

Regulatory Science and Emerging Technology in Japan

Enhancing safety and quality of life
through scientific research



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GSRS 20, Web VIRTUAL

Masamitsu Honma, Ph.D.
Deputy Director General
National Institute of Health Sciences
JAPAN

Regulatory Science in Japan

“Regulatory science is a science that makes accurate predictions, assessments, and judgments based on evidence to adjust the outcomes of science and technology to the most desirable form in harmony with people and society.”



By Dr. Mitsuru Uchiyama, Director General National Institute of Health Sciences, in 1987

“Promotion of Regulatory Science” was approved in the Fourth Science and Technology Basic Plan in Japan (August 2011: Cabinet Decision).

Sharing Roles in Regulation and Regulatory Science in Japan of Pharmaceuticals, Medical Devices, and Other Medical Products

● Ministry of Health, Labour and Welfare (MHLW)

- Basic policy, law, and official notices
- Authorization



● Pharmaceuticals and Medical Devices Agency (PMDA)

- Consultation, review, compliance assessment, inspection, and post-approval surveillance
- Collection and organization of information about adverse effects
- Development of regulatory guideline drafts and standards including JP
- Relief services for adverse health effects



● National Institute of Health Sciences (NIHS)

- Development and standardization of official evaluation methods and tests
- Development of technical guideline drafts (mainly on quality and nonclinical aspects)
- Testing adulterated and/or marketed products as OMCL
- Conducting research studies to accurately evaluate the quality, safety, and efficacy of medical products



● Japan Agency for Medical Research and Development (AMED)

- Grant program to facilitate medical R&D



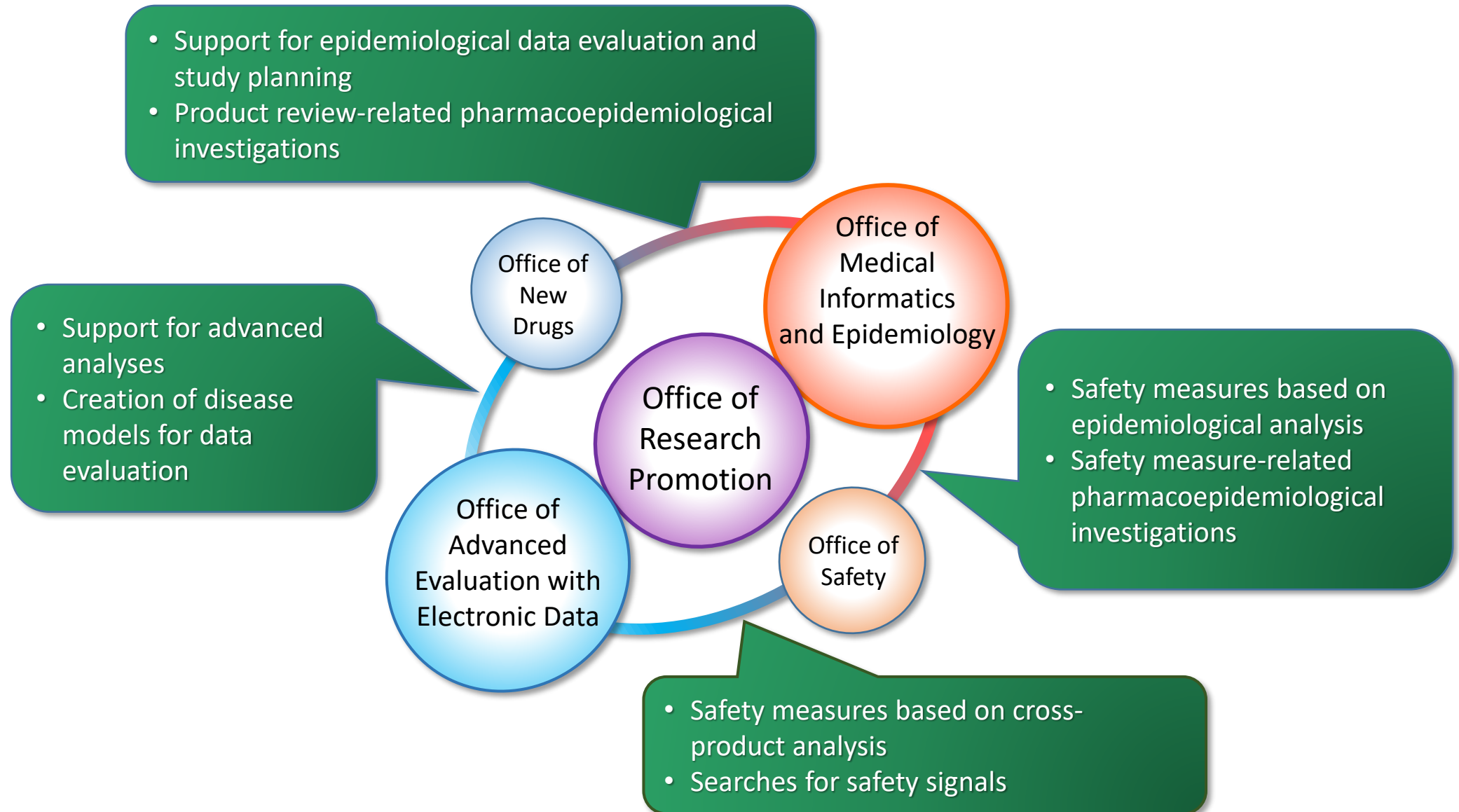
PMDA's Lead of Regulatory Science

Establishment of the Regulatory Science Center (est. April 2018)

- 1. Functions as the PMDA's command center**
- 2. Actively utilizes clinical trial data and electronic healthcare records**
- 3. Promotes innovative approaches to advanced therapies and technologies**
 - Horizon Scanning**
 - Science Board**
 - Real-World Data Utilization**



Regulatory Science Center of PMDA



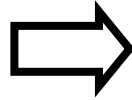
Horizon Scanning

Without Horizon Scanning...

