indicators of culture health	Optimization of perfusion conditions and early detection of abnormalities
Metabolic state	Time-course changes in glucose consumption and lactate production	Quantitative indicators of cellular activity	Early identification of functional decline or cell death
Barrier function	Real-time TEER measurements	Non-destructive functional assessment	Detection of barrier disruption and culture failure
Cell adhesion and growth	impedance-based monitoring of cell adhesion and morphology	Indirect indicators of cell status	Detection of cell detachment and spatial heterogeneity
Long-term stability	Consideration of sensor drift and biofouling	Key technical challenges for implementation	Ensuring reliability in long-term MPS culture

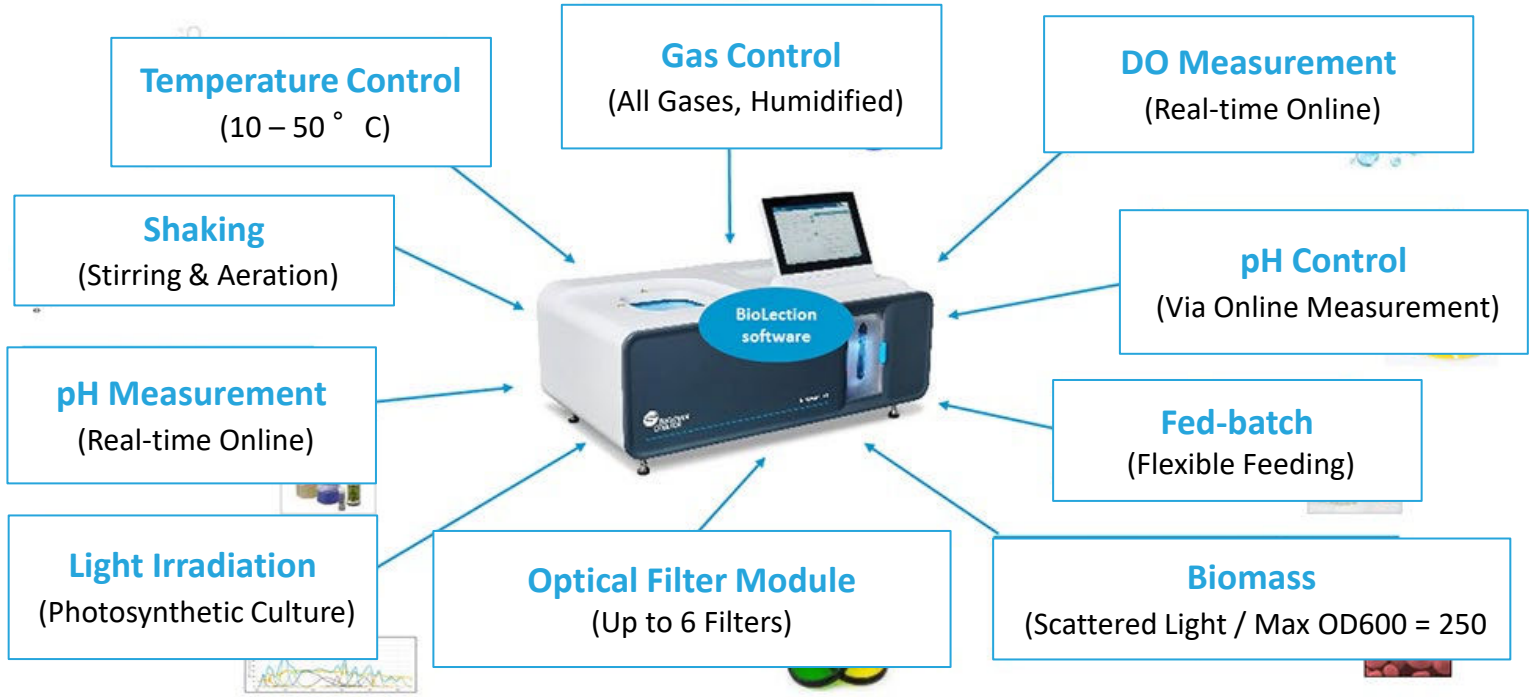
ACSBiomater.Sci.Eng.2021,7,2926−2948

Early Adopters of In-Line Cell Vital Monitoring

BECKMAN COULTER Life Sciences

BioLector XT

Microbioreactor



In-Line Cell Vital Monitoring

Medium flow rate

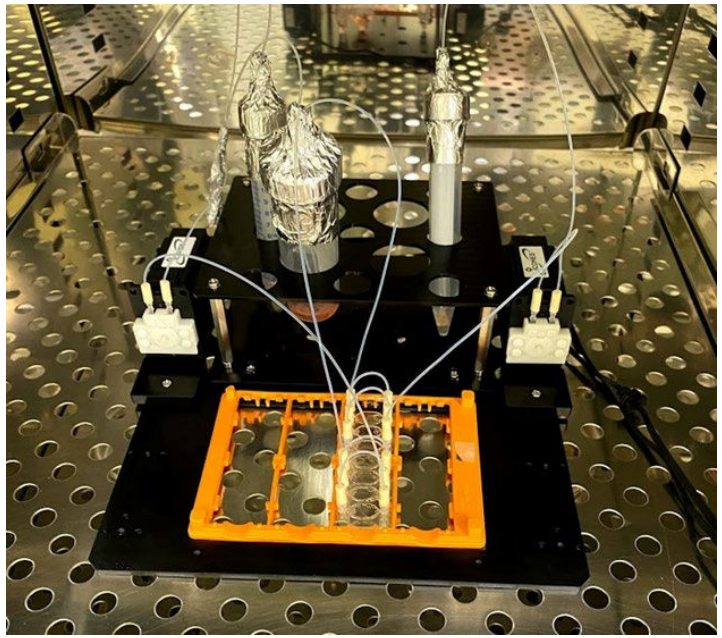
feedback

Medium Flow

pH

Dissolved Oxygen

Temperature



Morphology
Cell Number

Glucose

Lactate

Glutamine/
Glutamic Acid

Ammonium

Contamination

Cell Damage/
Function

Importance of "in-line monitoring"

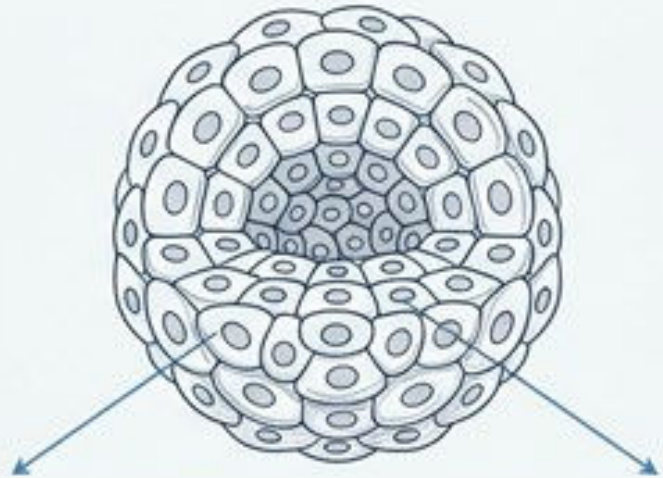
Utilization of "artificial scaffolds (biomaterials

Today's Agenda 3

Why 3D Cell Culture Now?

3D cell culture enables more in vivo-like data by reproducing cell–cell interactions and tissue-specific microenvironments that are not captured in 2D cultures.

