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Abstract

Asian Congress 2016 Co-Chairs Greeting

The Asian Congress on Alternatives and Animal Use in the Life Sciences (Asian Congress) 2016 is being organized by the Japanese Society for Alternatives to Animal Experiments (JSAAE) with the cooperation of the Alternatives Congress Trust (ACT), and the Organizing Committee is currently making preparations to begin registering participants from China, India, Japan, and Korea. The Asian Congress is scheduled to be held in November, 2016, at venues in the cities of Karatsu, Saga, and Fukuoka, Japan. The opening session will be held in Karatsu, followed by four days of scientific sessions and plenary lectures in Saga, and a closing session in Fukuoka, that will include the 29th JSAAE annual meeting and poster sessions focusing on Reduction, Refinement and Replacement (the Three Rs) of animal experiments.

The Asian Congress will be the first conference of its kind for researchers from Asia, and will afford an opportunity for promoting alternative methods to researchers in these places, where the concept of the Three Rs is just now achieving penetration. The Asian Congress is intended to achieve multiple missions, which will include disseminating information not just on the latest advances in including pure sciences but on practical applications of the Three Rs worldwide.

Co-Chair: **Hajime KOJIMA** (National Institute of Health Sciences)
Co-Chair: **Shigehiro OHDO** (Kyushu University)

Asian Congress 2016 Organizing committee:

Hajime KOJIMA (NIHS: co-chair)

Shigehiro OHDO (Kyushu Univ.: co-chair)

Satoru KOYANAGI (Kyushu Univ.)

Yasuyuki SAKAI (Tokyo Univ.)

Takaharu OGIWARA (Japan Cosmetic Center)

Shigehisa AOKI (Saga Univ.)

Hiroyuki MIYAZAKI (Japan Bio Products)

Asian Congress Program committee:

Hiroshi YAMAMOTO (Toyama Univ.: Chair)

Tsutomu Miki KUROSAWA (Kagoshima Univ.)

Eui-Bae JEUNG (Chungbuk National Univ., Korea)

Jufeng WANG (Pharmaron, China)

Muhammad Abdul Kader AKBARSHA (Bharathidasan Univ., India)

Troy SEIDLE (HSI, Canada)

Asian Congress Outline

Registration Fee:

Category	Advanced Registration	
	Early Bird	**Standard**
	Jun. 1st (Wed)～Jul. 31st (Sun), 2016	Aug. 1st (Mon)～Oct. 10th (Mon), 2016
Overseas	JPY25,000	JPY30,000

JPY: Japanese Yen

Registration Fee Includes:

- Admission to all sessions of both "Asian Congress 2016" & "the 29th JSAAE annual meeting".
- Printed Material (Program & Abstract Book)
- Coffee Breaks and Luncheon Seminars
- Welcome Party on November 15th (Tue)
- Gala Dinner on November 17th (Thu)

Social Program:

Welcome Dinner

Date : November 15th (Tue)
Time : 18:30-20:00
Venue : Nagasaki-sou
(ref. in Japanese only » http://nagasakisou.com/facility.php)

Gala Dinner

Date : November 17th (Thu)
Time : 19:00-21:00
Venue : Granada Suite
(ref. in Japanese only » http://www.granadasuite.com/fukuoka)

Joint Meeting

"The 29th JSAAE Annual Meeting"
Period : November 16 – 18, 2016
Venue : Kyushu University Centennial Hall
Organizer : Japanese Society for Alternatives to Animal Experiments (JSAAE)
President : Shigehiro OHDO (Kyushu University)

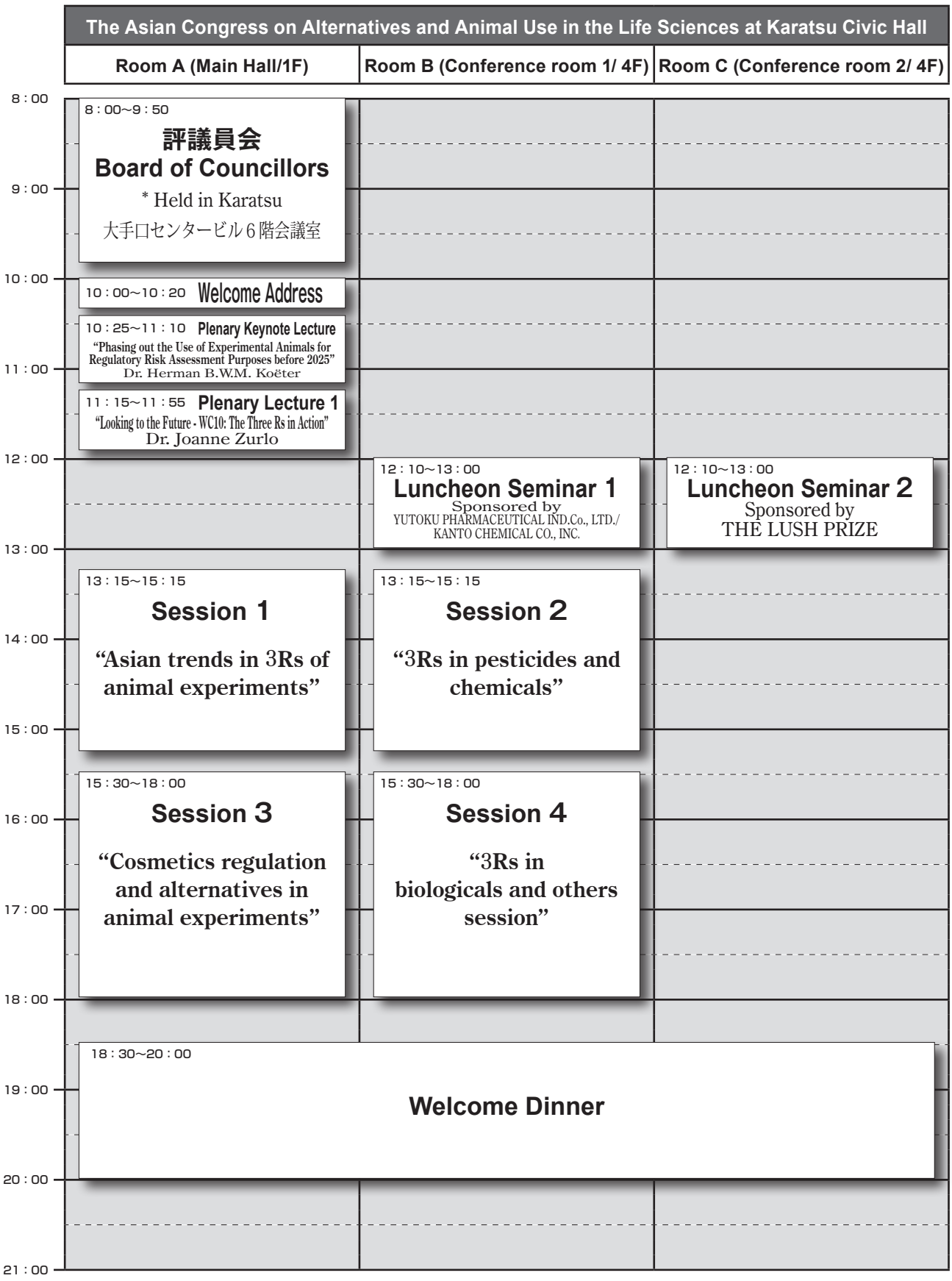
Social Tour

Date : November 16th (Wed)
Time : 12:00-17:00
Schedule : Karatsu Civic Hall ～ Karatsu City Sight-Seeing ～ Fukuoka

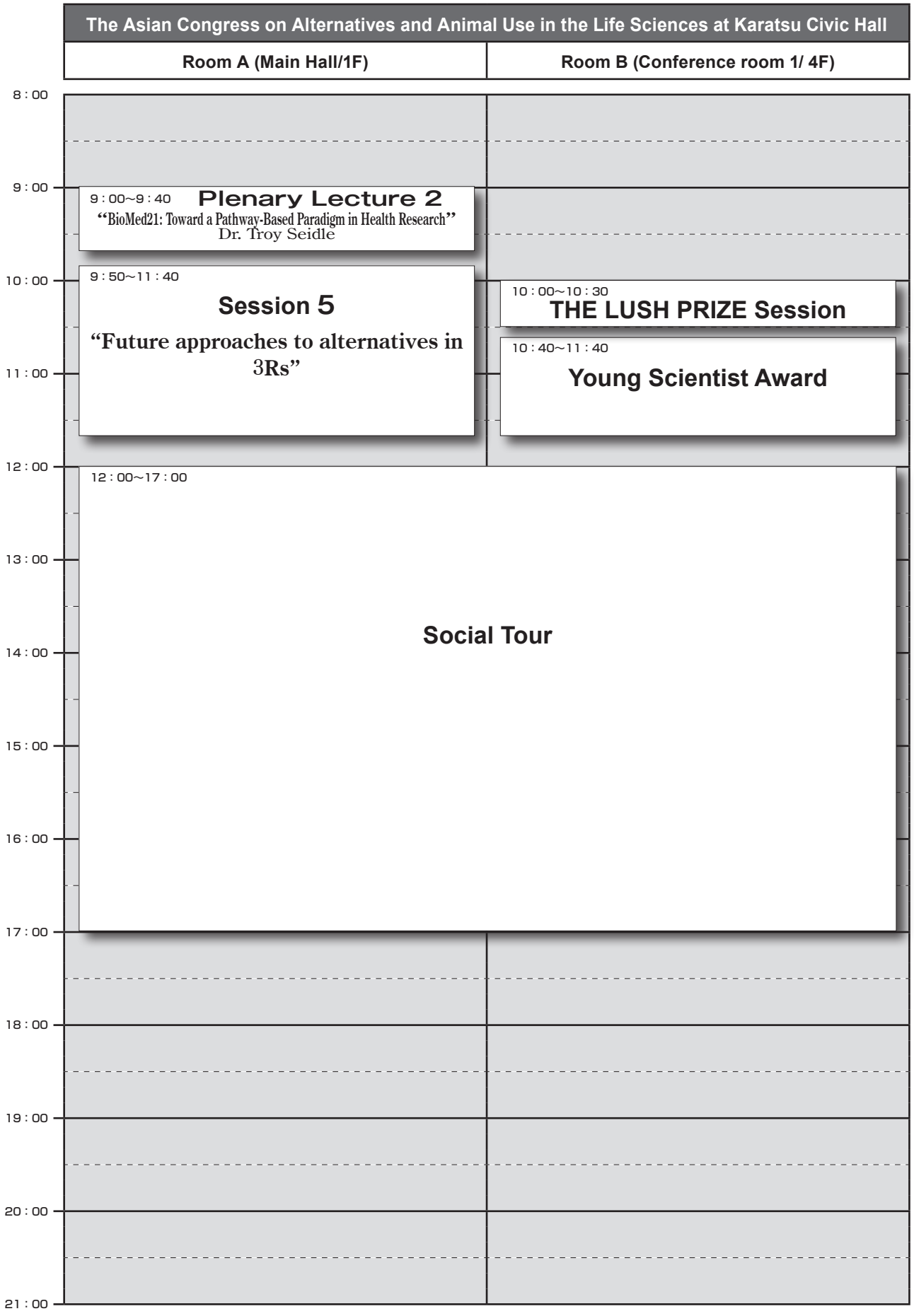
Time Schedule at a Glance

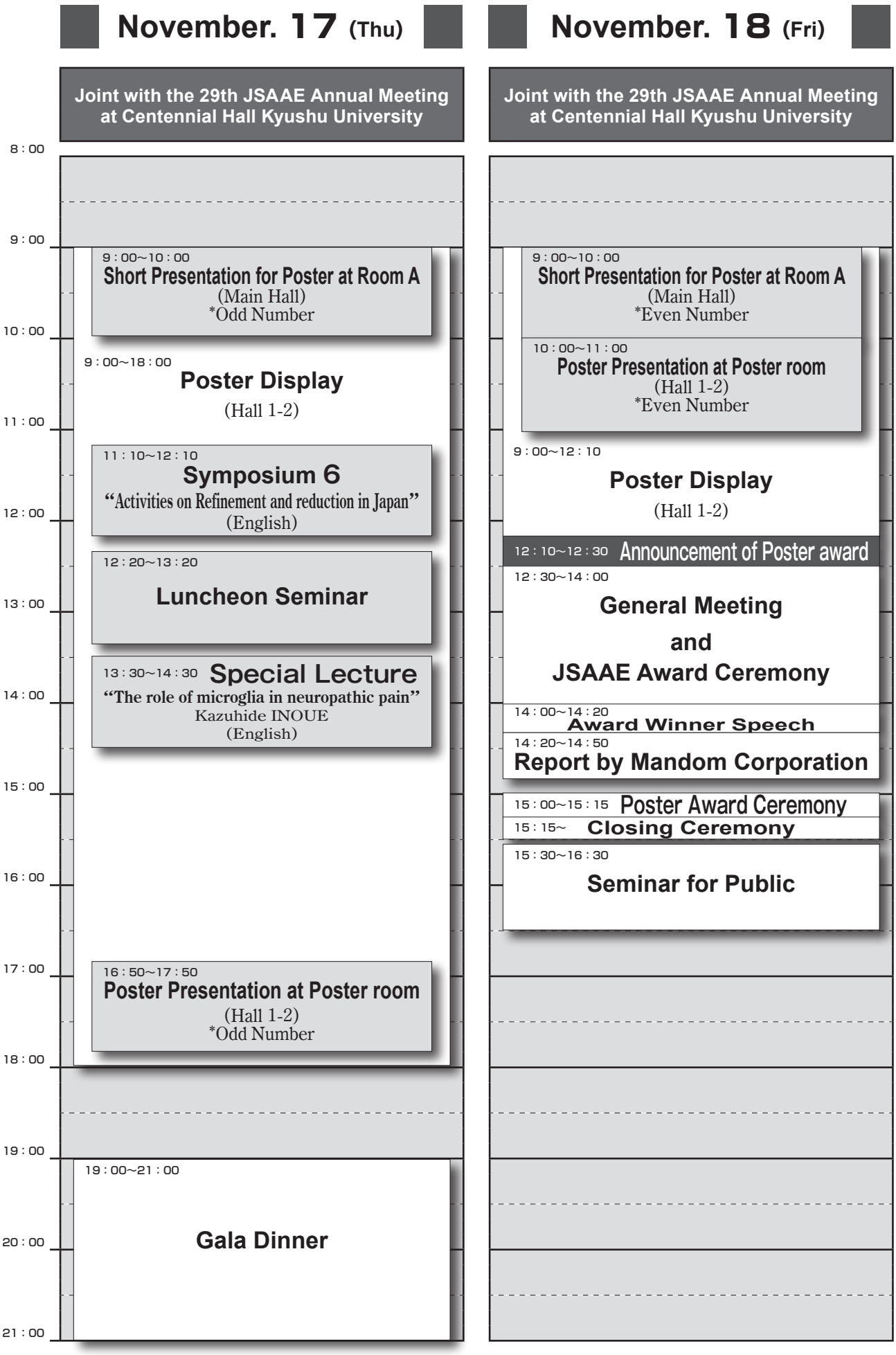
The Asian Congress on Alternatives and Animal Use in the Life Sciences, Karatsu, Saga, JAPAN

