English pages

## Report from the secretariat for The 14th Annual Meeting of the Japanese Society of Immunotoxicology

The 14th Annual Meeting of the Japanese Society of Immunotoxicology (JSIT 2007) was held at Hyogo Prefecture Civic Center in Kobe, Thursday, September 20 — Friday, September 21, 2007. The Sub-theme of this annual meeting was "Toxicogenomics and Immunotoxicology". In addition to 22 oral communications and 15 poster presentations, there were two invited lectures, a special lecture, a symposium, and a workshop during the meeting. Invited lecturers include Dr. Yukihiko Kitamura from Developmental Research Laboratories, Shionogi Co., Osaka who gave a talk about "Mast cells and KIT receptor tyrosine kinase" and Prof. Edith Smith from Oxford University, U.K. who spoke about "Drug induced allergy". A special lecture was presented by Prof. Tetsuro Urushidani from Doshisha Women's College of Liberal Arts who talked about "Prediction of hepatotoxicity using toxicogenomics project database (TG-GATEs)". The theme of the symposium was "Developmental immunotoxicology" and the speakers include Dr. Orie Nakamura from Osaka Medical Center and Research Institute for Maternal and Child Health, Osaka who presented "Molecular mechanism of specific immune system on maternal deciduas". Other speakers include Dr. Hayssam Khalil from Charles River laboratories, Canada, Dr. Gerhard F. Weinbauer from Covance Laboratories GmbH, Prof. Rodney R. Dietertl from Cornell University, USA, and Dr. Kenneth L. Hastings from FDA, USA who gave a talk about "Ontogeny and post-natal development of the rodent immune system", "Immune system development in the primate", Developmental immunotoxicity and critical windows of exposure for children's health", and "Regulatory concerns for developmental immunotoxicology", respectively. The workshop was divided into two sessions. One was "Evaluation of immunotoxicity using primates" that was introduced by Dr. Hiroshi Maeda from the Tokyo Pathology Center, Shin Nippon Biomedical laboratories, Tokyo and by Takayuki Okamura from Kashima laboratory, Mitsubishi Chemical Safety Institute, Kashima. The other was "The safety evaluation of monoclonal antibody pharmaceuticals" presented by Dr. Kiyoshi Kobayashi from Amgen K.K., Tokyo and by Dr. Tomoaki Inoue from Fuji Gotemba Research Laboratories, Chugai Pharmaceutical Co., Ltd., Gotemba. The "Annual Award" in JSIT 2007 was won by Dr. Tomoko Shindo from Hatano Research Institute, Food and Drug Safety Center, Kanagawa and "Encouragement Award" was by the Ph.D. student Miss. Ayako Nakayama from the Center for Fish and Wildlife Health, University of Berne, Switzerland & Kobe Women's College.

## The 15th Annual Meeting of the Japanese Society of Immunotoxicology (JSIT2008) (1st announcement)

September 11-12, 2008
Towerhall Hunabori, Edogawa, Tokyo, Japan

Invited plenary lecture "Immunotoxicology of innate immunity" (Prof. Stephen B. Pruett)
Plenary lecture
Master's lecture
Symposium "Immunotoxicity of nanoparticles (tentative title)"
Symposium "Gut-associated lymphoid organs and their regulations (tentative title)"
Workshop "Immunotoxicity and allergenicity of pharmaceuticals (tentative title)"
Oral and poster presentations

President: Jun-ichi Sawada, Ph.D. (National Institute of Health Sciences)
Secretary Office: TEL 03-3700-9453 FAX 03-3700-7438
E-mail jsit15@nihs.go.jp

## A prize for annual convention

### Murine Food Allergy Model with Oral Sensitization and Oral Challenge

Tomoko Shindo[1], Yukiko Kanazawa[1], Mami Furuya[1], Yoshiyuki Tazura[1], Kohichi Kojima[1] and Reiko Teshima[2]

[1]Hatano Research Institute, Food and Drug Safety Center, Kanagawa, Japan

[2]National Institute of Health Sciences, Tokyo, Japan

We have established murine food allergy model onset of immediate anaphylactic reactions by oral sensitization with oral challenge. The mice once administrated with ovalbumin showed the change of T cell population in mesenteric lymph node. It shows that mesenteric lymph node is an important organ for sensitization in this model. Then linoleic acid-lecithin mixture vehicle combined with sodium salicylate treatment as an essential factor of this model may provide food allergy by changing T cell population.