Limited Model
(Conventional 2D Culture)



More In Vivo-like Model (3D Culture)

- **Improved physiological relevance**: Reproduction of interactions with the extracellular matrix (ECM) as well as native cell morphology and polarity.
- **Enhanced predictive accuracy**: Demonstrates higher correlation with clinical outcomes in drug response and toxicity evaluation.
- **Understanding complex biology**: Enables the study of complex biology inaccessible to 2D culture, including tissue formation, cancer invasion and metastasis, and self-organization of organoids.

Multi-organ chip with Matured Tissue

NATURE BIOMEDICAL ENGINEERING | VOL 6 | APRIL 2022 | 351–371

nature biomedical engineering

ARTICLES

https://doi.org/10.1038/s41551-022-00882-6

Check for updates

A multi-organ chip with matured tissue niches linked by vascular flow

Kacey Ronaldson-Bouchard[1], Diogo Teles[1,2,3], Keith Yeager[1], Daniel Naveed Tavakol[1], Yimu Zhao[1], Alan Chramiec[1], Somnath Tagore[4], Max Summers[1], Sophia Stylianos[1], Manuel Tamargo[1], Busub Marcus Lee[1], Susan P. Halligan[1], Erbil Hasan Abaci[5], Zongyou Guo[5], Joanna Jacków[5], Alberto Pappalardo[5], Jerry Shih[6], Rajesh K. Soni[7], Shivam Sonar[8], Carrie German[8], Angela M. Christiano[5,9], Andrea Califano[4,7,10,11,12,13], Karen K. Hirschi[14], Christopher S. Chen[6], Andrzej Przekwas[8] and Gordana Vunjak-Novakovic[1,12,15] ✉