November. 15 (Tue)



November. 16 (Web)

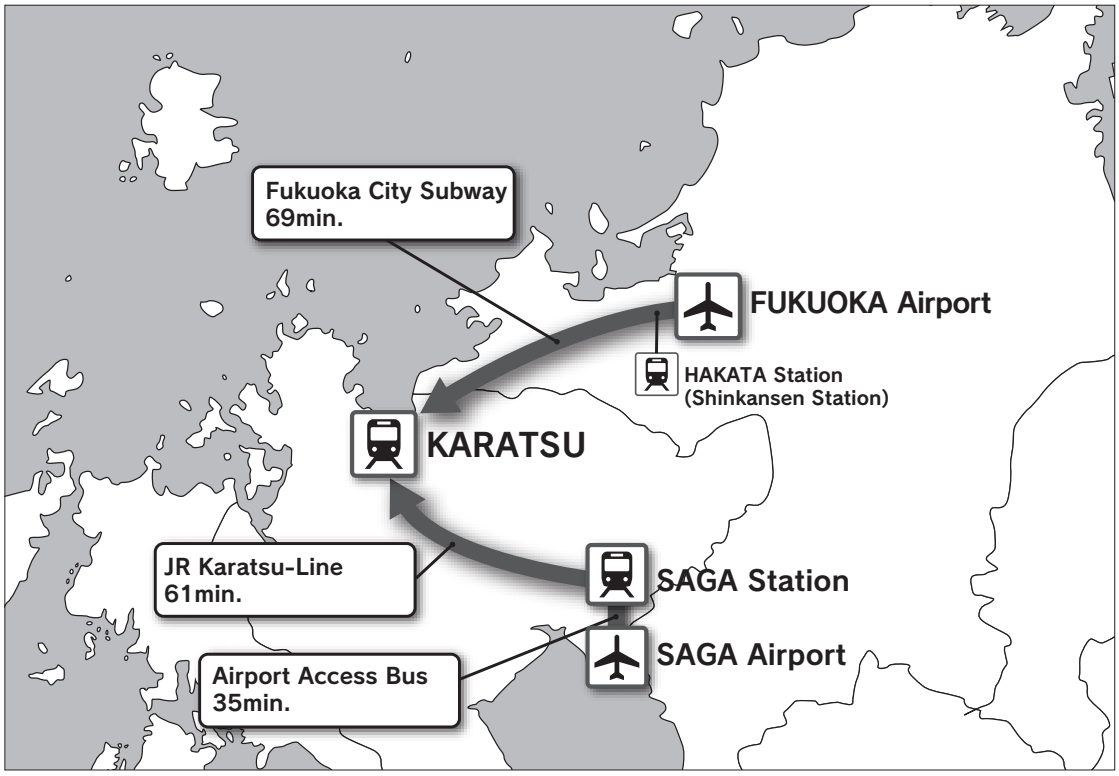



November. 17 (Thu)
November. 18 (Fri)
Joint with the 29th JSAAE Annual Meeting at Centennial Hall Kyushu University
Joint with the 29th JSAAE Annual Meeting at Centennial Hall Kyushu University
8 : 00
9 : 00
10 : 00
11 : 00
12 : 00
13 : 00
14 : 00
15 : 00
16 : 00
17 : 00
18 : 00
19 : 00
20 : 00
21 : 00
9 : 00～10 : 00
Short Presentation for Poster at Room A
(Main Hall)
*Odd Number
9 : 00～18 : 00
Poster Display
(Hall 1-2)
11 : 10～12 : 10
Symposium 6
"Activities on Refinement and reduction in Japan"
(English)
12 : 20～13 : 20
Luncheon Seminar
13 : 30～14 : 30 Special Lecture
"The role of microglia in neuropathic pain"
Kazuhide INOUE
(English)
16 : 50～17 : 50
Poster Presentation at Poster room
(Hall 1-2)
*Odd Number
19 : 00～21 : 00
Gala Dinner
9 : 00～10 : 00
Short Presentation for Poster at Room A
(Main Hall)
*Even Number
10 : 00～11 : 00
Poster Presentation at Poster room
(Hall 1-2)
*Even Number
9 : 00～12 : 10
Poster Display
(Hall 1-2)
12 : 10～12 : 30 Announcement of Poster award
12 : 30～14 : 00
General Meeting
and
JSAAE Award Ceremony
14 : 00～14 : 20
Award Winner Speech
14 : 20～14 : 50
Report by Mandom Corporation
15 : 00～15 : 15 Poster Award Ceremony
15 : 15～ Closing Ceremony
15 : 30～16 : 30
Seminar for Public

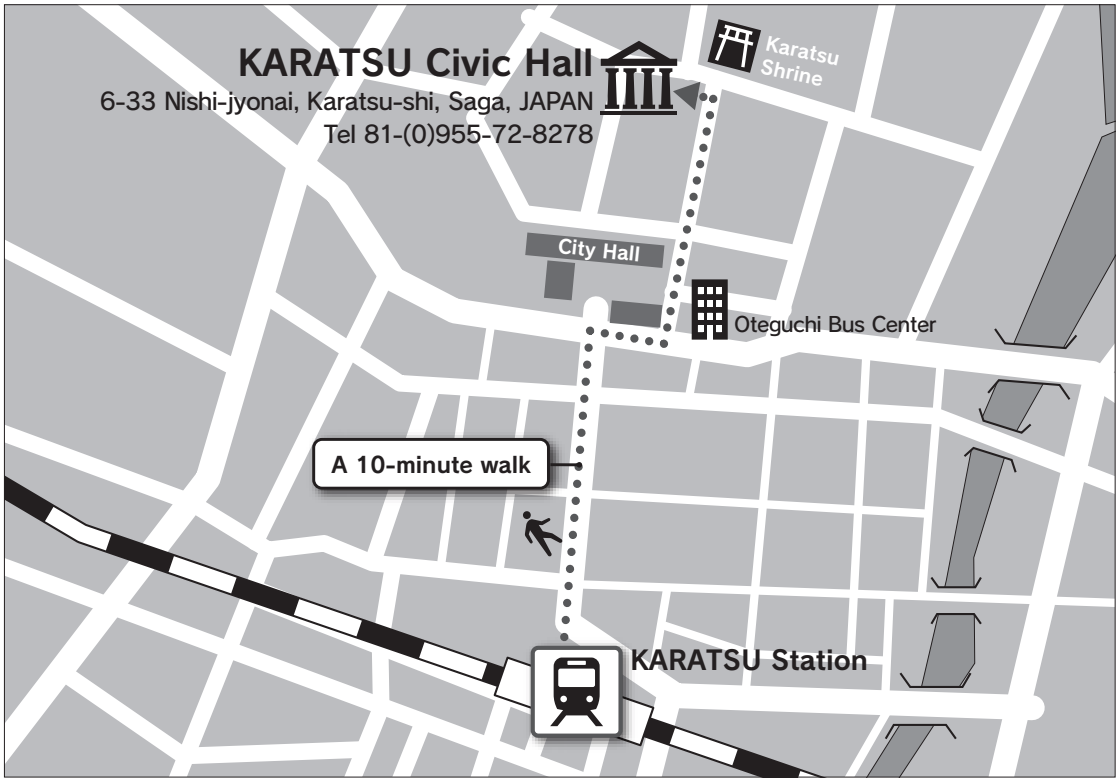
Asian Congress 2016 Access Information

Karatsu Civic Hall

■ From the Airport:

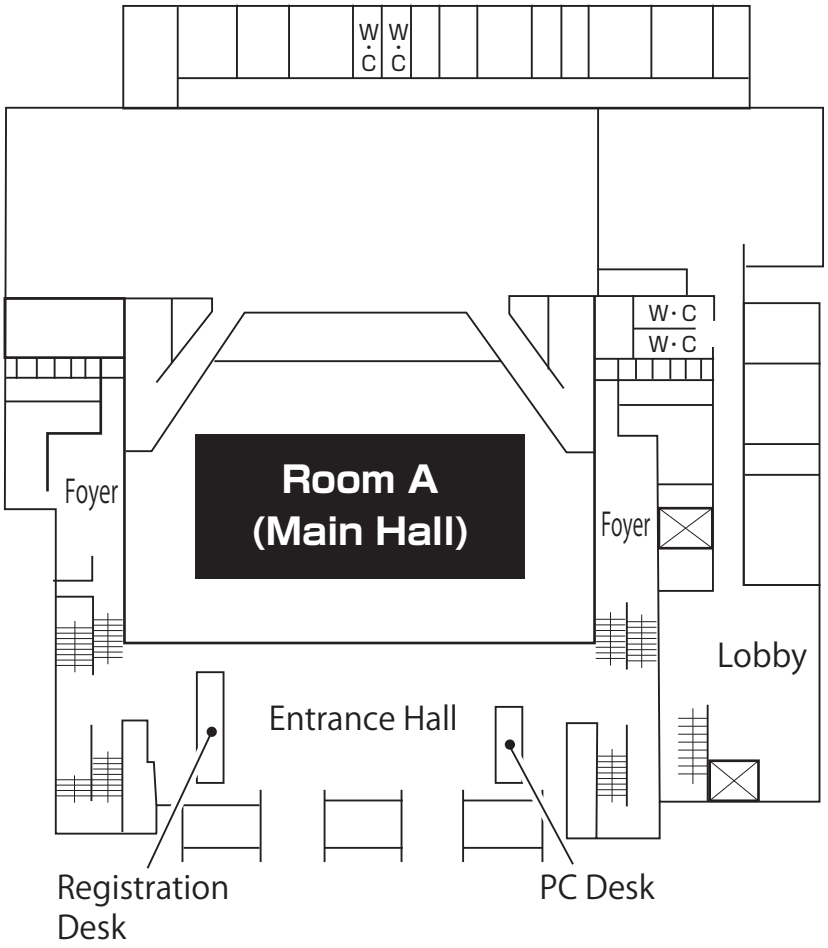


■ From the KARATSU Station:

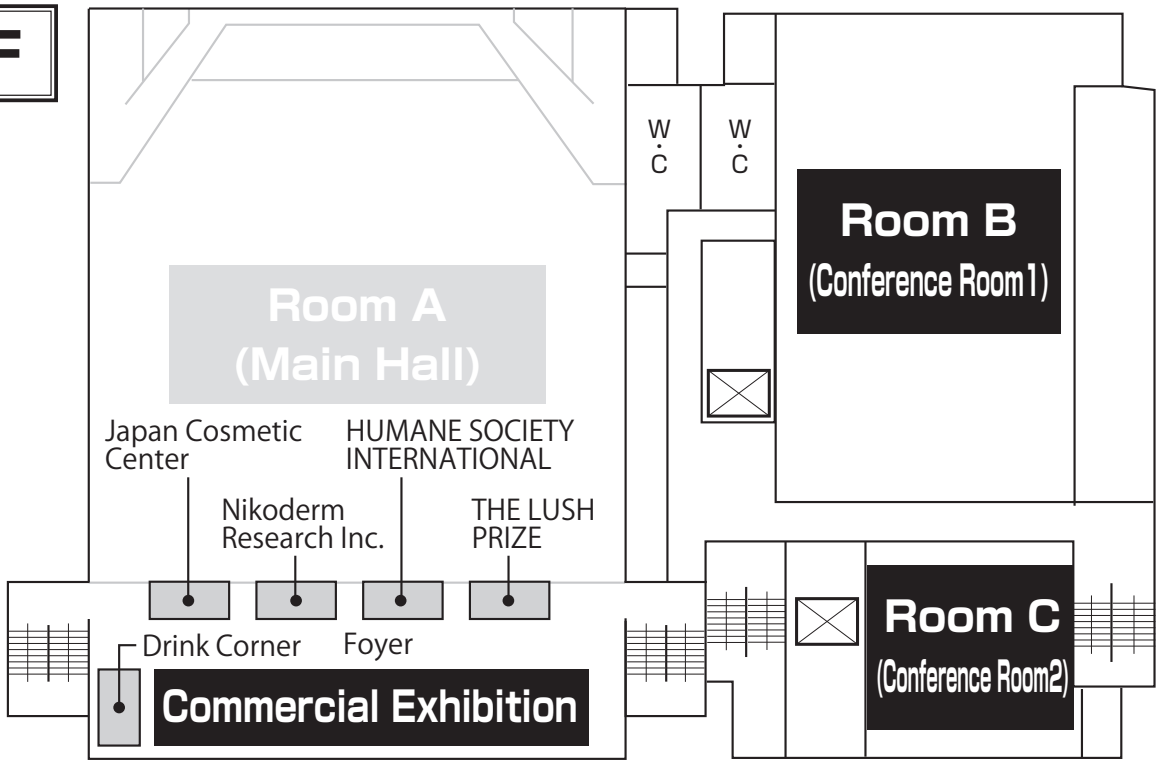


Floor Plan

1F



4F



Information for Participants

1. Registration / Information Desk

Place: 1F Entrance Hall, Karatsu Civic Hall
Date & Time: November 15 (Tue) 8:30 – 18:00
November 16 (Wed) 8:30 – 12:00

2. Advanced registrants

Please receive a Program & Abstract Book and a Name Card/Receipt at the Registration Desk on your arrival at Asian Congress 2016

3. Name Cards

All participants and exhibitors are required to wear their name cards displaying their name and affiliation during the congress and its social events.

4. Cloakroom

Place: 1F Information Desk, Karatsu Civic Hall
Date & Time: November 15 (Tue) 9:00 – 18:00
November 16 (Wed) 9:00 – 12:00
Note: Valuables and umbrellas will not be accepted.

