

GSRS23

2023.9.28 (Thu) 15:15-16:15

@Parma, Italy

Utilization of Cardiac MPS and Activities for Industrial Implementation and Regulatory Acceptance in Japan



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The opinions and information in this presentation are my own
and do not necessarily reflect the views and policies of MHLW and NIHS.

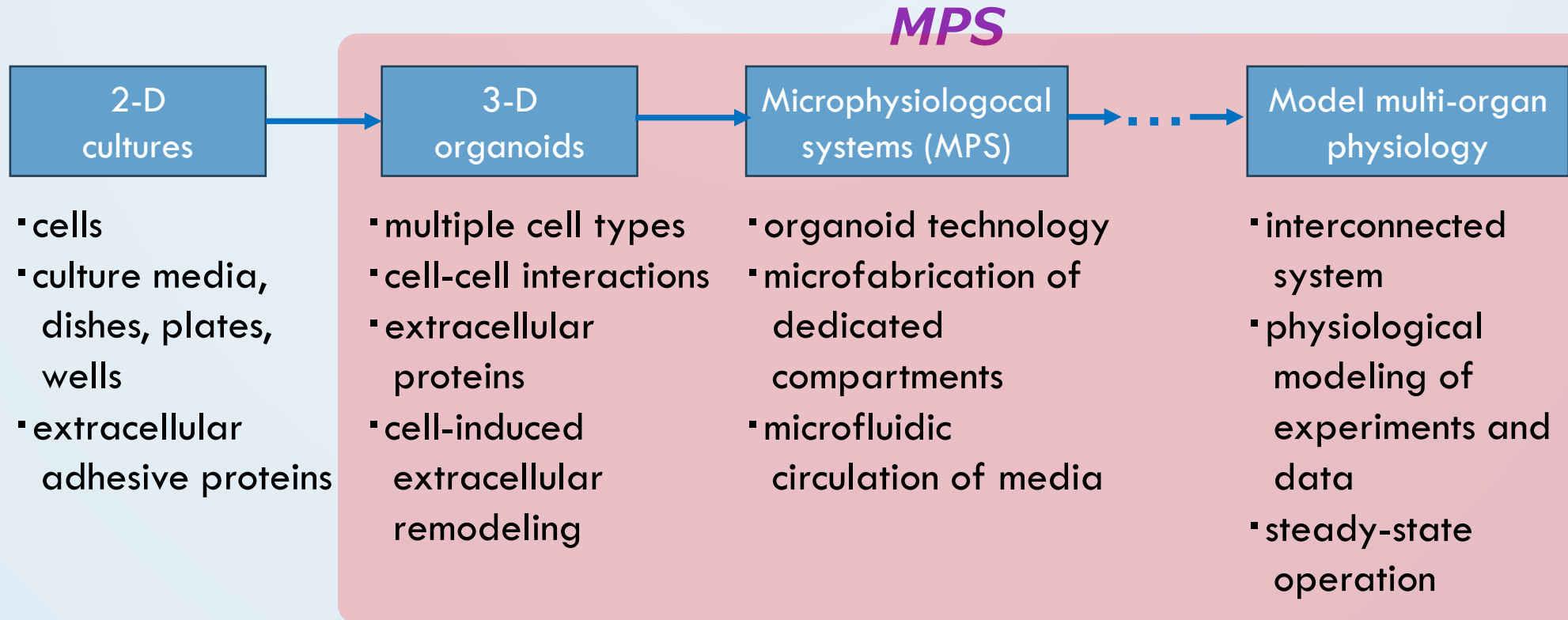
Today's topics

- ✓ ***What is MPS (microphysiological systems)?***
- ✓ *Utilization of cardiac MPS*
- ✓ *Our activities*

What is MPS (microphysiological systems)?

FDA's definition:

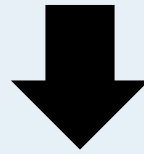
A microscale cell culture platform that models functional characteristics of specific human and animal tissues and organs in vitro by exposing cells to a microenvironment that mimics physiological aspects important to their function and pathology



MPS is next-generation drug discovery tools

Issues in drug discovery

- ❑ Limitations of human-derived samples and cells in pharmacokinetic studies
- ❑ Discrepancies between non-clinical and clinical trials regarding side effects
- ❑ Necessity of human-specific evaluation methods for novel modality drugs
- ❑ Promotion of alternative to animal testing etc...



We need to

- develop of human-specific *in vitro* evaluation system by using human-derived cells (ex: human iPS cells)
- improve and advance of human predictability by mimic to physiological micro environment

MPS is attracting attention as a next-generation drug discovery developmental tool

Trends in Pharmaceutical company

MPS-based organ/tissue model	No. of cases	Area of use (drug development phase)	MPS-supplier	End user
Blood vessel, vasculature	5	Target identification, validation and compound selection Discovery (scleroderma) System toxicology for consumer products Pharmacokinetics and pharmacology Target identification and validation	AIST Mimetas Mimetas Mimetas Mimetas	Daiichi-Sankyo Galapagos Philip Morris Undisclosed NovoNordisk
Bone marrow	4	Preclinical safety Preclinical safety Preclinical safety Preclinical safety	TissUse Emulate TissUse TissUse	AstraZeneca AstraZeneca Roche Bayer
Gut epithelium	4	Discovery (inflammatory bowel disease) Discovery Clinical development Preclinical safety	Mimetas Mimetas Mimetas Emulate	Galapagos Roche Roche Roche
Lung	3	Discovery (alveolus) Drug efficacy (epithelium) Preclinical safety	Wyss Wyss Emulate	Undisclosed Pfizer, Merck USA Roche
Liver	2	Pharmacological and toxicological effects Preclinical safety-assessment of species (rat, dog and human)	Emulate Emulate	AstraZeneca J&J, AstraZeneca
Ocular compartment	1	Discovery	Fh IGB/EKUT	Roche
Kidney epithelium	1	Pharmacokinetics and pharmacology	Mimetas	Undisclosed
Liver-Pancreas	1	Target validation / identification	TissUse	AstraZeneca
Liver-Thyroid	1	Preclinical safety – assessment of species-specificity (rat and human)	TissUse	Bayer
Skin-Tumor	1	Preclinical safety and efficacy	TissUse	Bayer

End User

- Daiichi-Sankyo
- Galapagos
- Philip Morris
- NovoNordisk
- AstraZeneca
- Roche
- Bayer
- Pfizer
- Merck
- J & J

MPS model

- Vasculature
- Bone marrow
- Gut epithelium
- Lung
- Liver
- Ocular compartment
- Kidney epithelium
- Liver-Pancreas
- Liver-Thyroid
- Skin-Tumor

Major pharmaceutical companies have already started using MPS and are using it for internal decision-making

Trends in Regulatory

Classical Complement Pathway
Inhibition in a “Human-On-A-Chip”
Model of Autoimmune Demyelinating
Neuropathies

John W. Rumsey et al

ADVANCED THERAPEUTICS

NCT04658472:

Proof-of-concept Study for SAR445088 in
**Chronic Inflammatory Demyelinating
Polyneuropathy (CIDP)**

FDA no longer needs to require animal tests before human drug trials

The FDA Modernization Act 2.0 was enacted at the end of 2022.