*Stakeholders :
unsure of
regulations...*



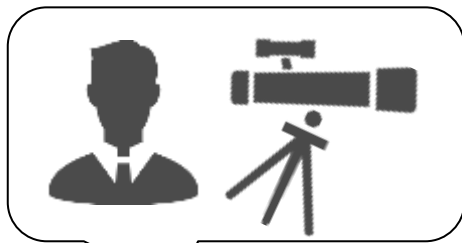
Report on
Technology A



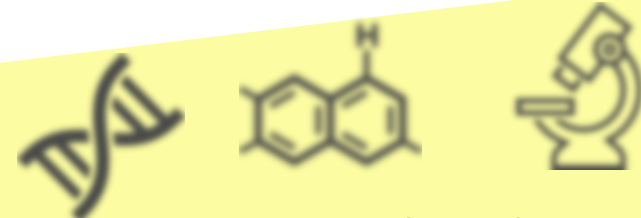
Regulator

*Regulators :
cannot keep pace
with accelerating
innovation...*

With Horizon Scanning...



Regulator



Emerging Technologies

- Proactively scan the horizon
for emerging trends and technologies*
- Make necessary regulatory preparations*

PMDA's Response to the COVID-19 Pandemic

Drugs

Active Ingredient	Brand Name	Applicant Company	Approval Date
<u>Remdesivir</u>	VEKLURY for Intravenous Injection	Gilead Sciences K.K.	May 7, 2020 (approved based on article 14-3 of the PMD Act)

Medical Devices

Japanese Medical Device Nomenclature (JMDN)	Brand Name	Applicant Company	Approval Date
Ventilator for general purpose	NKV-550 Series Ventilator System	NIHON KOHDEN CORPORATION	April 24, 2020
Bi-level positive airway pressure unit	Philips Respironics E30 ventilator	Philips Japan, Ltd.	May 1, 2020
Adult ventilator	Philips Trilogy Evo Series	Philips Japan, Ltd.	May 12, 2020

In Vitro Diagnostics

Japanese Medical Device Nomenclature (JMDN)	Brand Name	Applicant Company	Approval Date	Other Information
SARS-CoV-2 nucleic acid kit	2019-nCoV Fluorescence Detection Real-time RT-PCR Kitv	Sysmex Corporation	March 27, 2020	
SARS-CoV-2 nucleic acid kit	Loopamp Novel Coronavirus 2019 (SARS-CoV-2) Detection Kit	Eiken Chemical Co., Ltd.	March 31, 2020	
SARS-CoV-2 nucleic acid kit	cobas SARS-CoV-2	Roche Diagnostics K.K.	April 7, 2020	
SARS-CoV-2 nucleic acid kit	TaqPath Real Time PCR Reagent Kit for SARS-CoV-2	Life Technologies Japan Ltd.	April 20, 2020	
SARS-CoV-2 nucleic acid kit	Xpert® Xpress SARS-CoV-2 'Cepheid'	Beckman Coulter, Inc.	May 8, 2020	
SARS-CoV-2 antigen kit	ESPLINE SARS-CoV-2	Fujirebio Inc.	May 13, 2020	Review Summary 📄
SARS-CoV-2 nucleic acid kit	MEBRIGHT SARS-CoV-2 Kit	Medical & Biological Laboratories Co., Ltd.	May 21, 2020	

Mission

Conducting research studies (regulatory science) to accurately evaluate the quality, safety, and efficacy of pharmaceutical products, foods, and numerous chemicals in the living environment

Priority Researches

1. Enhancing the development of advanced medicines and medical devices

- Regenerative and cell medicine products, gene therapy products, highly modified antibody drugs, medium molecule peptide drugs, nucleic acid drugs, molecular target drugs, companion diagnostics, and radiopharmaceuticals
- New formulation/manufacturing technology and advanced quality control for continuous production, DDS, nanomedicine, and IoT
- Advancement of nonclinical test methods related to safety and efficacy evaluation for medical devices and medical materials
- Application of iPS cells for drug discovery and introduction to safety pharmacology
- Nonclinical and post-marketing evaluation method research corresponding to conditional early approval

2. Ensuring the safety of food, chemical, and living environment

- Assessing the safety of foods, food additives, food utensils, containers, and packaging by considering an increase in international food distribution
- Research on prediction/evaluation and management based on food risk analysis
- Food allergy research in which sensitization pathways are diversified
- Health risk assessment of chemical substances such as indoor air and household products and elucidation of the cause of pollution accidents
- Modernization of nonclinical safety test methods and development of animal replacement methods aiming at improving predictability in humans
- Enhancement and strengthening of various safety databases using ICT
- Development of the toxicity test method for the next generation

3. Supporting indispensable tests and inspections for health crisis management

- Testing and inspection as an Official Medicines Control Laboratories (OMCL) accompanying the internationalization of pharmaceutical GMP
- Tests and inspections to ensure the quality of generic drugs
- International standardization of Kampo preparations
- Structural analysis, structural-activity correlation analysis, analysis method, and database creation for countermeasures against dangerous drugs and illegal pharmaceutical products
- Response to food terrorism
- Response to widespread food poisoning
- Monitoring of radioactive contamination of food
- Monitoring residual pesticides in food
- Participation in compiling a compendial