5. PC Desk

Place: 1F Entrance Hall, Karatsu Civic Hall
Date & Time: November 15 (Tue) 9:00 – 17:00

6. Commercial Exhibition

Place: 4F Foyer
Date & Time: November 15 (Tue) 10:00 – 18:00
November 16 (Wed) 9:00 – 11:00
We are planning to hold a seal rally. All participants have a small gift, so please actively participate. The details will be announced at Exhibition sites and Information Desk.

7. Luncheon Seminars

Luncheon Seminars (with a lunch box): Take place at the lunchtime for Nov.15.
The Luncheon Seminars Tickets will be distributed based on the number of lunch boxes available. Please note that those who wish to have a lunch box need to obtain a Luncheon Seminars Ticket at the Ticket Counter below. If the Seminar Room has more seats than the number of Tickets distributed, you can attend the Luncheon Seminar without Tickets.

【Luncheon Seminar Ticket Counter】

Place: 1F Entrance Hall, Karatsu Civic Hall
Date & Time: November 15 (Tue) 9:00 – 10:30
* Tickets are distributed on the day of the seminars only.

* Tickets are limited to 1 ticket per person.
* Seats are limited, and it is first-come first-served basis. Please note that the Ticket Counter will be closed when all the seats are taken.
* Please note that the ticket will become invalid after 10 min. past of the seminar starting time.

8. Coffee and Tea Service

Place:	4F Foyer, Karatsu Civic Hall	
Date & Time:	November 15 (Tue)	10:00 – 17:00
	November 16 (Wed)	9:00 – 11:00

9. Break Room

Place:	Room B (4F Conference Room 2), Karatsu Civic Hall	
Date & Time:	November 15 (Tue)	13:30 – 18:00
	November 16 (Wed)	9:00 – 11:40

10. Free Wi-Fi

Free Wi-Fi is available. Details on access is to be announced at congress venue.

11. Emergency Contact Service

There will be no paging service available within the venue.

12. At the Congress Venue

- It is prohibited to record or film any portion of proceedings or inside the venue, without prior permission.
- Please turn off your mobile phone, or set it on silent /mute inside the venue.
- All areas in the congress venue are strictly non-smoking. Please smoke in the designated smoking areas only.

Information for Chairpersons and Speakers

To All Chairpersons

- Please come to see "Chairpersons/Speakers Desk" in Entrance Hall. We will provide you congress kits including a name card and Program & Abstract.
- Please be seated in the next chairperson's seat at latest 15 min. prior to the beginning of your session.
- Kindly be sure on session time schedule. We appreciate your corporation in organizing session schedule on time.

To All Speakers

- Please come to see "Chairpersons/Speakers Desk" in Entrance Hall. We will provide you congress kits including a name card and Program & Abstract.
- Please complete previewing presentation data at latest one hour prior to the beginning of your presentation at PC Desk on 1st Floor.

  [PC Desk operation hours and place]

  Place: 1F Entrance Hall, Karatsu Civic Hall

  Date & Time: November 15 (Tue) 9:00 – 17:00
- Please be seated in next presenter's seat at latest 15 minutes before your presentation time.
- The only equipment provided for presentation will be a PC projector. There will be no other projectors such as an overhead projector.
- During your presentation, you can forward your presentation slide by yourself by using a keyboard and a mouse on the podium.
- Please prepare presentations data transferred on a CD-R or USB memory stick and register at PC Desk. Kindly be sure to bring a back-up data as well.
- The OS and applications for the computer provided for presentations are as follows:

  OS: Windows 10

  Applications: PowerPoint 2013
- Do not use special or downloaded fonts.
- Image resolution is XGA (1024×768 pixel). Please set up the images with XGA.
- Windows Media Player is the only software that can be used to play a video data during your presentation.

  * The default codecs those are included in Windows Media Player. Using WMV is recommended.
- Do not save any other data than your presentation in the USB memory stick or the CD-R.
- Please run a virus check on your computer in advance.
- Please check your presentation data including images by pasting the data from host/main computer to another computer if the data is shown properly.
- All the copied data will be deleted by organizers appropriately after the congress end.

Program

Nov. 14 (Mon)

Room B (Conference Room 1 / 4F)

14:00～17:00 **Satellite Symposium AOP Training**

(Sponsored by Mandom Corporation)

Catherine WILLETT
Humane Society of the United States / Humane Society International, USA

Kellie FAY
US Environmental Protection Agency, USA

Nov. 15 (Tue)

Room A (Main Hall / 1F)

10:00～10:20 **Welcome Address**

Hajime KOJIMA
National Institute of Health Sciences (NIHS), Japan

10:25～11:10 **Plenary Keynote Lecture**

Chair: Yasuo OHNO
Kihara Memorial Yokohama Foundation for the Advancement of Life Sciences, Japan

"Phasing out the Use of Experimental Animals for Regulatory Risk Assessment Purposes before 2025"

Herman B.W.M. KOËTER
Chairman of the Alternatives Congress Trust (ACT), Italy

11:15～11:55 **Plenary Lecture 1**

Chair: Makoto HAYASHI
makoto International Consulting, Japan

"Looking to the Future - WC10: The Three Rs in Action"

Joanne ZURLO
Director of Science Strategy Center for Alternatives to Animal Testing (CAAT), Johns Hopkins Bloomberg School of Public Health, USA

13:15~15:15 Session 1 : Asian trends in 3Rs of animal experiments

Chairs: Tsutomu Miki KUROSAWA
Kagoshima University, Japan

Jufeng WANG
Pharmaron, China

AS1-1 "The 3R's change after 10 years activity of SNU-IACUC"

Jae-Hak PARK
Laboratory Animal Medicine, College of Veterinary Medicine, Seoul National University, Republic of Korea

AS1-2 "Trends in 3Rs of laboratory animal experiments (Bio-imaging in Singapore)"

Yi Quan Shawn TAY
Comparative Medicine, National University of Singapore (NUS) / Asian Federation of Laboratory Animal Science Associations (AFLAS), Singapore

AS1-3 "Zebrafish, *Danio rerio* as a replacement alternative"

Mangala GUNATILAKE
Dept of Physiology, Faculty of Medicine, University of Colombo, Sri Lanka

AS1-4 "The Role of an NGO in Implementing Non-Animal Testing and Training Methods in India"

Dipti M. KAPOOR
People for the Ethical treatment of Animals (PETA), India

AS1-5 "The Study of In Vitro Skin Sensitization Test Based on Integrating 3D Model to h-CLAT"

Shujun CHENG, et al.
Guangdong Inspection and Quarantine Technology Center, China

AS1-6 "Development of reconstructed human epidermal skin equivalent (EPiTRI) and validation of skin irritation test (SIT) protocol by using EPiTRI"

Huey-min LAI, et al.
Center for Drug Development, Industrial Technology Research Institute, Taiwan

AS1-7 "Preparation and characterization of Reconstructed Human Epidermis (RHE)"

Herlina B. SETIJANTI, et al.
Research Center for Drug and Food, National Agency of Drug and Food Control, Indonesia

AS1-8 "Alternative Research (3Rs) in the World, Asia and Japan"

Tsutomu Miki KUROSAWA
Joint Faculty of Veterinary Medicine, Kagoshima University, Japan

15:30~18:00 Session 3 : Cosmetics regulation and alternatives in animal experiments

Chairs: Sanae TAKEUCHI
P&G Innovation Godo Kaisha, Japan

Troy SEIDLE
Humane Society International, Canada

AS3-1 "Human living skin explant model as an alternative to animal experimentation for evaluation of cosmetic products, raw materials and finished products, activities and tolerance"

Elian LATI, et al.
BIO-EC LABORATORY, France

AS3-2 "Cosmetic regulation and alternatives to animal experiments in Thailand"

Neti WARANUCH, et al.
Cosmetics and Natural products Research Center, Faculty of Pharmaceutical Sciences, Naresuan University / Department of Pharmaceutical Technology, Faculty of Pharmaceutical Sciences and Center of Excellence for Innovation in Chemistry, Naresuan University, Thailand

AS3-3 "Cosmetic Regulation and Alternatives in Animal Experiments"

G.N. SINGH
Drugs Controller General (India), Central Drugs Standard Control Organisation, Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India

AS3-4 "Cosmetic regulation and alternative in animal experiments in China"

Rong KUANG
Zhejiang Institute for Food and Drug Control, China

AS3-5 "Face Alternative: Current Status in China"

Lu QIU
Shanghai Entry-Exit Inspection and Quarantine Bureau of China, China

AS3-6 "Development of Alternative Test Methods to Evaluate the Safety of Cosmetics"

Tae Sung KIM, et al.
National Institute of Food and Drug Safety Evaluation, Ministry of Food and Drug Safety, Republic of Korea

AS3-7 "Guidance on use of alternative methods for testing in the safety assessment of cosmetics and quasi-drug"

Hajime KOJIMA, et al.
Division of Risk Assesment, Biological Safety Research Center, National Institute of Health Sciences, Japan

Room B (Conference Room 1 / 4F)

12:10~13:00 Luncheon Seminar 1

(Sponsored by YUTOKU PHARMACEUTICAL IND.Co., LTD.
KANTO CHEMICAL CO., INC.)

A-LS1 "Unique cell culture techniques for *in vitro* research"

Shigehisa AOKI
Department of Pathology & Microbiology, Saga University, Japan

13:15~15:15 Session 2 : 3Rs in pesticides and chemicals

Chairs: Masahiro TAKEYOSHI
Chemicals Assessment and Research Center, Chemicals Evaluation and Research Institute, Japan

Judy STRICKLAND
Integrated Laboratory Systems, Inc. Contractor supporting the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), USA

AS2-1 "Development of 3D reconstructed human cornea-like epithelium, MCTT HCE™ from primary limbal cells, and its application for alternative to animal test"

Kyung-Min LIM
College of Pharmacology, Ewha Womans University, Republic of Korea

AS2-2 "Approaches to Reducing Animal Use for Acute Toxicity Testing: Retrospective Analyses of Pesticide Data"

Judy STRICKLAND, et al.
Integrated Laboratory Systems, Inc. / Contractor supporting the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), USA

AS2-3 "3R best practices in pesticide regulation in India"

Alokparna SENGUPTA
Research & Toxicology Department, Humane Society International, India

AS2-4 "Progress in deleting the 1-year dog study for the safety assessment of pesticides"

Horst SPIELMANN
Inst. For Pharmacy, Faculty for Biology, Chemistry and Pharmacy
Freie Universität Berlin, Germany

AS2-5 "Development of Read-across for Chemical Safety Assessment"

Takashi YAMADA, et al.
Division of Risk Assesment, Biological Safety Research Center, National Institute of Health Sciences, Japan

15:30~18:00 Session 4 : 3Rs in biologicals and others session

Chairs: Hiroshi YAMAMOTO
Toyama University, Japan

Katrin SCHUTTE
European Comission DG Environment, Belgium

AS4-1 "R&D status of alternative test methods for blood products in Korea"

Chiyoung AHN, et al.
Blood Products Division, National Institute of Food and Drug Safety Evaluation, Ministry of Food and Drug Safety, Republic of Korea

AS4-2 "Alternatives and Refinement for Animal Experimentation in Cancer Research"

Arvind INGLE
Scientific Officer 'F', Officer-in-Charge, Laboratory Animal Facility, ACTREC, Tata Memorial Centre, Navi Mumbai, India

AS4-3 **"Towards global harmonisation of 3Rs in biologicals – efforts of the EPAA Biologicals project team"**

Katrin SCHUTTE, et al.
Environment European Comission, DG Environment, Belgium

AS4-4 **"3Rs in Quality Control of human vaccines: opportunities and barriers"**

Sylvie UHLRICH, et al.
Sanofi Pasteur, France

AS4-5 **"Veterinary industry approach to 3Rs in Biologicals"**

Takeshi FUJII, et al.
Product Development & Regulatory Affairs, Zoetis Japan, Japan

AS4-6 **"VICH (International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Products) and Harmonization of Criteria to Waive TABST (Target Animal Batch Safety Test) for Vaccines for Veterinary Use"**

Koji OISHI
National Veterinary Assay Laboratory, JMAFF, Japan

Room C (Conference Room 2 / 4F)

12:10~13:00 **Luncheon Seminar 2**

(Sponsored by THE LUSH PRIZE)

A-LS2 **"An introduction to the Lush Prize 'Young Researcher Asia' awards"**

Rebecca RAM
Scientific Consultant, Lush Prize, UK

Nov. 16 (Wed)

Room A (Main Hall / 1F)

9:00~9:40 **Plenary Lecture 2**

Chair: Noriho TANAKA
Food and Drug Safety Center, Hatano Research Institute, Japan

"BioMed21: Toward a Pathway-Based Paradigm in Health Research"

Troy SEIDLE, et al.
Director of Research & Toxicology Department, Humane Society International, Canada

9:50～11:40 Session 5 : Future approaches to alternatives in 3Rs

Chairs: Yasuyuki SAKAI
Tokyo University, Japan

Mohammad A. AKBARSHA
Bharathidasan University, India

AS5-1 "The Use of Adverse Outcome Pathways (AOPs) to Support Chemical Safety Decisions within the Context of Integrated Approaches to Testing and Assessment (IATA)"

Catherine WILLETT
Humane Society of the United States / Humane Society International, USA

AS5-2 "Progress of alternative study in China"

Jufeng WANG
Pharmaron, China

AS5-3 "Mechanism based evaluation system for hepato- and nephrotoxicity or carcinogenicity using omics technology"

Fumiyo SAITO
Chemicals Assessment and Research Center, Chemicals Evaluation and Research Institute, Japan

AS5-4 "Stem cells and alternatives"

Eui-Bae JEUNG
College of Veterinary Medicine, Chungbuk National University, Republic of Korea

AS5-5 "Futuristic approach to alternative model organisms: Hydra stakes its claim"

Mohammad A. AKBARSHA, et al.
Mahatma Gandhi - Doerenkamp Center for Alternatives to Use of Animals in Life Science Education, Bharathidasan University, India

Room B (Conference Room 1 / 4F)

10:00～10:30 THE LUSH PRIZE Session

(Sponsored by THE LUSH PRIZE)

Chair: Hajime KOJIMA
National Institute of Health Sciences

"*In Vitro* Testing as a Scientifically Advanced Strategy for Regulatory Safety Compliance and Claim Support in the Global Cosmetics Industry"

Carol TREASURE, et al.
XCellR8 Ltd., UK

10:40~11:40 Young Scientist Award

(Sponsored by Japan Chemical Industry Association (JCIA)
Japan Anti-Vivisection Association (JAVA)
Japanese Society for Alternatives to Animal Experiments (JSAAE))

Chairs: Hiroaki TODO
Faculty of Pharmaceutical Sciences, Josai University, Japan

Horst SPIELMANN
Inst. For Pharmacy, Faculty for Biology, Chemistry and Pharmacy, Freie Universität Berlin, Germany

JCIA Award

"Evaluation of toxicants for the neural differentiation of human ESCs"

Jin Yong AN,et al.
Chungbuk National University, Republic of Korea

JAVA Award

"Preliminary Evaluation of Vascular Endothelial Growth Factor as a Biomarker for Alternative Skin Sensitization Test in HaCaT Keratinocytes"

Sae On KIM,et al.
College of Pharmacy, Seoul National University, Republic of Korea

JSAAE Award

"The effect on cellular function and microstructures of hepatic spheroids by using a novel method for loading ECM thin layer into spheroids"

Fumiya TAO,et al.
Yokohama City University, Japan

Phasing out the Use of Experimental Animals for Regulatory Risk Assessment Purposes before 2025

Herman B.W.M. KOËTER

Alternatives Congress Trust (ACT), Washington, DC, USA; Orange House Partnership, Brussels, Belgium and Lucca, Italy; Netherlands National Committee for the Protection of Animals Used for Scientific Purposes, The Hague, The Netherlands.

