

English pages

## AN UNKNOWN EPISODE OF THE PIONEER DAYS OF IMMUNOTOXICOLOGY

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First, I would like to thank for the president Junichi Sawada, board of directors, members of the Japanese Society of Immunotoxicology to bestow the title of the honorary member on me.

At the editorial staff's request, here, I would like to review details and background that I began to have the notion of immunotoxicology since 1974.

In the field of preventive medicine, at the process of the connection and treatment with many environmental matters, I felt strongly the necessity of forward-looking countermeasure but not backward countermeasure in the coming preventive medicine. In addition of that, I began to feel strongly the necessity of not only general toxic assessment but also individual toxic assessment of such body function as brain-nerve function, immunofunction and endocrine function.

### The 19<sup>th</sup> Annual Meeting of JSIT 2012 (Japanese Society of Immunotoxicology)

September 15-16, 2012

Auditorium (Daigaku ichigou-kan), The Jikei University School of Medicine

3-25-8 Nishishinbashi, Minato-ku, 105-8461 Tokyo, Japan.

Organizing Committee of the 19<sup>th</sup> Annual Meeting of JSIT

<http://jsit19.umin.ne.jp>

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Deadline for abstract submissions: June 26, 2012

The theme for this Meeting: "New aspects of diseases related to immunotoxicology"

### Program (Tentative Schedule)

#### ■ September 15, 2012 (Saturday)

##### • Special Lecture 1:

Prof. Henk van Loveren (Immunotoxicology Laboratory for Health Protection Research, National Institute of Public Health and the Environment)

##### • Luncheon Seminar 1:

Dr. Gary Bembridge (Huntingdon Life Sciences Ltd.)

##### • Award Lectures:

Dr. Eiko Koike

Dr. Yasumitsu Nishimura

##### • Educational Lecture 2:

Prof. Kazuhiro Kondo

(Department of Virology, The Jikei University School of Medicine)

##### • Workshop:

##### In vitro immunotoxicology

Dr. Emanuela Corsini (University of Milan, Italy)

Dr. Hitoshi Sakaguchi (Kao)

Dr. Takao Ashikaga (Shiseido)

Prof. Setsuya Aiba (Tohoku University School of Medicine)

Prof. Ai-Young Lee (Dongguk University, South Korea)

##### • Oral / Poster presentation

##### • Social gathering

Cafeteria Liebe (TAKAGI Nigo-kan)

#### ■ September 16, 2012 (Sunday)

##### • Special Lecture 2:

Dr. Motoyasu Ohsawa

(Hatano Research Institute, Food and Drug Safety Center)

##### • Educational Lecture 2:

Prof. Toru Miyazaki

(Laboratory of Molecular Biomedicine for Pathogenesis, Center for Disease Biology and

Integrative Medicine, Faculty of Medicine, The University of Tokyo)

• **Luncheon Seminar 2:**

Dr. Lawrence D Jacob (Principal Immunologist and Molecular Biologist, Bioanalysis and Immunology Group, Charles River Laboratories Preclinical services, Edinburgh)

• **Symposium:**

**Progress in research for immunotoxicology**

Prof. Kou Sakabe

(Department of Human Structure and Function, Tokai University School of Medicine)

Dr. Kenji Ishiwata

(Department of Tropical Medicine, The Jikei University School of Medicine)

Dr. Yasumitsu Nishimura

(Department of Hygiene, Kawasaki Medical School)

• **Oral presentation / Poster discussion**

• **Awards Ceremony**

Therefore, I began to aim at construction of scientific learning system of the toxicology to examine and evaluate individually the toxicity of such biofunction as brain-nerve function, immunofunction and endocrine function, and to be necessary for establishment of the risk assessment.

Of all the environmental chemical substances, organotin compounds were selected as the best substances having the possibility to cause many environmental matters in near future and to examine and evaluate individually the toxicity of body function.

While inducing the lesion of memory and olfaction, the aging of blood-brain barrier in brain-nerve systems, the lesion of generative function such as testis atrophy in endocrine systems, organotin made a great contribution to the study on the toxicology of immunofunction ( We advocated as immunotoxicology since 1974 ).

The immunotoxicological study on organotin gave many evidences and information by their property taking part in every immunoresponse systems.

For example, organotin induced severe thymus atrophy and suppression of T cell dependent immunofunction. Dialkyltin-induced thymus atrophy was due to necrosis

led with the inhibition of intracellular phospholipid transport between organelles by impairing the structure and functions of the Golgi apparatus and the ER, and the consequent inhibition of phospholipid metabolism and inhibition of the membrane-mediated signal transduction system leading to DNA synthesis via phospholipid turnover and  $Ca^{2+}$  mobilization and finally inhibition of cell proliferation.

This study on mechanism of dialkyltin-induced thymus atrophy led to the discovery of the suppressive effects on malignant cell proliferation system leading to the antitumor activity of organotin and the new mechanism of antitumor system via membrane-mediated signal transduction.

