Annual meeting on advancing 21st Century Toxicology,
The Center for Alternatives to Animal Testing and
the Animal-Free Safety Assessment Collaboration, May 12, 2021

AI, iPSC and MPS Projects for Systemic Toxicity

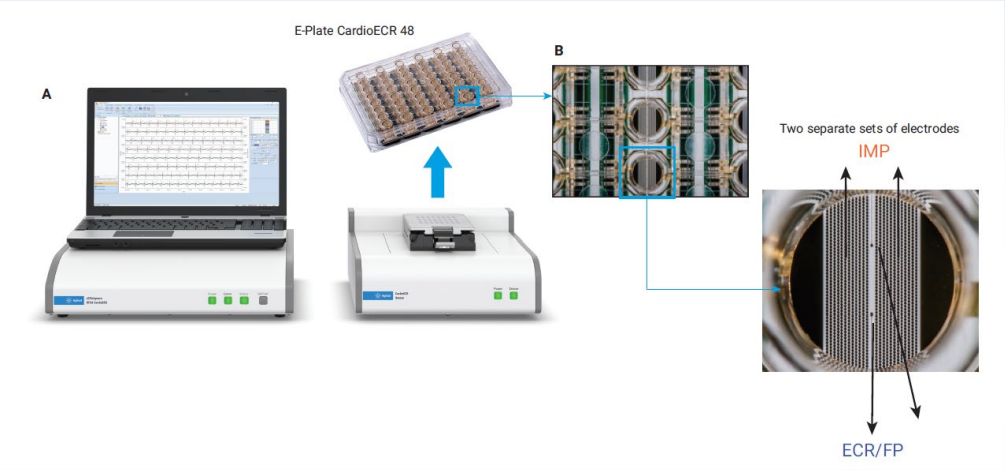
Hajime Kojima,
JaCVAM, NIHS, Japan

New approach methods (NAMs) for systematic toxicology in Japan

- For ICH S5 (R3), we are developing the NAMs for reproductive toxicity.
- For OECD TG, Japan is developing Detailed Review Papers (DRPs) on stem cell assay for reproductive toxicity and *in vitro* immunotoxicity with International drafting team.
- Big projects are going on the Microphysiological system (MPS) for PBPK and the AI system for repeat dose toxicity testing.

Pharmacological and toxicological tests using human iPS cells

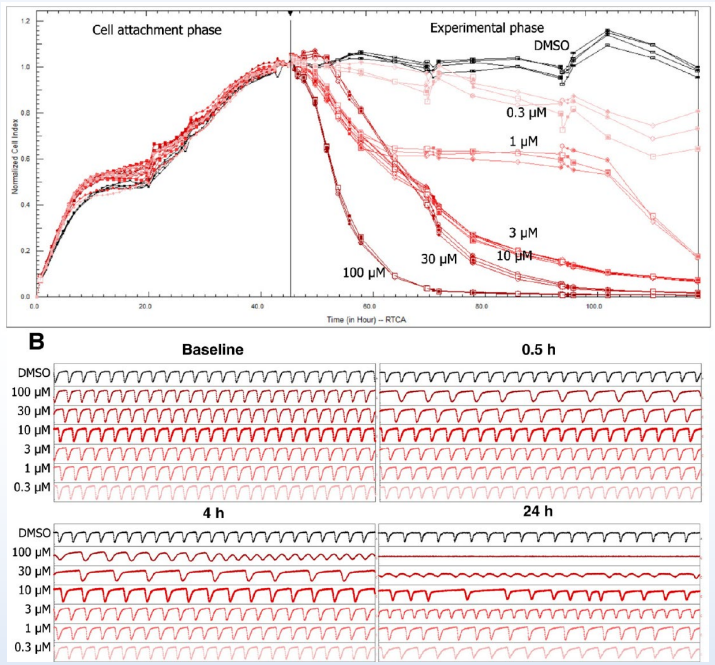
Cardotoxicity screening using Impedance-based assay



https://www.agilent.com/cs/library/applications/application-cardiac-safety-xcelligence-cardioecr-594-2076en-agilent.pdf

Measuring the impedance of iPS cell-derived cardiomyocytes, cardiomyocyte contraction and viability were stable in real time.