5 assays are written in the article as non clinical tests

(1)Cell-based assays

(2)Organ chips and microphysiological systems

(3)Computer modeling

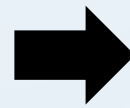
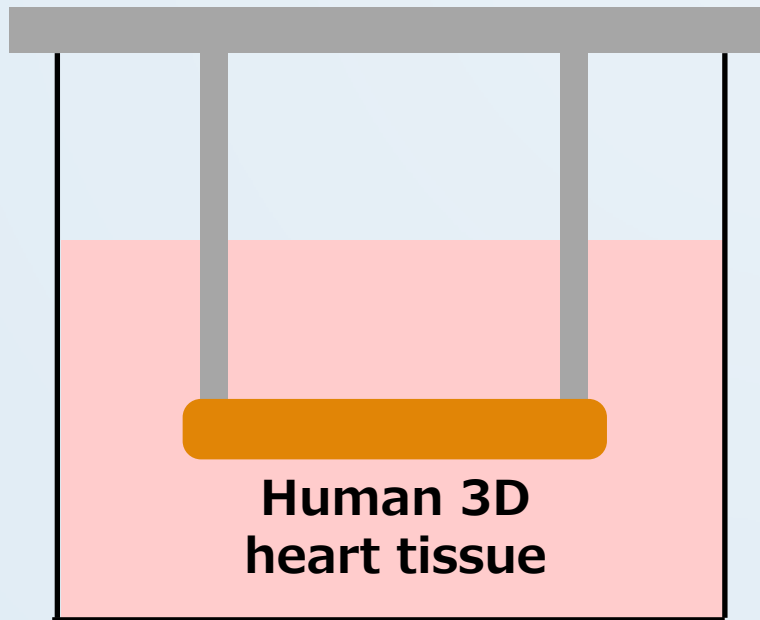
(4)Other nonhuman or human biology-based test methods,
such as bioprinting

(5)Animal test

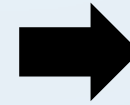
Today's topics

- ✓ *What is MPS (microphysiological systems)?*
- ✓ ***Utilization of cardiac MPS***
- ✓ *Our activities*

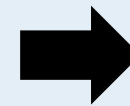
Utilization of cardiac MPS



- Improved human predictability
- Alternative to Animal Experiments

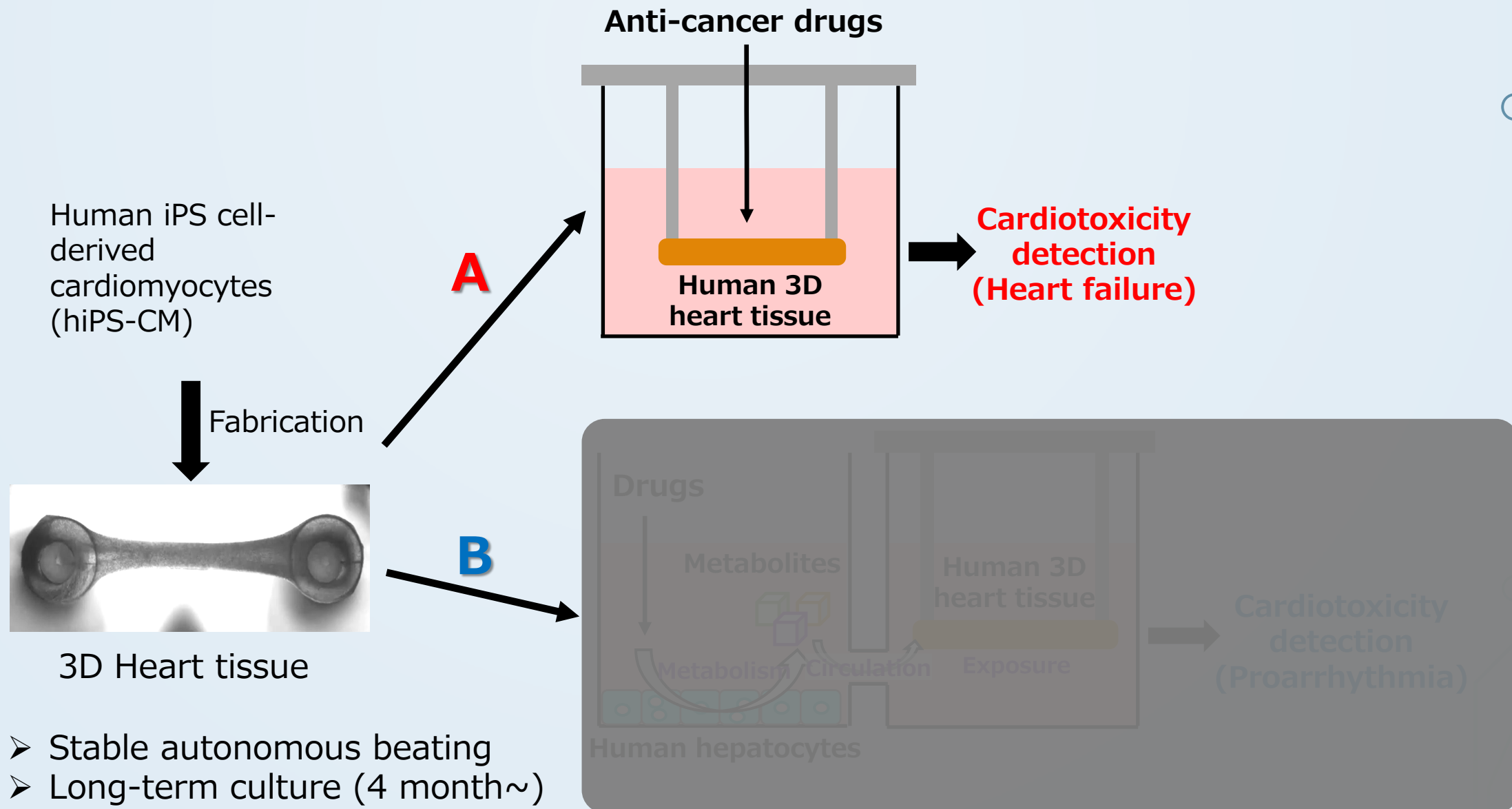


- Reproduction of myocardial contraction
(Drug responsiveness, gene expression, and organic changes)



