ImmunoTox Letter Digest

December, 2015

Report from the 22nd Annual Meeting of the Japanese Society of Immunotoxicology (JSIT2015)

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The 22nd Annual Meeting of the Japanese Society of Immunotoxicology (JSIT2015) was held at International Clock Tower Centennial Hall International Conference Hall, Kyoto University, Kyoto during September 10-11, 2015. The main theme of this meeting was "Revolutionary perspectives in the field of Immunotoxicology -Toxic effects and Disrupting effects-". The meeting consists of a special lecture, 2 educational lectures, one symposium and workshop, 2 luncheon seminars, JSIT Research Award Lectures, 11 oral presentations and 16 poster presentations including 3 student and young scientist presentations.

Special lecture

The influence of early immune signaling and the microbiome on immunomodulatory responses following exposure to the antimicrobial triclosan

(Stacey E. Anderson, NIOSH, Morgantown, WV)

Master's Lecture

1. Stress signaling and disease

(Hidenori Ichijo, Laboratory of Cell Signaling, Graduate School of Pharmaceutical Sciences, University of Tokyo)

2. Airborne fine particles and allergic rhinitis: elucidation of allergic rhinitis exacerbation mechanism and the development of therapeutic techniques using mouse model of allergic rhinitis

(Tomohiro Yoshimoto, Department of Immunology, Hyogo College of Medicine. Laboratory of Allergic Diseases, Institute for Advanced Medical Sciences, Hyogo College of Medicine)

Symposium

"Toxic' effect to 'disrupting' effect"

1. Aggravating effects of Asian sand dust and PM2.5 on lung inflammation and allergic inflammation

(Takamichi Ichinose, Department of Health Sciences, Oita University of Nursing and Health Sciences.)

2. Environmental chemical-induced inflammatory response and disruption of immune cell function

(Eiko Koike, Center for Environmental Health Sciences, National Institute for Environmental Studies)

3. Impact of exposure to environmental chemicals on obesity and obesity-related metabolic disorders.

(Rie Yanagisawa, Center for Environmental Health Sciences, Biological Impact Research Section)

4. Effects of prenatal and lactational exposure to low-doses of bisphenol A on murine brain development

(Kyoko Itoh, Department of Pathology and Applied Neurobiology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine)

5. Reproductive and endocrine disruption induced by environmental chemicals

(Taisen Iguchi, Okazaki Institute for Integrative Bioscience, National Institute for Basic Biology, National Institutes of Natural Sciences)

Workshop: “Immunotoxicity testing Q and A”

0. Immunotoxicity testing Q and A.

(Shigeru Hisada, Research and Development Division, ASKA Pharmaceutical Co., Ltd.; Tadashi Kosaka, Study Management Division, The Institute of Environmental Toxicology)

1. Current status of flow cytometry measurement at clinical laboratories

- To think about non-clinical measurement items -

(Atsushi Momobayashi, Molecular Genetic Analysis Department, LSI Medience Corporation)

2. Immunologic tests and evaluation of the risk for chemical-induced autoimmunity induced by chemicals in human

(Minoru Satoh, Department of Clinical Nursing, School of Health Sciences, University of Occupational and Environmental Health, Japan)

3. A case of evaluation of the immunotoxicity data having wide variations such as the production of antibody

(Takumi Ohishi, Gotemba Laboratory, BoZo Research Center Inc.)

4. Appropriate trial plan and analysis method for TDAR

(Satoru Fukinbara, Data Science Expert Committee, Drug Evaluation Committee, JPMA, Data Science Development Headquarters, Ono Pharmaceutical Co., LTD.)

In this year, “JSIT Research Award” was received by Dr. Jun-ichi Sawada (Pharmaceuticals and Medical Devices Agency). Title: Effects of genetic polymorphisms on anti-cancer drug-induced myelotoxicity.

“JSIT prize for encouragement” were received by Dr. Etsushi Kuroda, (Laboratory of Vaccine Science, WPI Immunology Frontier Research Center, Osaka University, Osaka), Title: The underlying mechanisms of particulate-induced immune responses and inflammations -Particulate adjuvant and immunotoxicity-, and Dr. Rie Yanagisawa (Center for Environmental Health Sciences, Biological Impact Research Section), Title: Impact of environmental pollutants on lifestyle related diseases -from the point of view of immunotoxicology-.

“The Best Presentation Award” was received by Dr. Eita Sasaki (Department of Safety Research on Blood and Biologicals products, Institute of Infectious Diseases). Title: Establishment for a next generation safety evaluating method for influenza vaccine and adjuvants using humanized mouse model.