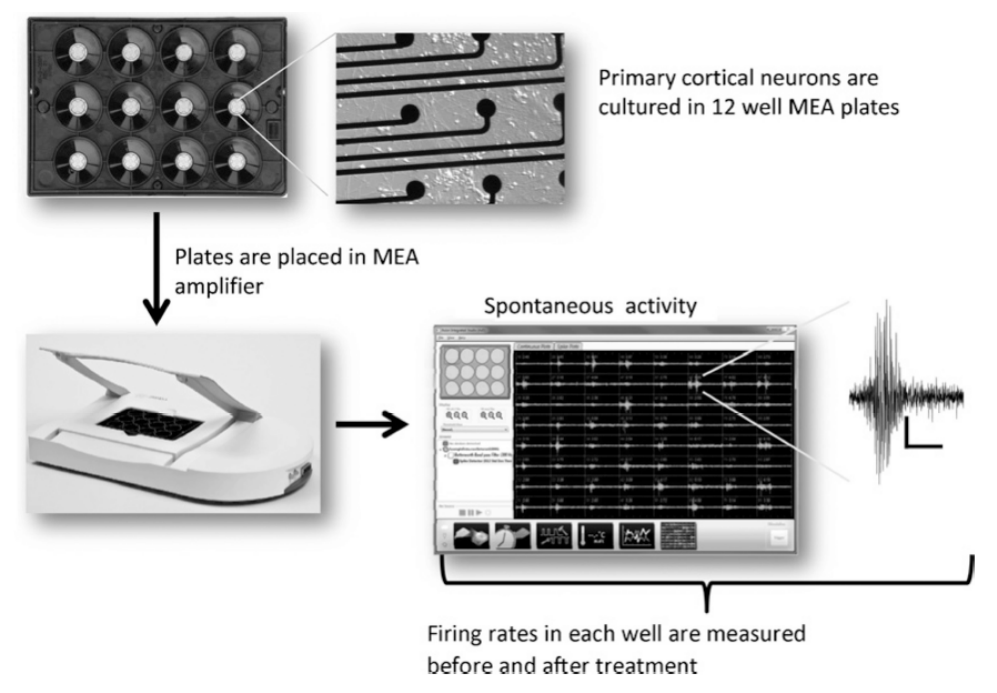
◆ Cytotoxicity (ex. Doxorubicin)



B. Koci et al. / Toxicology and Applied Pharmacology 329 (2017) 121–127

ICH S7B

Neurotoxicity screening using MEA

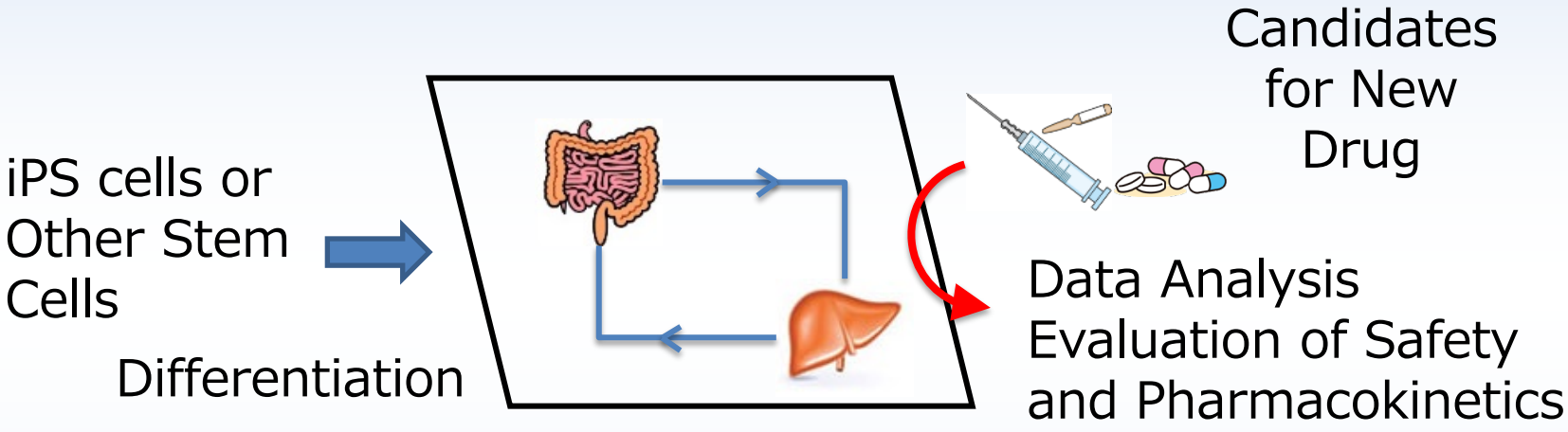


Using Micro-electrode array (MEA) system, the spike of iPS cell-derived neurons is measured.

ER. McConnell, Neurotoxicology. 2012 October ; 33(5): 1048–1057

The system for assessing Convulsive inducing action by machine learning

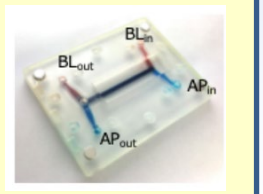
A Project Focused on Developing Key Evaluation Technology Aiming at Industrialization of Regenerative Medicine: Development of Platform Technology for Drug Discovery through Application of Regenerative Medicine

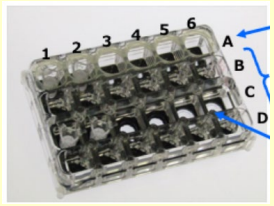


This project aims to develop an organ(s)-on-a-chip system by mounting organ cells derived from iPS or other stem cells on chips and devices that can be applied for safety and pharmacokinetic evaluations in the process of drug discovery.

