Session S405
Meeting at the Falls: ICATM Partner Updates

Update on recent activities at JaCVAM

HIRABAYASHI, Yoko
KOJIMA, Hajime
ASHIKAGA, Takao

Japanese Center for the Validation of Alternative Methods
Center for Biological Safety and Research
National Institute of Health Sciences
Japan

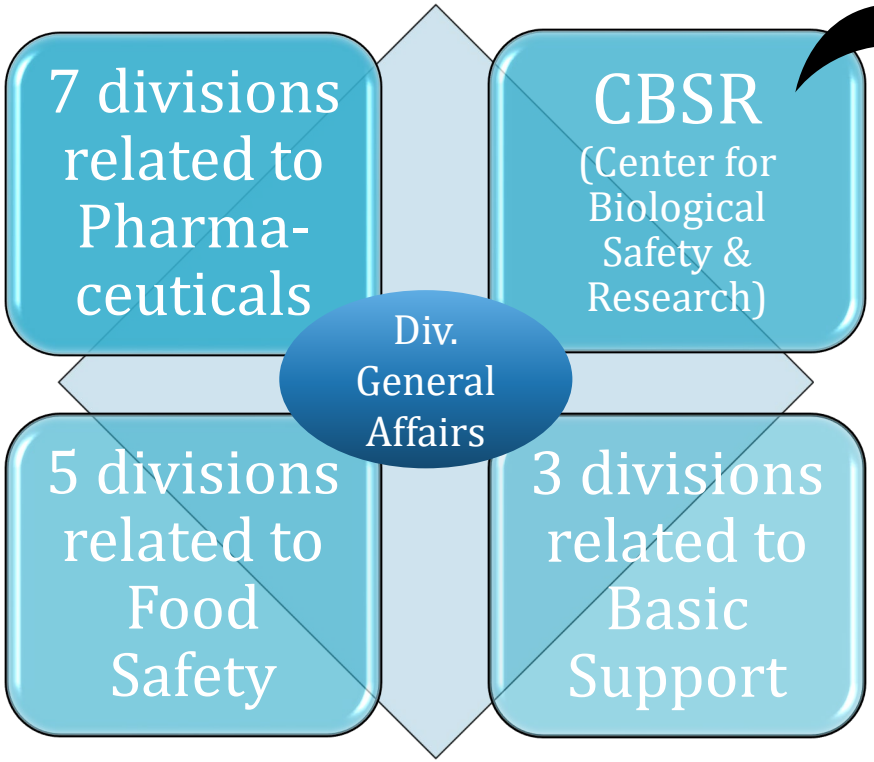
National Institute of Health Sciences (NIHS)

Enhancing safety and quality of life through scientific research

I have no financial relationships to disclose.

This presentation neither intend to represent, nor is restricted by, the policy of MHLW, Japan