- Cardiotoxicity Detection for Patient Safety

Utilization of cardiac MPS in my lab

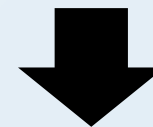


Impaired left ventricular contraction due to anticancer drugs

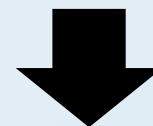
Anti-cancer drug	Frequency (%)	Frequency of use
Anthracyclin		
Doxorubicin	3-26	+++
epirubicin	0.9-3.3	++
idarubicin	5-18	+
alkylating agent		
cyclophosphamide	7-28	+++
ifosfamide	17	+++
Antimetabolite		
clofarabine	27	+
microtubule inhibitor		
docetaxel	2.3-8	++
Humanized monoclonal antibody (Molecular Targeted Therapeutics)		
bevacizumab	1.7-3	++
trastuzumab	2-28	++
proteasome inhibitor		
bortezomib	2-5	++
Small molecule tyrosine kinase inhibitors and kinase inhibitors (molecular targeted therapies)		
dasatinib	2-4	++
imatinib	0.5-1.7	+
lapatinib	1.5-2.2	+
sunitinib	2.7-11	+++

Issues of current test (Langendorff)

- Chronic toxicity testing is difficult due to the time-consuming nature of the heart removed from the individual.
- Some drugs have species differences in toxicity onset, and human extrapolation is unknown.



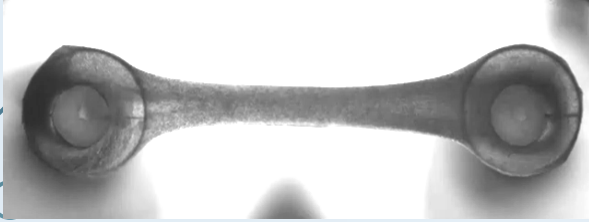
Need in vitro evaluation methods with high human predictability and detection of chronic toxicity



Use of human iPS cardiomyocytes

Contractility changes due to doxorubicin exposure

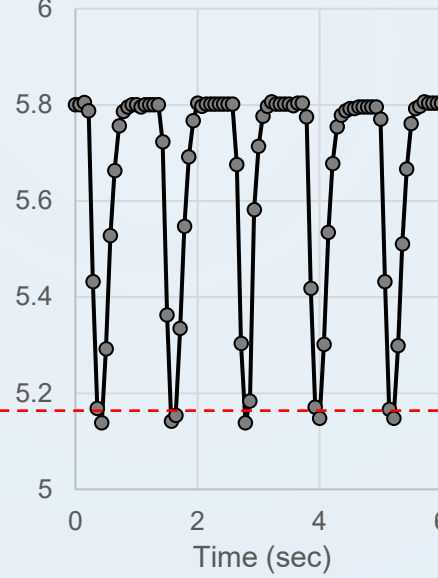
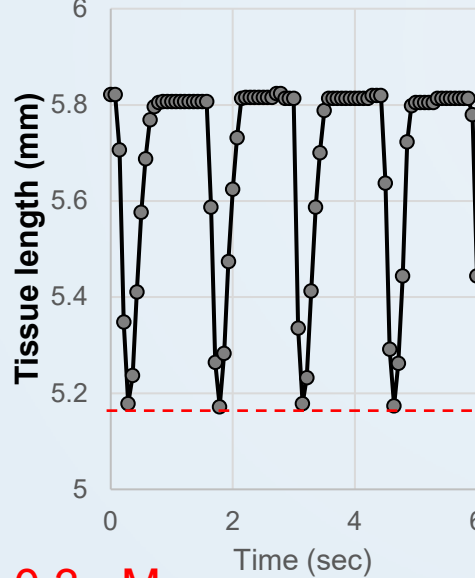
EHT



DMSO

Pre

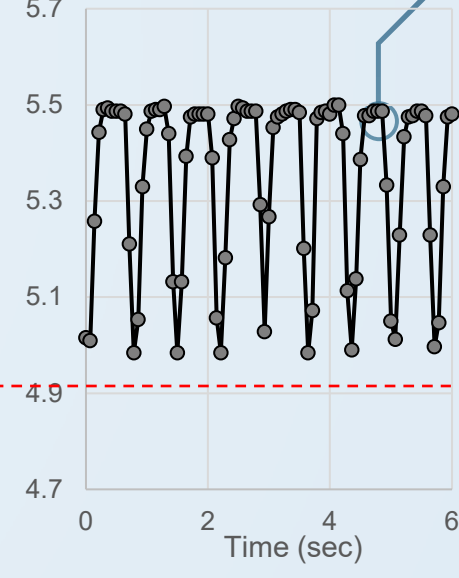
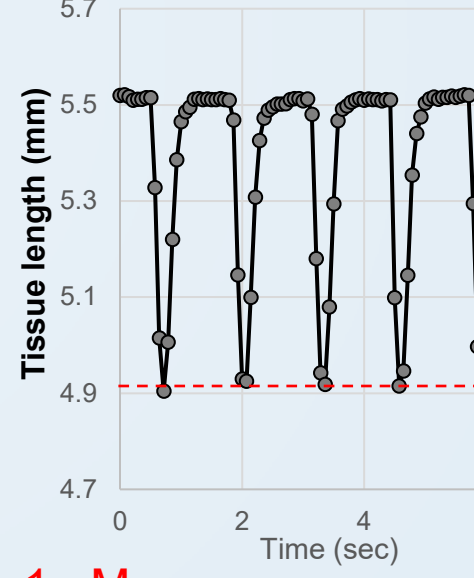
72 h