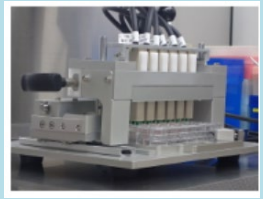
Initiatives for drug discovery of MPS in Japan

MPS devices Developed in Japan





Analysis equipment Developed in Japan



User Consortium among pharmaceutical researchers, suppliers and academia

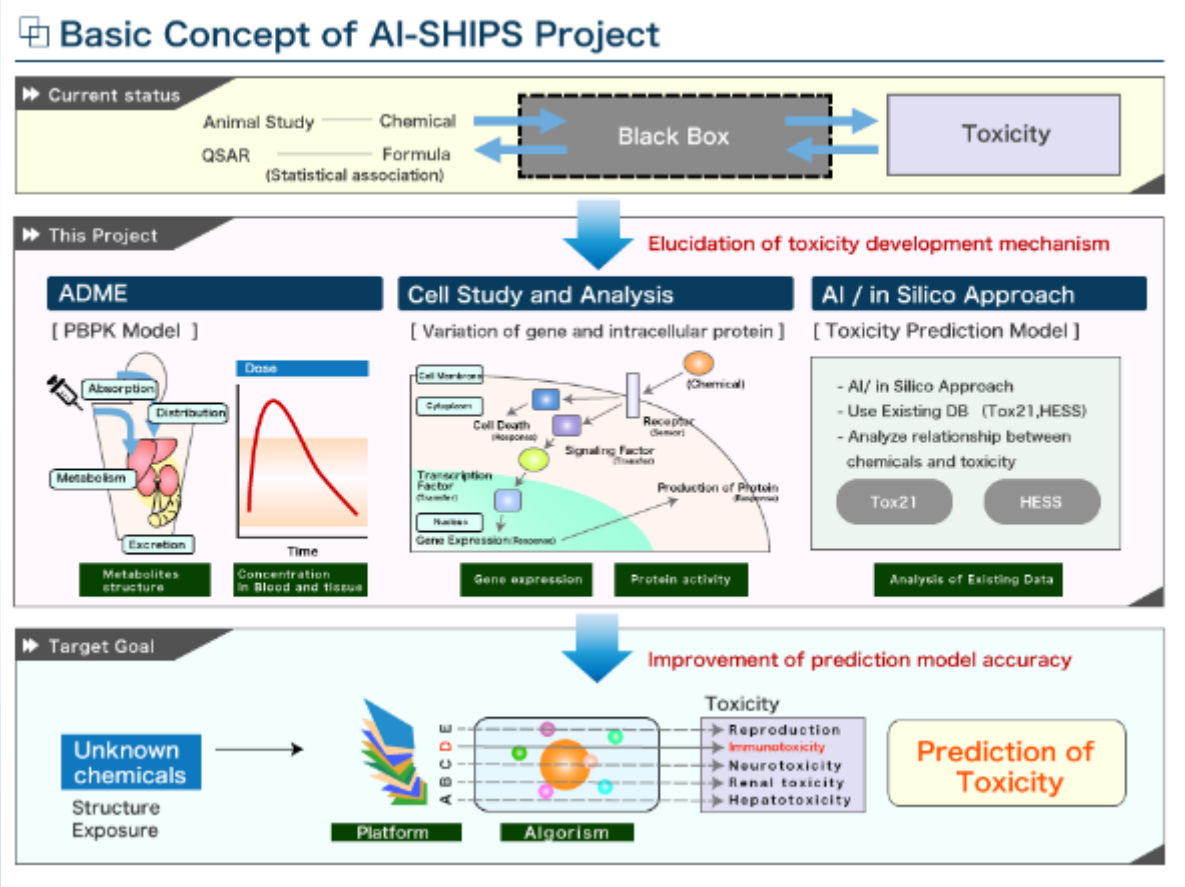
Stem Cell Evaluation Technology Research Association
事業内容 | SCA 幹細胞評価基盤技術研究組合 (scetra.or.jp)

⇒ Contributing to improving access to MPS

Development of in silico hazard prediction system using AI technology
-Repeat Dose toxicity-

METI (Ministry of Economy, Trade and Industry) consignment project *"Development of AI based next generation safety prediction system using related Big data"*