NIHS: Organization

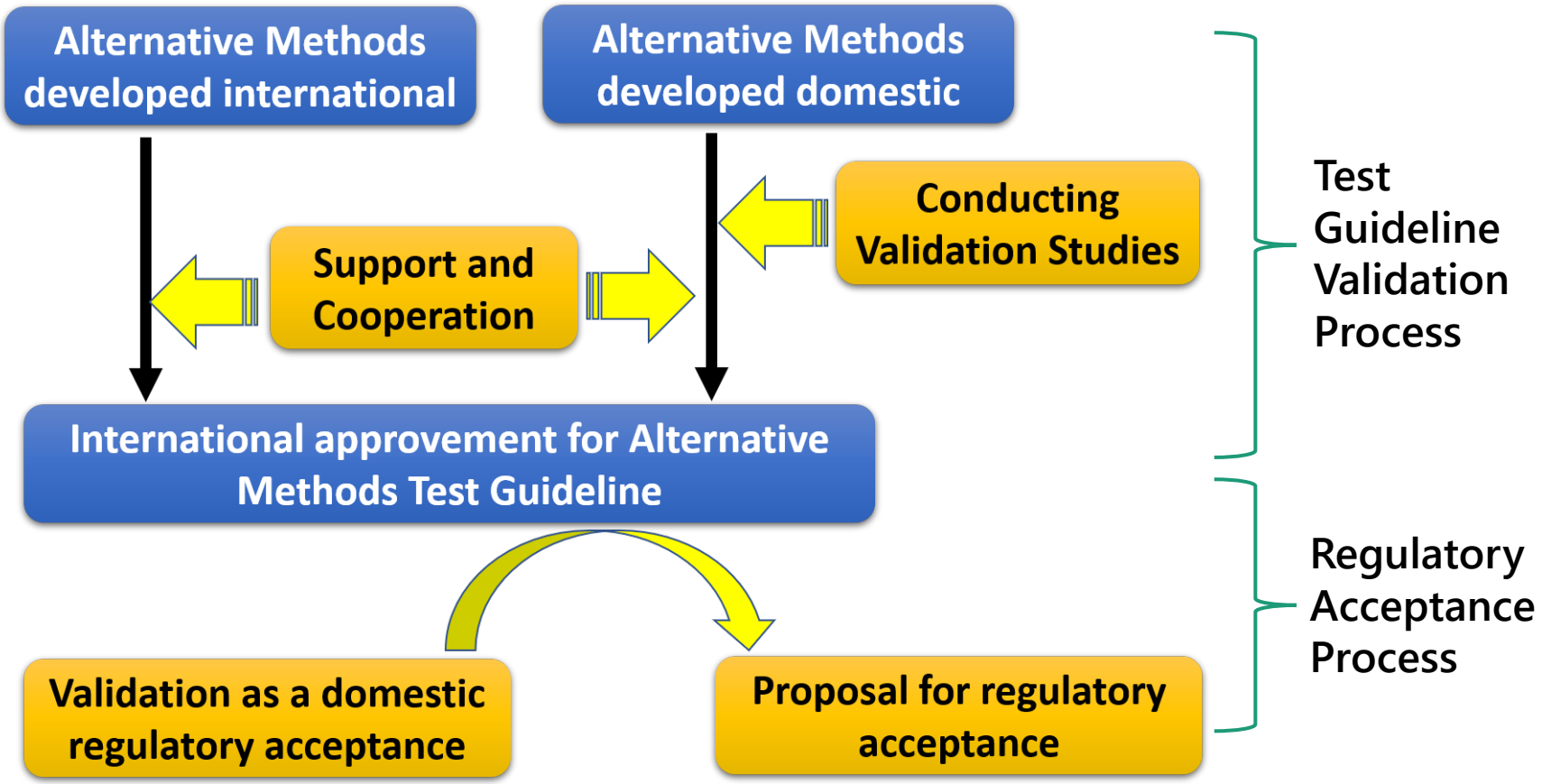


- Five Divisions related to Chemical Safety

and

- Experimental Animal Facility
- Japanese Center for the Validation of Alternative Methods (JaCVAM)

Flowchart of Activities



Number of Test Guidelines on human health that do not use animal testing in OECD (2022)

OECD:http://www.oecd.org/env/ehs/testing/oecdguidelinesforthetestingofchemicals.htm

Subject of evaluation	TOTAL	*in vitro*／*in chemico*
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**

40% (30／75) Achieved !

Test Guidelines on human health that do not use animal testing in OECD (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)