4. Integrated research in the fields of pharmaceuticals, foods, and chemicals

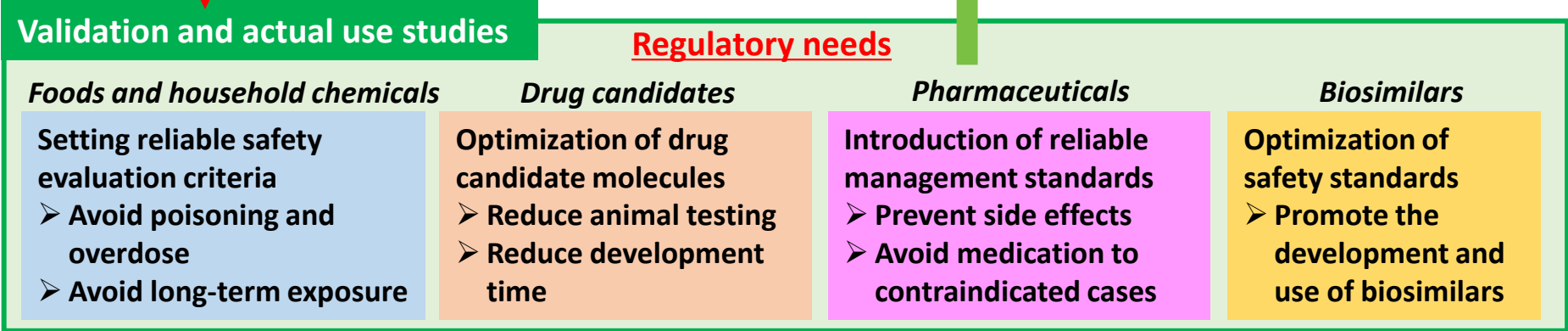
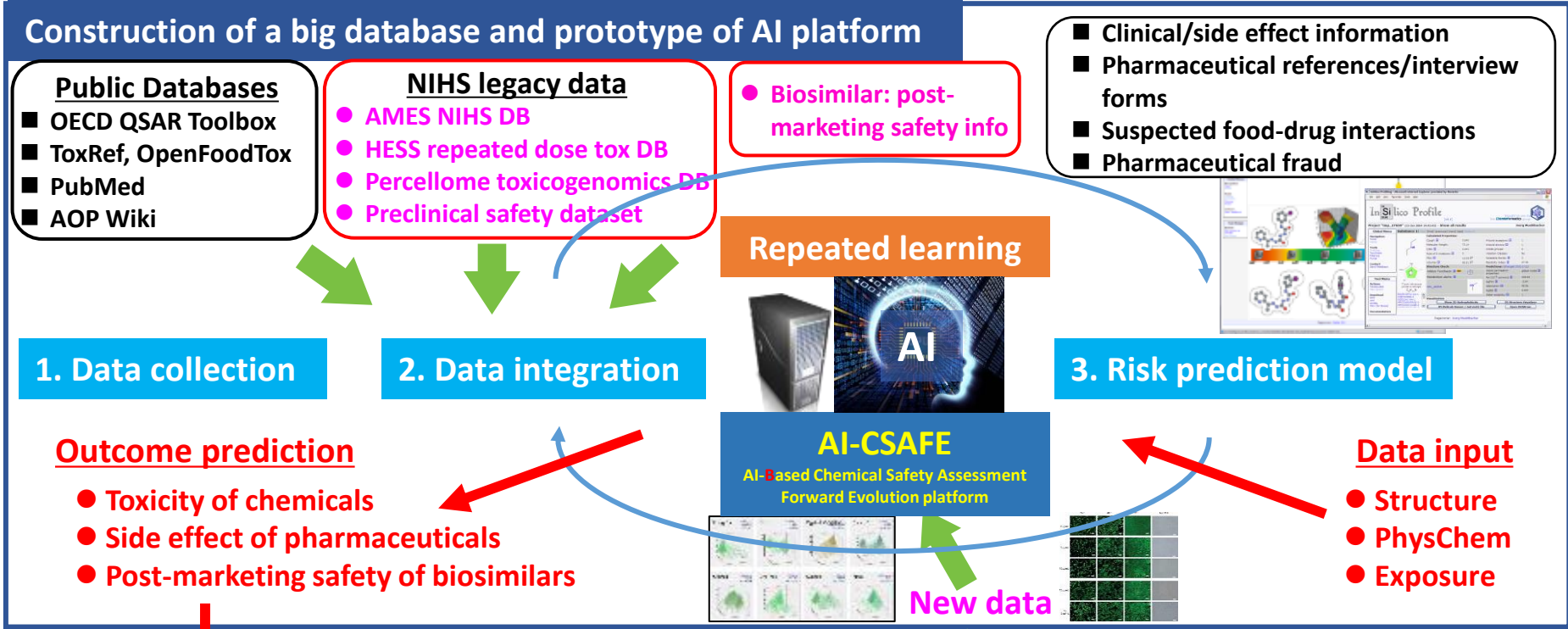
- Construction of the chemical safety big database and development of basic technology for predicting human safety of pharmaceuticals, foods, and chemicals using AI
- Research for social implementation of genome editing technology

Emerging Technologies Applied to Regulatory Science Research in NIHS

- ***In silico*/Deep learning/Artificial Intelligence (AI)**
- **OMICS; Toxicogenomics Technology**
- **Microphysiological System (MPS)/Body-on-Chip**
- **Desorption Electrospray Ionization-Mass Spectrometry (DESI-MS)**
- MRI for Animal Study
- Quantitative-NMR
- Atomic Force Microscopy (AFM)
- Next-Gen Sequencing (NGS)
- Cryo-Electron Microscopy
- iPS Cells
- Genome Editing Technology; CRISPR-Cas9



