ImmunoTox Letter Digest

June, 2019

## The 26th Annual Meeting of the Japanese Society of Immunotoxicology (JSIT2019)

**1. Date**

September 9-10th, 2019

**2. Venue**

Kitakyushu International Convention Center,
〒 802-0001 3-9-30, Asano, Kokura-Kitaku, Kitakyushu, Fukuoka

**3. President**

Minoru Satoh, MD, PhD
(Professor, Department of Clinical Nursing, University of Occupational and Environmental Health, Japan)

**4. Main theme of the meeting**

Immunotoxicology - from basic science to clinical medicine

**5. Meeting Secretariat**

Department of Clinical Nursing, University of Occupational and Environmental Health, Japan
Tomoko Hasegawa (Secretary General)
E-mail: jsit26-office@mbox.health.uoeh-u.ac.jp
URL: https://www.orbit-cs.net/jsit2019/index.html

**6. Program (tentative)**

**Sept 9-10**

Special seminar:" Immunotoxicology of inhaled nanoparticles and the implications for lung disease susceptibility"
James C. Bonner, Ph.D.
Professor, Toxicology Program, Department of Biological Sciences, North Carolina State University

Educational lecture:
Yoshiya Tanaka (University of Occupational and Environmental Health, Japan)
"Light and shadow of immunosuppressive drugs"
Kazuhiro Yatera (University of Occupational and Environmental Health, Japan)
"Environmental factor and pulmonary diseases"

Symposium: Inflammation and pathogenesis from view point of immunotoxicology
Yasuhiro Yoshida (University of Occupational and Environmental Health, Japan)
Yasuo Morimoto (University of Occupational and Environmental Health, Japan)
Yasumitsu Nishimura (Kawasaki Medical University)
Maiko Hajime (University of Occupational and Environmental Health, Japan)

Workshop
Organizer: Shigeru Hisada (Aska Pharmaceutical)
"Development of immunotoxicology AOP and its goal"
Hajime Kojima (National Institute of Health Sciences)
Shigeru Hisada (Asuka Pharmaceutical Co.)
Takumi Oishi (Bozo Research Center)
Shogo Matsumura (Asteras Pharmaceutical Co.)
Setsuya Aiba (Tohoku University)
Takao Ashikaga (National Institute of Health Sciences)

Oral session
Poster presentation and discussion
Luncheon Seminar

Social gathering
September 10, 18:30-20:30
JR Kyushu Kokura Hotel

The 8th Japanese Society of Immunotoxicology Award
(The 2018 JSIT Award)

## Immunotoxicological evaluation of food allergens

Reiko Teshima
Faculty of Veterinary Medicine, Okayama University of Science

We have been studying the properties of substances involved in particular food allergenic reactions and have conducted risk assessments. We have been focusing on the following two points: (1) the development of an evaluation method, and (2) the analysis of changes in allergenicity accompanying physical treatments of food allergens.

Regarding the first point, we constructed an in vitro digestion system using pepsin (SCG) or pancreatin (SIF) to predict the allergenicity of food proteins. Furthermore, we constructed an allergen database (ADFS) to enable searches for sequence homology and to predict cross-reactivity between novel proteins and known allergens.

Regarding the second point, we specifically searched for allergic reactions caused by hydrolyzed wheat protein (HWP), which was used as a quasi-drug, using both in vivo and in vitro methods. HWP (Glupearl 19S (GP19S)), which is used in facial soaps, was produced by the acid treatment of gluten (pH0.5-pH1.2) at 95℃ for 40 min. Reportedly, gluten treated with 0.1-N hydrochloric acid for 30 min at 100℃ exhibits a markedly increased IgE-binding capacity with patient sera, suggesting the generation of neoepitopes on the gluten after treatment. High-temperature acid treatments for a short time period resulted in the random degradation of gluten, producing mixed short and long peptides and leading to a smear pattern when examined using electrophoresis. Furthermore, glutamine deamidated (Q → E) peptides were produced during the treatment of gluten with acid and heat; this reaction may be responsible for the increase in sensitization. The appearance of a deamidated-epitope (QPEEPFPE) after the acid hydrolyzation of wheat gluten was examined using an epitope-specific monoclonal antibody (mAb INRA-DG1). The appearance of the epitope was observed after 30 min of heating under acidic conditions (pH of about 1). Western blotting using this mAb seems to be useful for identifying the existence of HWP-specific and highly sensitive epitopes.