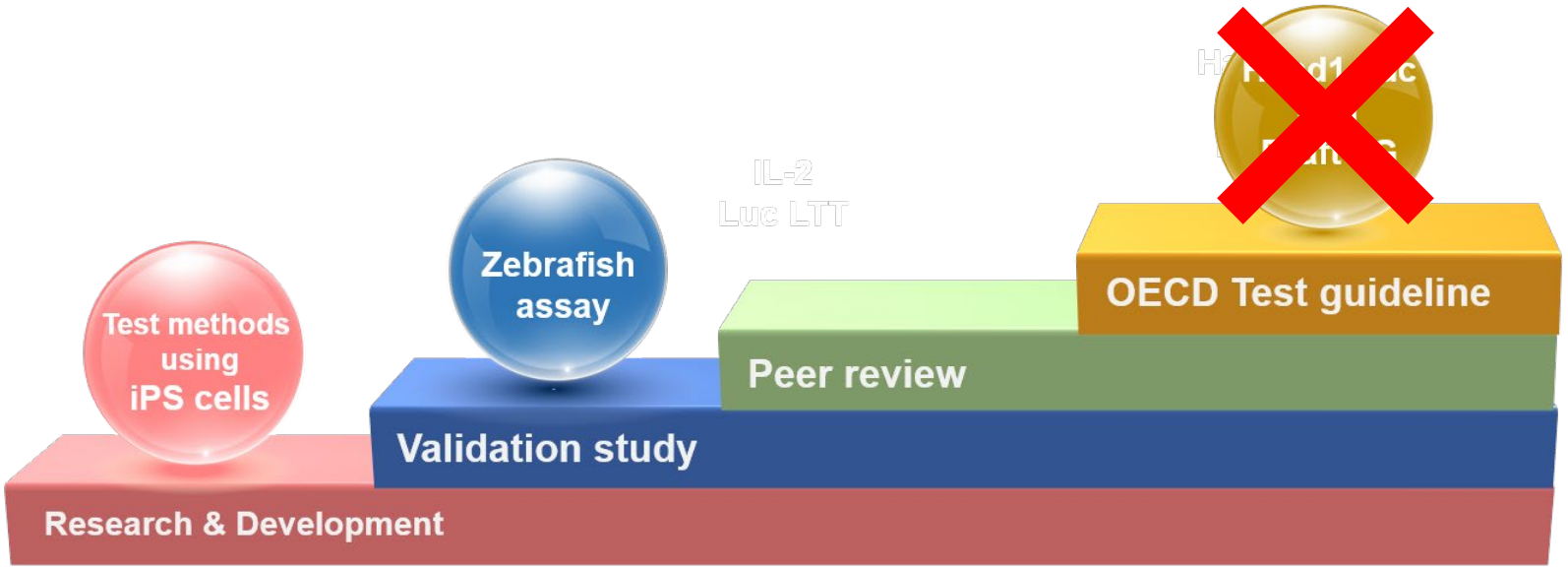
Red: Methods developed in Japan

Toward the development of NAM…

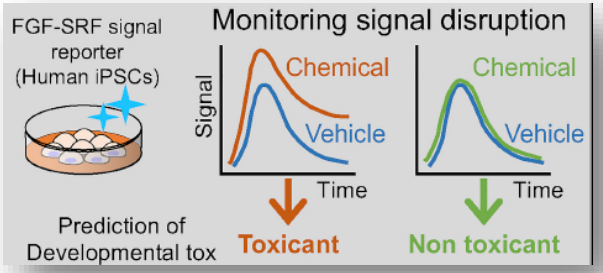
Test methods under development with JaCVAM: a challenge with a particular focus on general toxicity

1. Reproductive and Developmental Toxicity Tests
   - Test Method using human iPS cells
   - Test Method using Zebrafish fertilized eggs
2. Immunotoxicity Test
   - Standardize IL-2 Luc LTT and IL-1 Luc assay, and develop IATA (Integrated Approaches to Testing and Assessment)

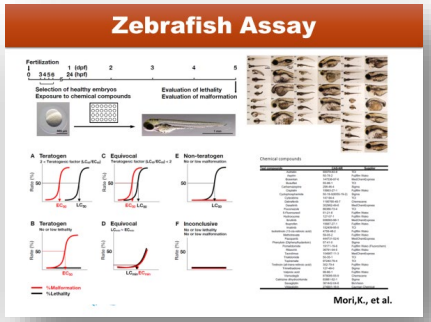
Reproductive Toxicity Tests

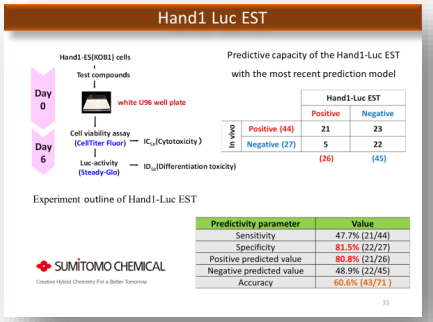


iSDT (integrated Signal Disruption Test)

