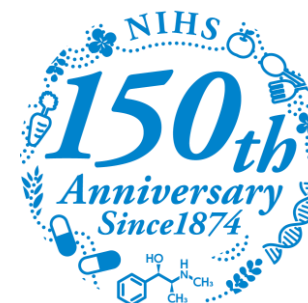


Activities of the Japanese Center for the Validation of Alternative Methods (JaCVAM), NIHS:

Development of new toxicity tests using NAM
and their use in regulations

HIRABAYASHI, Yoko , MD, PhD
Director of CBSR
National Institute of Health Sciences, Japan



Today's Talk

1. Introduction
2. Mission and organization of JaCVAM
3. Current activities toward the development of NAMs

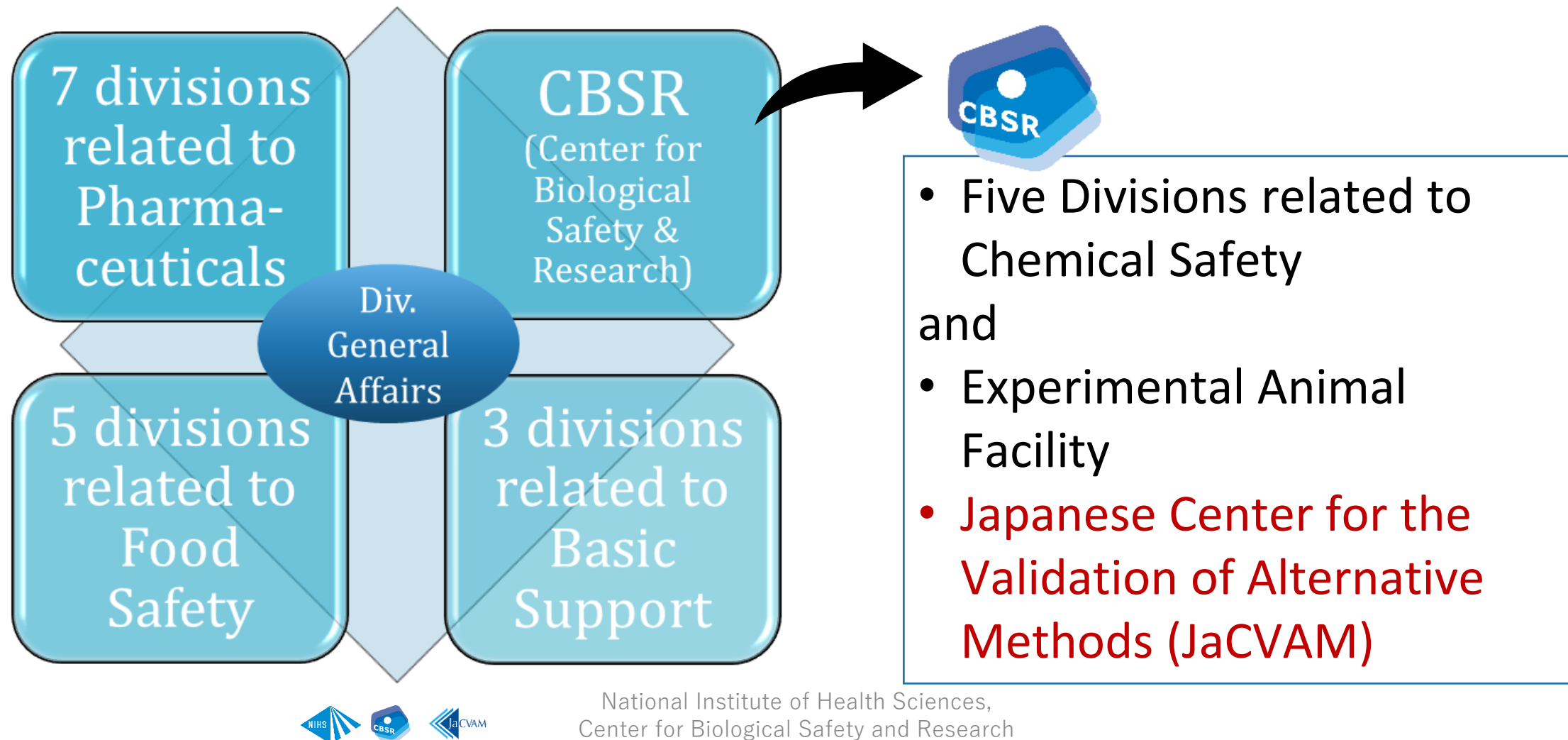
-
- I have no financial relationships to disclose.
 - This presentation neither intend to represent, nor is restricted by, the policy of MHLW, Japan

Introduction





National Institute of Health Sciences (NIHS)

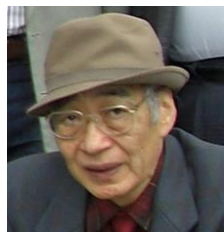
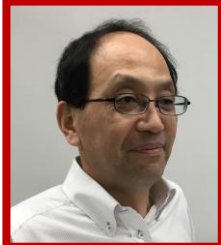




National Institute of Health Sciences



Center for Biological Safety and Research



15th Anniversary of JaCVAM

(Nov. 2020)



JRC
EURL ECVAM



ICATM



ICATM

International Cooperation on Alternative Test Methods

ICATM is a voluntary international cooperation of national organizations



Mission and organization of JaCVAM



TOP

About JaCVAM

JaCVAM Activities

Update on JaCVAM
and data

Submission of Alternative
Methods to JaCVAM

International Cooperation

JaCVAM affiliated
organizations



Policy and Mission:

JaCVAM's policy and mission is to promote the 3Rs in animal experiments for the assessing the safety of chemicals and other materials in Japan and establish guidelines for new alternative experimental methods through international collaboration.