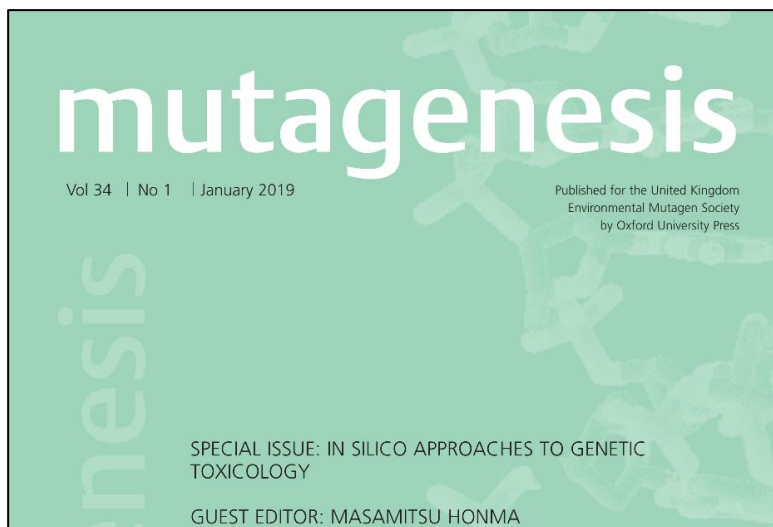
Development of chemical safety big database and AI-platform to support human safety assessment of pharmaceuticals, foods, and household chemicals



AMES/QSAR/AI International Challenge Project



Outcome of the 1st Project (-2017)



Mutagenesis 2019, 34, 3-16
doi:10.1093/mutage/gjz031
Original Manuscript

OXFORD
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Original Manuscript

Improvement of quantitative structure–activity relationship (QSAR) tools for predicting Ames mutagenicity: outcomes of the Ames/QSAR International Challenge Project

Masamitsu Honma*, Airi Kitazawa, Alex Cayley¹, Richard V. Williams¹, Chris Barber¹, Thierry Hanser¹, Roustem Saiakhov², Suman Chakravarti², Glenn J. Myatt³, Kevin P. Cross⁴, Emilio Benfenati⁴, Giuseppa Raitano⁴, Ovanas Mekenyan⁵, Petko Petkov⁶, Cecilia Bossa⁶, Romualdo Benigni^{6,7}, Chiara Laura Battistelli⁸, Alessandro Giuliani⁸, Olga Tcheremenskaia⁸, Christine DeMeo⁹, Ulf Norinder^{9,10}, Hiromi Koga¹¹, Ciloy Jose¹¹, Nina Jeliiazkova¹², Nikolay Kochev^{12,13}, Vesselina Paskaleva¹³, Chihae Yang¹⁴, Pankaj R. Daga¹⁵, Robert D. Clark¹⁵ and James Rathman^{14,16}

Division of Genetics and Mutagenesis, National Institute of Health Sciences, 3-25-26 Tononouchi, Kawasaki-ku, Kanagawa 210-9501, Japan, ¹Lhasa Limited, Granary Wharf House, 2 Canal Wharf, Leeds, LS11 5PS, UK, ²MultiCASE Inc., 23811 Chagrin Blvd Ste 305, Beachwood, OH 44122, USA, ³Leadscope, Inc., 1393 Dublin Road, Columbus, OH 43215, USA, ⁴Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Via G. Le Mura 159, Milano, Italy, ⁵Laboratory of Mathematical Chemistry, As. Zlatarov University, Bourgas, Bulgaria, ⁶Istituto Superiore di Sanita', Viale Regina Elena, 299 00161 Rome, Italy, ⁷Alpha-Pretox, Via G. Pascoli 1, 00184 Rome, Italy, ⁸Prous Institute, Rambla de Catalunya, 135, 3-2, Barcelona 08008, Spain, ⁹Svetox, Karolinska Institutet, Unit of Toxicology Sciences, Söderlärje 15136, Sweden, ¹⁰Department of Computer and Systems Sciences, Stockholm University, Box 7003, SE-164 07 Kista, Sweden, ¹¹Fujitsu Kyushu Systems Limited, 1-5-13 Higashihiru, Hakata-ku, Fukuoka 812-0007, Japan, ¹²IdeaConsult Ltd., 4 A. Kanchev str., Sofia 1000, Bulgaria, ¹³Department of Analytical Chemistry and Computer Chemistry, University of Plovdiv, 24 Tsar Assen St., Plovdiv 4000, Bulgaria, ¹⁴Molecular Networks GmbH and Altamira LLC, Neumeyerstrasse 28 90411 Nürnberg, Germany and 1455 Candlewood Drive, Columbus, OH 43225, USA, ¹⁵Simulations Plus, Inc., 42505 10th Street West Lancaster, CA 93534, USA and ¹⁶Chemical and Biomolecular Engineering, The Ohio State University, 151 W. Woodruff Ave. Columbus, OH 43210, USA

*To whom correspondence should be addressed. Division of Genetics and Mutagenesis, National Institute of Health Sciences, 3-25-26 Tononouchi, Kawasaki-ku, Kanagawa 210-9501, Japan. Tel: +81-44-270-6072; Fax: +81-44-270-6680; Email: honma@nihs.go.jp

Participants of the 2nd Project to improve QSARs and develop AIs to predict mutagenicity of chemicals substances (2020-)