## A prize for encouragement

### Understanding the immunotoxic mechanisms of benzo[a]pyrene in fish using the localization of an inducible cytochrome P450(CYP)-1A protein in piscine immune cells

Ayako Nakayama[1,4], Ivan Riesen[1], Elisabeth Eppler[2], Bernd Köllner[3], Kawai Shinichiro[4] and Helmut Segner[1]

[1]Centre for Fish and Wildlife Health, University of Berne, Switzerland

[2]University of Zurich, Switzerland

[3]Friedrich-Loeffler, Insel Riems, Germany

[4]Kobe College, Japan

Polycyclic aromatic hydrocarbons (PAHs) such as benzo[a]pyrene (BaP) are immunotoxic to fish. Metabolism of PAHs in immune cells has been implicated in PAH immunotoxicity in mammals, but for fish whether metabolic enzymes are present in immune cells and whether piscine immune cells have the capability to metabolite PAHs are still unknown. The highlight of this study was to be detected BaP-inducible CYP1A in piscine immune cells such as B-lymphocytes and granulocytes. Our finding could provide a clue to explain the immunotoxic mechanisms of PAHs in fish.

## Young power for immunotoxicological research

### Go west with asbestos! -along with my thinking about this society-

Yasumitsu Nishimura, Ph. D.

Assistant Professor/Lecturer

Dept of Hygiene, Kawasaki Medical School

I was introduced to asbestos in Hyogo College of Medicine, after completing my Ph. D. in the Graduate School of Medicine at Kyoto University. Prof. H. Iguchi taught me the study method to test the effect of asbestos-exposure using rats. After finishing the study about alveolar macrophages, Otsuki T. Prof. accepted me as a lecturer in Kawasaki Medical School. I am currently studying about the effect of asbestos-exposure on NK and NKT cells. In this process from Kyoto University to Kawasaki Medical School, that is, going west with asbestos, I realized the significance of the study about immunological effect of asbestos-exposure. I also understood social needs for immunotoxicological study and the importance of this society. I will continue to contribute to further development of this society.

## Participation Report for The 14th Annual Meeting of the Japanese Society of Immunotoxicology

### Greetings from the US

Contributed by Kenneth L. Hastings, Dr.P.H., D.A.B.T. (sanofi-aventis, USA)

As the year comes to an end, I would like to send greetings on behalf of your colleagues in the United States. It was a distinct pleasure to able to attend the 14th Annual Meeting of the Japanese Society of Immunotoxicology in September, and to have the opportunity to give a presentation at the meeting. I

have to say I was very impressed with the quality of presentations, the venue, and the interest of participants in immunotoxicology issues we are dealing with in the US. As it turns out, there is little difference between our issues and those dealt with in Japan. Partly, this is a result of the recently concluded negotiations resulting in publication of ICH S8. This document is one that we are proud of and is an example of how good science, careful preparation, and collegial relations can result in guidance that is both scientifically sound and serves to protect public health.

As I pointed out in my presentation, we have now to deal with the issue of developmental immunotoxicology. Although this topic is addressed in ICH S8, the guidance is not sufficiently detailed to be of any great value. Thus, we may need to address this issue in a future guidance, either as a stand-alone document or as part of a broader document on juvenile animal studies needed to enable clinical trials and marketing of drugs for pediatric patients. As I pointed out in my presentation, and as Professor Dietert discussed in detail, the developing immune system appears to be a uniquely sensitive target for xenobiotic toxicity. It is questionable whether current regulatory practices take this into account. It is also likely that with the emergence of biologic therapeutics which target the immune system the issue of developmental immunotoxicology will become even more important in the future. I was happy to see that research in this area appears to be alive and well in Japan.

On another note, please remember that the *International Journal of Immunotoxicology* is exactly that, an international journal. Your colleague Dr. Kazuichi Nakamura serves as an Editor, and we are very interested in continuing our relationship with your professional Society. We are very interested in contributions from Japan for publication in the Journal, and encourage submissions. Please keep us in mind the next time you are considering where you would like to submit your research results for publication.

Thank you very much for your hospitality, which as always in Japan was excellent. I very much enjoyed participating in your meeting and hope to have the opportunity to do so in the future.

