ImmunoTox Letter Digest

December, 2014

Report from the 21st Annual Meeting of the Japanese Society of Immunotoxicology (JSIT2014)

Seiichiro Himeno

Tokushima Bunri University, Fac. of Pharmaceutical Sci.

The 21st Annual Meeting of the Japanese Society of Immunotoxicology (JSIT2014) was held at International Conference Hall, Tokushima Bunri University, Tokushima, during September 11-12, 2014. The main theme of this meeting was "A Step forward in Imunnotoxicological Studies". The meeting consists of 2 special lectures, 1 educational lecture, symposium, workshop, 2 luncheon seminars, JSIT Research Award Lecture, 15 oral presentations and 23 poster presentations including 5 student and young scientist presentations.

Special lecture

1. Immunotoxicity of biologics. (Marc Pallardy, Universite Paris-Sud, France)
2. The mechanisms for zinc deficiency-associated dermatitis. (Tatsuyoshi Kawamura, University of Yamanashi, Department of Dermatology, Kofu, Japan)

Educational lecture

1. Molecular pathogenesis of hyper-IgE syndrome. (Yoshiyuki Minegishi, Institute for Genome Research, The University of Tokushima, Tokushima, Japan)

Symposium

"Next-generation Approach in Immunotoxicology"

1. Dynamics of complex biological systems determined/controlled by minimal subsets of molecules in regulatory networks. (Atsushi Mochizuki, Theoretical Biology Laboratory, RIKEN, Japan)
2. Chemical strategy for direct and indirect detection of protein-small molecule interactions: Drug target discovery and P450 substrate screening. (Naoki Kanoh, Graduate School of Pharmaceutical Sciences, Tohoku University, Japan)
3. A novel role of spleen-derived IL-10 in obesity-induced

The 22nd Annual Meeting of JSIT 2015 (Japanese Society of Immunotoxicology)

September 10–11, 2015

Kyoto University,
Clock Tower Centennial Hall International Conference Hall,
Kyoto-city, Japan.

Access:
http://www.kyoto-u.ac.jp/ja/access/campus/map6r_y.htm
Yoshida-Honmachi, Sakyo-ku, Kyoto, 606-8501

Theme:
"Revolutionary perspectives in the field of immunotoxicity -Toxic effects and Distrupting effects-"

The details of the 22nd Annual Meeting of JSIT 2015 are now under preparation. Two special lectures, 1 symposium, 1 educational lecture, and 1 workshop will be held.

Deadline for abstract submission:
June 26, 2015 (a tentative plan)

President:
Environmental Health Division,
Department of Environmental Engineering,
Graduate School of Engineering,
Kyoto University
Kyoto daigaku-Katsura, Nishikyo-ku, Kyoto 615-8540
Prof. Hirohisa Takano

Secretariat:
Akiko Honda
Phone: +81-75-383-3342
Fax: +81-75-383-3344
Email: jsit22-office@health.env.kyoto-u.ac.jp
Website: http://health.env.kyoto-u.ac.jp/jsit22-office (under construction)

systemic inflammation. (Koro Gotoh, Faculty of Medicine, Oita University, Japan)

4. New mechanism of action and potential biomarkers for vaccine adjuvant. (Ken J Ishii, Laboratory of Adjuvant Innovation, National Institute of Biomedical Innovation, Japan)

Workshop on Immunotoxicology Methods

"Toward the development of new test methods for xenobiotic-induced allergy and autoimmune diseases"

1. Autoimmune disorders and side-effects via immune systems that are caused by administering biotechnology-derived pharmaceuticals. (Tomoaki Inoue, Chugai Pharmaceutical Co. Ltd., Japan)
2. Splenic lesion in rats treated with antithyroid drugs – suggestive auto-antibody production. (Motoko Fukui, ASKA Pharmaceutical Co., Japan)
3. Animal model of immediate hypersensitivity induced by transdermal administration of food allergen. (Reiko Adachi, National Institute of Health Science, Japan)
4. The study of detection method for particulate environmental chemical-induced respiratory allergy. (Risako Nishino, The Institute of Environmental Toxicology, Japan)

In this year, "JSIT Research Award" was received by Dr. Motoyasu Ohsawa (Hatano Research Institute, Food and Drug Safety Center). Title: Immunotoxicity of environmental substances with special reference to heavy metals: Toxicological properties and evaluation. "The Best Presentation Award" was received by Dr. Eiko Koike (National Institute for Environmental Studies). Title: Effects of intratracheal exposure to bisphenol A on the immune system and central nervous system in a murine model of allergic airway inflammation. "The Student and Young Scientists Award" was given to Mr. Toshihiro Hirai (Graduate School of Pharmaceutical Sciences, Osaka University), Title: The effects of metal nanoparticles on onset of metal allergy, and Dr. Seiji Onuma (Graduate School of Pharmaceutical Sciences, Chiba University), Title: Preventive effects of the histamine H_4 receptor antatonist on worsening of itching induced by long-term topical glucocorticoid treatment.