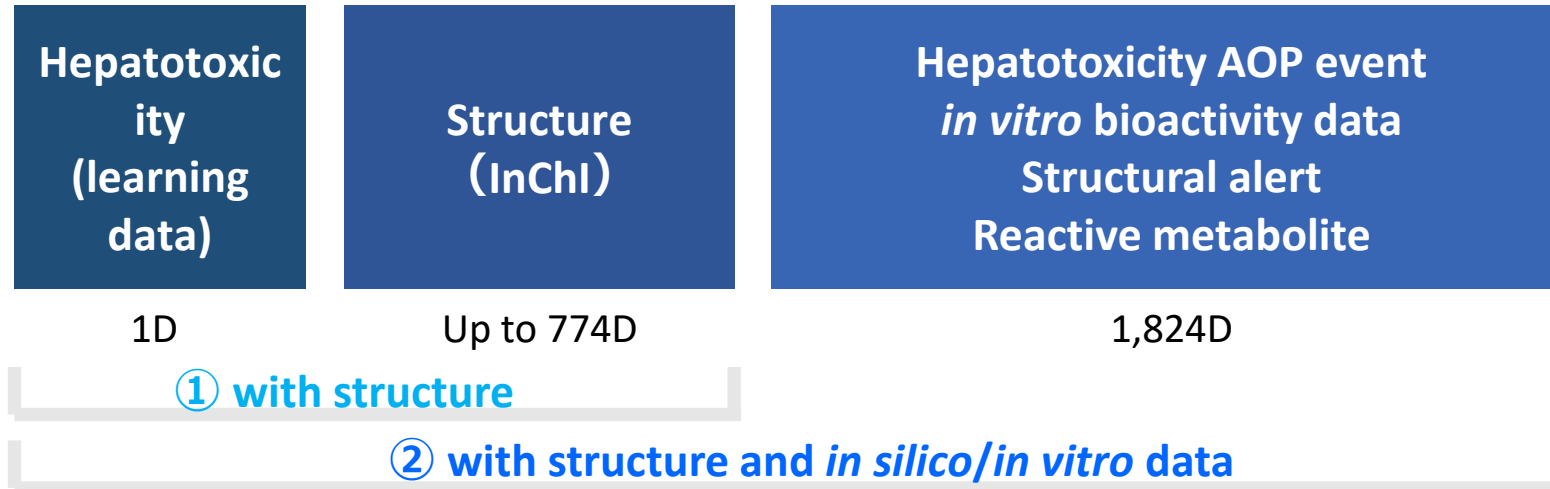
1. Shanghai Institute of Organic Chemistry China
2. Altox Ltd. Brazil
3. The Ohio State University USA
4. Leadscope, Inc. USA
5. Institute di Ricerche Farmacologiche Italy
6. IdeaConsult Ltd. Bulgaria
7. MultiCASE Inc. USA
8. Lhasa Limited UK
9. Istituto Superiore di Sanita Italy
10. Gifu University Japan
11. Massachusetts Institute of Technology USA
12. Simulations Plus, Inc USA
13. Chemotargets Spain
14. Bourgas University Bulgaria
15. The University of Sydney Australia
16. Meiji Pharmaceutical University Japan
17. Liverpool John Moores University UK
18. National Institute of Health Sciences Japan

http://www.nihs.go.jp/dgm/2nd_amesqsar.html



Hepatotoxicity Prediction Model and Literature Search Tool to Support Safety Assessment

(A) Hepatotoxicity model



(B) Literature search

Positive example

- 1 A maximum contaminant level for barium in drinking water has been set at 1 mg/L. This study examines for the first time, whether there are significant
- 2 Barium-containing overhead sootblowers are commonly used in metallurgical studies. On May 22, 2003, these sootblowers at a refinery plant in Olean, New York,
- 3 Acute barium salt poisoning may cause acute hypokalemia and result in respiratory paralysis and ventricular tachycardia/fibrillation. The early recognition of
- 4 Barium Chloride dihydrate (BaCl2.2H2O) was given for 92 days to B6C3F1 mice and Fisher 344/N rats in their drinking water at levels of 0, 125, 500,
- 5 Physicians, familiar with the common usage of barium medicinally as the contrast agent barium sulfate, may consider it an innocuous or at most a mild
- 6 For certain metal arc welding and other metal processing operations, compounds of barium are used as flux components. An osmium furnace generated f
- 7 We report in case of severe hypokalemia and focal muscle paralysis following a suicide attempt involving the calcium channel blocker verapamil.
- 8 Acute toxic cardioplegia due to barium carbonate (not poison) poisoning is described in two young patients. These cases very closely resembled Guillain
- 9 This study was conducted to determine how the bioavailability of a low concentration of barium (Ba) in drinking water is affected by the anion. Male S
- 10 Barium chloride dihydrate, a white crystalline granule or powder, is used in pigments, aluminum refining, leather tanning, and coloring, the manufacture
- 11 Because of the pioneering vision of certain leaders in the biomedical field, the last two decades witnessed rapid advances in the area of chemical mix
- 12 Because high barium concentrations (2-10 ppm) in human drinking water have been reported to be associated with elevated cardiovascular mortality,
- 13 Four men who resided in Scotland and who developed neurocysticercosis are described. These developed progressive massive fibrosis, from which
- 14 Long-term retention of 133Ba in the trachea from intratracheally administered BaSO4 particles was determined by both serial sacrifice and external sc
- 15 Groups of young adult rats of both sexes were exposed to 0, 10, 50, or 250 mg/liter (ppm) of barium as barium chloride in drinking water for 4, 8, or 13
- 16 A 19-year-old girl presented with a severe cardiac dysrhythmia after having ingested an unknown chemical. Lidocaine therapy improved the dysrhythm
- 17 A case of delirium overdone of barium sulphate in a psychiatric setting is presented, with resulting flaccid paralysis, malignant arrhythmia, resp arrest
- 18 The zero-mark case method has been proposed as an alternative to the no-observed adverse effect level (NOAEL) approach for assessing risk in c
- 19 Barium is an alkaline earth metal which has a variety of uses including in the manufacturing industry and in medicine. However, adverse health effects
- 20 Throughout the last 50 years, the paradigm for carcinogenicity assessment has depended on lifetime bioassays in rodents. Since 1997, the Internatio

Abstract of papers cited in international risk assessment reports

Negative example

Advances in asthma and allergic disease genetics: Is bigger always better?