JaCVAM Activities



Update on JaCVAM



Submission of Alternative
Methods to JaCVAM

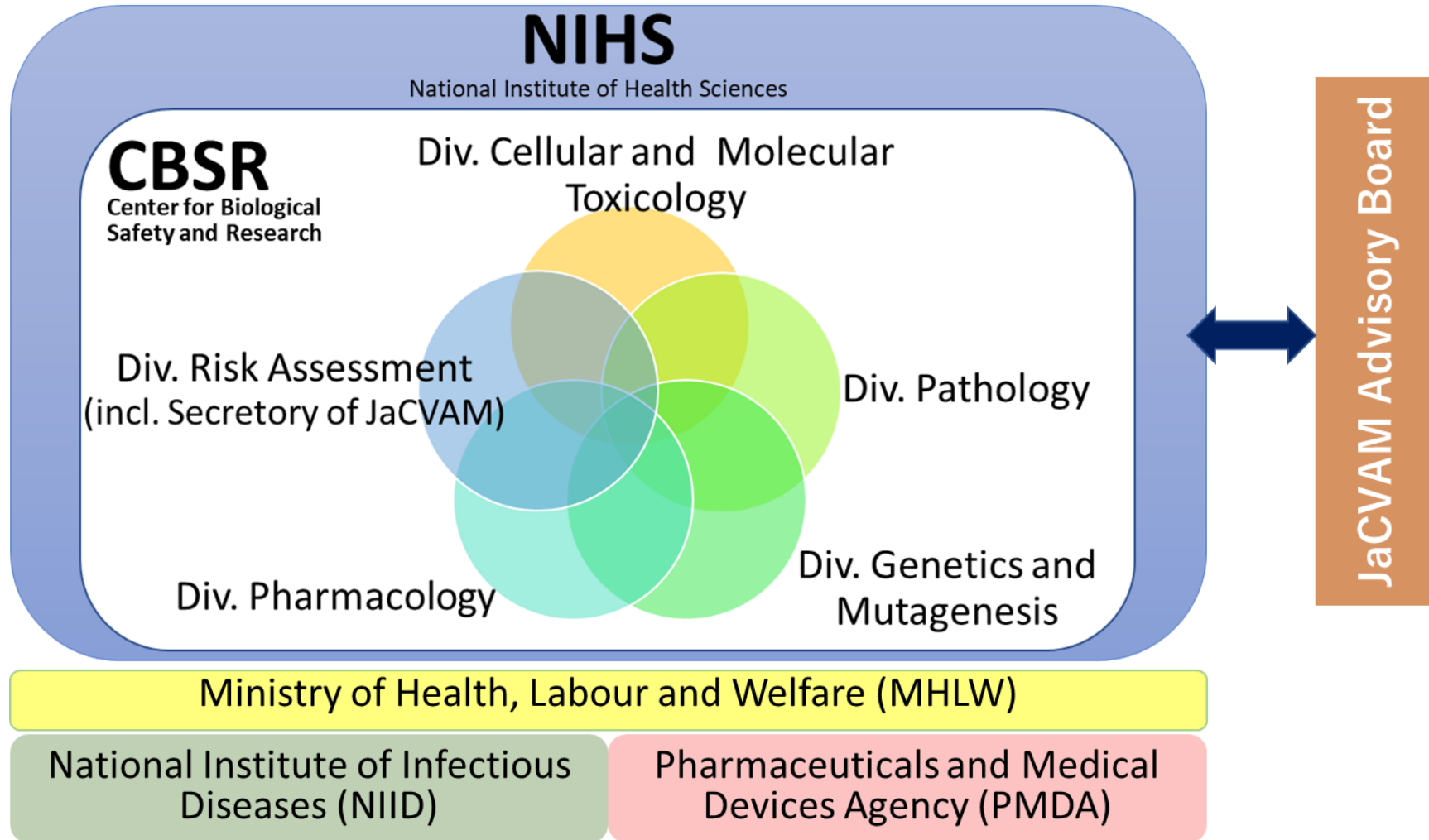


International Cooperation

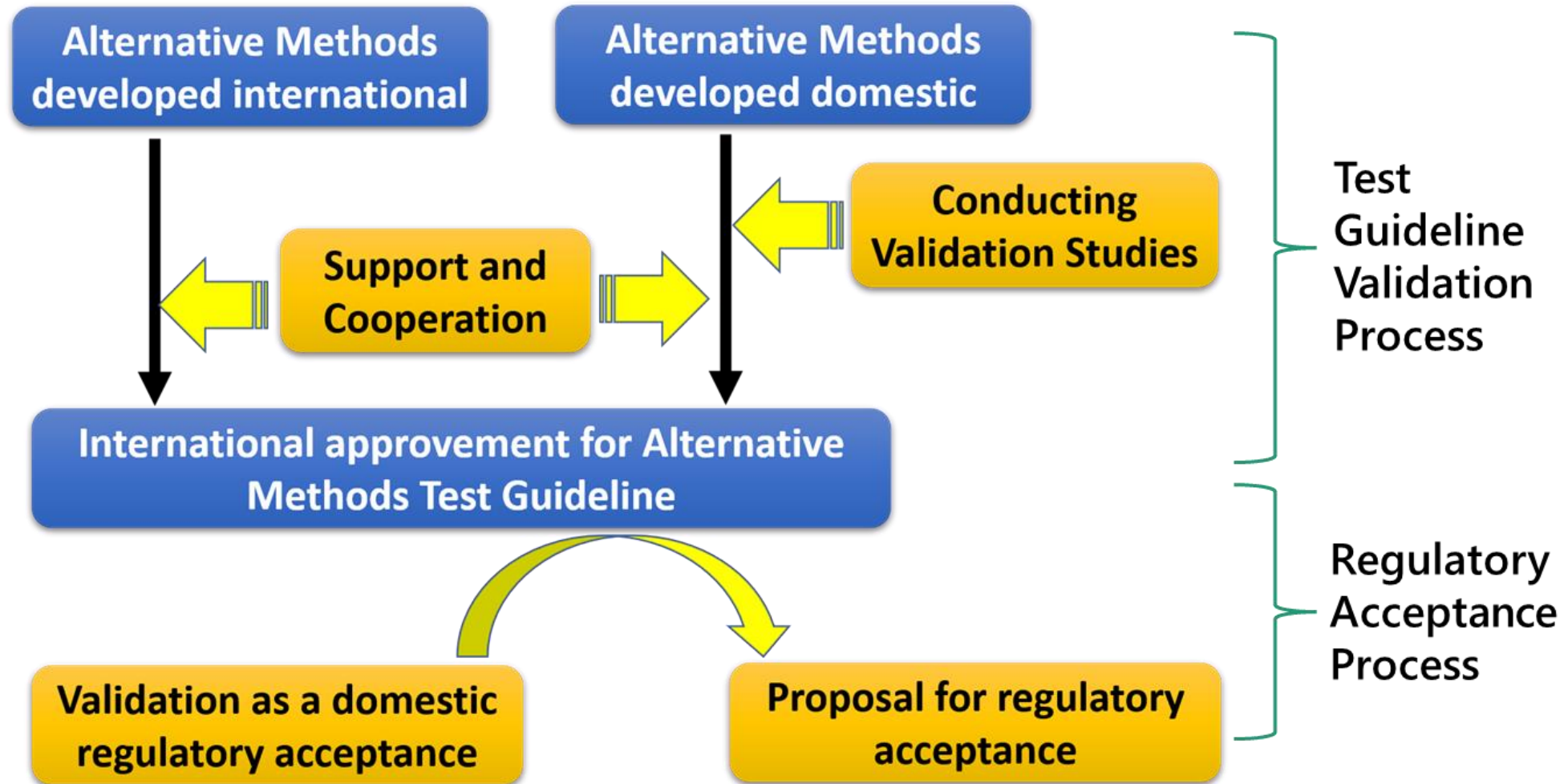


<https://www.jacvam.jp/en/index.html>

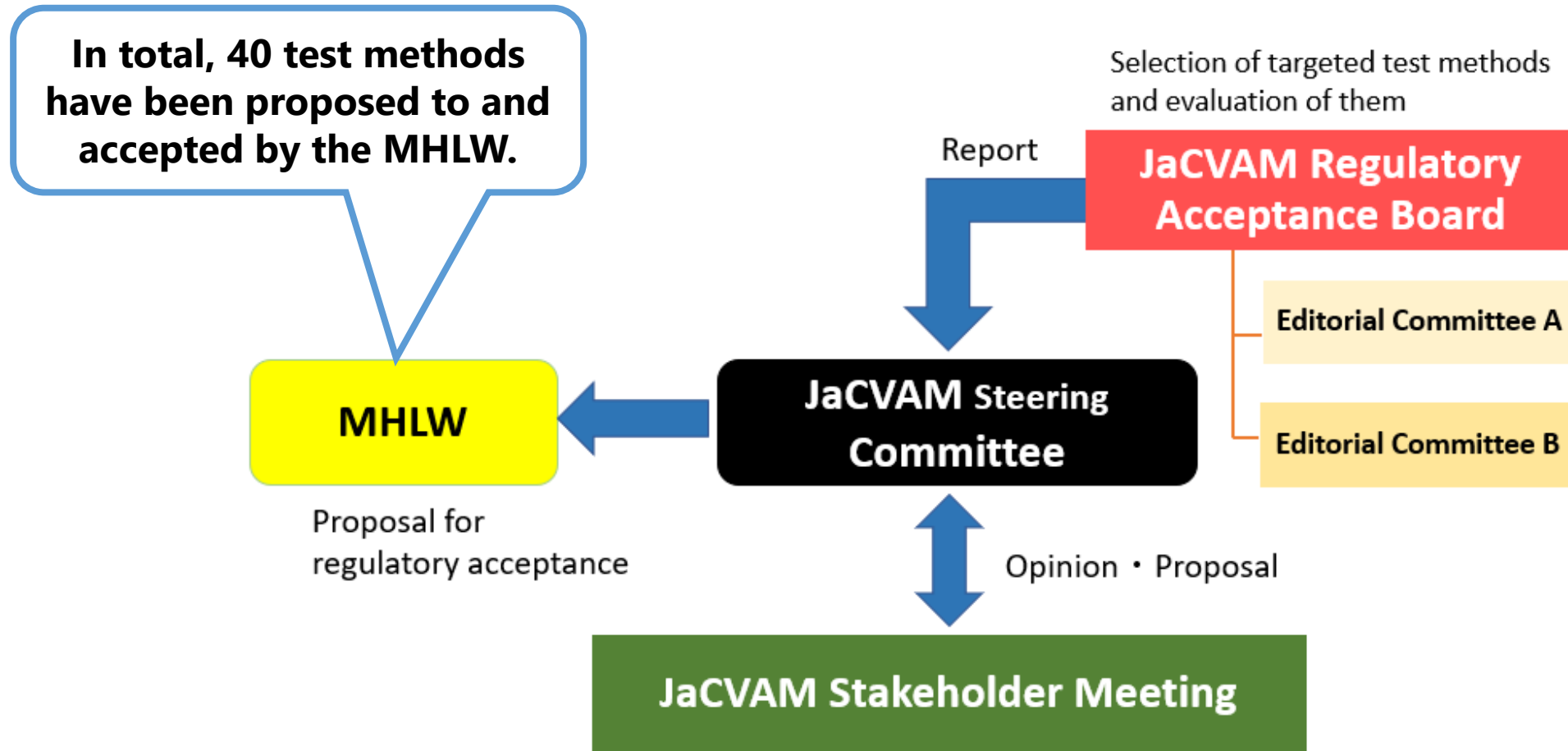
Steering committee of JaCVAM



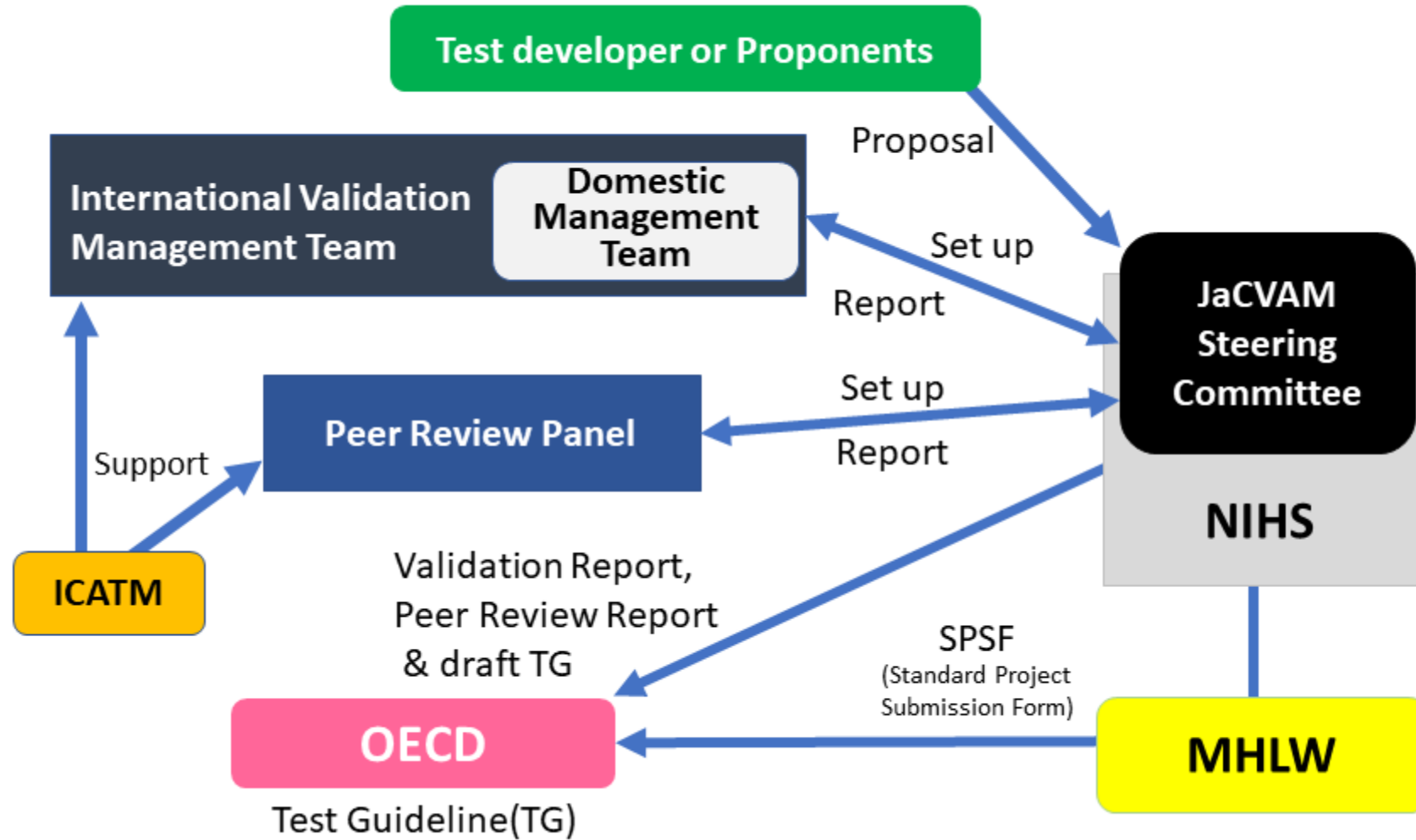
Flowchart of Activities



Regulatory Acceptance process



Test Guideline Validation process



Test Guidelines on human health that do not use animal testing

(as of 2022)

Subject of evaluation	TOTAL	<i>in vitro/in chemico</i>
Skin corrosiveness	3	3
Skin irritation	2	1
Phototoxicity	3	3
Eye Irritation	10	9
Skin sensitization	8	4
Percutaneous absorption	2	1
Genotoxicity	13	5
Endocrine Disruption	6	4
Other	28	0
SUM	75	30

OECD:<http://www.oecd.org/env/ehs/testing/oecdguidelinesforhetestingofchemicals.htm>

40% (30/75) Achieved !