Although for most of the new areas in chemical safety assessment such as nanotechnology applications and cloning global regulations have not yet been developed, there are currently in the EU already more than 20 Directives and Regulations in the food and feed safety area alone. In the existing legislation, experimental animal welfare considerations are hardly mentioned, let alone that guidance is provided on how to reduce the need for experimental animal use. What all these regulations have in common, is that they all aim at the safe use of chemical substances by having an understanding of their intrinsic hazards and risks.

The often heard argument that the regulatory community is unwilling to accept alternative data is a hoax. Regulators are open to new developments and do judge initiatives coming from others (academia, industry). Indeed, regulatory authorities today significantly differ from those of 25 years ago. They all have access to scientists who have full-time jobs, either in house or in the public sector. Scientists from the public sector are usually involved, on a part time basis, in regulatory risk assessment.

Despite all this, we are facing more than 35,000 chemicals and more than 3,000 food additives currently in use that have not yet been thoroughly tested for hazards and risks either in animal studies or 3R alternatives or a combination of these. During the last 30+ years we have all together managed to develop, validate and apply no more than a hand full of 3R alternatives in the domain of regulatory assessment. From this minute achievement one can only conclude that from an animal welfare point of view we are definitely on the wrong track. Therefore, the time has come to consider a radical change, a true transition to an animal-free assessment of the safety of chemicals, pharmaceuticals, food additives, pesticides, etc. A drastic transition requires brave decisions, not only at the level of regulatory authorities, but also from the users: the consumer who uses chemicals, the housewife who selects the processed food for her family, the farmer who need fertilizers and pesticides, the patient who eagerly wants access to the best medicines and the user of cosmetics. The lecture will propose a way by thinking out-of-the-box and aim at this point on the horizon where animals are no longer used.

Looking to the Future - WC10: The Three Rs in Action

Joanne ZURLO

Center for Alternatives to Animal Testing, Johns Hopkins Bloomberg School of Public Health

In 2017, the United States will host the Tenth World Congress on Alternatives and Animal Use in the Life Sciences (WC10) at the Washington Convention Center in Seattle. WC10 represents two milestones in the field of alternatives: it is the tenth in a series of Congresses that began in Baltimore in 1993, and it occurs on the tenth anniversary of the seminal publication of the National Academies *Toxicity Testing in the 21st Century – A Vision and a Strategy*. In order to appreciate the progress in promotion and implementation of the Three Rs, it is appropriate to look to the past. When the first World Congress was held in 1993, the science was in its relative infancy. The discussions focused more on the need for new technologies rather than on those available at the time. In the ensuing 27 years, the science has undergone a revolution with the advent of the human genome project, development of highly sensitive instrumentation, advances in cell culture, the marriage of bioengineering with cellular and molecular biology and further insight into animal behavior as relates to animal welfare. We are faced with new challenges such as how to handle big data, identifying new methods for evaluating efficacy and developing mechanisms for global acceptance of new technologies for regulatory purposes.

Perhaps the most significant change since the First World Congress has been the global acknowledgement of the importance of the Three Rs. In 1993, relatively few scientists around the world recognized the concept and the challenge at the time was to communicate the value of replacement, reduction and refinement of animal use to science, animal welfare and ethics. In the ensuing 23 years, the small alternatives community has grown substantially such that at the 2014 World Congress in Prague, there were representatives from 47 different countries. Recognition of the Three Rs is now enshrined in the laws and guidelines of many countries as well as in international guiding principles such as those from the World Organisation for Animal Health (OIE) and the Council for International Organizations of Medical Sciences (CIOMS)/International Council of Laboratory Animal Science (ICLAS). It can be assured that both science and animal welfare will only continue to progress with the upward trajectory of the Three Rs concept.

BioMed21: Toward a Pathway-Based Paradigm in Health Research

Troy SEIDLE[1)], Gillian R. LANGLEY[1)], Catherine WILLETT[1, 2)], Ian ADCOCK[3)], Francois BUSQUET[4)], Elena CSERNOK[5)], Christoph GIESE[6)], Kathrin HERRMANN[7)], Brigitte LANDESMANN[8)], Lindsay MARSHALL[1, 9)], Emily MCIVOR[1)], Alysson MUOTRI[10)], Fozia NOOR[11)], Katrin SCHUTTE[12)], Anja VAN DE STOLPE[13)], Hilde VAN ESCH[14)], Grzegorz WOSZCZEK[15)]

1) Research & Toxicology Department, Humane Society International
2) Animal Research Issues Section, The Humane Society of the United States
3) National Heart & Lung Institute, Imperial College London
4) Department of Biology, University of Konstanz
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8) Directorate General Joint Research Centre, European Commission
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Decades of repeated and costly failures to translate promising drug candidates from preclinical disease models to human therapeutic use warrant careful reconsideration by science funding bodies of the level of priority placed on animal models relative to emerging, human-specific tools in the biomedical research paradigm. Following an international workshop held in Brussels attended by experts from academia, governmental institutions, research funding bodies, and the corporate and NGO sectors, this consensus report analyzes, as case studies, five disease areas with major unmet needs for new treatments. In view of the scientifically driven transition toward a human pathway-based paradigm in toxicology, a similar paradigm shift would appear to be warranted in the domain of biomedical research: one that strategically incorporates advanced, human biology-based models and tools to understand disease pathways at multiple biological scales. Workshop participants recommend that science funding bodies prioritize human relevance as a key criterion for future research funding, commit substantial resources toward a comprehensive strategy to improve our mechanistic understanding of human disease, and fast-track the development and deployment of human-specific models to accelerate the identification and successful translation of new treatments to the clinic.

AS1-1 The 3R's change after 10 years activity of SNU-IACUC

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In order to do appropriate animal experiments, Animal Care and Use Program should be made. The program may be composed of the animal use, humane management, policy, the experimental process, the structure of the facility. Seoul National University IACUC started it role from 2005. Evaluation of animal experiments and facilities and protocols are performed as described in the PAM (post approval monitoring) guide. Through the continuing PAM, SNU try to extend the current animal room, construct new special purposed facilities, and renovate the old facilities. In addition, Seoul National University IACUC have presented the direction of the future of animal experiments in the following manner. 1. Efficient managing and interaction between animal experimentation facilities in SNU. 2. Establishing the sanitary conditions of the facility, 3. Improvement of the efficiency of animal experiments (clarifying of the purpose of animal experiments, the establishment of an appropriate animal model, detailed analysis of the results of animal experiments, ARRIVE, veterinary clinical trial center) 4. Consideration of safe and painless area for the animals (dividing breeding room from experimental zone, ensuring a comfortable housing environment). 5. Rapid and accurate judgment of IACUC, 6. Seeking ways of animal experiments to reduce the pains, 7. Using a suitable alternatives and mimicking human body.

AS1-2 Trends in 3Rs of laboratory animal experiments (Bio-imaging in Singapore)

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As announced on 8th January 2016, the Singapore Government has committed S$19 billion (~US$13.2 billion) to research investments over the next five years. Singapore Prime Minister Lee Hsien Loong added that approximately S$4 billion (~US$2.8 billion) will be invested each year from 2016 to 2020 on research, innovation and enterprise activities with Health and Biomedical Sciences as one of the four primary technology domains. Laboratory animal science professionals in Singapore are well – poised to support this well - funded health and biomedical sciences research activities including lab animal experiments with focus on the 3Rs until 2020. The NACLAR Guidelines on the Care and Use of Animals for Scientific Purposes was released in October 2004. The scope of the Guidelines covers all aspects of the care and use of animals for scientific purposes including their use in teaching, field trials, environmental studies, research, diagnosis, product testing, and the production of biological products. The aim of the NACLAR Guidelines is to promote humane and responsible care and use of animals for scientific purposes in Singapore. In essence, the NACLAR Guidelines are based on the principles of the 3Rs- Replacement, Reduction and Refinement. The Guidelines also outline the responsibilities of institutions, investigators and persons involved in the care and use of animals for scientific purposes. Currently, there are plans to revise the NACLAR Guidelines in the next 2 years. The use of medical technologies, such as non-invasive imaging, enables longitudinal studies in animals especially in the same study. These medical technologies are computed tomography (CT) scans and magnetic resonance imaging (MRI), combined together with imaging techniques are instrumental to achieving the reduction of the number of animals used. There are 3 main institutes equipped with core imaging technologies in Singapore. (A*STAR, NUS & Singhealth) Under the Agency for Science, Technology and Research (A*STAR) in Singapore, the Singapore Bioimaging Consortium (SBIC) is set up to foster and support the growth of multidisciplinary research activities in the field of bioimaging across local research institutes, universities and hospitals, in order to accelerate the development of biomedical research discoveries. SBIC has also recently founded the Translational Imaging Industrial Laboratory (TIIL) to offer an array of small animal preclinical imaging resources. Under National University of Singapore (NUS), Comparative Medicine Imaging Facility (CMIF) has both imaging technologies for the use of in vivo imaging of small and large animals. For small animals, imaging technologies include Rodent High Frequency Ultrasound, micro-Computed Tomography (CT) Whole Animal Imaging System, Micro positron emission tomography (PET) Whole Animal Imaging System, Magnetic resonance imaging (MRI) 7 Tesla system and Whole Animal Fluorescence/Bioluminescence Imaging System. For Large Animals, imaging technologies include Large Animal Computed Tomography (CT) system, Large Animal Magnetic Resonance Imaging (MRI) 3 Tesla system and C-arm Fluoroscopy system. Under Singhealth, SingHealth Advanced Bioimaging is equipped with the following specialist imaging equipment, including Micro-SPECT/CT, Micro-PET/MRI, Photo-Acoustic Scanner, Nonhuman Primate PET-CT, Ultrasound, digital C-arm fluoroscope. Singapore is committed to upholding the highest animal welfare standards and applies the 3Rs to NACLAR guidelines and its practices: Replacement, encouraging researchers to replace animals with alternative methods, such as computer models; Reduction, reducing the number of animals involved in research to the minimum necessary to obtain scientifically robust results; and Refinement, minimising any negative impact on animals by using state-of-the-art anaesthetics and bio-imaging equipment.

AS1-3 Zebrafish, *Danio rerio* as a replacement alternative

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With the development and acceptance of alternatives, interest of scientists has been deviating from the use of animals in their research work towards alternative models. This 'Alternative' concept is the 'Replacement' alternative that was indicated in the book; 'The Principles of Humane Experimental Technique' written by Russell and Burch in 1959. Although many methods of replacement have been developed and used by researchers, most of these are not **absolute** replacement models. As absolute replacement models should not involve whole animals and animal tissues, in many instances models used by researchers are **relative**. Relative replacement models include lower vertebrates, invertebrates or animals having lower level of sentience and tissues, cells, sera and embryos etc of animal origin. These relative replacement models of course reduce or prevent the use of conscious living vertebrates.

Among the widely accepted relative replacement models, the zebrafish and its embryo model have been of interest to the researchers due to its wide spectrum of scientific applicability. Applications of this model include developmental biology, oncology, toxicology, reproductive studies, teratology, genetics, neurobiology, environmental sciences, stem cell research and regenerative medicine. Scientific benefits of zebrafish, a native species in Sri Lanka, were introduced to Sri Lankan researchers at the Inaugural Scientific Conference of the Sri Lanka Association for Laboratory Animal Science (SLALAS) in January 2014 by Dr Francois Busquet, CAAT-Europe Policy Coordinator, University of Konstanz, Germany.

Being a fresh water fish, zebrafish and its developing stages are sensitive to changes in their immediate environment. These changes could cause mortality, and also affects all their activities and growth in developing stages. During this talk how zebrafish could be used as a replacement alternative model for water quality testing in order to address one of the long standing problems of public health concern, 'Chronic Kidney Disease of unknown origin' (CKDu) in certain Asian countries will be presented.

AS1-4 The Role of an NGO in Implementing Non-Animal Testing and Training Methods in India

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In recent years, People for the Ethical Treatment of Animals (PETA) India has worked with India's regulatory framework to expand the use of technologically advanced non-animal testing methods, computer software, and human-patient simulation models to replace and reduce the use of animals in biomedical experiments, biology education, and regulatory testing.

While these scientifically robust *in vitro* methods and simulations are becoming increasingly validated and available, they are not automatically accepted by regulatory and educational authorities. Furthermore, even regulatory acceptance by authorities does not guarantee that they will be implemented by industry, institutions, or educators. PETA India has sought to bridge these gaps by collaborating with all parties to promote the preferential use of scientifically robust non-animal methods. For example, we have worked with India's Central Insecticide Board to harmonise India's use and acceptance of non-animal strategies with that of other countries.

Recognised and registered as an expert member in several subcommittees of Indian regulatory departments, PETA India works to raise awareness of non-animal testing methods and lobbies for the replacement of animal use in regulatory testing whenever possible. Examples of recent successful collaborations between PETA India and Indian regulatory authorities include the ban on animal testing for cosmetics and household products, the decision to stop requiring duplicative testing for new drug registrations, and regulatory consideration of non-animal tests for acute dermal and ocular toxicity that replace the Draize rabbit tests.

PETA India is also actively involved is the modernisation of biomedical teaching techniques by replacing the use of animals with more effective human-simulation software for medical, dental, pharmacy, and life sciences curricula across the country. PETA India has been actively updating the respective regulatory authorities with information on modern non-animal teaching tools as well as providing donations to professional schools for simulation software.