Nathan Schachter, MD, PhD,* Elio Rodriguez, PhD,† Stephan Weidinger, MD,* and Carole Ober, MD* Chicago, IL and Kiel, Germany

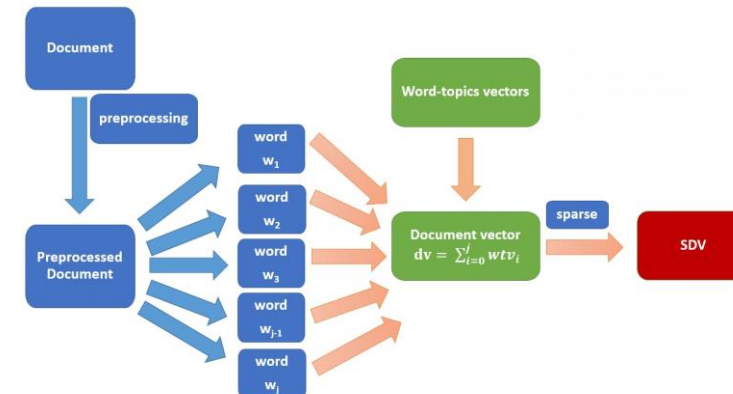
This review focuses on genome-wide association studies (GWAS) of asthma and allergic diseases published between January 1, 2018, and June 30, 2019. During this time period, there were 38 GWAS reported in 39 articles, including the largest performed to date for many of these conditions. Overall, we found that childhood-onset asthma is associated with the most independent loci compared with other defined groups of asthma and allergic disease cases, although asthma and moderate-to-severe asthma are associated with fewer genes, which are largely a subset of those associated with childhood-onset asthma. There is significant genetic overlap between asthma and allergic diseases, particularly with respect to childhood-onset asthma, which involves genes that reflect the importance of barrier function biology, and to HLA region genes, which are the most frequently associated genes overall in both groups of diseases. Although the largest GWAS in African American and Latino/Latina populations were reported during this period, they are still significantly underpowered compared with studies reported in populations of European ancestry, highlighting the need for larger studies, particularly in patients with childhood-onset asthma and allergic diseases, in these important populations that carry the greatest burden of disease. (J Allergy Clin Immunol 2019;144:1495-506.)

Key words: asthma, allergic disease, genetics

The past 18 months have witnessed tremendous strides in our understanding of the genetic architecture of asthma and allergic diseases. These advances are primarily the result of increasingly large genome-wide association studies (GWAS) that have

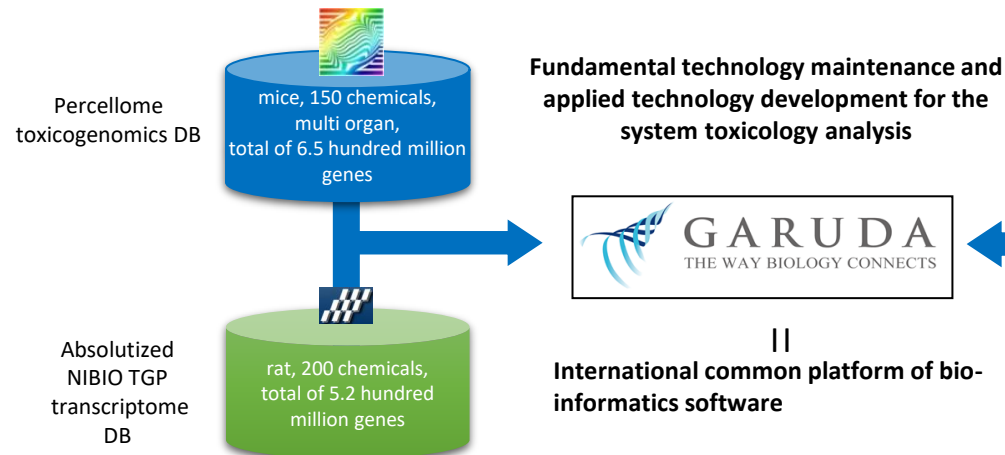
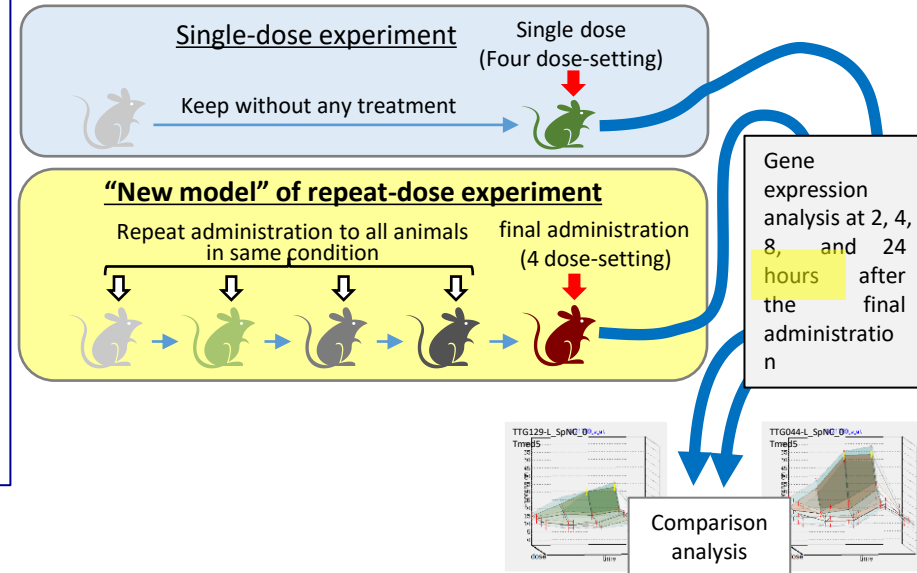
OVERVIEW OF LESSONS LEARNED: BIGGER IS NOT ALWAYS BETTER

The concept of using large sample sizes for genetic studies that "bigger is better" is based on the realization early on that genetic variants conferring risk for asthma and allergic diseases have small effects and therefore will be detected only in very large samples. Moreover, because of the substantial multiple testing burden in genome-wide studies, large sample sizes are needed to obtain P values that meet the criteria for genome-wide significance (typically at $P < 5 \times 10^{-8}$). Although it is generally true that bigger is better, the quest for larger and larger samples is a double-edged sword, with tradeoffs between gains of power caused by larger samples and loss of power caused by increased clinical, environmental, and genetic heterogeneity among cases, an inherent feature of very large samples. These tradeoffs are well illustrated by the GWAS of asthma and allergic diseases published over the period covered in this review.