Test Guidelines on human health that do not use animal testing

(as of 2022)

Subject of evaluation	ID No. of Test Guideline
Skin corrosiveness	430, 431 (incl. 5 RhE models), 435
Skin irritation	439 (incl. 6 RhE models)
Phototoxicity	432, 495, 498
Eye Irritation	437, 438, 460, 467, 491, 492 (incl. 4 ChE models), 492b, 494, 496
Skin sensitization	442C (ADRA, DPRA, kDPRA), 442D, 442E (h-CLAT, U-SENS, IL-8 Luc assay, GARD™Skin) , 497
Percutaneous absorption	428
Genotoxicity	471, 473, 476, 487, 490
Endocrine Disruption	455 (incl. 3 test methods), 456, 458, 493 (incl. 2 test methods)

Red: Methods developed in Japan

Current activities toward the development of NAMs

New Approach Methods (NAMs)

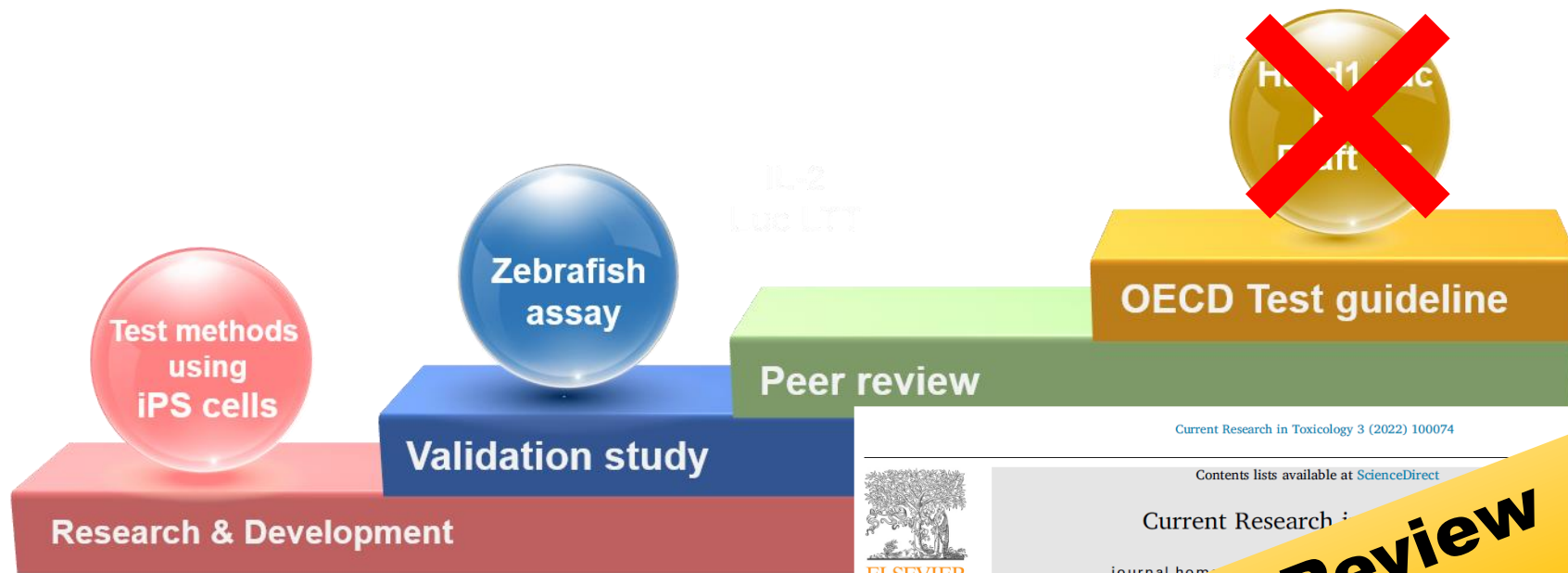
Any technology, methodology, approach, or combination that can provide information on chemical hazard and risk assessment to avoid the use of animal testing (US EPA)

Toward the development of NAMs

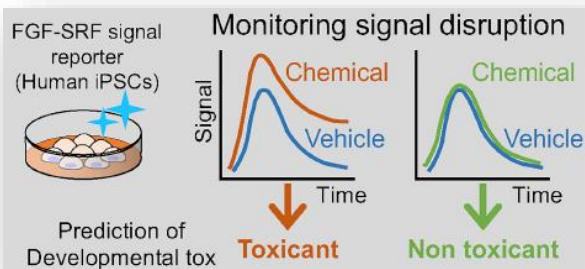
Test methods under development with JaCVAM:
a challenge with a particular focus on general toxicity

1. Reproductive Toxicity
2. Immunotoxicity
3. Toxicokinetics using Microphysiological system (MPS) models

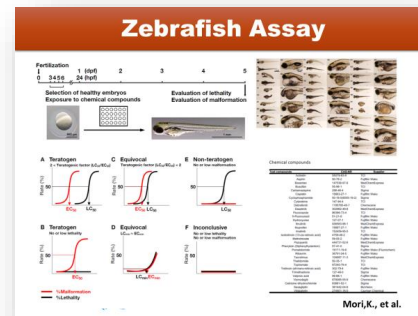
Reproductive Toxicity Tests



iSDT (integrated Signal Disruption Test)