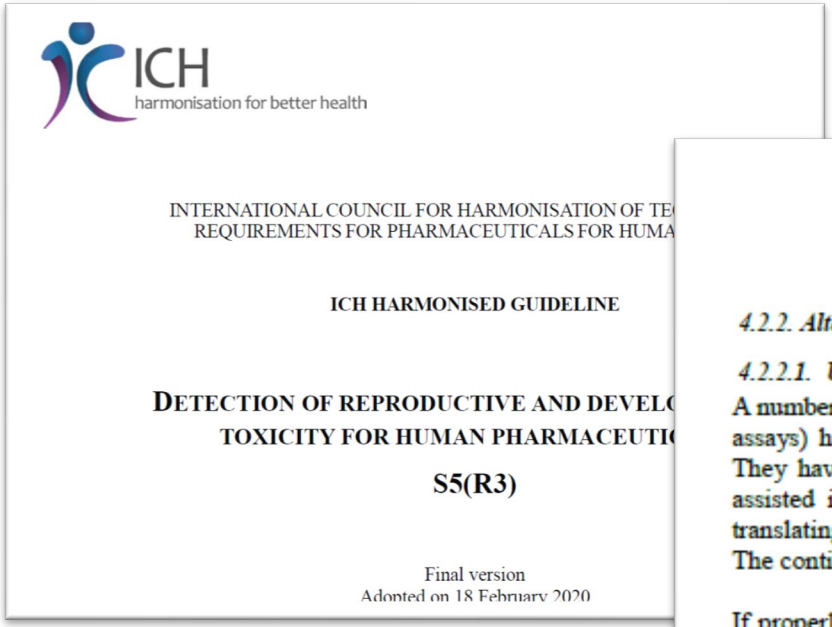


Kanno S, Okubo Y et al: iScience, 2022





ICH guidelines specify the use of alternative test methods


ICH
harmonisation for better health

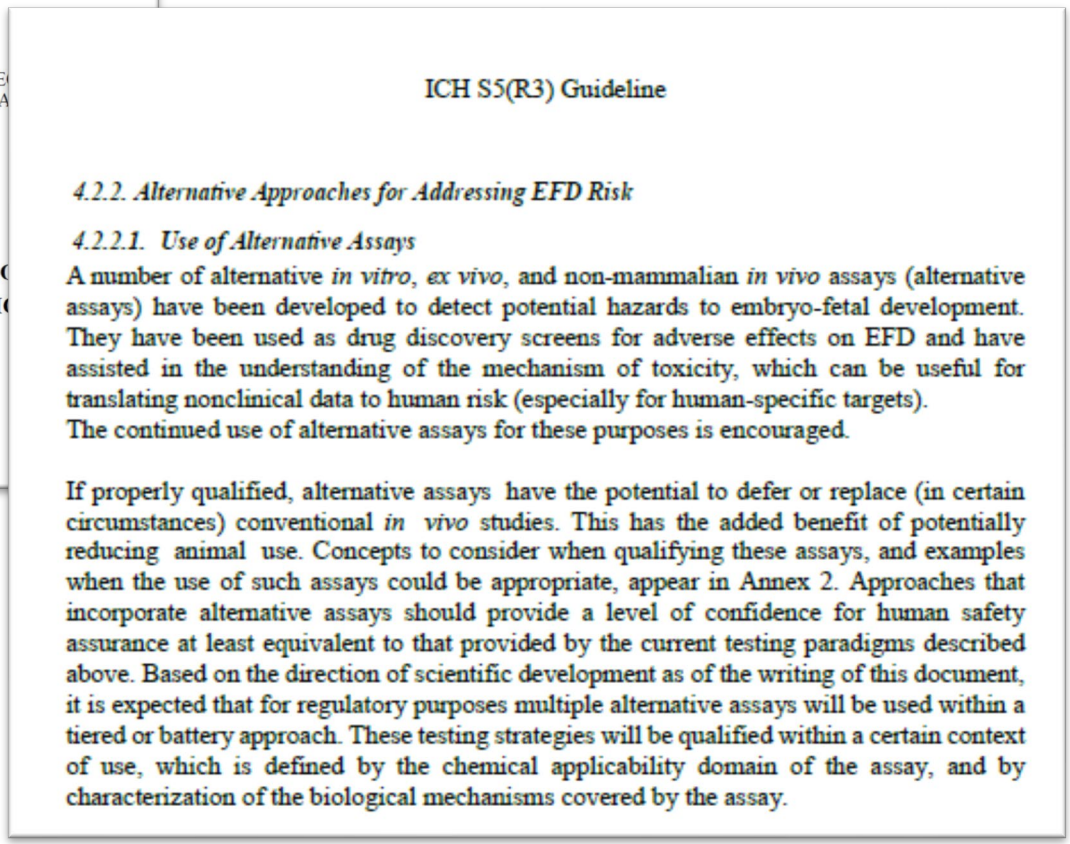
INTERNATIONAL COUNCIL FOR HARMONISATION OF TE
REQUIREMENTS FOR PHARMACEUTICALS FOR HUMA

ICH HARMONISED GUIDELINE

DETECTION OF REPRODUCTIVE AND DEVELO
TOXICITY FOR HUMAN PHARMACEUTI

S5(R3)

Final version
Adopted on 18 February 2020


ICH S5(R3) Guideline

4.2.2. Alternative Approaches for Addressing EFD Risk

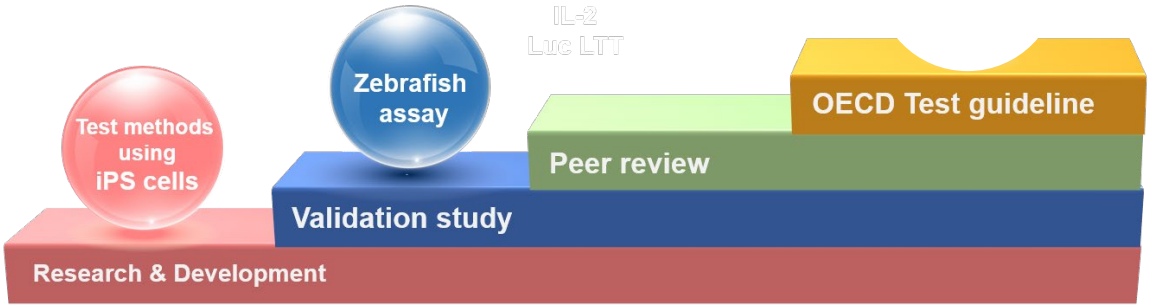
4.2.2.1. Use of Alternative Assays

A number of alternative *in vitro*, *ex vivo*, and non-mammalian *in vivo* assays (alternative assays) have been developed to detect potential hazards to embryo-fetal development. They have been used as drug discovery screens for adverse effects on EFD and have assisted in the understanding of the mechanism of toxicity, which can be useful for translating nonclinical data to human risk (especially for human-specific targets).
The continued use of alternative assays for these purposes is encouraged.