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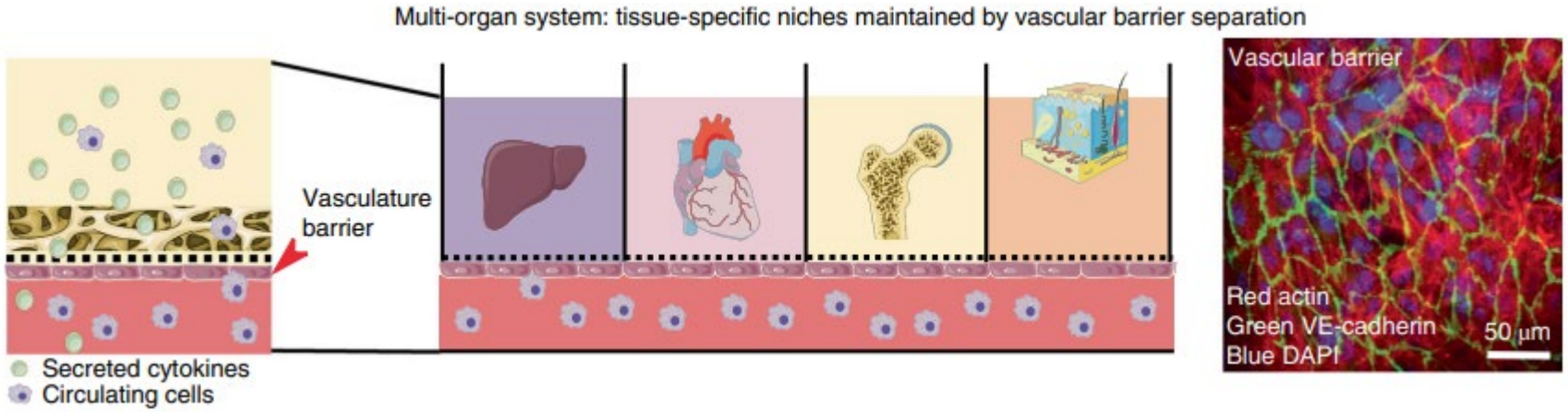
Published online: 27 April 2022



Considerations for Developing CYP Induction Assays in Hepatocytes Insights from a Multilaboratory Study

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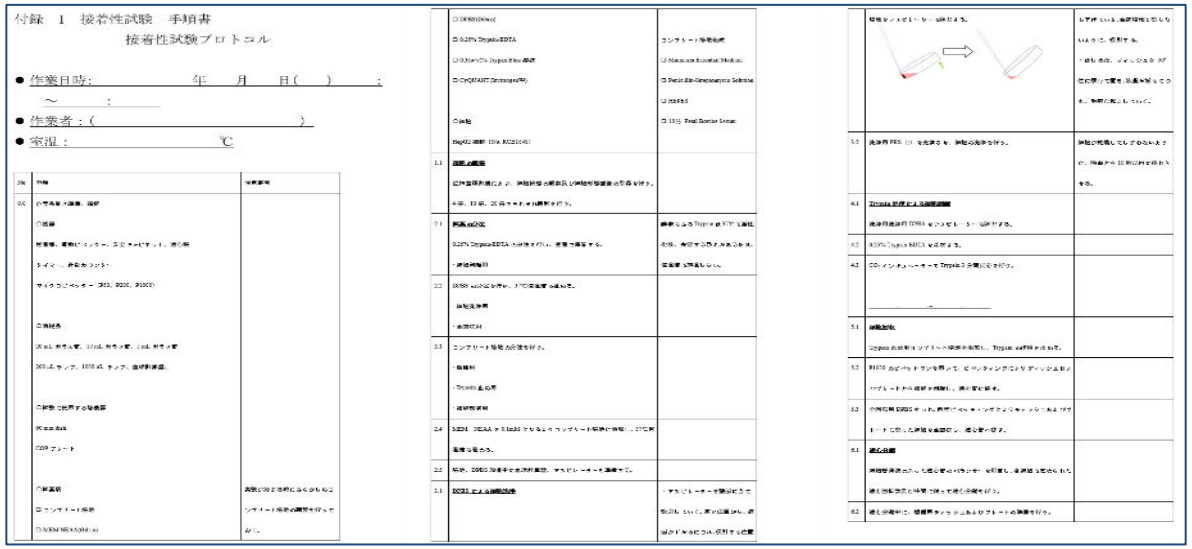
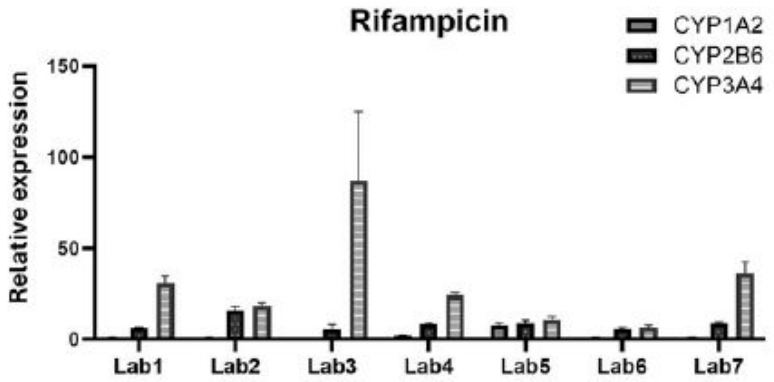
journal homepage: www.elsevier.com/locate/ejcb