Kanno S, Okubo Y et al: *iScience*, 2022



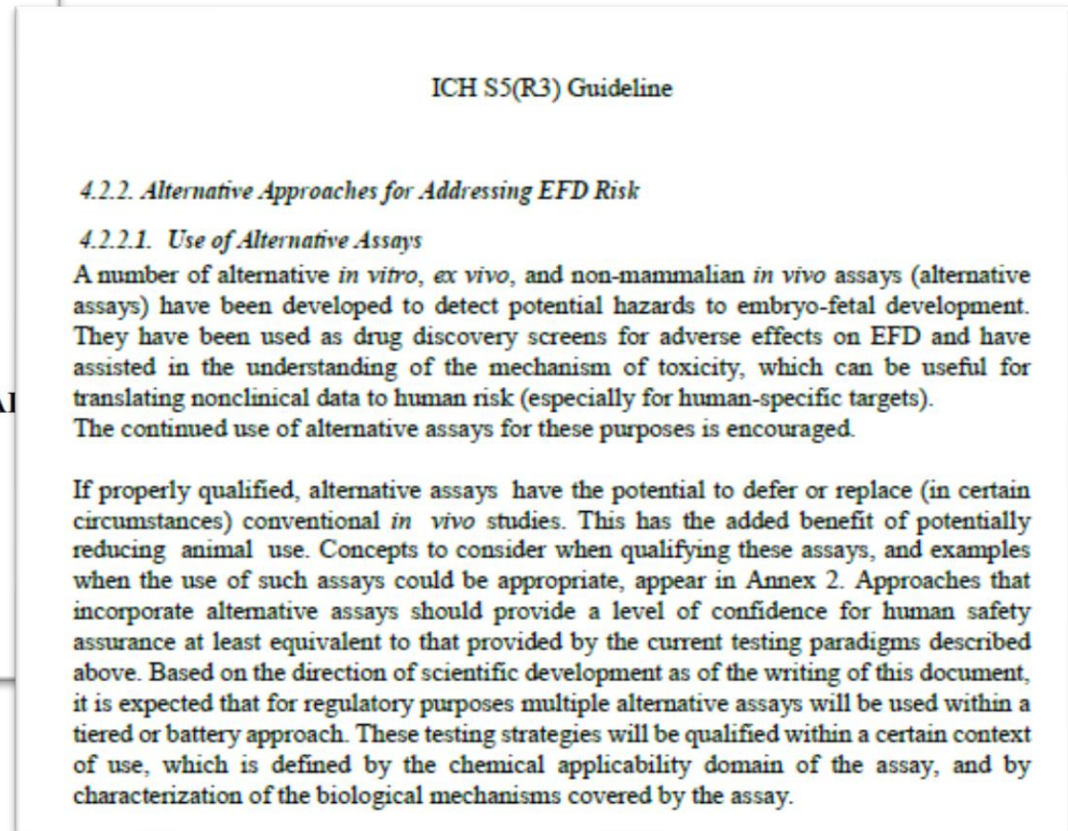
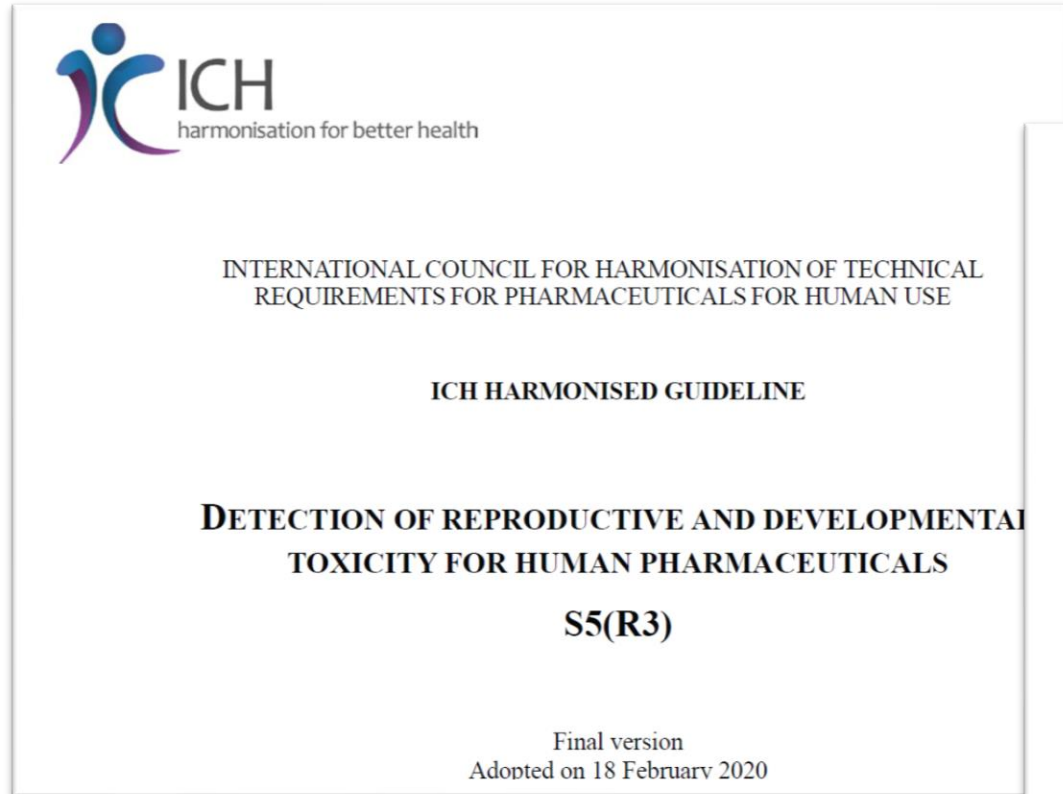
Detailed Review Paper (DRP)

<https://doi.org/10.1016/j.crto.2022.100074>



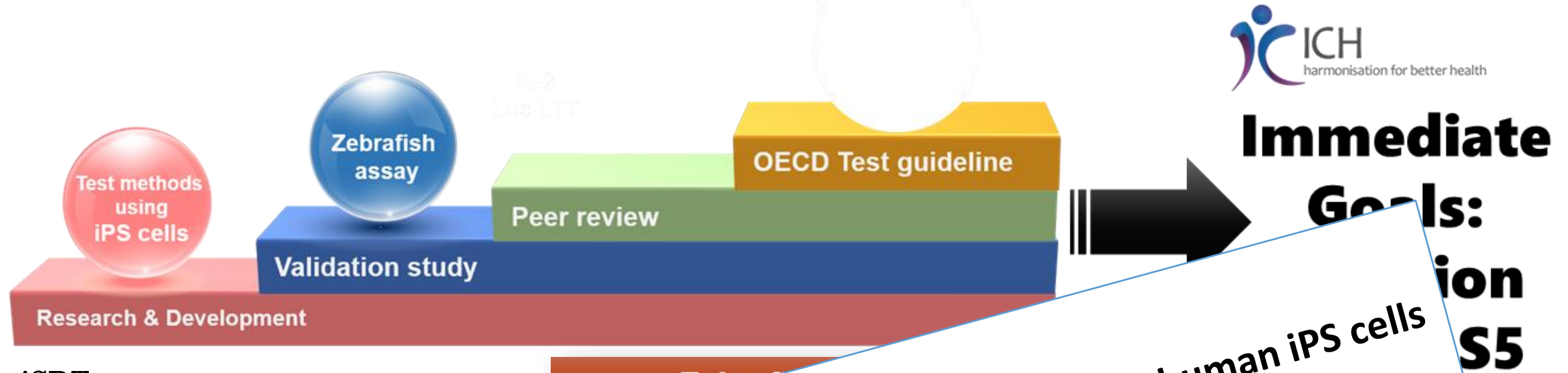
National Institute of Health Sciences,
Center for Biological Safety and Research