This presentation will discuss progress to date as well as the obstacles still to be overcome in order to achieve complete adoption of testing guidelines approved by the Organisation for Economic Cooperation and Development and full replacement of animal use in biomedical experiments.

AS1-5 The Study of In Vitro Skin Sensitization Test Based on Integrating 3D Model to h-CLAT

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[Introduction] Skin is an important barrier for the human body to block the external materials, and it will defend against hazardous substances by special reactions. Allergic contact dermatitis is a type IV delayed hypersensitivity cutaneous immune reaction, which is important for chemicals classification and identification as well as safety assessment. During the induction phase of skin sensitization, keratinocyte, Langerhans cells (LC) play a critical role, especially, the three dimensional epidermis with multi-layer keratinocyte and metabolism similar with normal epidermis.

[Methodology] Construction of human cell line activation test (h-CLAT) method and it was combined with HaCaT keratinocytes, eventually, the Episkin™ skin model was combined in h-CLAT also, three type different integrated skin sensitization methods were build. By monitoring the cell viability, cell surface marker CD54 /CD86 and relative fluorescence intensity of cells surface after the cells was exposed substances, in order to format a complex test strategies and assessment plans for skin sensitization powerful potency of chemicals and personal care products. The study was divided into three parts: I, replication of h-CLAT, adjustment of h-CLAT, II, combination HaCaT cells with h-CLAT to assess situation of skin sensitization for substances, III, the study for combination Episkin™ with h-CLAT to assess skin sensitization.

[Results] Firstly, the h-CLAT method was constructed in the lab by self-validated. Secondly, the keratinocyte was attached the h-CLAT, and detection of IL-18 by the kit. As a result, the IL-18 was significant increase in HaCaT cells only and co-culture system($P < 0.05$). Subsequently, THP-1 cells was exposed the non-toxic dose of IL-18 combined with DNCB, the results showed that there was no significant difference between the double substances treatment group and the DNCB group ($P > 0.05$). Following, the co-culture system was used to detect the positive skin sensitization and negative skin sensitization substances, it was found that compared the h-CLAT to co-culture system, the CD86/CD54 fluorescence intensity did not significantly enhanced ($P > 0.05$). However, under the same conditions, the irritation and the sensitization of the materials can be detected in one in vitro test method, and to screen preliminarily the exposed dose of substance for the 3D skin model. Lastly, in order to optimize the HaCaT keratinocyte and THP-1 cells co-culture model, the co-culture system was constructed by the biological activity of Episkin™ skin model and THP-1 cells, and it was used to screen 17 kinds of substances in the skin sensitization test. Eventually, it was found that to compare pure THP-1 cells and THP-1 cells and HaCaT keratinocytes co-culture system with Episkin™ skin model and THP-1 cells co-culture system, the relative fluorescence intensity in the Episkin™ skin model and THP-1 cells co-culture system was increased significantly ($P < 0.05$) by tested the 10 positive substances. Finally, 16 kinds of cleaning products were tested.

[Conclusions] Through the study of known skin sensitization positive standard substances and negative materials to establish h-CLAT, as well as the plant extract were distinguished correctly in ability of skin sensitization. At the same time, in order to strengthen the single cell detection system, HaCaT cells was co-cultured with the h-CLAT, and discriminated sensitive positive substance and negative material accurately and a test method based on IL-18 to detect skin sensitivity and stimulation was formed. Finally, for more fit the action that the cosmetic products, the personal care products and other substances reaction in human skin, and then the model h-CLAT combined with 3D skin model was built. Hence, the recognization and assessment of 10 kinds of skin sensitive positive materials, 7 negative materials and 16 kinds of cleaning product were tested. The results show that the system could make correct judgment for skin sensitization materials, and the physical type of substances became more suitable with 3D model than normally cell testing.

AS1-6 Development of reconstructed human epidermal skin equivalent (EPiTRI) and validation of skin irritation test (SIT) protocol by using EPiTRI

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Topical exposure to chemicals and cosmetic products can lead to various adverse skin effects. Corrosion and irritation are commonly regarded as two major categories among these adverse effects. Corrosive substances irreversibly damage the skin beyond repair, while irritant substances lead to a reversible local inflammatory reaction caused by the innate (non-specific) immune system of the affected tissue. Some chemicals trigger an irritant response after repeated exposure of the same skin area (=cumulative irritants), other chemicals may even cause irritation after a one-time exposure (=acute irritants). Current regulatory requirements focus on the assessment of the acute irritation potential of chemicals and cosmetics in order to support the risk management. Data on skin irritation effects are required by REACH and EU's Cosmetic Regulation as well as pharmaceutical and medical devices premarket approval required by authorities in many countries.

Internationally accepted test methods for skin irritation testing (SIT) include the traditional in vivo animal test as well as in vitro test methods. However, there is a trend changed from in vivo to in vitro testing due to the 3R (replacement, reduction, refinement) requirement resulted from recent animal testing ban. All accepted in vitro test methods are based on the RhE technology (Reconstructed human Epidermis) validated by ECVAM. RhE models use normal human keratinocytes that, during culturing, form a multi-layered epidermis including a stratum corneum at the top and can function as a barrier.

There are only few RhEs which have been validated for SIT being approved by ECVAM, and none of them are of Chinese heredity. ITRI has started some years ago in house based on our culture experience of cells isolated from human donors, the cell expansion (scale up) technology, and our own GTP/GMP facilities. So far, a multi-layered epidermis composed of well differenciated stratified stratum corneum, granulosum, stratum spinousum and basal layer and with reproducible barrier function was developed and used for skin irritation testing in accordance to OECD439 guideline.

In this presentation, we reported the progress of development of reconstructed human epidermis (EPiTRI) and the aim to develop the skin irritation testing protocol by using EPiTRI for validation. Quality control parameters for EPiTRI such as structure morphology of tissue, thickness, TEER (Trans-epithelium electrical resistant), lipid profile were investigated to study the correlation with barrier function. After obtaining satisfied quality control data, we conducted the validation process. During the development of skin irritation testing protocol, several important parameters were evaluated for obtaining better statistical accuracy of data when compared with data from in vivo testing. These important parameters includes pre-incubation time, post-incubation volume, chemical exposure time, washing method, etc. A result of sensitivity of 100%, specificity of 70% and accuracy of 85% was obtained in current Phase I validation status. The study shows that the human epidermal skin equivalent EPiTRI could possibly provide as an in vitro model to evaluate the skin irritation and a reliable SIT method has been developed accordingly.

AS1-7 Preparation and characterization of Reconstructed Human Epidermis (RHE)

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During the last decade, the use of animals for research purposes and specially for cosmetic safety testing has been a sensitive matter. Major progress was made in the replacement of animal experiments, including the approved in vitro approaches for regulatory skin irritation, based on the OECD principles was developed by using reconstructed human epidermis (RHE). The model was obtained by culturing normal human keratinocytes.

The purpose of this study was to preparation of 3D-Reconstructed Human epidermis (RHe) models from primary human keratinocytes from Indonesian skin.

Reconstructed human epidermis are composed of a dermal compartment containing human skin fibroblasts embedded in a collagen matrix and human keratinocytes seeded on top to form the epidermis. Reconstructed human epidermis models are composed of human keratinocytes seeded on a polycarbonate membrane to form the epidermis.

We have established techniques for the preparation of the 3D Reconstituted Human epidermis from normal Human epidermal Keratinocytes primary keratinocytes and characterized this model. Key stages in the cell culture of 2D and 3D epidermis were identified. The 3D-RHE showed the correct histological structure containing all layers of human epithelium.

AS1-8 Alternative research (3Rs) in the world, Asia and Japan

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Alternative research is currently conducted all over the world and its recent progress is remarkable as 3Rs research. The laboratory animal welfare research and practice was started in 1950s and they are accelerated from 1980. CAAT leads this field in USA and the 1st World Congress for Alternatives was held in 1993. ECVAM is the leading organization for alternative research in Europe and then International academic organizations activate this field. In Asia, JSAAE was founded in 1984 and JSAAE collaborates many international organizations in this field. Consequently, the 6th World Congress was invited to Tokyo in 2006. The 6th World Congress had 3 satellite meetings in other Asian parts, namely Beijing, Seoul and Kyoto. This means that the 6th World Congress is a milestone of expansion of alternative research into Asian region. Indeed, the KSAAE was founded in the year of 2006. AFLAS is one of other remarkable activities of alternative research. The first congress was held in Nagasaki in 2004 and the congress held every two years and in this year, Singapore is a host for this congress. The important subjects discussed in the congress include laboratory animal welfare and 3Rs with other subjects in laboratory animal science. The AFLAS membership is now expanded to 11.

In Japan, JSAAE has a center position to propagate 3Rs activities. The initial activities of JASSE were focused on cosmetics. However when animal welfare law took 3Rs as key words, 3Rs concept is well recognized biomedical research organizations. The practical activities of 3Rs are held by JALAM, JSLAE and JAEAT as education and training sessions and then 3Rs is now expanding to be recognized by industries.

Accordingly, world activities of 3Rs are now accepted in Asian countries widely and the Asian Congress of Alternatives Karatsu is organized. In the future, the World Congress is expected to be planned in Asia again.

AS2-1 Development of 3D reconstructed human cornea-like epithelium, MCTT HCE™ from primary limbal cells, and its application for alternative to animal test

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Several alternative *in vitro* methods to evaluate ocular irritancy have been developed. Recently, the first 3D reconstructed human cornea-like epithelium (RhCE) model, EpiOcular™ has been approved by OECD as the validated reference method (VRM) for *in vitro* eye irritation test. Other RhCE models like SkinEthic HCE, Labcyte Cornea model and MCTT HCE™ are also within validation or under the peer review stage as generic models with equivalent performances. MCTT HCE™ is prepared from primary human limbal cells obtained from the remainder tissues during corneal transplant. MCTT HCE™ reproduces well cornea-like characteristics with respect to biomarker expression, histological appearance and barrier function. Using this model, new genomic and lipid biomarkers specific to eye irritants like cornifelin and EGR-1 have been discovered, which will give an important insight into the cornea pathophysiology. In addition, its performance are being examined and validated according to OECD TG492 performance standards. We anticipate MCTT HCE™ to become another validated RhCE model in near future. Moreover, its applicability towards the testing of medical device has been explored and promising results were obtained, suggesting that MCTT HCE™ model may an important tool for the research of human cornea.

AS2-2 Approaches to reducing animal use for acute toxicity testing: retrospective analyses of pesticide data

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Regulatory agencies use data from in vivo rodent acute oral and dermal toxicity tests to determine potential systemic toxicity of chemical products following ingestion and topical skin exposure. These data are used to derive an LD_{50} value (dose expected to produce lethality in 50% of the animals tested) for assigning hazard classification and labeling, to protect human health and the environment when handling and transporting chemicals. In this study, we considered whether acute oral toxicity hazard classifications for pesticide formulations and active ingredients (AI) could be used to assign acute dermal toxicity hazard classifications using the U.S. Environmental Protection Agency (EPA) categorization system and the Globally Harmonized System of Classification and Labelling of Chemicals (GHS). This retrospective analysis used high-quality acute toxicity data for 612 formulations and 298 AI extracted from various EPA toxicity reports, peer-reviewed publications, and databases. Hazard classifications based on rat oral LD_{50} values were compared to hazard classifications based on rat dermal LD_{50} values for the same substance. The concordance of oral and dermal hazard classification was 56% for formulations and 61% for AI using the EPA system and 69% for formulations and 55% for AI using the GHS system. Overprediction of dermal hazard was 44% for formulations and 35% for AI using the EPA system and 30% for formulations and 41% for AI using the GHS system. Underprediction of dermal hazard was 1% for formulations and 4% for AI using the EPA system and 1% for formulations and 3% for AI using the GHS system. While concordance overall was modest, the very low underprediction rates show that acute oral hazard categories are sufficiently protective for acute dermal hazard classification. Use of oral hazard data to also classify dermal hazard would obviate the need to perform acute dermal toxicity tests for classification and labeling and thereby reduce the number of animals used for acute systemic toxicity testing of pesticides. This project was funded in whole or in part with Federal funds from the NIEHS, NIH under Contract No. HHSN2732015000410C.

AS2-3 3R best practices in pesticide regulation in India

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India is the largest manufacturer of pesticides in Asia and is taking steps to align its registration data requirements and testing guidelines with "3R best practices" that have achieved global recognition through the OECD as well as by other major markets. Each year, several hundred new pesticide active ingredients and formulations are tested in some 30 GLP certified laboratories in India, which still includes the so-called acute toxicity "six-pack", along with a host of subchronic and chronic studies that can consume as many as 10,000 rodents, rabbits, dogs, fish, birds and other animals for a single new food-use active ingredient. India has already taken some positive steps, including removing the 1-year dog study requirement, and showing openness to greater use of combination studies, e.g., assessing genetic toxicity parameters such as micronucleus formation as part of a 90 day general toxicity study rather than as two separate tests. However, more work is needed to ensure the timely uptake of all available and future OECD 3R guideline methods, innovative testing strategies, and non-testing approaches such as waivers, read-across, and computational modeling, particularly as movement continues toward a paradigm shift based on understanding of "adverse outcome pathways" (AOPs). Ongoing, timely updates to regulatory data requirements to make use of all available, valid 3R testing and non-testing approaches is a common challenge in all countries and regulated product sectors. This presentation will discuss Humane Society International's work with India's Central Insecticide Board & Registration Committee and industry stakeholders to revise regulatory requirements to reflect the state-of-the-art in 3R best practices, and perspectives regarding future opportunities, both in India and Asia generally.

AS2-4 Progress in deleting the 1-year dog study for the safety assessment of pesticides

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A review of publications on pesticides assessing the need for 1-year toxicity studies in dogs was performed. Four key peer-reviewed papers with different approaches investigated the value of a 1-year dog study in addition to a 3-month study. Despite different databases and approaches, each concluded with the recommendation to limit the testing of pesticides in dogs to a duration of 3 months. The weight of evidence (WoE) approach of this review reinforces these conclusions.