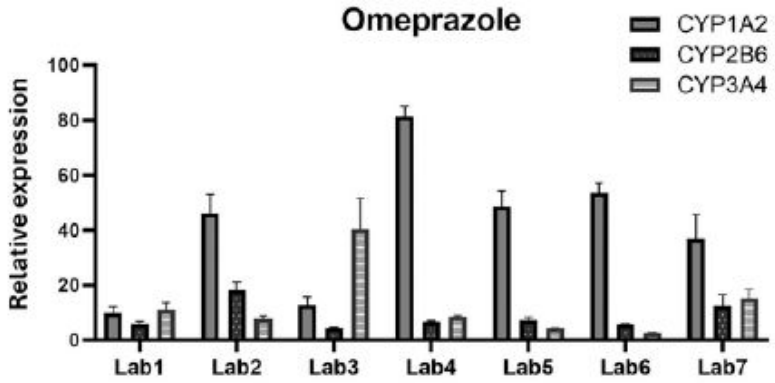
Considerations for developing CYP induction assays in hepatocytes: Insights from a multilaboratory study

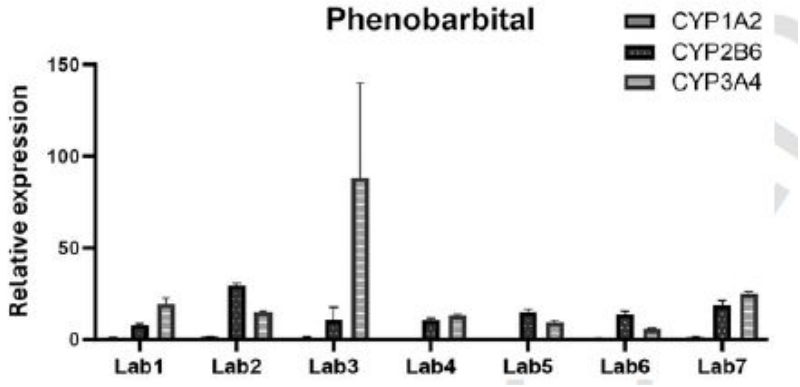
Hiroko Toyoda[a, b], Ayaka Nozue[a], Yuki Nishida[c], Yasuko Yakabe[a], Yasuhiko Aiki[a], Yukiko Ueyama-Toba[d, e], Kazuo Takayama[d], Hiroyuki Mizuguchi[d, e], Chihiro Mori[f], Yu-suke Torisawa[f], Yoko Sakai[g, 1], Takahiro Iwao[g], Tamihide Matsunaga[g], Shinichiro Horiuchi[h], Daiju Yamazaki[h], Seiichi Ishida[h, 2], Nobuhiko Kojima[i], Kosuke Inamura[j], Yasuyuki Sakai[j], Masaki Nishikawa[j], Ikue Mihara[b], Takafumi Akabane[b], Yuzuru Ito[a, c, *]

Standard Operating rocedures (SOPs)









3D Cell Culture: Three Major Approaches

3D Cell Culture Approaches

1. Scaffold-based Approaches

Mimicking the structure of native tissues

Use ECM-like support structures to guide cell adhesion, growth, and differentiation; widely used in tissue engineering and regenerative medicine.