0.1 μ M

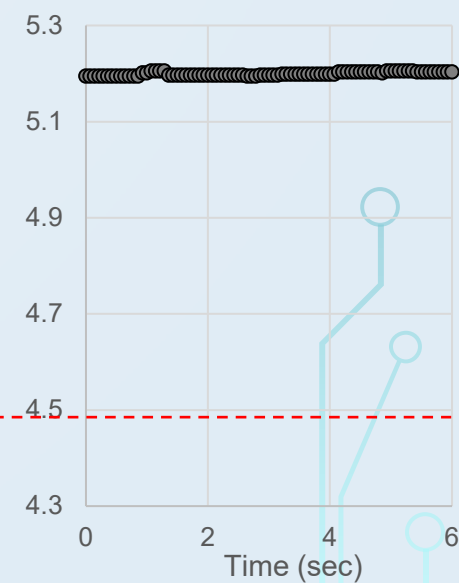
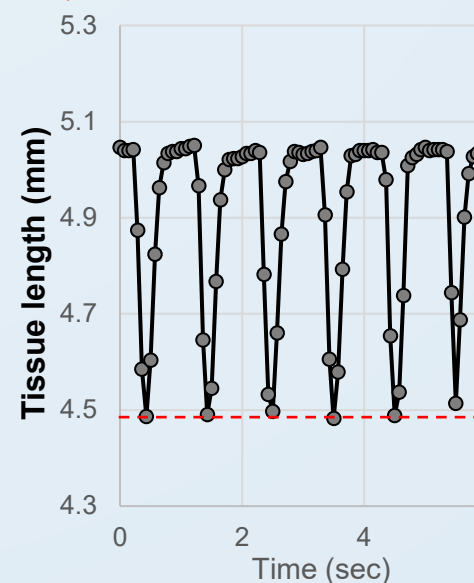
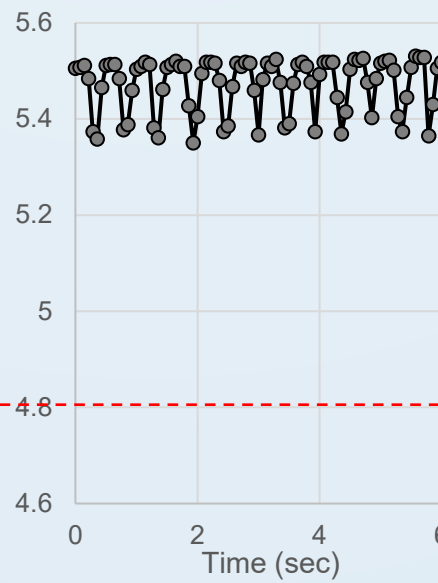
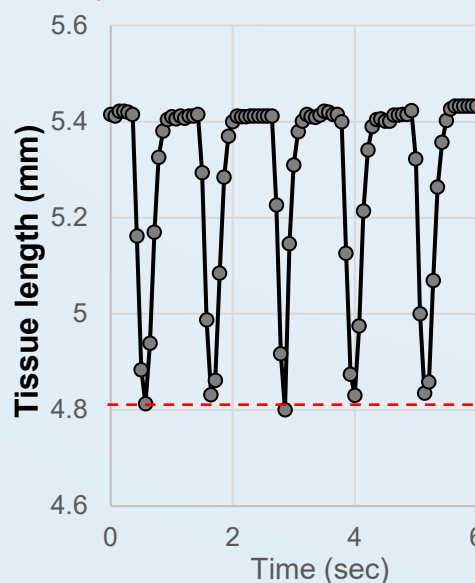
Pre

72 h



0.3 μ M

1 μ M



Doxorubicin(DOX):
Anthracyclines

First choice for systemic cancer treatment

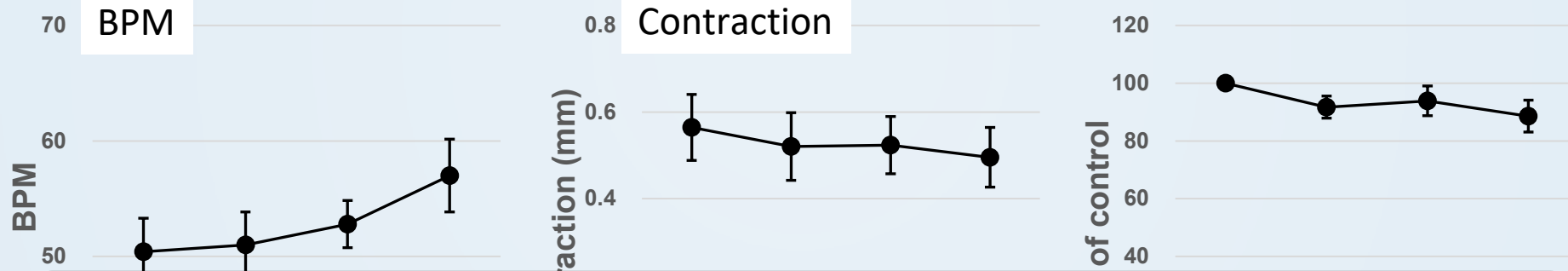
Application schedule:

0 (Pre) 24 48 72 h

↑↑ DOX application
↑ Contractility measurement

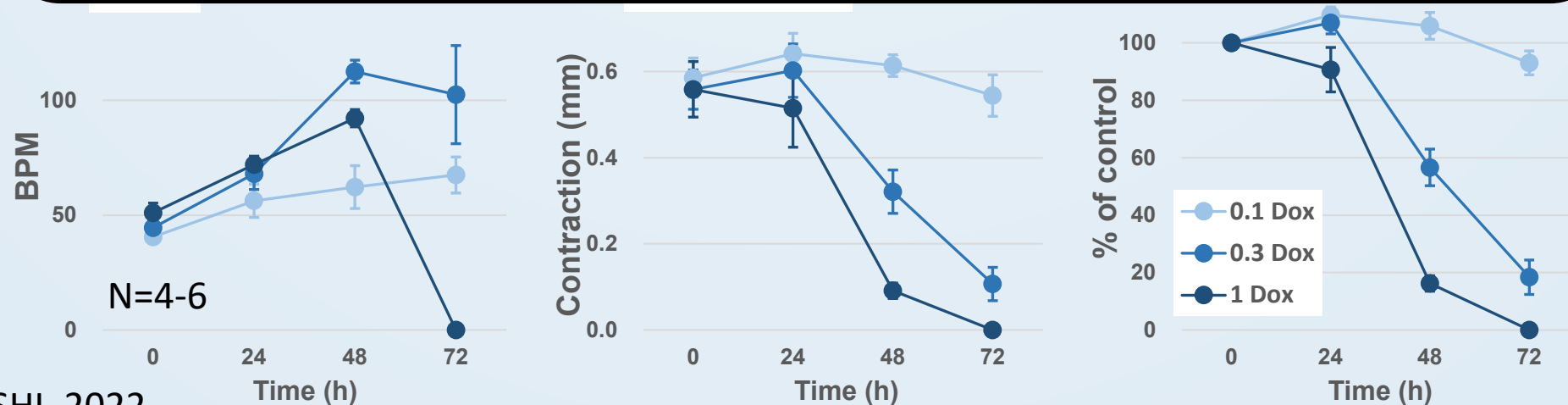
Contractility changes due to doxorubicin exposure