If properly qualified, alternative assays have the potential to defer or replace (in certain circumstances) conventional *in vivo* studies. This has the added benefit of potentially reducing animal use. Concepts to consider when qualifying these assays, and examples when the use of such assays could be appropriate, appear in Annex 2. Approaches that incorporate alternative assays should provide a level of confidence for human safety assurance at least equivalent to that provided by the current testing paradigms described above. Based on the direction of scientific development as of the writing of this document, it is expected that for regulatory purposes multiple alternative assays will be used within a tiered or battery approach. These testing strategies will be qualified within a certain context of use, which is defined by the chemical applicability domain of the assay, and by characterization of the biological mechanisms covered by the assay.

EFD: embryo fetal development

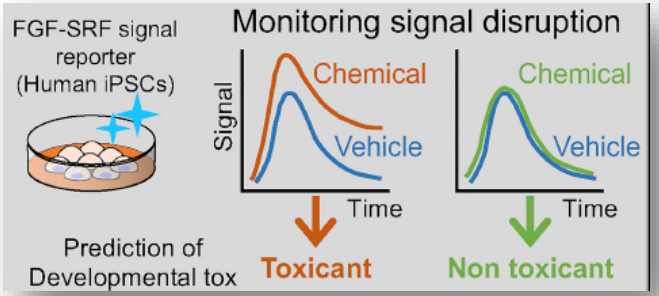
Reproductive Toxicity Tests



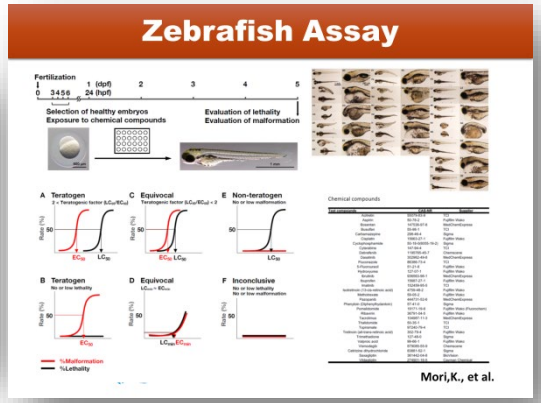
ICH harmonisation for better health

Immediate Goals: inclusion in ICH S5

iSDT (integrated Signal Disruption Test)

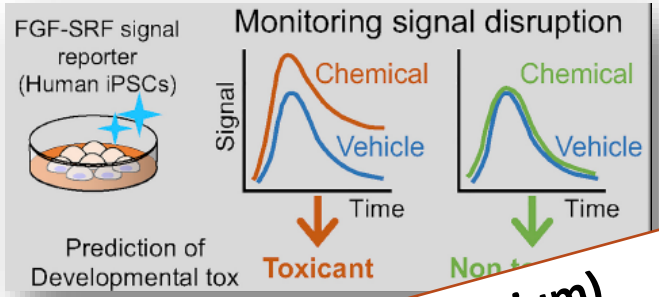


Kanno S, Okubo Y et al: iScience, 2022



Attempting to develop a new test method using human iPS cells

iSDT (integrated Signal Disruption Test)