“The Student and Young Scientists Award” was given to Mr. Takato Kusakabe (Laboratory of Adjuvant Innovation, National Institute of Biomedical Innovation, Health and Nutrition (NIBIOHN), Laboratory of Vaccine Science, Immunology Frontier Research Center (IFReC), Osaka University). Title: Application of hydroxypropyl-β-cyclodextrin, a small compound as a potent DAMPs inducer, for mucosal adjuvant.

I would like to appreciate all the participants who actively joined presentations and discussions.

The Best Presentation Award

Establishment for a next generation safety evaluation method for influenza vaccine and adjuvants using humanized mouse model

Eita Sasaki[1], Takuo Mizukami[1], Haruka Momose[1], Kazunari Kamachi[2], Hiroshi Yamada[3], Ken J Ishi[4,5], Isao Hamaguchi[1]

[1]Department of Safety Research on Blood and biologicals products, Institute of Infectious Diseases
[2]Department of Bacteriology II, Institute of Infectious Diseases
[3]National Institutes of Biomedical Innovation, Health and Nutrition. Toxicogenomics and Informatics Project
[4]National Institutes of Biomedical Innovation, Health and Nutrition. Laboratory of Adjuvant Innovation
[5]Laboratory of Vaccine Science, Immunology Frontier Research center, Osaka University

Aim: Vaccination is a most beneficial and universal tool to prevent infectious disease. To ensure the safety of vaccinations, the abnormal toxicity test (ATT, also known as general safety test) have introduced to the vaccine rot release testing. Recently, many types of influenza vaccines and adjuvants were developed to enhanced immunogenicity. To cover many types of influenza vaccine, we tried to develop new safety test using gene expression profiling. We successfully identified 20 biomarker genes to evaluate the safety of influenza vaccine. On the other hand, extrapolation of the result from animal experiment to human is important for safety assessment. Therefore, in present study, we attempted to establish a next generation safety testing method for vaccine and adjuvant using humanized mouse model.

Materials and Methods: Human peripheral blood mononuclear cells (PBMC)-engrafted NOG mice were used as a huPBL-mouse model. The vaccines using this study are following: inactivated whole trivalent influenza vaccine (WPV); HA influenza vaccine. The vaccine was intraperitoneally injected to the mouse at a dose of 0.5 mL/mouse. The day following the vaccination, the lung and blood were collected and analyzed leukocyte population, gene expression.

Results and Discussion: Stable engraftment of human PBMC in huPBL-mouse was observed after 2 weeks of transplantation. Both human CD4 and CD8 positive cells were also detected in the PB after 2 weeks transplantation. Similar to T cell lineage, $CD19^{+}$B cell could also be seen in the PB after 2 weeks after transplantation. We could detect more than 50% of human CD45 positive cells derived from donor human PBMCs at 3 weeks after the transplantation. These preliminary result suggest that vaccine treatment for safety evaluation should be carried out at 3 weeks after the PBMC transfer. In addition, the some biomarker genes expression were increased in WPV vaccinated mice compared with SA-treated mouse.

Based on these results, the new vaccine safety test method using Hu-PBL-mouse might be useful for safety assessment of human and the possibility of the extrapolation for the marker genes were partially indicated.

The Student and Young Scientists Award

Application of Hydroxypropyl-β-cyclodextrin, a small compound as a potent DAMPs inducer, for mucosal adjuvant

Takato Kusakabe

(Laboratory of Adjuvant Innovation, National Institute of Biomedical Innovation, Health and Nutrition (NIBIOHN), Laboratory of Vaccine Science, Immunology Frontier Research Center (IFReC),Osaka, Japan)

My name is Takato Kusakabe working in National Institute of Biomedical Innovation, Health and Nutrition (NIBIOHN). I am very happy and honored to be the best Young presenter Award at the 22th Annual Meeting of the Japanese Society of Immunotoxicology. I would like to appreciate the support from the selection committee and give special thanks to my research professor Dr. Ken Ishii, Dr. Etsushi Kuroda and other colleagues in my laboratory for supporting throughout the progress.

In this study, we tried to apply hydroxypropyl-β-cyclodexrin (HP-β-CD) for mucosal adjuvant. Mucosal vaccine is an attractive and valid alternative to current vaccines because it has a potential to induce local immune responses at the site of entry of the pathogens. However intranasal routes are generally less immunogenic and frequently induce tolerance. To resolve these problems, safe and effective adjuvants for mucosal vaccines are required. Recently, we reported that HP-β-CD has the adjuvant activity and induces antibody responses. This adjuvant effect is similar to Alum, which is the most widely used adjuvant in human. Because Alum is particle adjuvant, it is difficult to use for mucosal administration. Accordingly, taking advantage that HP-β-CD is soluble to water, we tried to apply HP-β-CD for mucosal adjuvant. We found that intranasal (i.n.) administration of HP-β-CD functioned as adjuvant and induced not only systemic but also mucosal immune responses. In addition, HP-β-CD by i.n. administration induced a low antigen-specific IgE responses. For the clinical use of HP-β-CD as mucosal adjuvant, intranasal administration of HP-β-CD-adjuvanted influenza hemagglutinin split and inactivated whole-virus influenza vaccine result in the secretion of vaccine-specific antibody and protected mice against a lethal challenge with influenza virus. These results suggest that HP-β-CD may be a potent mucosal adjuvant for seasonal and pandemic influenza vaccine.