0.1% DMSO



On the basis of in vitro results, it is unclear whether extrapolation to humans is possible.

⇒ Need to confirm correlation with in vivo



Strategy of the research

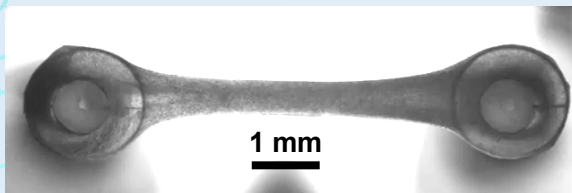
<Issues in heart>

Extracted Heart Langendorff
Evaluation of contraction impairment
due to anti-cancer drugs

Chronic toxicity undetectable
human extrapolation unknown

Advanced *in vitro* cardiac
contraction evaluation methods

Human 3D heart tissue



Common
compounds

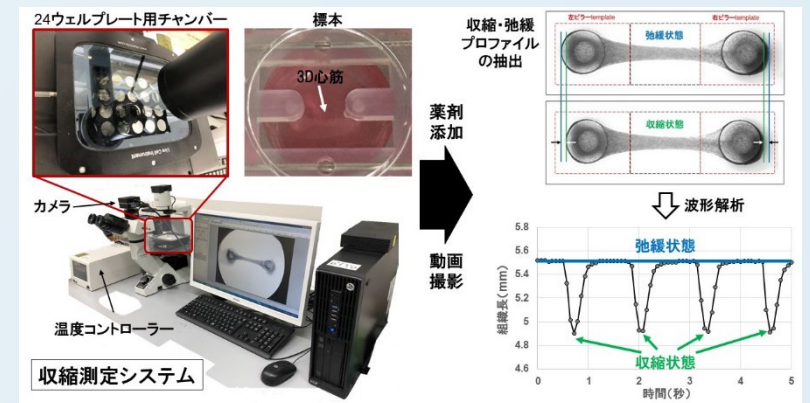
① *In vivo* data

< Human echocardiography >

- Echocardiographic parameters
- LVEF (left ventricular ejection fraction)
- LVEDP (left ventricular end-diastolic pressure)
- GLS (myocardial strain)

② *In vitro* data

< Human 3D heart tissue >

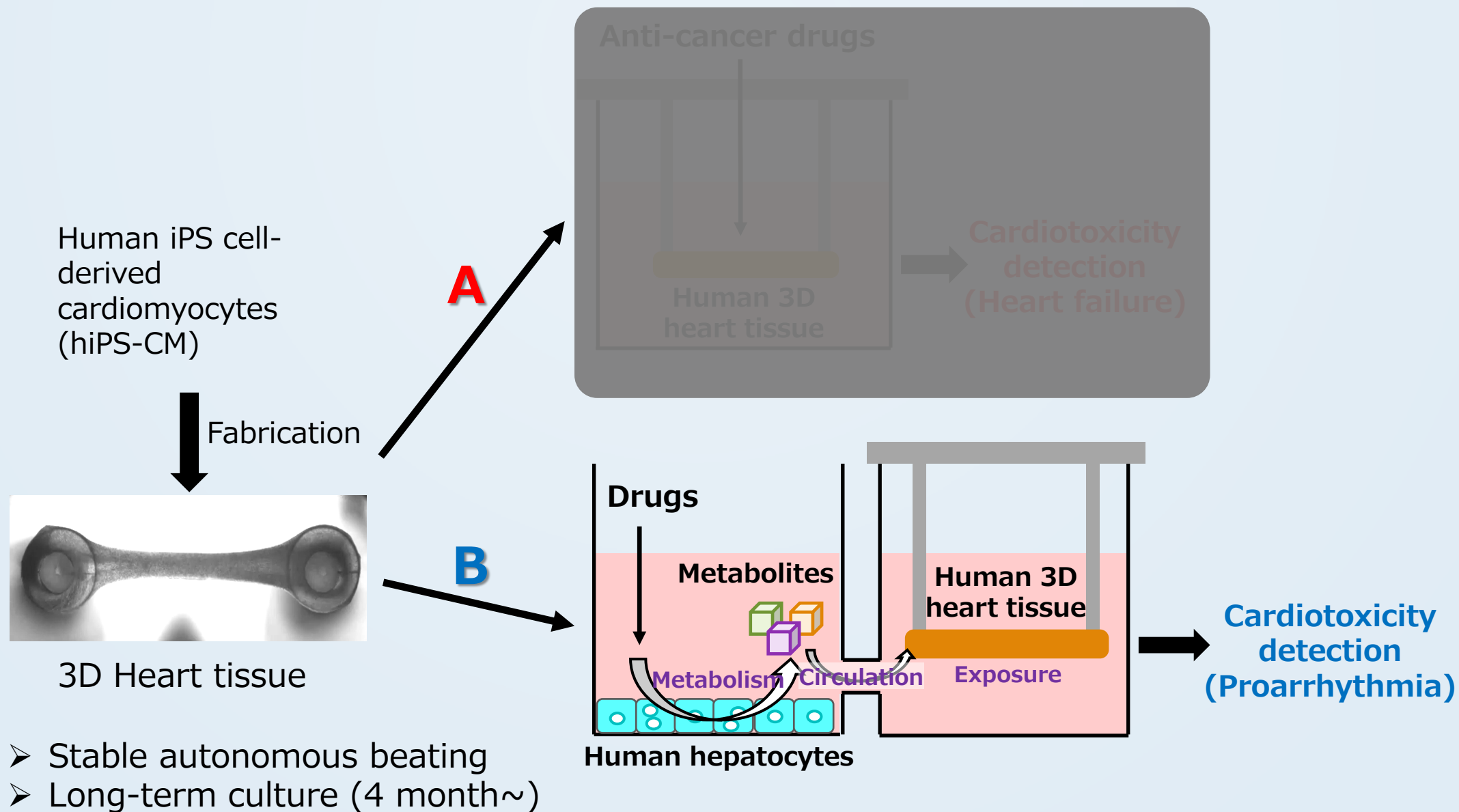


Contractility
Contraction and relaxation velocity

③ IVIVE

Comparison and correlation validation of *in vivo* and
in vitro data to identify translational parameters