ICH guidelines specify the use of alternative test methods



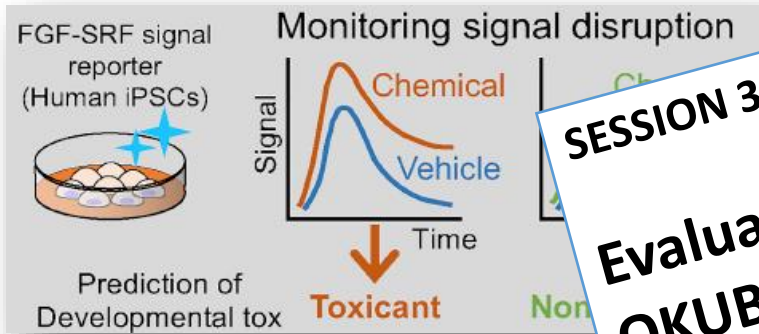
EFD: embryo fetal development

Reproductive Toxicity Tests



Immediate Goals:
Harmonisation S5

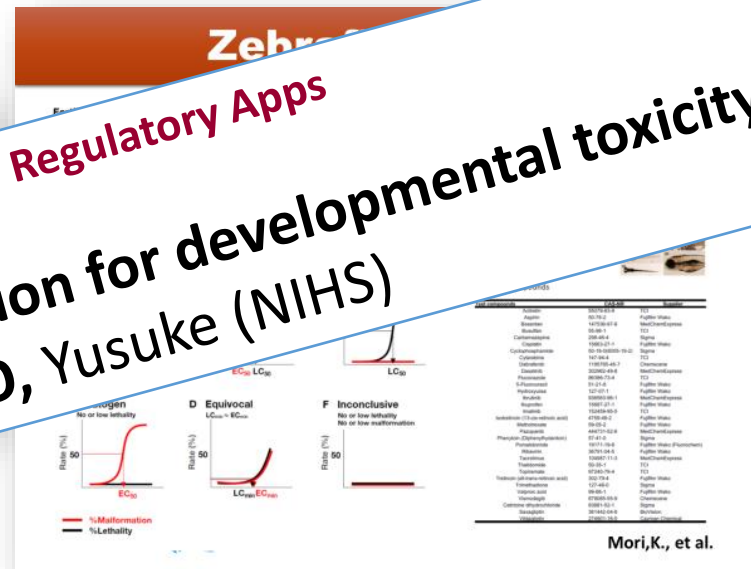
iSDT (integrated Signal Disruption Test)



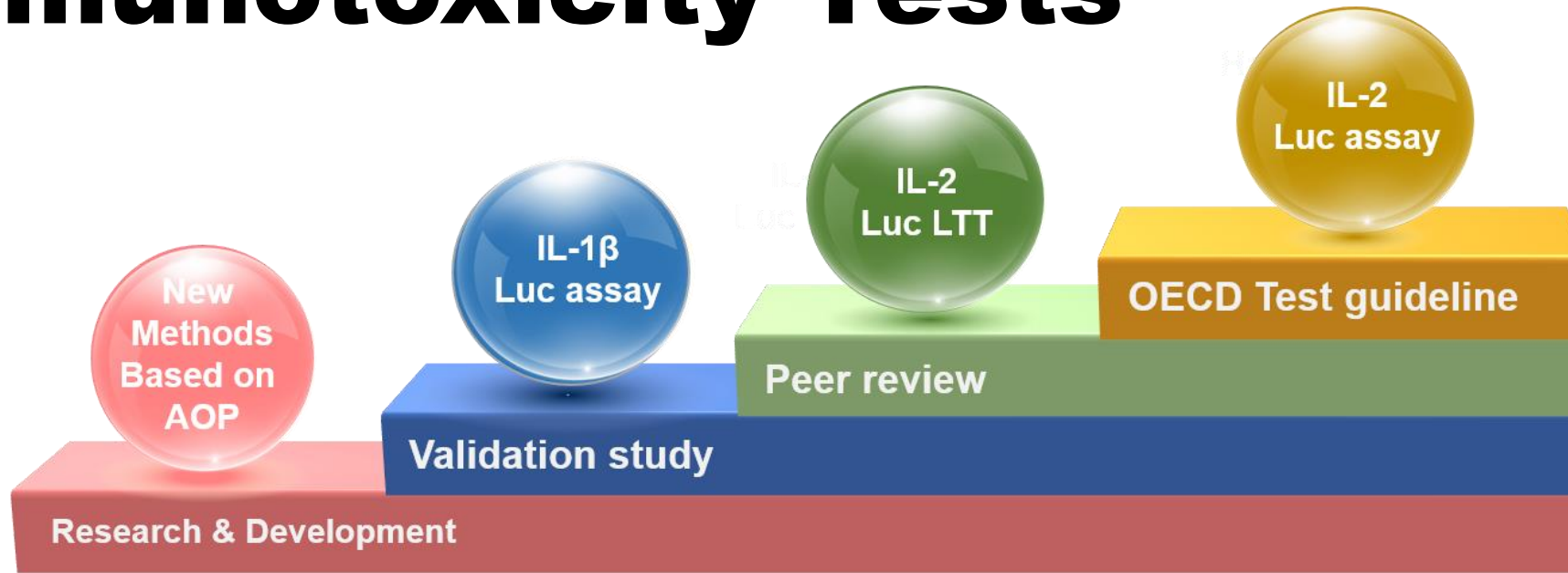
Kanno S, Okubo Y et al: *iScience*, 2022

SESSION 3 | Regulatory Apps

Evaluation for developmental toxicity using human iPS cells
OKUBO, Yusuke (NIHS)



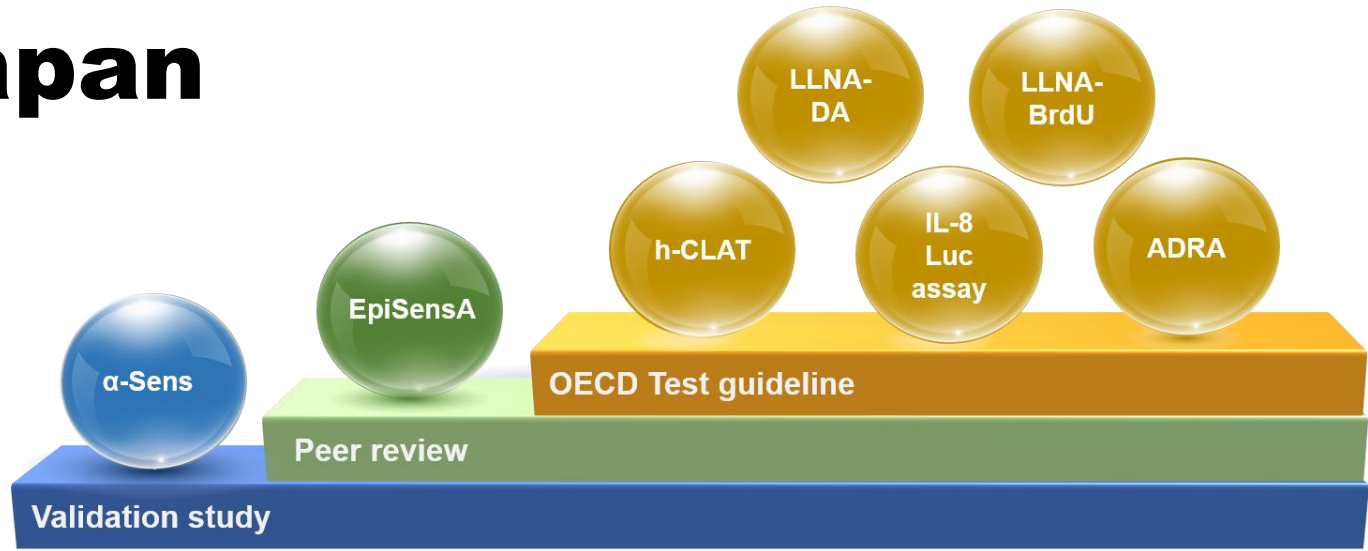
Immunotoxicity Tests



Development phase of alternative immunotoxicity testing methods

1. Developed three AOPs for immunotoxicity
2. Created DRPs for immunotoxicity testing, primarily for test systems to detect immunosuppression
3. Develop test methods based on AOPs
4. Validation studies of the developed assays are conducted and the assays that make up the Multi-ImmunoTox Assay (MITA) are converted to TGs.
5. Finally, an IATA was developed using TG as the core, combined with other information.