AI-based
Substances
Hazardous
Integrated
Prediction
System project



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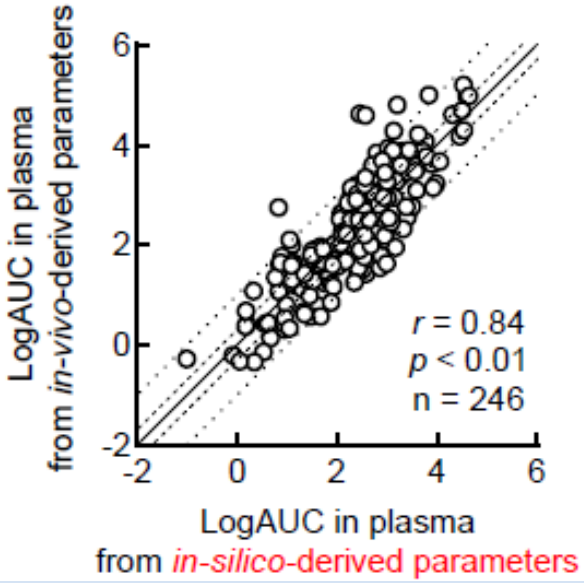
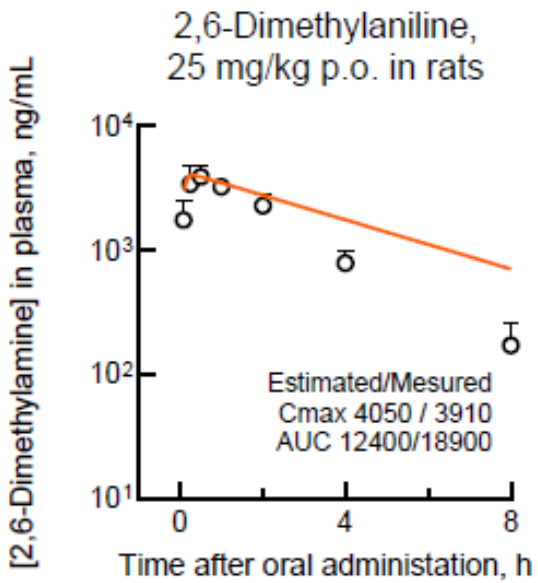
Comparison of dynamic simulation and measured values using rat after pharmacokinetic determination

Deep Learning

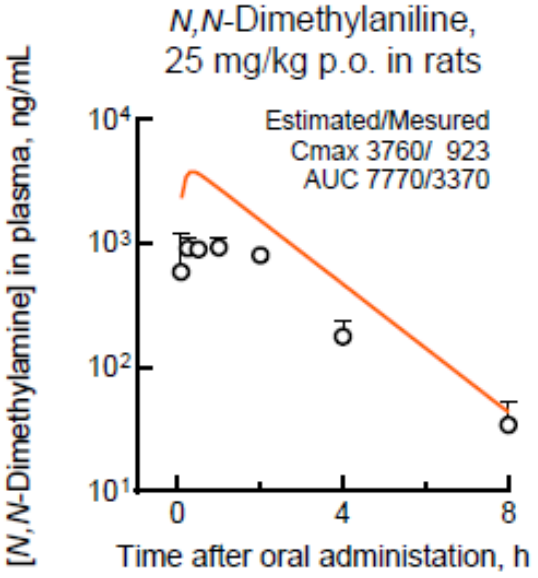
Kamiya, Yamazaki et al., Chem Res Toxicol 34, 507-513, 2021



ka	14.7
V1	1.02
CLh,int	0.903



ka	8.49
V1	0.672
CLh,int	3.15



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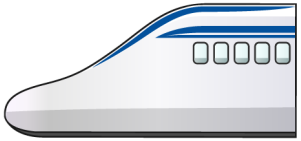
Translational research science using advanced technology

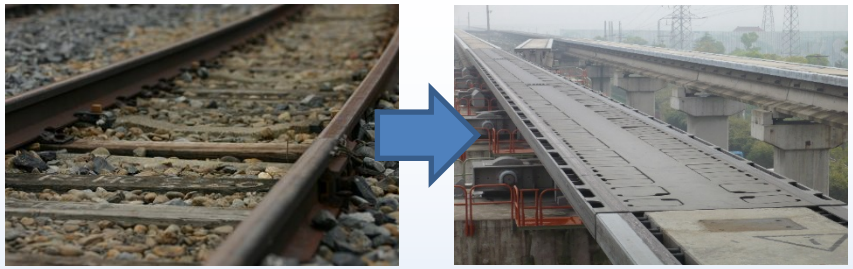
Original technology

Regulation

Advanced technology



Maglev



It is necessary for new technology to optimally regulations based on international harmonization with industry, government, and industry.

From Dr. Naraoka, SCA

Summary

Japan has a long history and many experiences regarding alternative method developing and …

In order to accelerate achievement of new approach methods for systemic toxicology in every regulatory fields (chemicals, pharmaceuticals and foods, etc.), we needs International collaborative partners who are sharing the common goal.