Utilization of cardiac MPS in my lab



Liver-cardiac model

Drug	Year of withdrawal	Reason(s) for withdrawal from market
Dilevalol	1990	Hepatotoxicity
Triazolam	1991	Neuropsychiatric reaction
Terodiline	1991	QT interval prolongation and TdP
Encainide	1991	Proarrhythmias
Fipexide	1991	Hepatotoxicity
Temafloxacin	1992	Hypoglycaemia, haemolytic anaemia and renal failure
Benzarone	1992	Hepatotoxicity
Remoxipride	1993	Aplastic anaemia
Alpidem	1993	Hepatotoxicity
Flosequinan	1993	Excess mortality possibly due to proarrhythmia
Bendazac	1993	Hepatotoxicity
Soruvudine	1993	Myelotoxicity following drug interaction
Chlormezanone	1996	Hepatotoxicity and severe skin reaction
Tolrestat	1996	Hepatotoxicity
Minaprine	1996	Convulsions
Pemoline	1997	Hepatotoxicity
Dexfenfluramine	1998	Cardiac valvulopathy and pulmonary hypertension
Fenfluramine	1998	Cardiac valvulopathy and pulmonary hypertension
Terfenadine	1998	Drug interaction, QT interval prolongation and TdP
Bromfenac	1998	Hepatotoxicity following prolonged administration
Ebrotidine	1998	Hepatotoxicity
Sertindole	1998	QT interval prolongation and potential for TdP
Mibefradil	1998	Statin-induced rhabdomyolysis following drug interaction and concerns on other potential drug interactions, including the risk of TdP
Tolcapone	1998	Hepatotoxicity
Astemizole	1999	Drug interactions, QT interval prolongation and TdP
Trovafloxacin	1999	Hepatotoxicity
Grepafloxacin	1999	QT interval prolongation and TdP
Troglitazone	2000	Hepatotoxicity
Alosetron	2000	Ischaemic colitis
Cisapride	2000	Drug interactions, QT interval prolongation and TdP
Droperidol	2001	QT interval prolongation and TdP
Levacetylmethadol	2001	Drug interactions, QT interval prolongation and TdP
Cerivastatin	2001	Rhabdomyolysis following drug interactions
Rofecoxib	2004	Myocardial infarction and strokes

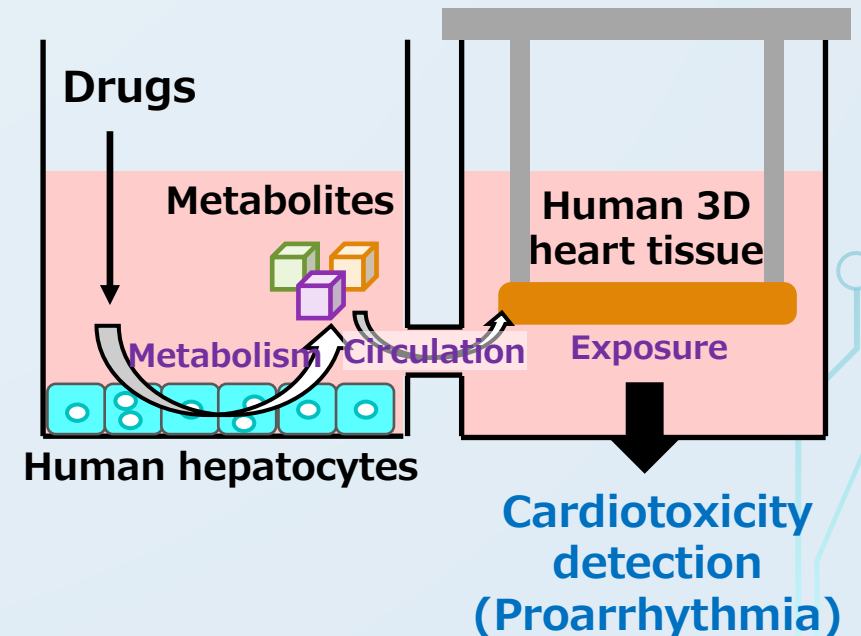
Current issue

- ✓ Cardiotoxicity such as arrhythmogenesis is a major consideration in drug development.
- ✓ Previously, some drugs were withdrawn from the market due to arrhythmogenesis associated with drug interactions.