Kanno S, Okubo Y et

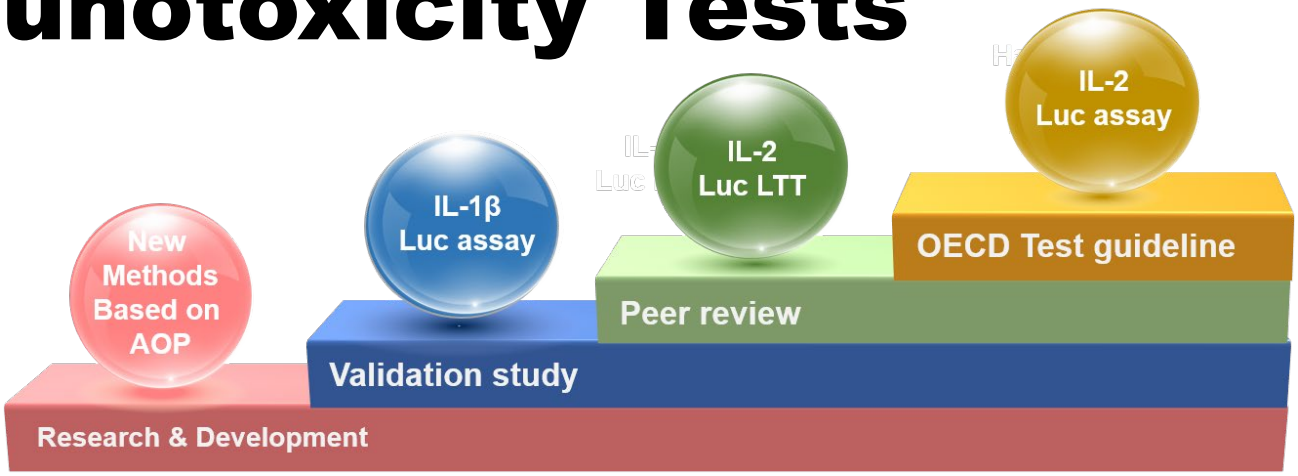
Session S450 (Symposium)

New Approach Methods for Developmental and Reproductive Toxicity Testing

#137 Developmental toxicity Test using human iPS cells based on signal disruptions induced by chemical substances

OKUBO, Yusuke (NIHS)