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

Photos: http://p.bunri-u.ac.jp/jsit2014/photo.html

The Best Presentation Award

Effects of intratracheal exposure to bisphenol A on the immune system and central nervous system in a murine model of allergic airway inflammation

Eiko Koike[1], Rie Yanagisawa[1], Tin Tin Win Shwe[1], Hirohisa Takano[2]

[1]National Institute for Environmental Studies, [2]Kyoto University

Recently, experimental and epidemiological studies raise concerns about endocrine disruption and allergy related to exposure to chemicals in consumer products. Bisphenol A (BPA) is an environmental chemical which exhibits hormone-like properties. BPA is widely used in the manufacture of polycarbonate plastics and epoxy resins. These materials are found in some consumer products and food containers. BPA is being increasingly associated with adverse health effects including allergy such as asthma in children.

In the present study, we investigated the effects of intratracheal exposure to BPA (0.0625, 1.25, 25 nmol/body/wk) on the immune system and central nervous system using an allergic airway inflammation model induced by ovalbumin (OVA) in 6-week-old C3H/HeJ Jcl male mice. Following exposure to BPA, the changes of several parameters of the immune system and central nervous system were examined.

Co-exposure to OVA and BPA (low- and medium-dose) significantly enhanced airway inflammation and Th2 cytokine production such as IL-13, IL-33, KC, and RANTES, compared with OVA alone. OVA-specific Ig (IgE, IgG_1, IgG_{2a}) production was also tended to enhance by co-exposure to OVA and BPA. In lung local lymph nodes, total cell numbers and Th2 cytokine production (IL-4 and IL-5) were significantly greater in the OVA+BPA (low- and medium-dose) group than in the OVA group. Central nervous system parameters were examined only in the high-dose BPA. OVA+BPA group had poorer ability to discriminate between old and new objects by novel-object-recognition test than the vehicle or BPA group.

Moreover, memory function-related gene expression (NMDA receptor subunit NR2B) in hippocampus was also decreased in the OVA+BPA group compared with the vehicle group. These results suggest that BPA exposure throughout childhood may disrupt immune responses and central nervous system function in allergic mice.

The Student and Young Scientists Award

The effects of metal nanoparticles on onset of metal allergy

Toshiro Hirai

Laboratory of Toxicology and Safety Science,
Graduate School of Pharmaceutical Sciences,
Osaka University, Osaka, Japan

I am very privileged to receive the students/young scientist best presentation award at the 21st annual meeting of the Japanese Society of Immunotoxicology and would like to appreciate the support from the selection committee. I would also like to give special thanks to my research professor Dr. Yasuo TSUTSUMI, Dr. Yasuo YOSHIOKA, Dr. Kazuma HIGASHISAKA and other colleagues in Laboratory of Toxicology and Safety Science for supporting throughout the progress.

Until now, metal ions have been thought to be an only form of metal which penetrate into our body. However, the recent study revealed that not only ions, but also metal nanoparticles, which could penetrate our barrier, were naturally occurred from bulk metal. In this study, we investigate the effects of metal nanoparticles on onset of metal allergy compared with the effect of metal ions. In the results, we showed that the metal nanoparticles were stronger sensitizer than metal ions and could be the cause of onset of metal allergy. We hope that our results contribute the future prevention of metal allergy.

Preventive effect of the histamine H_4 receptor antagonist on worsening of itching induced by long-term topical glucocorticoid treatment

Seiji Onuma

Department of Geriatric Pharmacology and Therapeutics,
Graduate School of Pharmaceutical Sciences, Chiba University

I'm very honored to receive the Students & Young Scientist Award at the 21st Annual Meeting of JSIT 2014. I would like to sincerely thank you to the committee.

Topical application of glucocorticoid (GC) is the first-line therapy for the treatment of chronic skin diseases. However, long-term topical GC often increases side effects, even pruritus (itching). Previously, we reported that long-term topical GC application to TNCB-induced chronic dermatitis model mice exacerbated pruritus[1]. Histamine is one of the mediators of pruritus and histamine H_4 receptor (H_4R) is gathering attention as "pruritus receptor." In this study, we investigated whether H_4R antagonist could suppress pruritus of glucocorticoid-induced pruritus model mice.