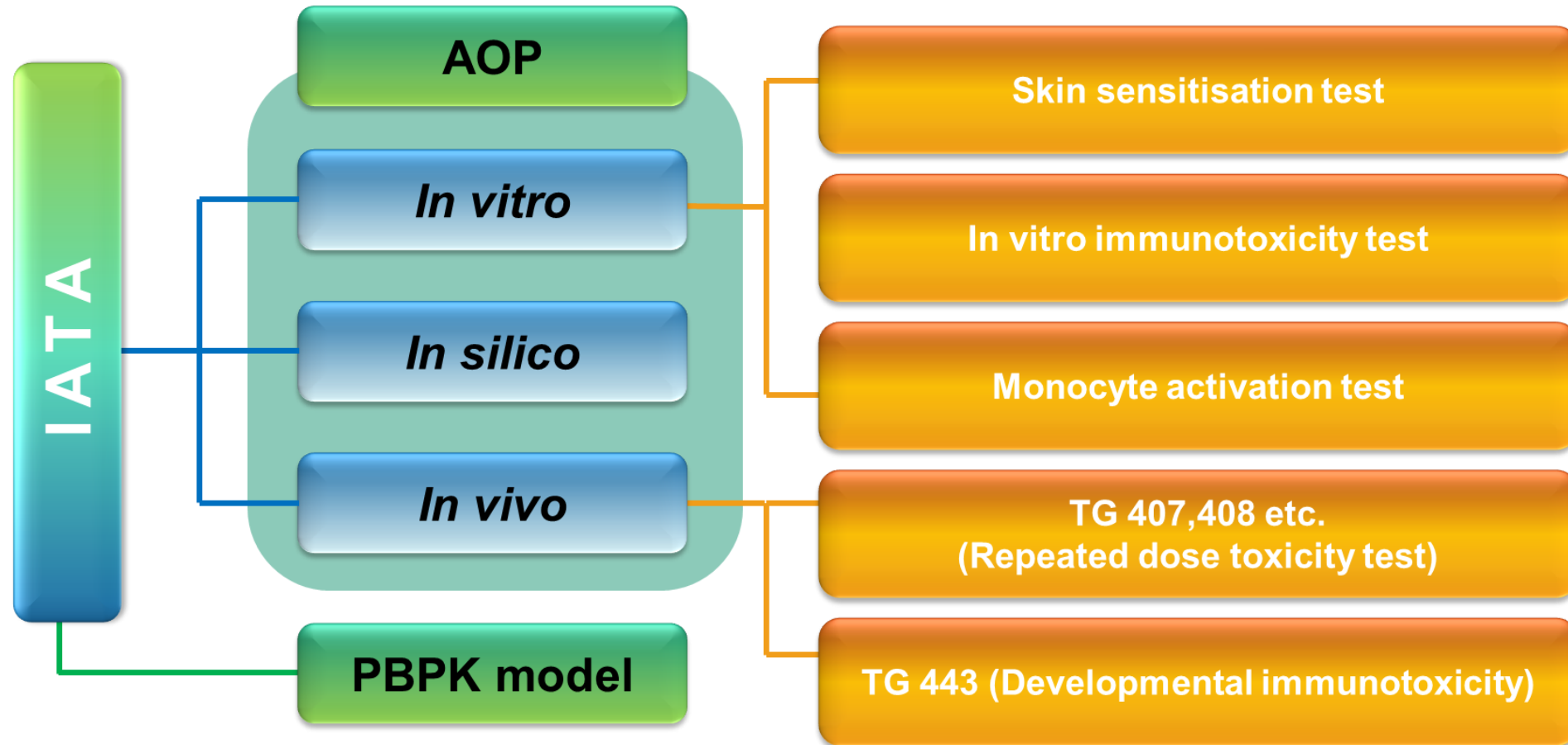
Skin sensitization tests developed in Japan



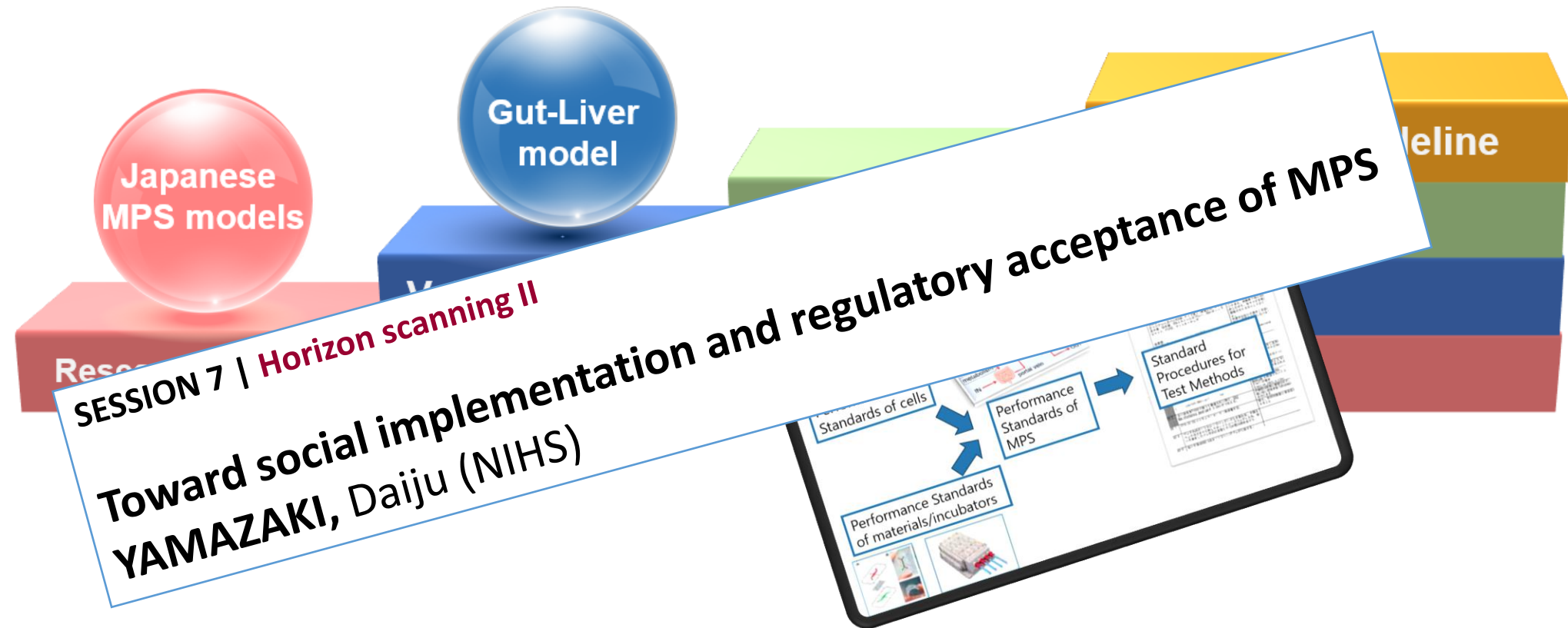
Monocyte activation tests



Future Plan: Development of IATA for Immunotoxicity Tests



Toxicokinetics using MPS models



Other collaborative activities

Project of Ministry of Economy, Trade and Industry (METI)