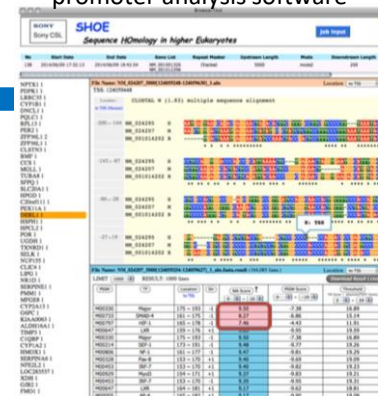
Toxicogenomics Study (Percellome project)

- **Prediction of repeated-dose toxicity from the existing data of single-dose experiments**
 - ✓ **Noncoding RNA expression analysis** of repeated-dose mice's liver
 - ✓ **Analysis of epigenetic mechanism**
genome DNA methylation analysis of repeated-dose mice's liver
- **Integration with the rat transcriptome data of NIBIO Toxicogenomics Project**
- **"Open Data" service of the Percellome DB and International common platform of bio-informatics software**

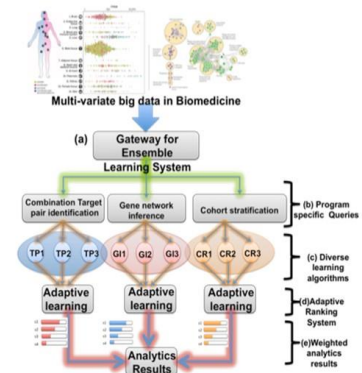


Joint research with bioinformatics research group

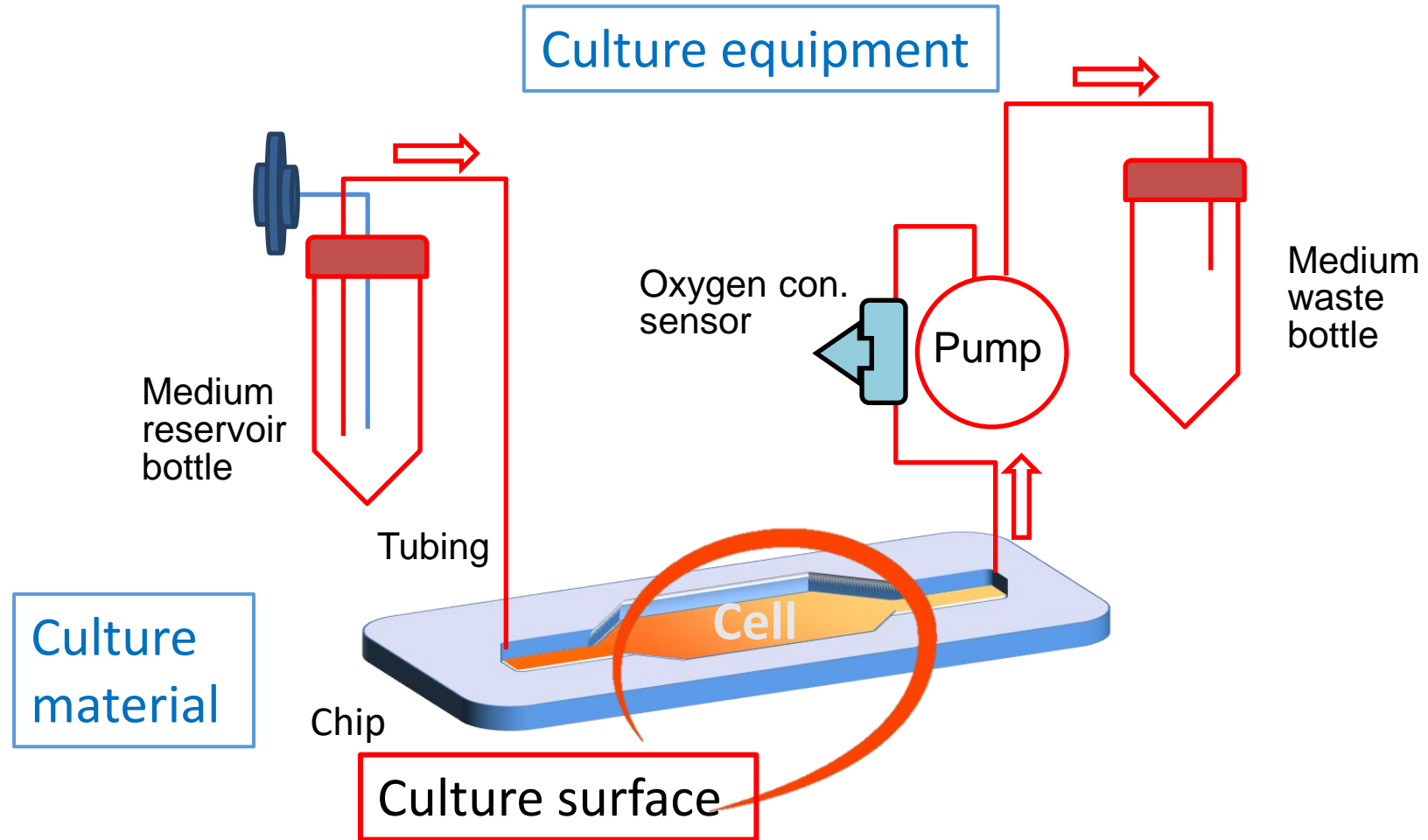
In-house development of promoter analysis software