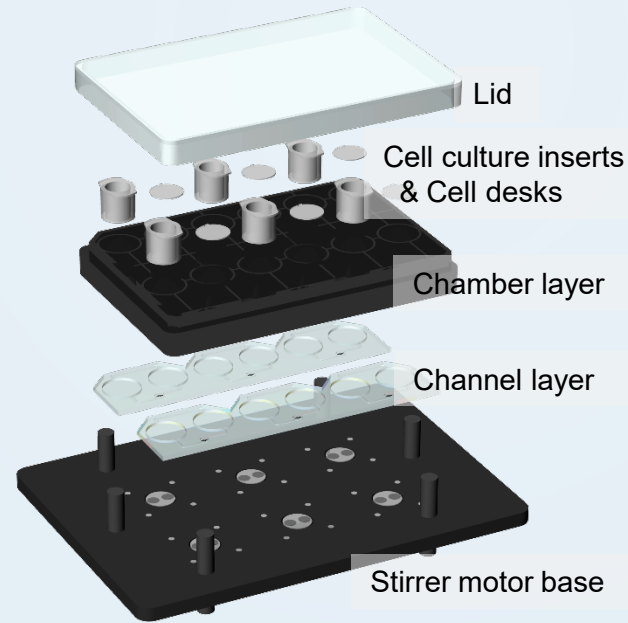
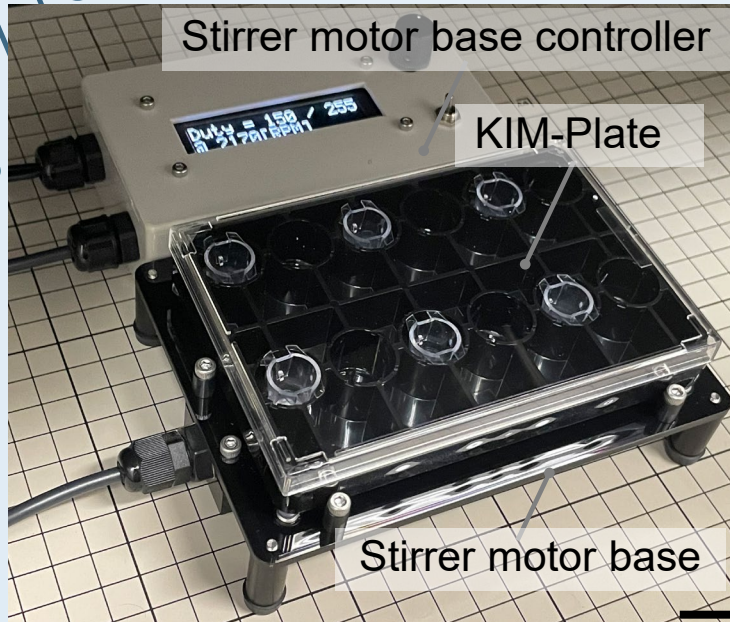
➡ A predictive system for cardiotoxicity such as arrhythmogenesis via drug metabolism is required.

- Cardiotoxicity (14/34 case)
- Drug interaction (5/14 case)

Rif. Pharmacogenetics, Report (2005) by the Council for International Organizations of Medical Sciences (CIOMS)



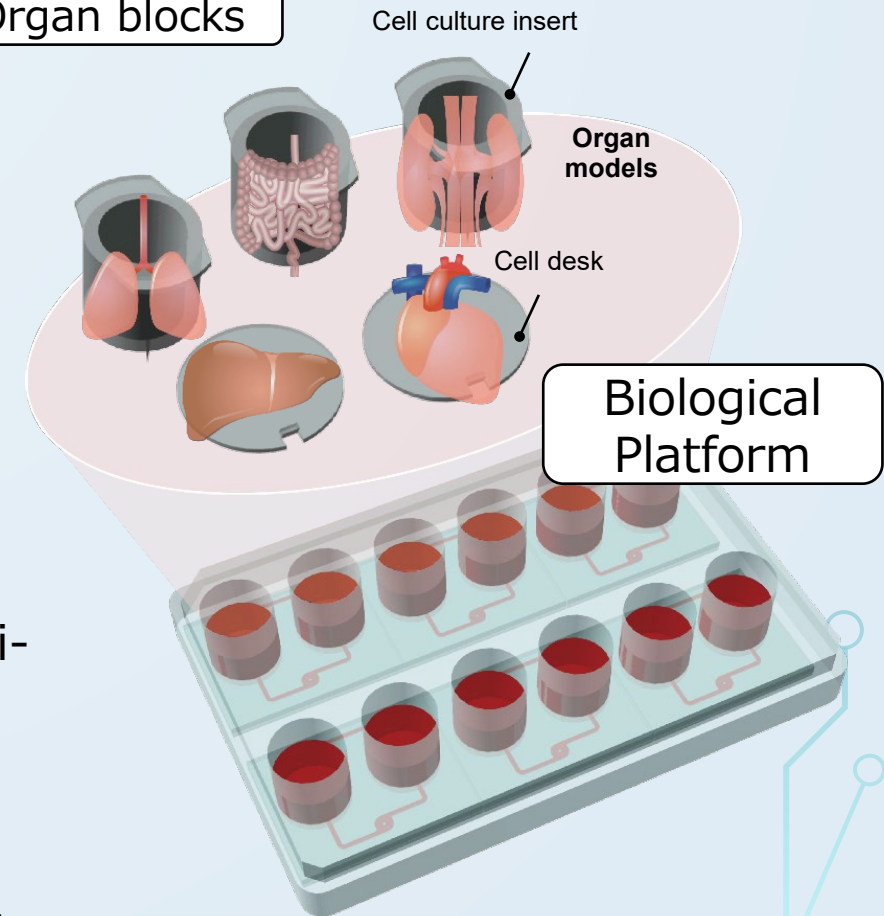
MULTIORGAN MPS PLATFORM



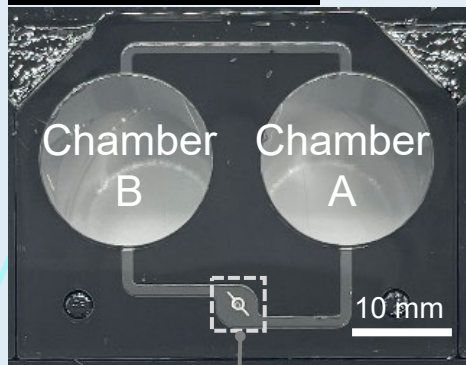
Shinha K, et al., *Micromachines*, 2021

Platform x Organ block

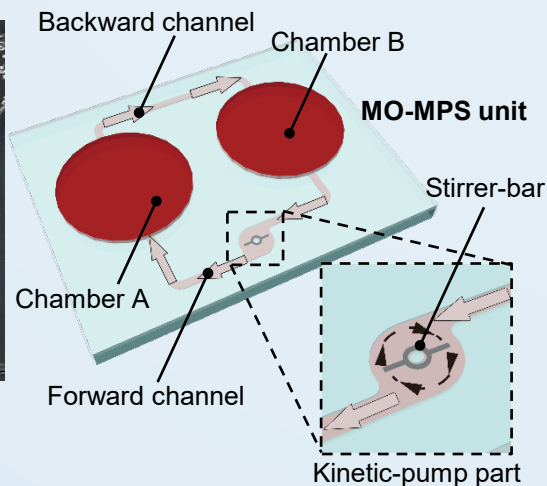
Organ blocks



Backside view



Kinetic-pump part



1. Organ blocks are prepared using a conventional multi-well plate before experiments.
2. Move the organ blocks into the platform for coculture.