Immunotoxicological Research

The effects of air pollutants on respiratory and immune system

Akiko Honda

(Kyoto University)

The aim of my study is 1) to elucidate the effects of air pollutants such as Asian sand dust particles (ASD) and particulate matter with aerodynamic diameter ≤ 2.5 μm (PM2.5) on respiratory diseases, especially asthma, 2) to clarify the mechanism by which air pollutants cause development/exacerbation of asthma, 3) to identify the responsible components and factors of air pollutants contributing to asthma. We provided evidence that ASD reduced cellular viability and facilitated pro-inflammatory responses in airway epithelial cells, and that ASD also activated the network of antigen presenting cells (APC) and subsequent immune response via lymphocyte. Furthermore, we indicated that the difference in the events of ASD and in heat-sensitive components adhered to ASD could enhance the health effects (J. Appl. Toxicol., 34:250-257, 2014). Subsequently, we examined the effects of

heat-sensitive components adhered to ASD such as Bjerkandera adusta (B.ad) or Benzo[a]pyrene (BaP) on respiratory and immune system. The research results indicated that B.ad rather than BaP contributed to development/exacerbation of asthma, especially to the immune system via APC.

The final goal of our research is to contribute to the prevention and treatment strategy of the health effects caused by air pollutants, and to suggestion of monitoring components.

Words from New councilors

Greeting to becoming a new councilor member

Kiyoshi Kushima

Drug Safety Research Labs., Drug Discovery Research, Astellas Pharma Inc.

I would like to take opportunity to express my sincere appreciation to the Board of Directors of the Japanese Society of Immunotoxicology for accepting me as a councilor. The approval gives me great pleasure.

I started research of immunology at Hiroshima University, where the role of $CD4^-CD8^-$ (double negative) T cell and γδ-T cell in the hormone-stress-immune network was explored. After joining to Astellas Pharma Inc., I have been engaged in an evaluation of adverse effect, especially immunotoxicology/developmental immunotoxicology of developing drugs. Throughout my research, effects on immune function of non-steroidal inflammatory drugs (NSAIDs) were indicated in rat pups exposed through dams. Further, my recent interest is to clarify the mechanism of drug-induced severe allergy/hypersensitivity, i.e. Stevens-Johnson syndrome and toxic epidermal necrolysisa, since these adverse events are sometimes fetal for patients. In addition to the research activities, I am involved in making Adverse Outcome Pathway (AOP) of immunosuppressant to develop the alternative test assay of animal testing, as a member of AOP committee of JSIT. I will continue to make an effort to work on drug allergy and immunotoxicolology with helpful advice and support from JSIT members.

Words from New councilors

Greeting to becoming a new councilor

Masahiro Takeyoshi

Chemicals Evaluation and Research Institute, Japan

I would like to thank members of the Board of Directors of the JSIT for accepting me to serve as a councilor. I started my career at Chemicals Evaluation and Research Institute (CERI) in Hita city, Oita Prefecture, engaging in Local Irritation, Sensitization and Antigenisity studies of chemicals. Then I am currently managing the development work for safety evaluation method for chemicals based on omics technology, such as genomics, proteomics and metabolomics, and assay methods for biological activities for biologics in a laboratory at Saitama Prefecture.

Guinea pig prediction test for skin sensitization of chemicals employs skin reaction as an endpoint to decide positive/negative judgment, and it may makes ambiguous judgment. My research driving force in these days was to clarify the judgment of sensitization test results. So I have tried to elucidate the antigen reactive lymphocyte by cytokine release after cloning the guinea pig interleukin-2 cDNA. And I also introduced the technique of local lymph node assay from Dr. Ian Kimber, and then developed the non-RI alternative of this method that was endorsed as OECD TG442b.

I will try to make meaningful contributions to the Japanese Society of Immunotoxicology. I hope to inspire your further guidance and encouragement.

Real Voices of International Immunotoxicologists

What non-Japanese scientists think about immunotoxicology? What they have experienced and will do future. Their comments would allow us to realize the significance of study about immunotoxicology. This time, we interviewed Dr. Stacey Anderson from National Institute for Occupational Safety and Heath, USA. Let's go to hear his voice. What do you feel and get from it?