As one may expect, for each of the reviews, there are limitations and doubts as to the comprehensiveness. The US EPA has considered this point and came in their expanded and updated review of 2006 the clear conclusion that for pesticide risk assessment, dog studies should not be longer than 3 months. There is no doubt that a repeat-dose study of 3 months' duration in dogs is needed and this point is not in dispute. However, the WoE based on all of the reviews together, and in particular Spielmann and Gerbracht (2001), Doe et al (2006), Baetcke et al (2005), and US EPA (2006), allows the clear conclusion that a 12-month dog study in addition to a 3-month study is of little value and the requirement for this study should be eliminated from the list of mandatory studies to be performed in the safety assessment for pesticides.

In the entire databases analyzed in the four main publications critically reviewed here, there are at most 3–4% of compounds in which the results of a 12-month dog study may have influenced a reference dose. The combined WoE from the four reviews is considered clearly sufficient to drop the 12-month dog study for pesticides and limit the dog studies to 3 months. The fact that the approaches for each review were different but came to very similar results strengthens the argument further. In cases, in which the dog appears to be substantially more sensitive than the rat in 3-month studies or shows a different spectrum of findings, a thorough comparative evaluation for kinetics, allometric comparisons, and differences in dynamics is indicated. Simply applying a generic or chemical-specific uncertainty factor is not an acceptable default. The WoE from the reviews individually, and even more so from their combined considerations, supports the conclusion that without compromising human safety routine, dog testing is needed but can be limited to studies of 3 months' duration, for which improvements of the design should be considered, as suggested in some of the reviews.

Therefore, based on a balanced combination of science and animal welfare considerations, those national requirements still insisting on a 12-month dog study for the registration of a pesticide should be updated as soon as possible to harmonize with the US EPA and the EU and eliminate the requirements for dog studies beyond 3 months. Thus, from the perspective of implementing the 3Rs concept into regulatory safety testing of pesticides, the routine inclusion of a 1-year dog study as a mandated regulatory requirement is no longer justifiable and a globally harmonized approach should be taken to match the latest legislation of the European Union and the US EPA.

AS2-5 Development of read-across for chemical safety assessment

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The latest chemical management policies require the toxicological evaluation of marketed but untested chemicals. On the other hand, reduced animal testing is desired for animal welfare and economic reasons. Read-across is regarded as a method for predicting endpoint information for one substance (target substance), using data from the same endpoint from other substances (source substances) which are selected based on similarity in the context of structure, properties and mechanism of action. It is recognized as one of the alternative approaches to fill data gap for regulatory decisions.

Repeated dose toxicity is one of the key regulatory endpoints in the course of human risk assessment of chemicals. The toxicity refers to the toxicological effects in mammals occurring as a result of repeated exposure to a substance. After repeated administration of test chemical at high, medium and low doses, the toxicological profile is characterized in terms of identification of potential target organs and determination of No Observed (Adverse) Effect Level (NO(A)EL). Given the difficulty in building a mechanistically transparent Quantitative Structure-Activity Relationship (QSAR) models for the complicated toxicological endpoints to assess, read-across by forming a robust group of chemicals (often referred to as a category) therefore has potential as a useful method to fill the data gap.

We have developed Hazard Evaluation Support System (HESS) Integrated Platform. HESS has a supportive function to group structural analogs into toxicologically meaningful categories based on the concept of adverse outcome pathways (AOPs). The system is linked to HESS DB, which contains full data set at all tested doses of repeated-dose toxicity studies, most of which were conducted in accordance with GLP principles in Japan. The DB also has reference information on Absorption, Distribution, Metabolism, and Excretion (ADME) and mechanisms of induction of toxicity for some of those chemicals. Use of the HESS platform supports to perform read-across by category approach to predict the primary toxicity of untested chemicals in a transparent and interpretable manner. We have successfully developed several case studies on read-across assessment for repeated-dose toxicity using HESS.

There is growing interest to establish best practices for conducting and evaluating read-across in the context of regulatory decisions. Technical guidance is available for chemical grouping. However, guidance on how to practically apply read-across is still missing especially in terms of selecting analogs and uncertainty analysis. The OECD is currently conducting work on the Integrated Approaches to Testing and Assessment (IATA) case studies, which includes the efforts to examine grouping approaches and exchange of the experiences among the member countries. A goal of this work is to achieve a harmonized approach to the implementation of IATA for regulatory decision-making. This knowledge and experience will increase the understanding of the process of category formation and use of read-across.

AS3-1 Human living skin explant model as an alternative to animal experimentation for evaluation of cosmetic products, raw materials and finished products, activities and tolerance.

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The business of cosmetics and toiletries is thriving. The action of the cosmetic products must be assessed in order to guarantee the consumer an outcome in compliance with what is alleged by the producer. Tolerance for both raw materials and finished goods must be controlled in order to rule out any threat of irritation. Several cellular models can be used for this assessment, such as simple cell culture, reconstructed skin, or human skin explants maintained in survival. The observation of the results can be made either by optical microscopy or fluorescence lighting, after performing histological staining or immunostainings.

The skin in survival was especially developed in the years 1980 following prohibition to use laboratory animals for the studies of activities and tolerance of the cosmetic products. The explants are prepared with residues from plastic surgery operations. The skin is cleaned, the fat tissue is excised and the explants are cut out with a punch of the desired diameter.

Explant of human skin maintained in survival, *ex vivo* model, is a very interesting model because it contains all the cells and all the structures of a healthy human skin. It is perfectly adapted to the studies of screening of actives as well as to the description and evaluation of the activity of a cosmetic formulation. The product to be tested can be applied in topic or can be dissolved in the culture medium, even both at the same time. It can receive repetitive applications with a long survival, or be exposed to a stress (irradiation UV) acute or chronic.

Explants can be maintained long time in survival in our own culture medium, the BEM, confidential formula developed by BIO-EC

Studies showed a good maintenance of general morphology and a good cellular answer during a time of survivals being able to go up to 20 days in particular conditions. But 10 to 12 days of survival are sufficient to evaluate the activity of a raw material or a cosmetic formulation.

Keratinocytes cells preserve their capacity of division and differentiation. The cells of Langerhans keep their mobility and their reactivity. The melanocytes answer well against UV stimulation while remaining in basal position. The stimulation of the components of the dermal epidermal junction is very clearly visualized by several specific Immunostainings. Also the restructuring activities in the dermis.

Many types of evaluation were selected to show the possibilities of this model: Evaluation of the cutaneous tolerance, anti-age activity, whitening activity, healing activity……..

AS3-2 Cosmetic regulation and alternatives to animal experiments in Thailand

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Regulation and standard testing methods for cosmetic products in Thailand are under supervision of Thailand FDA according to newly issued Cosmetic Act B.E. 2558 (2015). Skin irritation, eye irritation and allergic reaction are the primary concern for the product safety according to the FDA point of view. Therefore, skin irritation test, photo toxicity test, ocular irritation test and transdermal permeability test are suggested for cosmetic product registration in Thailand. Alternatives to animal testing according to OECD Test Guidelines or other equivalent methods are accepted. Cell culture using 3D's based standard protocol is recently encouraged to be used for product safety evaluation. Product efficacy can also be done by *in vitro* and *in vivo* studies. A label-free testing for steroid 5α-reductase inhibitor using LC-QTOF-MS/MS is currently developed in our research facility for hair product development in an alternative to hamster flank gland and rat liver microsome models. The method was successfully applied to quantify S5αR inhibitory activity of some Thai herbal extracts. The sample product developed from this study method was clinically proofed and already transferred to the cosmetic company.

AS3-3 Cosmetic Regulation and Alternatives in Animal Experiments

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Manufacture and import of cosmetics are regulated in India under the provisions of the Drugs and Cosmetics Act, 1940 and Rules, 1945 made thereunder. Under the said Act and the Rules, no cosmetic can be manufactured or imported for sale except in accordance with the conditions of License/Registration Certificate issued by the Licensing Authority. The Cosmetics in finished form included under Schedule S of the said Rules are required to conform to the Indian Standards specifications laid down from time to time by the Bureau of Indian Standards (BIS), the National Standards Body of India set up under the Bureau of Indian Standards Act, 1986.

The Constitution of India provides that it is the fundamental duty to protect and improve the natural environment including forests, lakes, rivers and wildlife, and to have compassion of living creatures. Keeping this in view and the development of non-animal testing methods for safety evaluation of cosmetics, the Central Drugs Standard Control Organisation, in the Government of India took a landmark decision in May, 2014 prohibiting use of animals in testing of cosmetics. Apart from this, import of cosmetics which have been tested in animals in other parts of the world has also been prohibited in the country in October, 2014.

The Bureau of Indian Standards (BIS) is continuously engaged in developing standards employing alternative non-animal tests for safety evaluation of cosmetic products. Skin irritation test and eye irritation test (Draize Tests in Rabbits) were removed from the Indian Standard (IS) in 2007. In February, 2014, the IS 4011 was amended specifying that when there is a need for safety evaluation of cosmetic products to demonstrate absence of oral toxicity and/or oral mucosal irritation, the manufacturer shall submit the safety data based on alternative non-animal test methods to the Licensing Authority for their consideration and approval.

India is now a nation where cruelty free cosmetics are available. In doing so, India has maintained its commitment to safeguard both animals and humans.

AS3-4 Cosmetic regulation and alternative in animal experiments in China

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The system of cosmetic regulation in China such as classification, registration and toxicological evaluation methods and the development of Animal Alternative Toxicology (AAT) in cosmetic safety evaluation will be introduced in this presentation.

Cosmetics are classified as two categories for special use with 9 subcategories such as hair dye and whitening and for non-special use such as face mask and body lotion. Experimental animals such as rabbit and guinea pig are used for evaluating the eye irritation, skin irritation, phototoxicity and skin sensitization. In recent years, many labs in China especially ZJIFDC have verified several non-animal test methods such as 3T3 phototoxicity test, BCOP, CAMVA, EIT, SIT, and so on. We are validating these methods for evaluating the safety of finished product.

AS3-5 Face alternative : current status in China

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China is the second largest cosmetics consumer market of the world, with huge volume of cosmetics retail sales of cosmetics, and, there are nearly 4 thousands of enterprises. About safety supervision is an important responsibility. For a long time, we have adopted the <Hygienic Standard for cosmetics> to carry on the safety testing to the domestic cosmetics and import-export cosmetics. But, we are also constantly making progress in alternatives for cosmetic safety assessment. SFDA has issued the new policy that does not force the animal test in 2014 for cosmetics safety assessment. About 11 relevant industry standards have been published and used. We gained practical experience in method establishment, validation, transformation, international cooperation in last ten years, although there is a gap with international steps. In some testing institutions, the alternatives have been carried out daily, even using the latest OECD standards and Integrated test. We have completed a validation work on Episkin (China) model for dermal irritation test in 2012 according to OECD protocol between 5 labs. They are all good jobs to build the foundation for Chines alternatives work. Of course, only a small part of the body has ability to do so. In order to match international regulations, trade needs, and animal welfare, to enhance efficiency, we may need to make new pattern to do better. We should take part in the international or regional cooperation organization so that join more validation work, share information, collaborate for method establishment, and results of recognition, etc. Inside China, we should continue to promote non-animal test idea, strengthening cooperation among universities, testing institutions, research institutions. As the Chinese government called for the development of the real economy, more and more Chinese cosmetics enterprises will be get bigger. Giving companies more idea about non anima test is very important at the present. This is conducive to the companies can reasonably choose the test method, and understanding. In today's China, this is still entirely government oriented thinking. And, that's just what needs to be changed.

AS3-6 Development of alternative test methods to evaluate the safety of cosmetics

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Since European laws related to cosmetics were revised in 2013, it has become more important to evaluate the safety of cosmetic products and ingredients by employing alternative test methods (ATMs). The Ministry of Food and Drug Safety (MFDS) also revised regulation on functional cosmetics in 2013 to accept ATMs as an appropriate tool to assess the safety of cosmetics. This year, the Cosmetics Act was amended with the aim of banning animal testing. The Korean Center for the Validation of Alternative Methods (KoCVAM) joined the International Cooperation on Alternative Test Methods (ICATM) in March 2011 and has participated in 4 validation management teams and 10 peer review teams led by ICATM partners. KoCVAM, together with the MFDS, is making efforts to promote the regulatory use of ATMs for cosmetics. The MFDS has constantly adopted harmonized OECD ATM guidelines and offered regular educational programs in order to disseminate ATMs in Korea. Since 2007 until now, a total of 12 OECD Test Guidelines have been introduced in Korea for the safety assessment of cosmetic ingredients and products. The *In Chemico* Skin Sensitization Test Method (Direct Peptide Reactive Assay) was adopted in April this year. In addition, the LLNA:BrdU-FCM developed in Korea was approved for its inclusion in the OECD work plan at the 28th WNT meeting in April 2016. KoCVAM will actively cooperate with ICATM members to develop ATMs that reflect the 3R principles for regulatory purpose and enhance animal welfare.

AS3-7 Guidance on use of alternative methods for testing in the safety assessment of cosmetics and quasi-drug

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According to the MHLW (the Ministry of Health, Labour and Welfare) notification, Japan in 2011, JaCVAM (Japanese Center for the Validation of Alternative Methods) decided to accelerate new *in vitro* testing methods to take advantage of this opportunity to strongly impact testing throughout Japan. Therefore, the members are coordinating the Guidance on the use of alternative test methods in safety assessment of cosmetics and quasi-drugs since 2012. The members have consists on dermatologists, delegates of cosmetic companies, the technical officers of PMDA (Pharmaceuticals and Medical Devices Agency) and specialists of NIHS (National Institute of Health Sciences) and this member is on-going to make drafting the guidance based on the OECD test guideline and/or JaCVAM evaluation document per each alternative test method.

Until now, the following guidances have been approved by MHLW.

- ✓ "Guidance on the use of alternative test methods for skin-sensitization and phototoxicity in safety assessment of cosmetics and quasi-drugs (Appendix 2: Guidance on the use of the in vitro 3T3 NRU phototoxicity test as an alternative test method in safety assessments of cosmetics and quasi-drugs)" dated April 26, 2012
- ✓ "Guidance on the use of alternative test methods for skin-sensitization (LLNA:DA, LLNA:BrdU-ELISA) in safety assessments of cosmetics and quasi-drugs" administrative notice dated May 30, 2013,
- ✓ "Guidance on the use of the Bovine Corneal Opacity and Permeability (BCOP) test as an alternative method for testing ocular irritation in the safety assessment of cosmetics and quasi-drugs" dated February 4, 2014
- ✓ "Points of consider for ocular irritation testing in the safety assessment of cosmetics and quasi-drug, dated February 27, 2015
- ✓ "Guidance on use of the Isolated Chicken Eye (ICE) test as an alternative method for testing ocular irritation in the safety assessment of cosmetics and quasi-drugs" dated November 16, 2015

AS4-1 R&D status of alternative test methods for blood products in Korea

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Currently, animal tests are practiced for the lot release of blood products such as human serum albumin, immunoglobulin, coagulation factor, etc. The aim of our study is to develop alternative test methods for blood products.