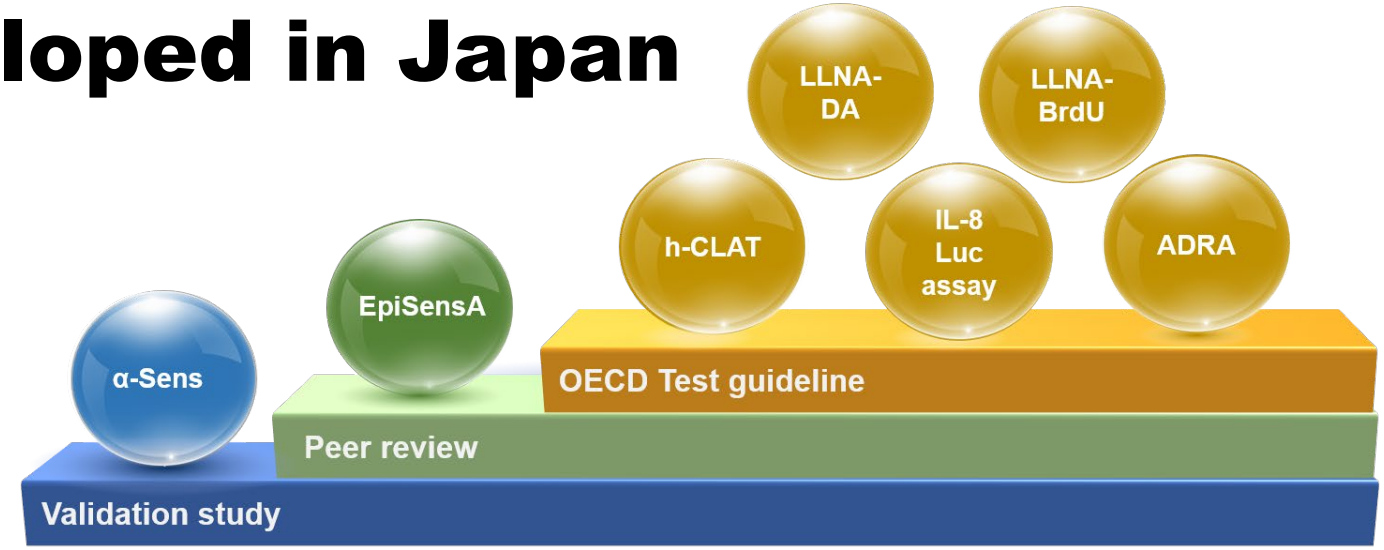
Immunotoxicity Tests



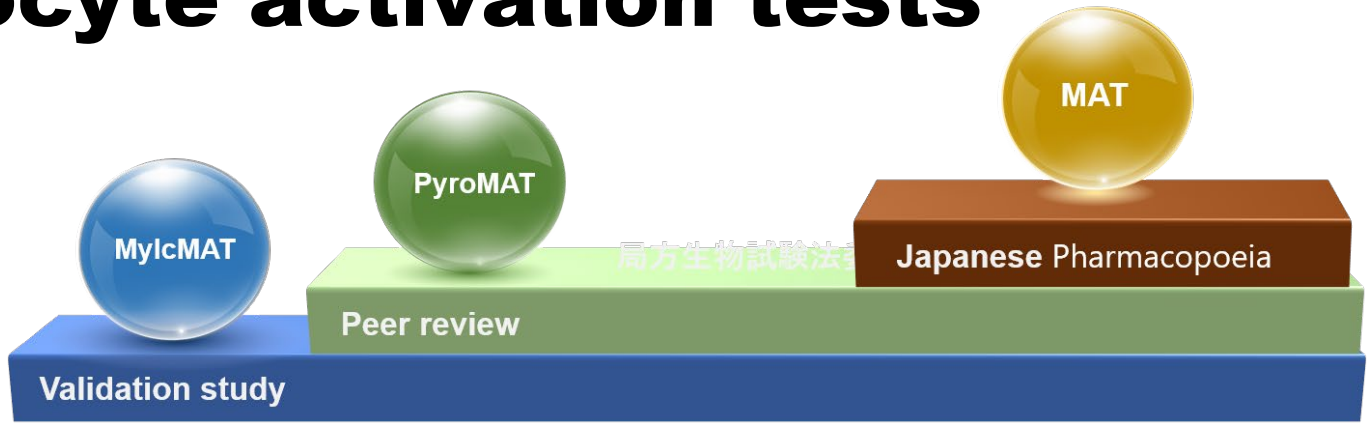
Development phase of alternative immunotoxicity testing methods

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.

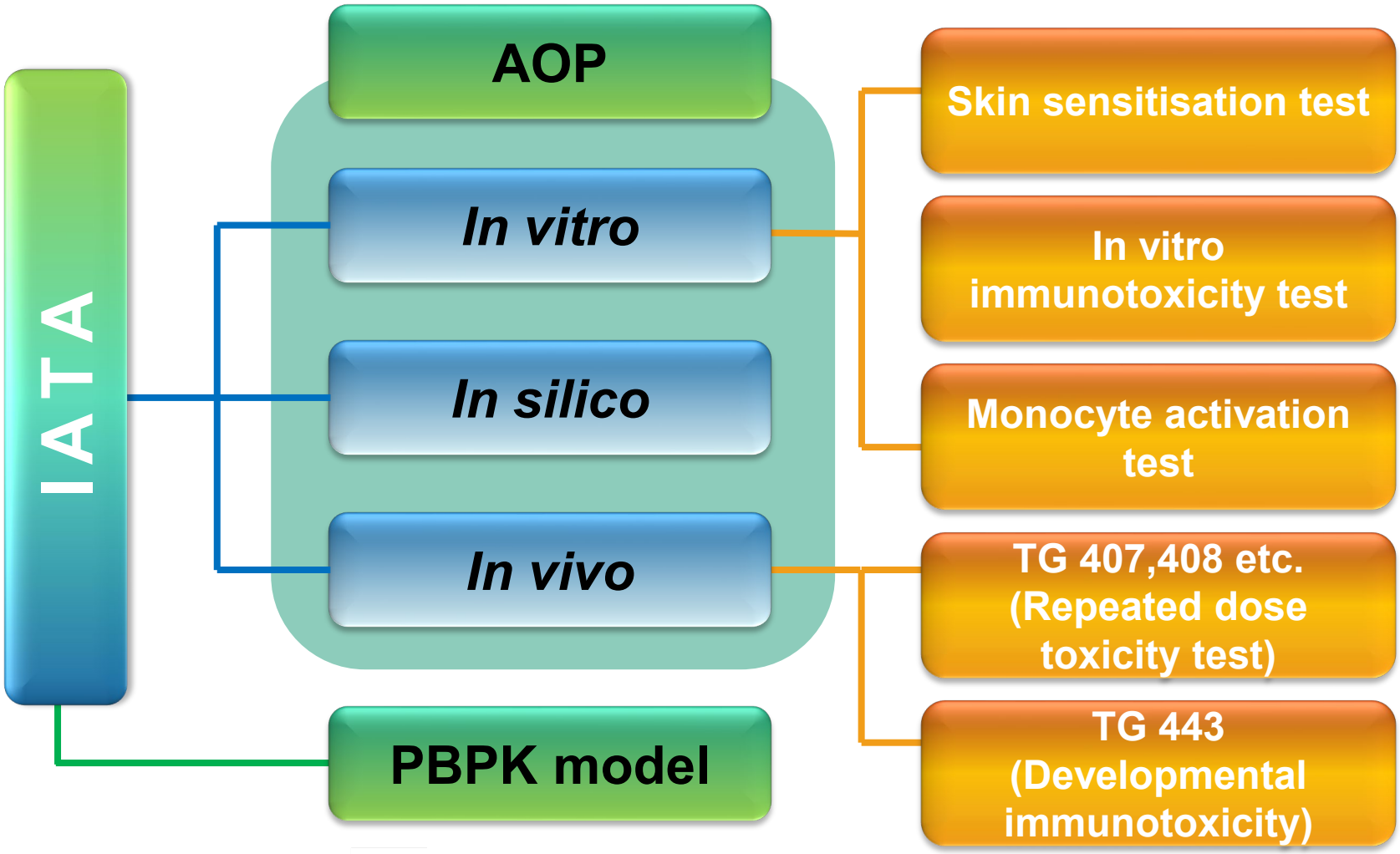
Skin sensitization tests developed in Japan