Organ block@Kimura Lab

How to Use

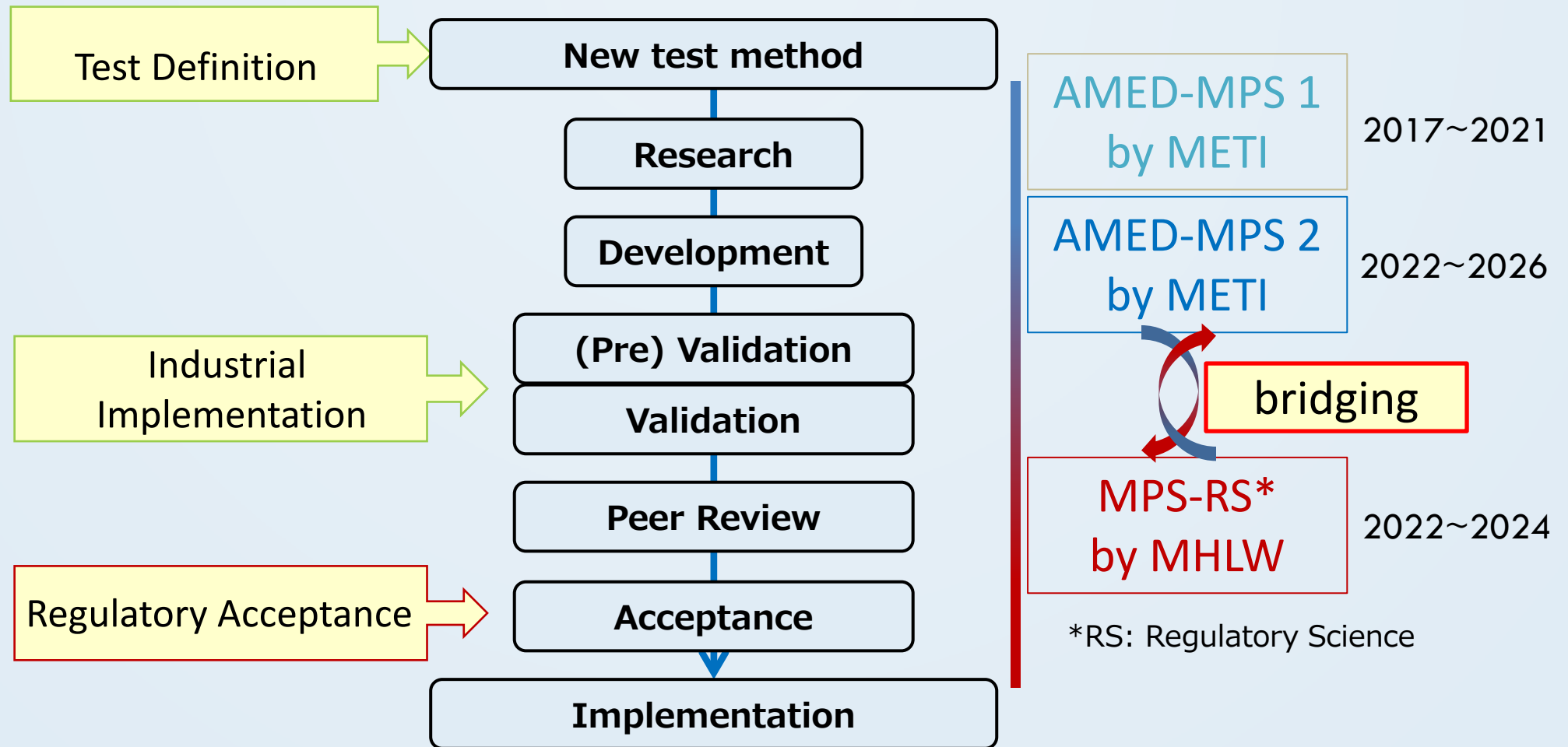


Collaboration with Prof. Kimura (Tokai Univ.), Prof. Sakai (Univ. of Tokyo), Sumitomo Bakelite

Today's topics

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- ✓ *Utilization of cardiac MPS*
- ✓ ***Our activities***

MPS projects in Japan



AMED MPS-RS project (2022~2024)

Principal Investigator: Seiichi ISHIDA (NIHS/Sojo Univ.)



NIHS-CBSR

Yoko HIARABAYASHI (Director)

Kaoru SATO

Daiju YAMAZAKI



Sojo Univ.

Taku MATSUSHITA

Collaborators

Kazushige MAKI (PMDA)

Yuzuru ITO (Univ. Tsukuba)



National Institute of Health Sciences (NIHS)

Center for Biological Safety and Research (CBSR)



The National Institute of Health Sciences (NIHS) conducts testing, research, and studies toward the proper evaluation of the quality, safety, and efficacy of pharmaceutical products, foods, and the numerous chemicals in the living environment.

MPS Consortium for Industrial Implementation and Regulatory Acceptance (MPS実用化推進協議会)

Objective:

Promotion of the development of guidelines for test methods using MPS originating in Japan

Just Launched!!
mps-kyogikai@nihs.go.jp



Regional Chapter

- Asia-Pacific
- Europe and Africa
- Americas.

MPS Consortium for Industrial Implementation and Regulatory Acceptance

(MPS実用化推進協議会)

Member (until 7/31)

Category	Count
Total	149
Pharmaceutical company	20
CRO	9
Food company	3
Laboratory equipment company	26
Reagent manufactures	34
Cell manufactures	13
Logistics company	1
Academia	30
Government	8
Others	5

Activities

21st Aug 2023 Kickoff symposium

Participants number of attendees: 148 (include guest)

Jan 2024

Annual meeting

- Plenary lecture
- Symposium
- Poster presentation
- Exhibition etc

Acknowledgement

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Kaoru Sato
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National Institute of Genetics

Noritaka Masaki
Akatsuki Kimura

Kanazawa University

Yuto Tanaka
Yusuke Masuo
Yukio Kato

Tokai University

Hiroshi Kimura

University of Tokyo

Yasuyuki Sakai

Sojo University

Yuji Komizu
Seiichi Ishida
Taku Matsushita

Tsukuba University

Osamu Ando
Yuzuru Ito

Sumitomo Bakelite



国立研究開発法人 日本医療研究開発機構
Japan Agency for Medical Research and Development