Stacey Anderson, Ph.D.

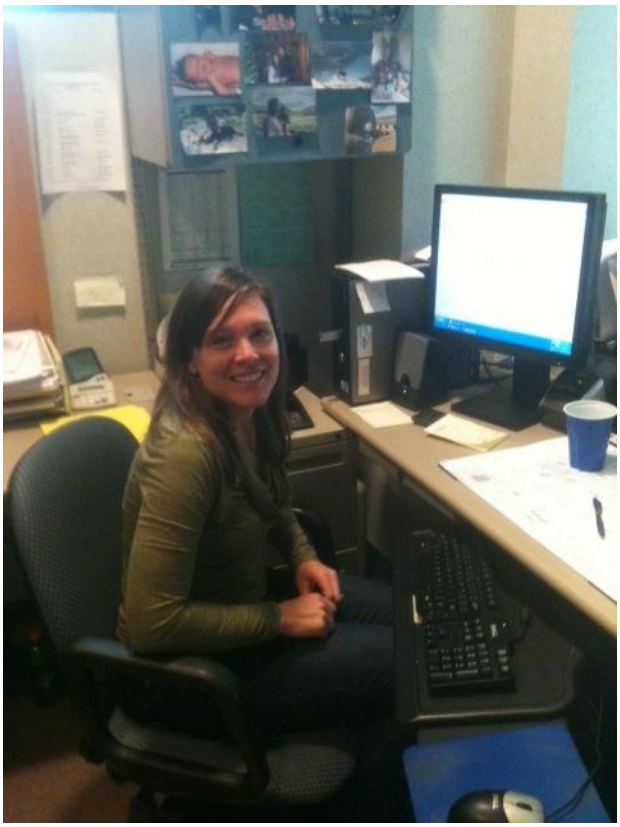
National Institute for Occupational Safety and Heath
Team Leader, Hazard Identification and Immunotoxicolgy
Allergy and Clinical Immunology Branch
1095 Willowdale Dr. M/S 4020
Morgantown, WV 26505

Q1. What was the most impressive event for you in your trip to Japan this time?

I would like to start by saying that my first trip to Japan was impressive in many ways. I found Kyoto to be a truly unique place with tremendous amounts of beauty and culture. In addition, the organizers and hosts of the meeting made my husband and I feel very welcomed. Their descriptions of the local cuisine and customs were much appreciated. I would also like to say that I was very impressed by the large number of immunotoxicologists in Japan especially since it is considered a relatively new field of science.

Q2. What is the most exciting thing in your career to date.

After 11 years in the field of immunotoxicology, I would have to say that the most exciting thing that has happen in my career is watching how my team has evolved during that time. I have mentored and worked with numerous technicians, student interns, and post-docs during that time. It is very rewarding to me to know that I have contributed to their success. My first doctoral student is planning to graduate in May and has already accepted a post-doctoral position in a very respected laboratory. It is a wonderful feeling to know that I was part of her growth and development into an independent thinking scientist.



Dr. Stacey Anderson

Q3. What are the things you are doing energetically, right now?

We have a lot going on in my laboratory right now! I used my lecture as an opportunity to try and capture the key areas of research that we are currently focused on and excited about. We are really interested in understanding how chemicals influence allergy and asthma. One important class of chemical that we have been interested in are antimicrobials and disinfectants. While this classification covers a very large number of chemicals, we have identified several conserved and unique mechanisms by which this kind of chemical can influence hypersensitivity responses. We feel that this research has identified several novel mediators of allergic disease such as the innate immune system, additional T-cell pathways, the microbiome, and regulatory RNA.

Q4. What is required for breakthrough in immunotoxicology research in the future, do you think?

Over the last decade there has been a remarkable increase in the incidence of allergic disease and one potential contributor is the increasing number of chemicals in production with an estimated 700 new chemicals introduced annually. Before we can reduce the incidence of this disease we must understand the responsible agents and the underlying mechanisms. The field of immunotoxicology is very dynamic especially with respect to the immunology component. It seems that something new is discovered every week in the field of immunology and that is why it is very important to stay on top of the current trends in this field. These new discoveries can provide important new areas of research for immunotoxicologists which may help us to better understand the effects of chemicals on the immune system. Recently components of the innate immune system have been identified to be important regulators of the adaptive immune response. However, there is very limited research investigating how chemicals affect the innate immune system and ultimately hypersensitivity or other abnormal immune responses. A better understanding of these aspects of the immune system may help to guide immunotoxicological research efforts. It is very important that we expand our way of thinking to encompass novel mediators of allergic disease, such as the innate immune system, in our efforts to treat and prevent chemical-induced immune disorders.