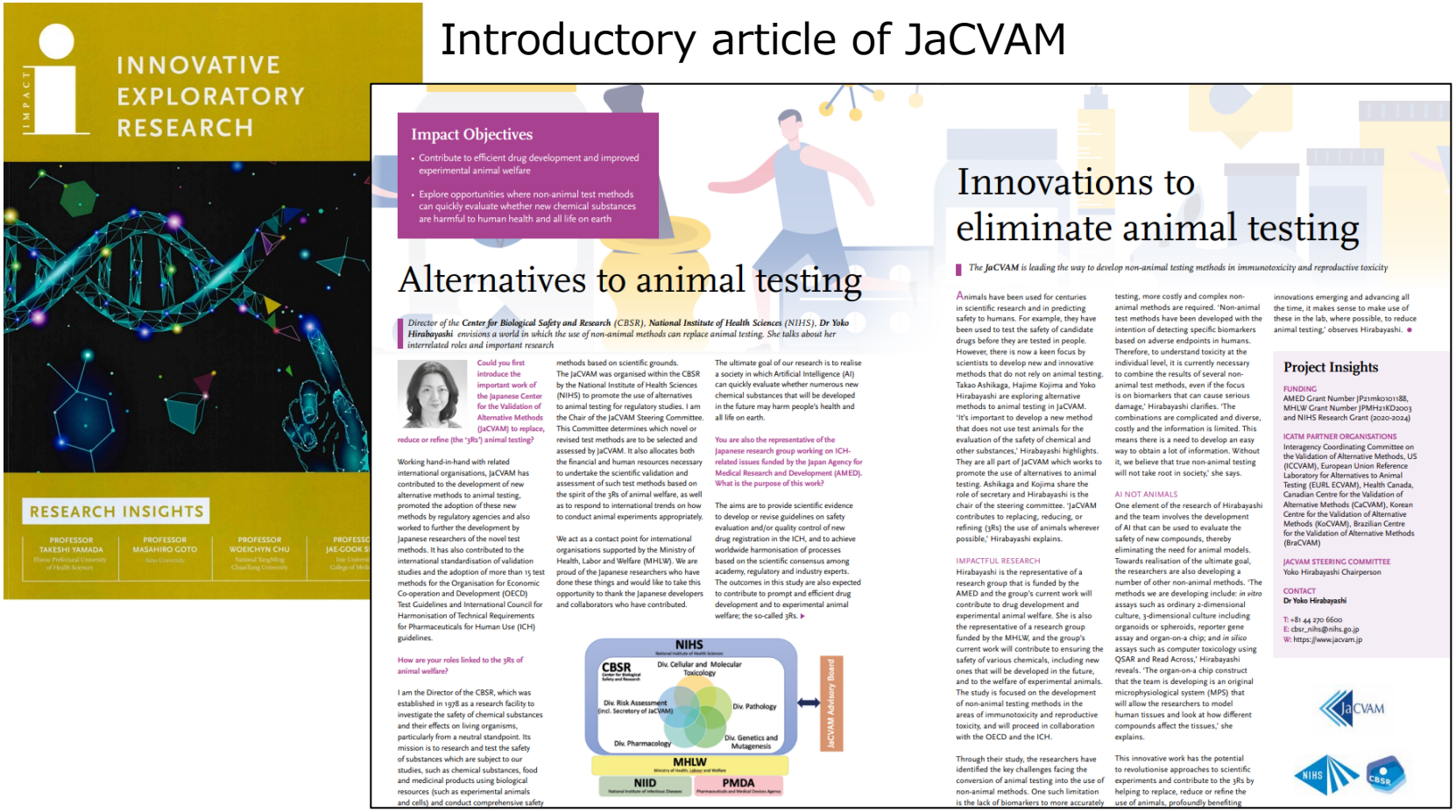
Monocyte activation tests



Future Plan: Development of IATA for Immunotoxicity Tests



Introductory article of JaCVAM



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https://www.ingentaconnect.com/content/sil/impact/2021/00002021/00000008/art00017#

Thank you very much for your attention