Oral administration of JNJ39758979 or JNJ28307474, the selective H_4R antagonists, decreased scratching counts, the index of pruritus, of TNCB-induced chronic dermatitis model mice. Furthermore, JNJ28307474 significantly decreased ear thickness of mice, the index of inflammation, which was significantly suppressed by repeated DEX application. From these results, it was indicated that H_4R antagonists could be useful drug for preventing exacerbation of pruritus induced by long-term topical glucocorticoid treatment.

I would also like to express my greatest gratitude to Prof. Akihiro HISAKA, Assoc. Prof. Katsunori YAMAURA, Res. Assoc. Hiromi SATO and emeritus Prof. Koichi UENO. Additionally, I would like to give special thanks to Janssen Research & Development, LLC for generous provision of H_4R antagonists.

Reference

1) Yamaura *et al. J Toxicol Sci.* 2011; 36(4): 395-401

Symposium Report

Completion of the symposium titled "Next-generation Approach in Immunotoxicology"

Eiko Koike[1], Ryosuke Nakamura[2], Yasumitsu Nishimura[3], Yasuo Yoshioka[4]

[1]Center for Environmental Health Sciences, National Institute for Environmental Studies, Japan

[2]Division of Medicinal Safety Science, National Institute of Health Sciences, Japan

[3]Department of Hygiene, Kawasaki Medical School, Kurashiki, Japan

[4]Laboratory of Toxicology and Safety Science, Graduate School of Pharmaceutical Sciences, Osaka University, Osaka, Japan

At the 21st annual meeting of JSIT, Tokushima, we've organized and completed the symposium titled "Next Generation's Study for Immunotoxicology". At the beginning of plan about this symposium, we had reconfirmed the increases in hazardous risks derived from current progress of sciences and techniques and the newly accumulated information about relationship between immune functions and diseases, resulting in the conclusion that we had to learn borderless sciences and reinforce Immunotoxicology more. Therefore, the present symposium was focused and organized on the points of "prevention", "exploration", "resolution" and "application", in which we could have listened the four interesting and highly suggestive talks.

First, Dr. Atsushi Mochizuki (Theoretical Biology Laboratory, RIKEN, Japan) gave us his special talk, titled "Dynamics of complex biological systems determined/controlled by minimal subsets of molecules in regulatory networks". In his talk, the networks of biological molecules and genes and the relationships among them were explained in a simple manner by mathematical methods, which allowed us to recognize the significance of those theoretical techniques to obtain clear-cut conclusion from various kinds of OMICS analyses.

Next, we had an intelligible presentation titled "Chemical strategy for direct and indirect detection of protein-small molecule interactions: Drug target discovery and P450 substrate screening" from Dr. Naoki Kanoh (Graduate School of Pharmaceutical Sciences, Tohoku University, Japan), about chemical biology from basic to advanced study. Their unique technology that enables small molecules to be conjugated to a solid phase by a functional group-independent manner convinced us that the chemical biology has a great potential not only to explore target molecules but also to evaluate immunotoxicity of drug candidates.

Next, Dr. Koro Gotoh (Faculty of Medicine, Oita University) gave us a lecture on "A novel role of spleen-derived IL-10 in obesity-induced systemic inflammation" including a preventive point of view. In his talk, inability of the spleen to synthesize anti-inflammatory IL-10 was shown to induce systemic chronic inflammation in obesity. Because the contribution of the environmental pollutants is concerned for the increase of lifestyle-related chronic inflammatory diseases, we learned development of the new immunotoxicological study for the elucidation of the toxicological mechanism is needed.

At last, Dr. Ken J Ishii (National Institute of Biomedical Innovation) gave us a lecture on "New mechanism of action and potential biomarkers for vaccine adjuvant". The actual mechanisms of vaccine adjuvants have been not immunologically understood for a long time, with a famous sarcastic remark "Immunologist's dirty little secret", although the research and development of adjuvants has a history of more than 80 years. In his talk about the novel mechanisms of several adjuvants, we learned the strong relationship between the research of vaccine adjuvant and immunotoxicity.

Young power for immunotoxicological research

Effects of inflammatory cytokines on accumulation of manganese in human neuronal cells

Hitomi Fujishiro

Laboratory of Molecular Nutrition and Toxicology, Faculty of Pharmaceutical Sciences, Tokushima Bunri University

Exposure to an excess amount of manganese (Mn) causes neurological symptoms similar to Parkinson's disease.