MatriMix
架橋コラーゲンシート
Genocel
HYDROX
CelGlu

Bio-Spun™ Scaffold

2. Scaffold-free Approaches

Promoting cellular self-organization

Rely on cellular self-assembly on low-adhesion surfaces to form spheroids or aggregates; commonly applied in drug screening and developmental biology.

3. Specialized Applications

Addressing specific research needs

Designed to meet advanced research demands, such as controlling cellular alignment and automating culture processes.

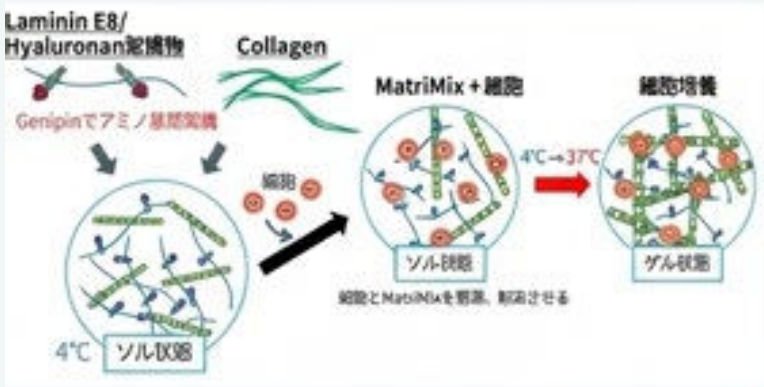
Biologically Derived and ECM-Mimetic Scaffolds: Enhanced Biomimicry

MatriMix
(FUJIFILM Wako Pure Chemical / Nippi)

技術:
コラーゲン+ラミニンE8断片+ヒアルロン酸。4°Cでゾル状、37°Cでゲル化する温度応答性。

特徴:
オルガノイド形成に特化。成分が明確でロット差が少ない。高い透明性で観察に適す。

主な用途:
腎臓、腸、肝臓、がんオルガノイドの分化誘導。



ad-MED Vitrigel®2
（関東化学株式会社）

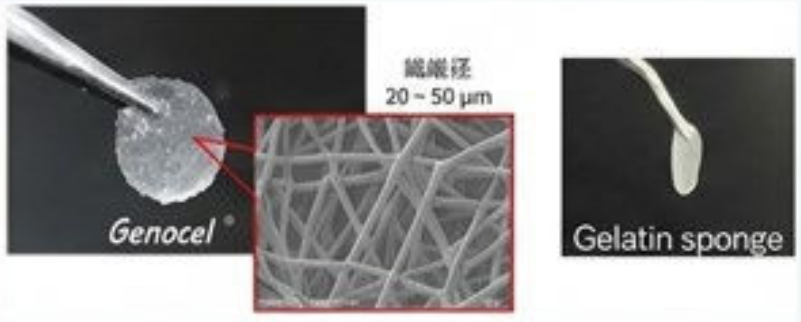
技術：高密度コラーゲン「ビトリゲル®膜」を用いた細胞培養用インサート（脱水・ガラス化により生体結合組織様構造を再現）。
特徴：高い細胞接着・伸展性／液相–液相・液相–気相培養対応／両面共培養可／高透明・低自家蛍光
主な用途：上皮・3D組織モデル、共培養・相互作用解析、薬物透過性・毒性評価、生体模倣in vitro評価系。