Apply machine-learning technology

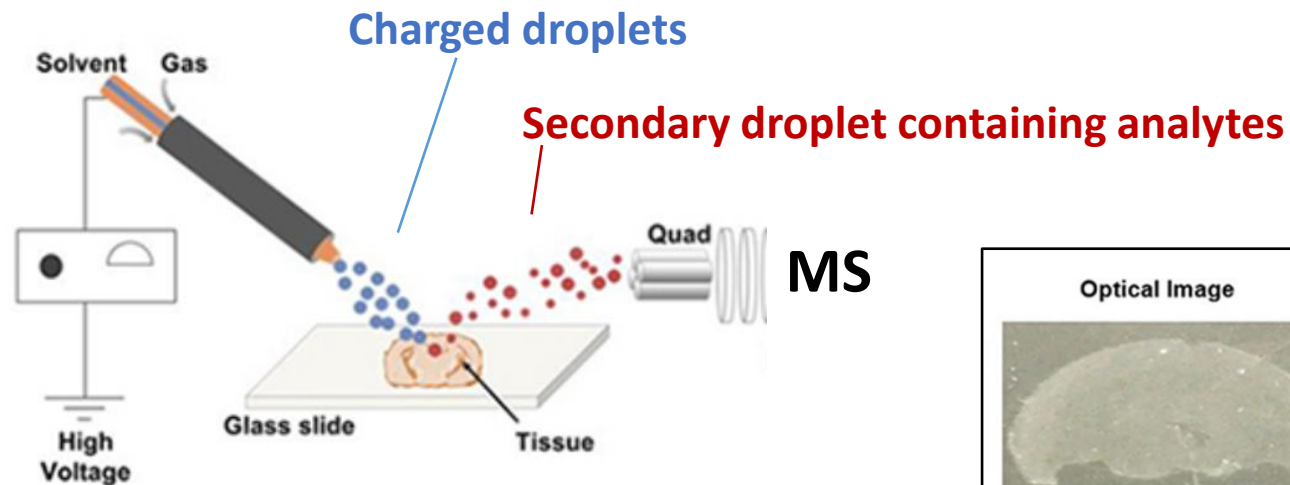


Microphysiological System (MPS): Body-on-a-Chip

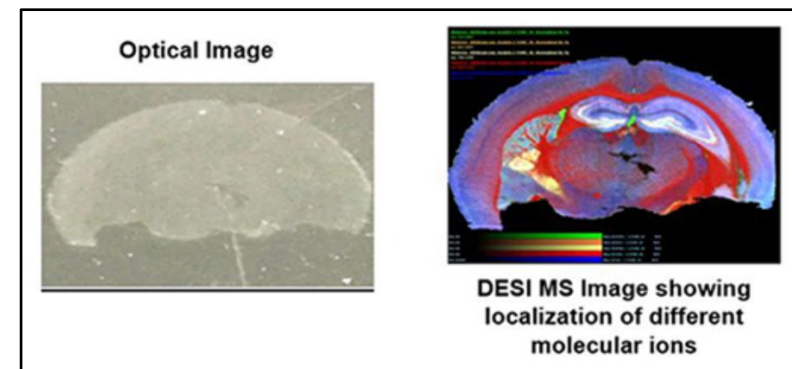


Desorption Electrospray Ionization-Mass Spectrometry (DESI-MS)

- Qualitative and quantitative research method
- Ambient analysis technique to visualize the spatial localization and distribution of molecules without sample preparation
- Compatible with histopathological workflows such as H&E staining



https://www.waters.com/waters/ja_



NIHS's Response to the COVID-19 Pandemic

■ Supporting the development of COVID-19 drugs

- Study on safe and effective inhalation method for pulmonary inhalation drugs

■ Ensuring reliability of *in vitro* diagnostics for the COVID-19 infection

- Development of a PCR primer crossing analysis system for COVID-19 diagnostics
 - <http://www.nihs.go.jp/mtgt/covid-19info.html>
- Validation of performance of COVID-19 PCR diagnostic kits
- Validation of performance of COVID-19 antibody diagnostic agents
- Supply of positive controls for COVID-19 antibody diagnosis and standardization

■ Dissemination of scientific information on the COVID-19 pandemic (pharmaceuticals, diagnostics, and foods)

- <https://www.nihs.go.jp/sars-cov-2/index.html>



Summary

- **Regulatory science contributes to newly developed prevention, diagnosis, and treatment for diseases and establishes a system that can lead the results to practical use of pharmaceuticals and medical devices as soon as possible, which promotes life innovation (realization of a healthy and long-lived society by creating innovative medicines and medical devices originating in Japan).**
- **PMDA established the “Regulatory Science Centre” expecting it to play a central role in the incorporation of innovation into the regulatory system.**
- **PMDA identifies emerging technologies at a very early stage and properly evaluates whether they are effective in product development (Horizon Scanning).**
- **NIHS develops and maintains guidelines for the evaluation and development/examination of efficacy/safety of pharmaceuticals, medical devices, and regenerative medicine products and conducts research related to them based on regulatory science.**
- **NIHS incorporates emerging technologies to scientifically accurately assess the quality, safety, and efficacy of the effects of drugs, foods, and chemicals on humans.**
- **PMDA and NIHS are currently working on solving the COVID-19 pandemic, supporting the development of therapeutic drugs and medical devices, improving diagnostic technology, and disseminating scientific information on COVID-19.**

Thank you for your attention !!



<http://www.nihs.go.jp>