Zinc (Zn) transporters such as Zrt, Irt-related protein 8 (ZIP8), and ZIP14 have been shown to have affinities for Mn as well as Zn, but their roles in Mn uptake in neuronal cells remain unclear. The introduction of siRNA of ZIP14 decreased the uptake of Mn, suggesting an important role of ZIP14 in Mn uptake in human SH-SY5Y neuroblastoma cells. The pretreatment of SH-SY5Y cells with interleukin-6 (IL-6) markedly increased the accumulation of Mn, which could be partly explained by the increased uptake of Mn^{2+} due to IL-6-induced up-regulation of ZIP8 and ZIP14. The treatment of SH-SH5Y cells with IL-6 clearly decreased the expression level of ZnT10 and decreased the Mn excretion efficiency. Pretreatment of SH-SH5Y cells with TNFα or IL-1β also up-regulated gene expression of ZIP8 and ZIP14, and decreased the mRNA levels of ZnT10. Thus, the enhancement of the production of inflammatory cytokines in the brain might be related the aberrant Mn accumulation and the development of neurodegenerative disorders.

Words from new councilors

Greetings to becoming a new councilor member

Daigo Sumi

Faculty of Pharmaceutical Sciences, Tokushima Bunri University

At the beginning, I would like to take this opportunity to express my gratitude to the doctors and seniors who recommended and accepted me as a councilor member of the Japanese Society of Immunotoxicology.

I obtained a Ph.D. with a research focus on the anti-atherosclerotic effects of nitric oxide at the Graduate School of Medicine of Nagoya University. After graduation, I worked for 3 years as a Post Doctoral Fellow at the Dr. Louis J. Ignarro (a 1998 Nobel Laureate in Medicine) Laboratory at the David Geffen School of Medicine at UCLA. Following that work, I undertook the study of biological reactions involving environmental chemicals at Tsukuba University (Professor Yoshito Kumagai Laboratory). More recently, I joined the Faculty of Pharmaceutical Sciences at Tokushima Bunri University, where I have been investigating various aspects of metal-induced immunotoxicology under the mentorship of Professor Seiichiro Himeno.

Arsenic is an environmental pollutant derived from the Earth's crust. Populations around the world have been exposed to arsenic-polluted well water and thereby chronic arsenic poisoning, which causes hyperkeratosis, cancer, diabetes, cardiovascular disease, and other diseases. I have been examining the hypothesis that chronic exposure to arsenic gives rise to these disorders via dysfunctions of the immune system. My results indicate that the functions of natural killer (NK) cells and T cells are affected by arsenic exposure. I am currently investigating the mechanisms underlying the dysfunctions of NK cells, T cells, and immunological function among individuals chronically exposed to arsenic in Bangladesh.

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

Mineral oil exposure and human autoimmunity

Minoru Satoh, MD, PhD

Professor

Department of Clinical Nursing

School of Health Sciences

University of Occupational and Environmental Health, 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 as a rheumatologist for 10 years before moving to the United States for research in 1991. My original plan was to spend 2-3 years there and come back to continue my career as a rheumatologist-researcher, however, I ended up spending 22 years for research in the US until I took a position at University of Occupational and Environmental Health (UOEH) last year. Throughout my career, I have been working on clinical significance and mechanisms of autoantibody production, in particular role of chemicals and other environmental factors in autoimmunity. A mouse model of lupus-like autoimmunity we discovered, induced by a component of mineral oil pristane, became a standard

model of chemically-induced lupus. Since the roles of mineral oil exposure in induction of autoimmunity in human have not been well studied, I would like to focus my future research on this area, taking an advantage of the unique environment of UOEH and with help from members of the JSIT. I will continue to work on autoimmunity using an international network and contribute to the research in immunotoxicology and the JSIT from a view of a rheumatologist specialized in autoantibody research.

As the councilor of the Japanese Society of Immunotoxicology

Takamasa Kido

Department of Public Health and Environmental Medicine,
The Jikei University School of Medicine

I take very honored to be the councilor of the Japanese Society of Immunotoxicology. I would like to thank Professor Yanagisawa, Dr. Tsunoda and seniors who recommended my appointment to the committee of the Japanese Society of Immunotoxicology.

During my graduate student days in the master course at Kitasato University Graduate School of Medical Sciences, I focused on the immunotoxicity of petroleum-derived cleaning solvent for dry cleaning in *in vitro* study. The mRNA expressions of cytokines related to inflammation and allergy in J774.1 cells exposed to the cleaning solvent or PCE were elevated.

In addition, I participated in the study evaluating the toxicity of multi-walled carbon nanotubes (MWCNT). My role in the study was the evaluation of mRNA expressions in splenocytes after whole body inhalation of MWCNT. Relative mRNA expression of *IL-1β* in macrophages from the female rats exposed to 5 mg MWCNT/m3 was significantly higher than in control rat cells. For lymphocytes, the cells from male and female rats in the MWCNT-exposed groups had significantly lower *IL-2* values than control rat cells.

I continues the study for immunotoxicity of essential trace element, zinc as Research assistant at Department of Public Health and Environmental Medicine, The Jikei University, School of Medicine.