Genocel®
（京都医療設計 / 日本毛織）

技術:
ゼラチンのみで構成された不織布構造（繊維径 20-50 μm）。

特徴:
湿潤状態でも形状を保持し、収縮しない。
半透明で培養中の観察が可能。

主な用途:
幹細胞培養、細胞シート作製、スフェロイド形成。



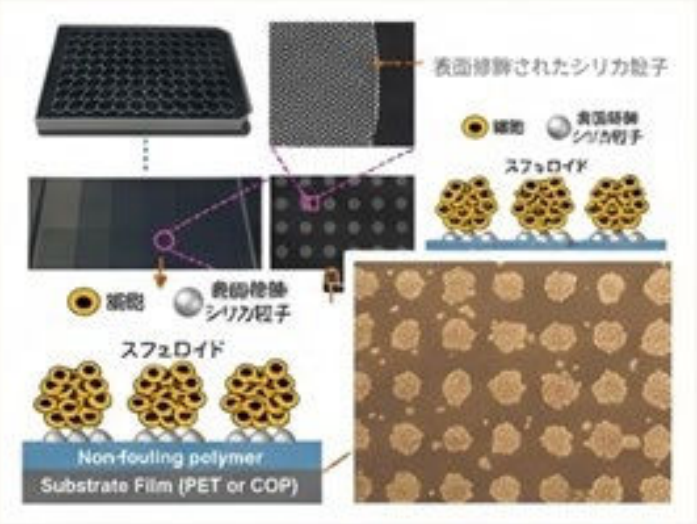
Patterned and Microstructured Plates: Precise Control of Spheroid Positioning and Geometry

PAMSELL (ANK Co.)

技術：RGD配列で修飾したシリカ粒子を高密度に配列した「Micropad」構造。

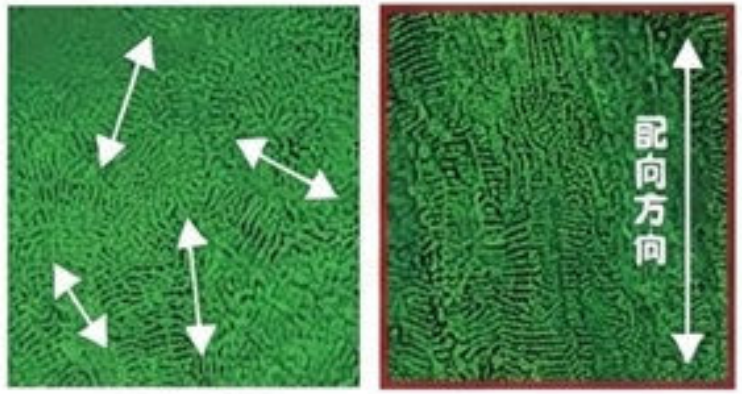
特徴：Micropad上でスフェロイドが安定して付着。培地交換が容易で、その場での顕微鏡観察に最適。

主な用途：自動化ハイスループットスクリーニング（HTS）、イメージングベースのアッセイ。



CellArray-Heart™

- 技術：細胞を一方向に配向させる微細ストライプ構造を持つポリスチレン製基材。
- 特徴：播種するだけで心筋細胞などを一方向に配向させ、成熟した形態と機能（一方向への収縮）を誘導。
- 主な用途：薬剤の心毒性評価、再生医療研究、骨格筋細胞・線維芽細胞の配向培養。



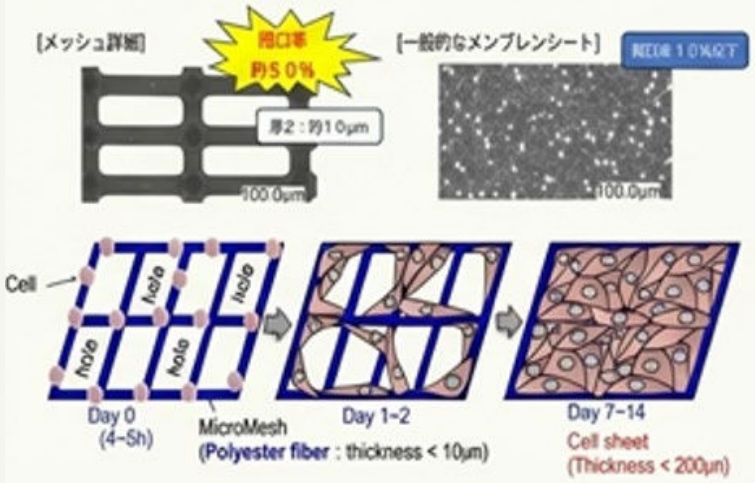
一般的な基材　CellArray-Heart™

Meshtable® (水田製作所)

技術：厚さ10μm未満の微細なポリエステル繊維メッシュ。開口率約50%。

特徴：酸素・栄養供給を維持し、厚みのある細胞シート (最大200μm) を形成。
メッシュごと脱着可能で、両面からの観察や共培養も可能。

主な用途：細胞シート工学、化学物質の代謝・透過性評価、再生医療。



Foundational Technologies for MPS Qualification

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FDA Advances Drug Development Innovation by Establishing ISTAND as Permanent Qualification Program

FDA Voices

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07/31/2025

Regulated Product(s)
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Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program