As outlined above, we have been conducting research on immunotoxicological evaluations of food allergens from both basic and applied aspects.

The 7th Japanese Society of
Immunotoxicology Prize for Encouragement

**Promotion of Developmental ImmunoToxicology (DIT) assessment and Adverse Outcome Pathway (AOP)**

Kiyoshi Kushima
Drug safety research labs., Astellas Pharma

It is my great pleasure and honor to be awarded the JSIT prize for encouragement. I would like to express my sincere thanks to all of the members of the awarding committee.

My research history on an immunotoxicology started when I was graduate school student. The experience I had during the student taught me the depth and fun of immunotoxicology research. After graduation, I joined pharmaceutical company, where my research activity on a developmental immunotoxicology (DIT) initiated. Immune systems in pups, that is immature compare to that in adults, show different profiles in the effects on the chemical exposure. We have reported the effects on the development of immunity in rat pups delivered from the dams exposed by non-steroidal anti-inflammatory drugs (NSAIDs) during the gestation period. Indomethacin, acetyl salicylic acid, or diclofenac sodium salt was administered once daily to pregnant rats on days 18-21 of gestation. Indomethacin decreased the serum anti-KLH IgG antibody titer in 3-week old male rats, while the serum levels of anti-KLH IgM, total IgM, and IgG unchanged. These changes disappeared in 8-week-old pups. Incubation of spleen cells isolated from the 3-week-old pups with mitogen resulted in a suppression of Th2 cytokines, suggesting that a change in the release of Th2 cytokines might involve the suppression of antibody production. These results will contribute to the development of a technique for the assessment of developmental immunotoxicity.

We are now contributing the development of Adverse Outcome Pathway (AOP), that is a new program lead by OECD. JSIT testing methodology committee established AOP working group in 2015, in which we submitted a AOP regarding the suppression of T-cell dependent antibody response by the calcineurin inhibitor. The AOP successfully passed an internal review, and external review is expected to start soon.

In the end, I would like to express my deepest appreciation to all of the people who involved, supported and advised me for my research.

Immunotoxicological Research

## Chronic arsenite exposure induces cellular senescence in mouse B lymphoma cell line A20 cells

Kazuyuki Okamura
National Institute for Environmental Studies

Epidemiological studies have reported that chronic arsenite exposure induces immunosuppression, however, the mechanisms are still controversial. Our previous study suggested that arsenite exposure induced suppression of lymphocytes proliferation, leading to immunosuppression, *in vivo*. The gene expression changes observed by arsenite exposure *in vivo* were well reflected in mouse B lymphoma cell line A20 cells *in vitro*. Thus, we further investigated the mechanisms of arsenite induced suppression of cell proliferation in A20 cells. After 24 hours arsenite exposure, we clarified that cell proliferation was inhibited via cyclin-dependent kinase inhibitor p16 induction followed by p130 increase and G0/G1 arrest. We further showed that long-term arsenite exposure until 14 days induced morphological changes of the cells, which was not observed in 24 hours exposure. In addition, strong induction of G0/G1 arrest via p130, appearance of senescence-associated β-galactosidase positive cells and irreversible growth suppression were observed in the cells after long-term arsenite exposure. These features are consistent with cellular senescence. We also found that the expression of activation-induced cytidine deaminase (*Aid*) was prominently up-regulated, and several DNA repair-related enzymes were down-regulated after long-term arsenite exposure. These results suggested that long-term arsenite exposure induces cellular senescence via DNA damage accumulation in lymphocytes.