We have studied an in vitro potency assay for human tetanus immunoglobulin(hTIG) which is administered for prophylaxis or treatment of tetanus. Its potency is most commonly determined by measuring toxin-neutralizing efficacy in animals. In line with the international effort to replace the use of animals, we set up an in vitro assay method based on an enzyme-linked immunoassay and conducted validation studies for the method. All validation parameters including accuracy, precision, specificity, linearity and range satisfied the defined specification. The comparison between in vivo and in vitro methods with 3 different hTIG products indicated very high correlation. In addition, in vitro potency data for 48 lots of hTIG final products satisfied the regulatory criteria for lot release. Taken together, these results suggest that the in vitro method could be a good alternative to the in vivo method.

We have also studied monocyte activation test(MAT) as an alternative for the rabbit pyrogen test(RPT). MAT is an in vitro test method measuring the amount of pyrogenic cytokines released from monocytes exposed to pyrogens. We have used cryopreserved rabbit peripheral blood mononuclear cells(PBMNC) as a source of monocytes and employed ELISA to measure the release of pyrogenic cytokines. We compared the results obtained by RPT and MAT for some critical pyrogens, and examined the possibility to replace RPT to MAT by correlation analysis. The results show that: (1) Rabbit PBMNC worked satisfactorily. (2) The secretion of pyrogenic cytokines such as IL-1beta, IL-6, TNF-alpha were increased in proportion to increase of the concentration of the pyrogens. (3) Increase of pyrogenic cytokines released in MAT is highly correlated with the temperature rise in RPT.

AS4-2 Alternatives and refinement for animal experimentation in cancer research

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Globally cancer is a major public health issue and is a second biggest cause of deaths. Cancer researchers plays important role in investigating new modalities of diagnosis and treatment. This includes discovering the faulty genes and molecules that cause cancer, investigating how the disease grows and spreads, developing and testing new treatment and tests, and exploring how our immune system can help fight tumours. Animal models have played a major role in understanding this disease and anticancer drug discovery. In cancer research most commonly used animal species are mice, rat, hamster, rabbit, Guinea pigs or fishes and amphibian. When animals are used for research, it is the moral duty of the scientist to avoid or minimize discomfort, distress, and painful situations. The regulations and policies help to ensure animals are treated humanely. If a procedure involves more than momentary or slight pain or distress, it must be performed using appropriate pain relieving drugs (e.g. sedatives, analgesia or anesthesia). In India the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) and Institutional Animal Ethics Committee (IAEC) has been instrumental in avoiding the animal usage or if not possible, to reduce the number of animals used for the experimentation. The IAEC also ensures that the number of animals used for the research in each groups are enough to yield statistically valid results; appropriate species of animal is used for the project; humane experimental endpoints have been established and appropriate methods of euthanasia are being utilized. Use of different cell lines in tissue culture system offers a great relief from use of animals at the same time provide important clues before embarking the animal experiments. Use of spontaneously developing tumor models like leukemia, lung cancer, brain cancer and breast cancer caused by MMTV or any other aetiology etc. are encouraged rather producing these diseases in the animals. Efforts are also targeted towards use of 'artificial tumor' tissue grown from the 'stem cells' or a combination of tumor cells and tumor stromal cells etc. Beside the alternatives, refinement also plays important role in reducing the animal usage in cancer research. Use of T- and B-cell deficient animals as shown by the use of flow-cytometry; use of rodent pathogen free animals; use of genetically proven animal models; use of appropriate no. of cells and volume for injection; use of appropriate route of injection; use of properly genotyped/ phenotyped animal models helps to reduce the no. of animals used for the respective research and also yield authentic and reproducible results. We are aware that avoiding animal usage is impractical. To some extent animal use can be minimised in cancer research. However, cancer research will always warrant use of whole body system to evaluate the new strategies for diagnosis and treatment of cancer. The lecture will highlight the available alternatives and refinements for animal experimentation and will end with a positive note that if coupled with the refinements, even a minimised number of animal usage shall also yield the meaningful and acceptable results.

AS4-3 Towards global harmonisation of 3Rs in biologicals – efforts of the EPAA Biologicals project team

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The European Partnership for Alternative Approaches to Animal Testing (EPAA) maintains a project team to promote the use and global harmonisation of 3Rs in the quality control of Biologicals, including vaccines. The Biologicals team convened an international workshop in 2015 which achieved consensus to actively encourage the deletion of general safety tests (e.g. abnormal toxicity tests in mice and/or guinea pigs, target animal batch safety tests) for vaccines from legal requirements and guidance documents, such as pharmacopoeia monographs, World Health Organisation (WHO) recommendations, and World Organisation for Animal Health (OIE) guidelines.

These tests have become obsolete through the introduction of Good Manufacturing Practice and, most importantly through the use of adequate and stringent quality control measures. Advanced process understanding, in-process controls, validation of the manufacturing process and release testing complying with international standards are also part of modern vaccine development and render the general safety test in animals obsolete.

With respect to vaccine potency tests, workshop participants identified international convergence on the scientific principles of the use of appropriately validated in vitro assays in place of in vivo methods as overarching goal. In pursuing this goal, it was considered essential to include key regulators and manufacturers early on in the corresponding discussions. As an outcome of such discussions, collaborative studies to advance new assays should be initiated as appropriate.

The presentation will summarise the scientific background to the recommendations and key conclusions of the workshop* and will report on the important follow-up steps launched at the level of the European Pharmacopeia and WHO.

* link to the workshop report:
https://circabc.europa.eu/sd/a/4a081e45-f19f-47f7-8d8d-65f4f10fccff/ihb%20sept%202015%20report.pdf

AS4-4 3Rs in quality control of human vaccines: opportunities and barriers

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The 3Rs principles – Replacement, Reduction, Refinement – have been established in 1959 and since then have been adopted widely and particularly in Europe with the European Directive 2010/63/EU. The demand for implementing 3Rs is not only coming from legislators but also the general public who is more and more sensitive on the ethics of animal use in research, as in other fields. The vaccine industry has been committed to the 3Rs principles for several years, including animal welfare as well as for reducing and replacing animal use in research, non-clinical safety and analytical testing.

Whereas animal testing has been successfully removed from lot release testing of well-characterized human vaccines, large numbers of laboratory animals continue to be used for safety and potency quality control testing for established inactivated vaccines such as rabies, pertussis, diphtheria, and tetanus.

Moreover, specifications for human vaccine batch approval often differ for various parts of the world, resulting in either duplication of animal testing or partial implementation of 3Rs for some vaccines when distributed worldwide. This reinforces the need for enhancing international harmonization and cooperation efforts in order to support more rapid progress towards worldwide reduction, refinement, and replacement of animal use for human vaccines testing.

The presentation will briefly review the use of laboratory animals in human vaccines research and testing and will describe the vaccine manufacturing industry's commitment and its concrete programs for implementing 3Rs principles in R&D and industrial operations processes. It will highlight the successes as well as the barriers that are encountered when implementing 3Rs principles, as well as the ongoing efforts that include external collaborations with other industries, public organizations and Health Authorities for the acceptance of alternative methods.

AS4-5 Veterinary industry approach to 3Rs in biologicals

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The 3Rs and animal welfare are key to the animal health pharmaceutical industry. In the context of biologicals the main area where animals are still used, with the exception of product registration, is in the routine batch release testing. Advances in manufacturing quality controls through GMP and in science and technology mean that it is now possible to move towards a much more integrated consistency approach to quality control. The approach is based on building in quality through the process to reduce the need for animal tests on finished product to ensure safety and efficacy. The target animal batch safety test has already been removed by VICH and industry and regulators are working on other alternative testing approaches for potency testing. The presentation will outline the in vitro first approach that industry now takes to batch testing but also outline the challenges faced in transitioning old products to new tests and in addressing questions such as stability with in vitro testing. Examples of types of technology being used will be provided along with some of the collaborative projects running in Europe on specific areas to develop and validate new tests. In vitro test methods provide many benefits to industry and should ultimately improve the quality and consistency of biological products (mostly vaccines).

AS4-6 VICH (International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Products) and harmonization of criteria to waive TABST(Target Animal Batch Safety Test) for vaccines for veterinary use

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VICH is "International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Products", an international program between the US, Japan and the EU with Australia, New Zealand, Canada and South Africa as observers. It brings together in a unique discussion Forum the Regulatory Authorities and Industry representatives from these countries/regions.

The role of VICH is to harmonize technical requirements for data necessary for registration of a veterinary medicinal product through the development and implementation of VICH Guidelines with the objective to establish and implement harmonized requirements for veterinary medicinal products in the VICH regions. The requirements meet high standards of Quality, Safety and Efficacy to protect animal health & welfare, public health and the environment, by minimizing the use of test animals and costs of product development.

In 2007 the VICH Steering Committee agreed a "Statement of principle on 3Rs", reiterating its ambition to minimize animal testing and specifically expressed its support for the 3Rs principle – replacement, refinement and reduction of animal in research.

General batch safety test for veterinary vaccines as the Laboratory Animal Batch Safety Test (LABST) or the Target Animal Batch Safety (TABST) has been required to demonstrate that a vaccine does not cause abnormal local or systemic reactions in the VICH regions through the ages. However, the LABST had been removed from European Pharmacopoeia monographs for veterinary vaccines in 1997, and the TABST in a stepwise approach until its complete deletion in 2013. From these backgrounds, Europe proposed to VICH to aim at harmonization of general batch safety tests across the VICH regions in order to minimize the need to perform separate studies for regulatory authorities of different countries. Due to the great divergence in requirements between the regions, it was concluded to a stepwise approach with the first step to harmonize the criteria on data requirements for waiving of the TABST for **inactivated vaccines** in regions (US and Japan), and respective VICH GL50 came into force in 2014.

A comparable guideline for **live vaccines** is under development and discussions on steps towards waiving possibilities for LABST are ongoing.

AS5-1 The use of Adverse Outcome Pathways (AOPs) to support chemical safety decisions within the context of Integrated Approaches to Testing and Assessment (IATA)

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There are scientific, social, economic, practical and regulatory pressures stimulating the development and use of streamlined chemical testing and assessment approaches, including increased reliance on non-animal methods. Advances in biological understanding as well as in experimental technologies (e.g. 'omics tools, cell culturing, reconstructed tissues) have allowed the consideration of dramatically different approaches to chemical safety assessment than those traditionally practiced. Increasingly, combinations of non-testing and non-animal test methods are replacing apical animal tests. The Organization for Economic Cooperation and Development (OECD) is developing guidance and coordinating the infrastructure to support this approach, first by organizing the development of Adverse Outcome Pathways (AOPs). An AOP is the collected chemical and biological information about a particular biological pathway. The OECD has developed guidance for building and assessing AOPs, and is coordinating development of the AOP Knowledge-base (AOP-KB) for collecting and using this information. The goal is to collect as much AOP-related information as possible, ultimately linking AOPs through common Key Events to form a more complete description of biology. The AOP-KB also accepts information about the perturbations of these pathways caused by chemical exposure – information can be used to design prediction models. AOPs can form the logical basis for the integration of information and the design of integrated testing strategies (ITS), within the context of an integrated approach to testing and assessment (IATA), to inform hazard or risk determination. An IATA is designed to address a specific question, and may include exposure or regulatory considerations, depending on the context. AOP-supported IATA can improve the efficiency of hazard or risk assessment by focusing testing on needed information and improve confidence in decisions by providing weight-of-evidence support. Regulatory application of IATA can also facilitate harmonized use of new, non-animal methods and strategies. The OECD AOP and IATA for skin sensitization is a potential example: the OECD has published the AOP and guidance for using it to support chemical categories and ITS. An IATA for skin sensitization is in development by the European Union Reference Laboratory for alternatives to animal testing (EURL-ECVAM); interim results suggest that an AOP-supported IATA containing an ITS of three non-animal methods can predict human results better than animal tests.

AS5-2 Progress of alternative study in China

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In the presentation, it introduced the progress of alternative study in China. At 1997, the basic concept of alternative method was described for the first time in the certain proposal regarding the development of laboratory animal science issued by China State Commission of Science and Technology. The alternative to animal experimentation as a project has been brought into the State plan of scientific research management. In 2001, in national program in the construction of condition for science and technological research addressed establishment of regulation for animal welfare, which is put forward clearly and definitely as an important content of legal management of laboratory animal. In the regulation for laboratory animal, alternatives to lab animal as one part of animal welfare is added in the document. Also, the government provided funds to support the explorative research in this aspect. There were a lot progresses in cosmetic evaluation and drug safety assessment.

AS5-3 Mechanism based evaluation system for hepato- and nephrotoxicity or carcinogenicity using omics technology

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A number of chemicals are existing in our surroundings and are needed to be served for the assessment for safe use, while most of their hazard information are limited. Accordingly the development of efficient hazard assessment system for chemicals has been required. Especially, a promotion of the 3Rs (Replacement, Reduction, Refinement) policy and development of promising in vitro alternative test methods are moving forward in the fields of toxicological studies. Therefore, we have been developing a carcinogen prediction systems based on the gene expression profiles focusing on omics technology that enables mechanism based evaluation of toxicity by using reduced number of animals and multiple toxicological endpoints in an animal study. We participated the 5-year ARCH-Tox project of the Ministry of Economy, Trade and Industry (METI) as Tox-Omics aiming to develop a new testing approach that allows evaluation of the multiple endpoints (hepato-/ nephrotoxicity, carcinogenicity and neurotoxicity) in a 28-day repeated dose toxicity study by some set of marker genes selected based on toxicity mechanism such as MoA (Mode of Action) / AOP (Adverse outcome pathway).

We report here the development process of mechanism based evaluation system focused on chemical induced hepato- and nephrotoxicity or hepatic and renal carcinogenicity by using gene expression analysis with DNA microarray. As a case study, MOA/AOP was constructed from the gene expression profile and histopathological findings of carbon tetrachloride (hepatotoxicity) and cisplatin (nephrotoxicity). Consequently, we developed an advanced toxicity evaluation system for hepato- and nephrotoxicity or hepatic and renal carcinogenicity based on toxicity mechanism. We also developed a new prediction system named "CARCINOscreen®" for evaluating the carcinogenic potentials of chemicals using the gene expression profiles of liver and kidney from rats after a 28-day repeated administration. The prediction system could predict the carcinogenicity potential of training chemical set including carcinogens and non-carcinogens with an accuracy more than 90%.