Trialkyltin-induced thymus atrophy was caused by apoptosis led with the induction of expression of Fas / Fas L, no expression of Bid, decrease in the membrane potential, followed by high expression of cytochrome c and loss of mitochondrial function (mitochondria involvement), and ultimately high increases in the activities of caspase-8, -9, and -3, high expression of CAD (which fragments DNA), no expression of ICAD (CAD inhibitor).

Organotin led to the inhibition of Zn-dependent thymic hormone activity and the disorder of differentiation and maturation of T-lymphocytes in the thymus, followed by the disorder of immunoresponse system.

Further, the studies on the phospholipid metabolism-mediated signal transduction system advanced to the studies on arachidonic acid cascade system, and consequently led to the discovery of prostaglandin system-mediated anti-inflammatory action of organotin.

In connection with these studies on organotin, many international conferences aiming at the development of a new bioactive substance became to be held in foreign countries since 1980.

In 1984, the International Seminar on the Immunological System as a Target for Toxic Damage was held at Grand Duchy of Luxembourg. This was the first conference that immunotoxicology began to be defined internationally as one of the domain of research.

In Japan, First Workshop on Heavy Metals *Immunotoxicology of Metals* (promoted by the Japanese Society for Hygiene ) was held in 1984. This was the first conference held under the name of Immunotoxicology in Japan.

Our study on "Immunotoxicological Research of

Environmental Chemicals” was given in trust as Grant Program A (30 million yen) of Grants-in-Aid for Scientific Research (KAKENHI) of Monbusho (now Monbu Kagakusho) (Ministry of Education, Culture, Sports, Science and Technology) in 1985. This was the first Government Grant given under the name of Immunotoxicology in Japan.

In 1986, I published “Chapter 9: Suppression of cell proliferation by certain organotin compounds” in *Tin and Malignant Cell Growth* (CRC Press, Boca, Raton, Florida, USA).

In 1991, I published “Chapter 3: Immunotoxicological Test of Metals” in *Vol. 10 “Immunotoxicology” of Chair of Toxicological Test* (Chijin Shokan). This was the first publishing in collected form with pharmaceuticals and metals as environmental chemicals in Japan.

After 20 years since 1974 when we advocated as immunotoxicology, the Japanese Society of Immunotoxicology started in 1994.

### Young power for immunotoxicological research

#### The effects of environmental chemicals of allergic disorders

Rie Yanagisawa

(National Institute for Environmental Studies)

When I was a master’s student, I studied murine strain differences in allergic airway inflammation following the exposure to diesel exhaust particles (DEPs). Since 2000, I have engaged again in the assessment of health effects caused by DEPs in National Institute for Environmental Studies. DEPs, contain a variety of environmental chemicals, can enhance various respiratory diseases, however, it was not clear which components in DEP are associated with the aggravation of various respiratory diseases such as allergic airway inflammation. I have elucidated that extracted organic chemicals in DEP, rather than residual carbonaceous nuclei of DEP after extraction, exaggerated allergic airway inflammation through the enhancement of Th2 responses. Next, I undertook the establishment and validation of ‘in vivo screening’, which can detect the health effects of environmental chemicals such as Di-(2-ethylhexyl) phthalate (DEHP). Furthermore, I have elucidated that maternal exposure to DEHP during neonatal periods

enhanced atopic dermatitis-like skin lesions related to mite allergen in males, but not in females. In future, I would like to focus on the effects of maternal exposure to environmental chemicals on allergic diseases in descendants. In addition, I would like to focus on the difference in the susceptibility to chemicals by the sexes.

#### Report of the attendance of 51th SOT meeting

Reiko Teshima

(National Institute of Health Sciences)

The 51th SOT (Society of Toxicology) meeting of USA was held at Moscone Convention Center in San Francisco during March 12-15, 2012.

On the third day (March 14) morning, SOT-ISS (Immunotox speciality section) - proposed symposium “the allergenicity and immunomodulatory effect of food substances” was held. Dr. Gregory S. Ladics (Dupont Agricultural Biotechnology, Wilmington, DE, USA) and I organized the symposium as chairpersons and 5 speakers presented their data and discussed with audiences.

The title of 5 speakers were as follows; 1. Structural and functional biology of allergenic food proteins by Prof. Heimo Breiteneder (Medical University of Vienna, Vienna,), 2. Role of dietary triglycerides in the immune response to concomitantly ingested protein antigens by Dr. Eric Eckhardt (University of Kentucky, Lexington, KY, USA), 3. Anti-allergic effects of a specific mixture of oligosaccharides or combined with a probiotic strain (synbiotics) by Dr. Leon Knippels (Danone Research, Wageningen, Netherlands), 4. Food sensitization and its induction by immunomodulating factors by Dr. Tomoko Shindo (Research Institute, Hadano Kanagawa, Japan), 5. In vitro provocation study by Dr. Ryosuke Nakamura (National Institute of Health Sciences, Japan).

The symposium presented several hypotheses regarding the role that dietary triglycerides and synbiotics may play in the development of oral tolerance as well as the role immunomodulating factors (e.g., environmental factors) may play in breaking oral tolerance to protein allergens. Additionally, the structural and functional biology of allergenic food proteins were discussed along with in vitro models to predict the potential cross-reactivity of food proteins.