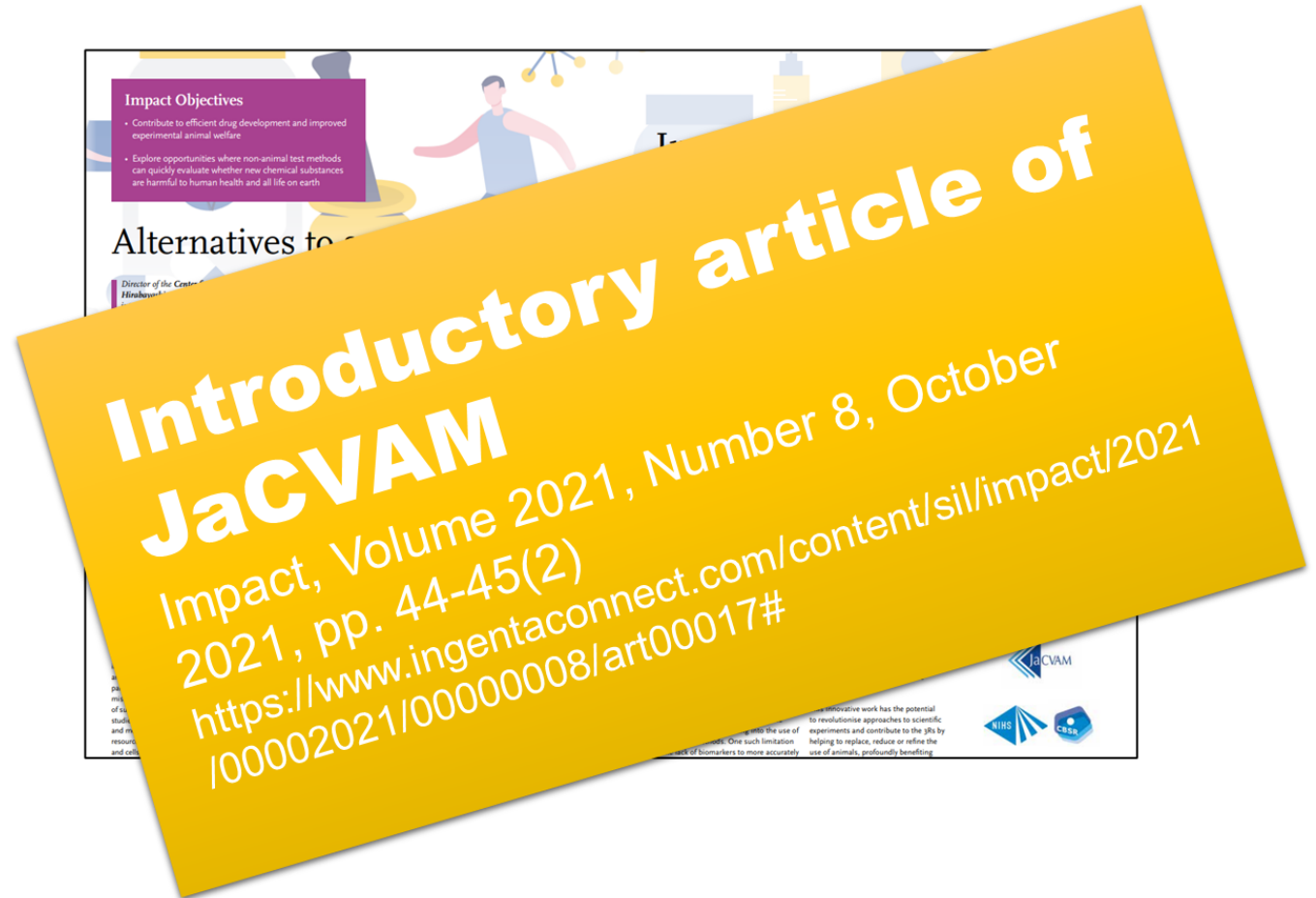
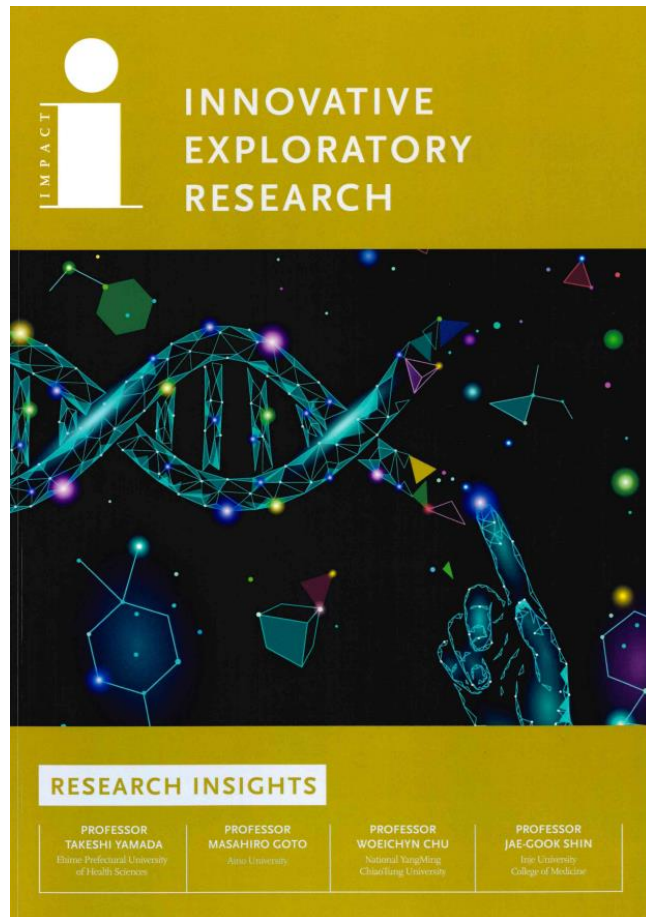
Development of basic technology to support drug discovery by applying regenerative medicine technology:

Toward Industrial Implementation & Regulatory Acceptance of MPS

Development of Next-generation Safety Prediction Methods Using Artificial Intelligence Based on Toxicity-related Big Data: **AI-SHIPS Project**

Challenges in trying to apply to regulatory use





Thank you very much for your attention