The marker genes established in this study are promising to develop new effective in vitro testing methods in future. Furthermore, metabolomics and proteomics techniques may be powerful tools for identification of toxicity mechanisms since the changes in gene expression levels may not always relate with the phenotype.

AS5-4 Stem cells and alternatives

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Toxicity tests are necessary for assessing the safety or hazards of several substances in various fields. Alternative tests based on the 3R principles (reduction, refinement, and replacement) have been proposed to overcome some of the drawbacks of animal experiments and avoid unethical procedures. Developmental toxicology is an important field to assess undesirable effects on the development of an organism, including malformation, growth retardation, embryo lethality, and malfunction. In vitro systems for testing developmental toxicity are capable of providing more rapid, precise, and relevant information than some animal studies, are an economical approach characterized by a low compound requirement and short duration, and are classified into: cell culture (e.g., EST), organ culture (e.g., MM assay), and embryo culture (e.g., WEC assay, CHEST and FET). Embryonic stem cells (ESCs) have the capacity to self-renew and the ability to generate differentiated cells. Embryoid bodies (EBs) act as the onset of differentiation and are useful for evaluation of developmental toxicity. Two types of stem cells—mouse and human ESCs—were used to screen the developmental toxicity of chemicals. Mouse EST suggested by ECVAM has been used to assess the 50% inhibitory dose of chemicals in three endpoints; viability of undifferentiated ESCs (IC_{50} D3) and mouse fibroblasts (3T3 cells, IC_{50} 3T3), and differentiation of ESCs into cardiomyocytes (ID_{50}). In our study, the area of mouse EBs replaced cardiomyogenesis of ESCs to reduce the need for time-consuming and laborious processes. Twenty compounds, including non-embryotoxic and embryotoxic/teratogenic chemicals, were evaluated by this modified EST, termed EBT. Section images of EBs were obtained using a phase-contrast microscope and EB area was analyzed using image analysis software. The area of EBs was dose-dependently reduced by chemicals, and ID_{50} mEB value is derived from the logarithmic graph. To evaluate and classify the developmental toxicity of chemicals, our EBT-based prediction model reflected inhibition of cell viability and reduction in EB area. To compensate for species-specific differences between human and mouse, human ESCs were used to assay the developmental toxicity of well-known chemicals: dexamethasone, hydroxyurea, indomethacin, cytosine arabinoside, 5-fluorouracil (positive control), and penicillin G and ascorbic acid (negative controls). Human EST assays involved three end points; the doses that reduced viability by 50% (IC_{50}) in undifferentiated and differentiated human ESCs and in human fibroblasts (hMRC-5). To examine the effects of toxicants on cellular functions, hybridization to Affymetrix GeneChips of samples exposed to toxic (5-fluorouracil and indomethacin) or non-toxic chemical (penicillin G) for 5 days was performed. The development, cell cycle and apoptosis-related transcriptome were significantly changed by toxicants. In conclusion, exposure to toxicants results in increased cell death and inhibition of cardiac differentiation in both mouse and human ES cells. Developmental toxicity testing using human ES cells can be used to overcome the problems caused by differences between species. Mouse EBT is a novel toxicological screening system, and will facilitate rapid evaluation of embryo-toxic compounds.

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AS5-5 Futuristic approach to alternative model organisms: Hydra stakes its claim

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Use of mammalian models for toxicological risk assessment of chemicals is in practice for well over 50 years. The data generated in these models are meant for extrapolation to humans. This practice has all along remained controversial in view of the species differences. The advances in molecular biology techniques have revolutionized the toxicological risk assessment with rapid, less expensive and highly relevant systems to evaluate the risks imposed by the toxic chemical substances even at low concentrations in a manner very precise. These advances urged the U.S. EPA and NRC to develop a strategy and vision for toxicity testing in 21st century. The EU also has come up with the REACH legislation. Tox-21c and REACH legislation envision a paradigm shift in toxicity testing and propose the use of emerging technologies based on non-animal methods for better understanding of chemical-environment interaction, and also emphasize the adoption of animals belonging to the lower levels of taxonomic hierarchy, which are lesser sentient, for *in vivo* toxicity testing. Motivated by these developments we aimed at establishing hydra, a simple organism belonging to Phylum Cnidaria, as a model organism for toxicity testing of chemical entities. Hydra, with its simple body structure and biology, is simpler than the vertebrate animal models but much complex compared to the cultured cells which make it an amenable system for assessment of chemical entities. Besides, hydra offers advantages such as easy to culture, reproduces fast, cost-effective and highly sensitivity to inorganic pollutants. Moreover, the whole genome sequence of hydra revealed that most of the genes are conserved in which sense it offers advantage over even in the most routinely used invertebrate model organisms such as *Caenorhabditis elegans and Drosophilla melanogaster*. The data to be presented, generated in our lab during the past few years,have demonstrated the suitability of hydra for toxicity testing of nanomaterials as well as their bulk counterparts.We have standardized a number of assays which measure responses to exposure of chemicals at whole organismal, developmental, physiological, cellular, behavioral and molecular levels. Acute and chronic studies performed with sub-lethal doses demonstrated that hydra can be used as viable bio-indicator for early warning of pollutants. ROS, as the main causative factor underlying multiple manifestations of toxicities of the chemicals, has been shown to be generated in the lysosomes. Moreover, a suite of molecular assays affirmed that DNA damage, cell cycle arrest and apoptosis are the sequel to chemical exposure-induced ROS as is the case in higher animal models. Thus, the use of hydra as a viable organism to elucidate the mechanism of toxicity infliction by environmental chemicals would aid in the bettering of aquatic chemical risk assessment.

YSA : Award Winners Session

Session: Nov.16, Wed 10:40-11:40
Venue: Room B (Conference Room 1/4F)
Chairs: Hiroaki TODO, Faculty of Pharmaceutical Sciences, Josai University, Japan
Horst SPIELMANN, Inst. For Pharmacy, Faculty for Biology, Chemistry and Pharmacy, Freie Universität Berlin, Germany

JCIA award

Sponsored by Japan Chemical Industry Association (JCIA)

Jin Yong AN (Chungbuk National University, Republic of Korea)
Evaluation of toxicants for the neural differentiation of human ESCs

(ref. p.198 poster P-79)

JAVA award

Sponsored by Japan Anti-Vivisection Association（JAVA）

Sae On KIM (College of Pharmacy, Seoul National University, Republic of Korea)
Preliminary Evaluation of Vascular Endothelial Growth Factor as a Biomarker for Alternative Skin Sensitization Test in HaCaT Keratinocytes

(ref. p.201 poster P-82)

JSAAE award

Sponsored by Japanese Society for Alternatives to Animal Experiments (JSAAE)

Fumiya TAO (Yokohama City University, Japan)
The effect on cellular function and microstructures of hepatic spheroids by using a novel method for loading ECM thin layer into spheroids

(ref. p.184 poster P-64)

In Vitro Testing as a Scientifically Advanced Strategy for Regulatory Safety Compliance and Claim Support in the Global Cosmetics Industry

C. L. TREASURE, B. SIM, N. BELOT, A. EDWARDS, C. ROSCOE, C. LONGMORE

XCellR8 Ltd, The Innovation Centre, Sci-Tech Daresbury, Keckwick Lane, Daresbury, Cheshire WA4 4FS, UK

There is currently a global shift towards non-animal tests for both safety and efficacy (claim support) within the cosmetics and personal care industry. In addition to the ethical advantages of moving away from animal testing, *in vitro* methods provide a scientifically advanced route to compliance with a range of key legislation, including the European Cosmetics Regulation 1223/2009 and REACH. Many *in vitro* safety tests now have full international approval in the form of OECD Test Guidelines, for key endpoints including skin and eye irritation, skin corrosion and sensitisation. In addition, non-regulatory methods can provide extremely valuable information at an early stage of the product development process, in terms of both safety profiling and efficacy assessment for claim support purposes. *In vitro* studies using human cells enable the generation of data with direct relevance to human responses, giving detailed mechanistic information about interactions of finished products and ingredients with the human body. XCellR8 is a UK-based laboratory exclusively devoted to *in vitro* testing, with Good Laboratory Practice (GLP) accreditation to conduct regulatory safety testing for the global market. The company is committed to the full replacement of animal-derived components in cell culture methods to provide fully human-based *in vitro* models. XCellR8 works with Lush and a number of other leading cosmetic companies and ingredient suppliers, enabling them to comply with legislation and create safe and innovative new products.

A-LS 1 Unique cell culture techniques for *in vitro* research

Shigehisa AOKI

Department of Pathology & Microbiology, Saga University

Cell culture is a well-established standard technique and a fundamental tool in biology. Challenging of a novel culture technique can open up new fields of cosmetics, pharmacology and medicine. To mimic biological microenvironment, an artificial microenvironment for cultured cells is consists of complicated factors, including cell–cell interactions, liquid factors, scaffold material, and physical stress. To solve the important problem, we previously established novel techniques and demonstrated the effectiveness of a three-dimensional culture system, and further established two simple culture techniques: air–liquid interface (ALI) and fluid flow stress (FFS). A three-dimensional collagen gel culture techniques can easily replicate cell–cell interactions in vitro. As skin is constantly exposed to air, the ALI system closely mimicked the physical circumstance of skin and maintained the homeostasis of the epidermis and dermis. The ALI culture system also clarified the possibility of skin regeneration through ectopic mesenchymal cell involvement. Fluid streaming and shear stress were recently demonstrated to constitute the critical microenvironment for various cell types. The FFS culture technique demonstrated that fluid streaming induced epithelial–mesenchymal transition of mesothelial cells, leading to peritoneal fibrosis. Our novel culture techniques will hopefully open up new fields of cosmetics, pharmaceutical development and medicine.

A-LS 2 An introduction to the Lush Prize 'Young Researcher Asia' Awards

Rebecca RAM

Scientific Consultant, Lush Prize UK

The Lush Prize is very pleased to attend the 29th Annual Meeting of the Japanese Society for Alternatives to Animal Experiments and announces the launch of the **Young Researcher Asia Awards**.

The award welcomes young scientists from across Asia, up to 35 years old at time of application, who wish to follow a career in animal-free toxicology. Applicants complete a nomination explaining their research, including how they would use a bursary of approx. 1,800,000 JPY (10,000 GBP). To date, a total of 37,800,000 JPY (210,000 GBP) has been awarded to nineteen international young researchers for 21st century toxicology projects.

Many scientists find that access to funding for research into non-animal technologies can be a barrier. The Lush Prize wants to change this, and encourage young researchers to develop a career in toxicology without harming animals by offering bursaries to allow them to advance in this area.

The Lush Prize is now in its fifth year and awards a total of 45,000,000 JPY (250,000 GBP) annually to initiatives working to end the use of animals in toxicology testing. There are six categories of award: Science; Training; Young Researcher; Lobbying and Public Awareness. The sixth category is the Lush Black Box Prize which offers, in any one year, the full 45,000,000 JPY for a key breakthrough in human toxicology. The Prize has been very pleased to award winners from across the Asia region previously. For further details please visit http://www.lushprize.org/past-years/

Many initiatives are directed at the '3Rs': reduction, refinement, and replacement of the use of animals. The Lush Prize seeks only to support projects working on the *genuine replacement* of animal tests and is the largest reward in its field.

Nominations open for the Lush Prize open in April each year. Judging is carried out by a panel of experts from around the world – scientists, politicians and campaigners. Winners participate in a conference and attend a prestigious awards ceremony. Full details of the Young Researcher Award http://www.lushprize.org/awards/young-researcher-prize/ and other award categories are available on the Lush Prize website www.lushprize.org

Asian Congress 2016

謝　辞 ／ Acknowledgements

本大会を運営するにあたり，下記の企業もしくは団体様から
格別なご協力をいただきましたことを，ここに記して深謝いたします.

The 29th Annual Meeting of Japanese Society for Alternatives to Animal Experiments (29JSAAE) would gratefully acknowledge the following companies and organizations for financial and in kind contributions received in support of the Congress.

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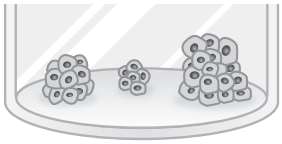

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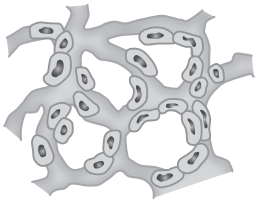

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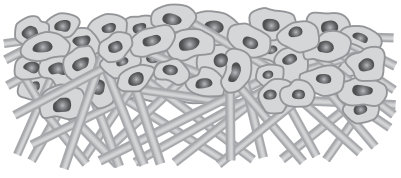

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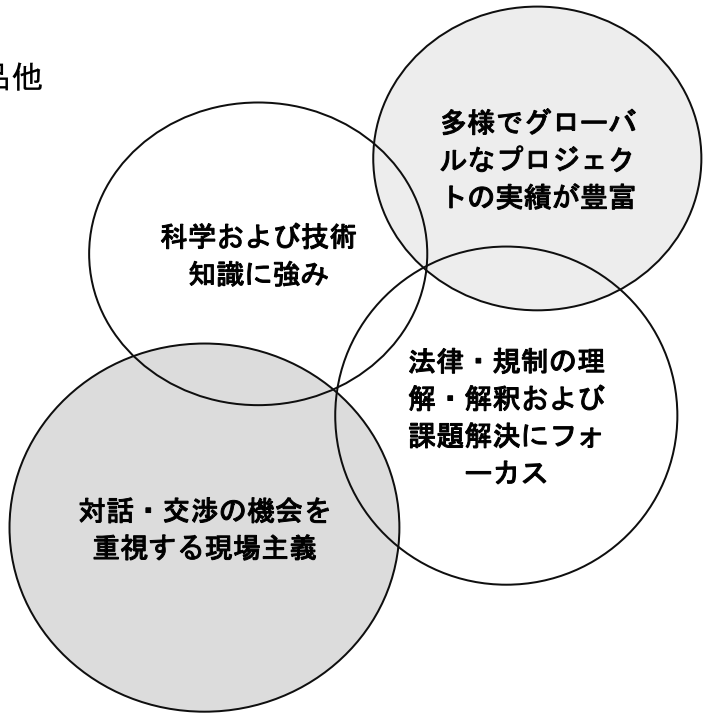

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