## Travels in Immunotoxicology and in Japan

Contributed by Edith Sim, BSc, M.A., D. Phil. (Director of Graduate Training Medical Sciences Division, Professor of Pharmacology, University of Oxford, UK)

Firstly, it is a great pleasure to thank Dr. Kazuichi Nakamura and Professor Shin Yoshino, as President, who invited me to attend the 14th Annual Meeting of the Japanese Society for Immunotoxicology in Kobe and to give a lecture on Drug induced Autoimmunity. Dr. Nakamura also invited me to speak at the Shionogi & Co., Ltd. in Osaka to deliver a lecture on Drug Induced Allergy. Both experiences have been extremely rewarding both scientifically and culturally. The Japanese Society for Immunotoxicology is a vibrant scientific society with talks from young scientists which were highly polished. The talk by Dr. Orie Nakamura on developmental immunotoxicology showed beautiful staining techniques for following expression of markers as they appear during foetal development. The poster session was also most impressive.

I am very grateful indeed for the opportunity to meet with fellow scientists and also to sample some of the outstanding Heritage sites which we visited. I greatly appreciate the opportunity to visit these sites which was only possible through the kindness and friendship of Dr. Kazu Nakamura and also his young colleague and students from the Kobe Pharmaceutical University.

I arrived in Japan on 19th September with my husband, Prof. Bob Sim, and travelled from Narita to Kobe by train. Dr. Nakamura had arranged an excellent hotel near the centre of Kobe which allowed my husband and I to visit the harbour area on 20th September, including the Earthquake Memorial Park. We were particularly impressed by the architecture and sculpture in this beautiful city. That evening Dr. Nakamura met us at the hotel together with Dr. Ken Hastings and Prof. Rod Dieter. We were escorted to the conference Banquet on a ship from which we were able to see a major feat of engineering — the 3.9 Km long Akashi Kaikyo Suspension Bridge.

At the banquet, I was unprepared but very pleasantly surprised to be able to express my gratitude to Dr. Nakamura and Prof. Yoshino for the invitation to the conference and the opportunity to visit Japan for the first time.

On 20th September, we arrived at the conference. It was extremely interesting to hear the presentations on developmental immunotoxicology. Science is best served in a multi-disciplinary way. Basic research at the whole organism and also at the organ, protein and gene level all add together to aid in our understanding of a subject. From the perspective of an applied discipline where legislation results from the research, a full description of events at the whole animal level through systemic investigation is essential. If there can also be a layer of understanding at the molecular level this can open up new avenues for investigation and ultimately for legislation. The sessions on appropriate animal models for understanding immunotoxicity and windows of vulnerability were fascinating for a molecular scientist, which is my own area. The caution expressed by Dr. Lawrence in relation to the use of toxicogenomics was enlightening but again brings home the message that understanding at many levels can be helpful both in understanding immunotoxic reactions and subsequently informing the legislative process as was emphasized by Dr. Ken Hastings.

My own presentation which should have been entitled Drug Induced Autoimmunity covered work with which I have been involved over many years at the molecular level. The drug hydralazine, and also procainamide, induce, in certain individuals, a condition which resembles Systemic Lupus Erythematosus (SLE). In drug-induced SLE, as well as in idiopathic SLE, immune complex clearance is disrupted and immune complex deposition is frequently associated with deficiencies of the early components of the classical complement pathway (C1, C4 and C3). These components promote the solubilisation and clearance through phagocytosis of immune complexes. I used hydralazine-induced SLE as a model system for understanding multi-factorial disease where the drug is the environmental trigger. Hydralazine interferes with the role of the complement cascade in clearing these complexes. During this process, hydralazine itself becomes covalently bound to the complement proteins inhibiting the solubilisation and also the phagocytosis of immune complexes such that they persist and become deposited at inappropriate sites and hence SLE can develop. It is possible that hydralazine, covalently bound to the activated complement component C4, may act as an immunogen also. This was an interesting point raised during the thoughtful questions which were asked.

Particularly in relation to the previous presentation on genomics, it turns out that the major predisposing factor in hydralazine-induced SLE is the ability of an individual to metabolize the drug. The metabolism of hydralazine is catalysed by the enzyme arylamine N-acetyltransferase and individuals can be either fast or slow acetylators with slow acetylators being those who develop the immunotoxic reaction. The molecular basis of the polymorphism in acetylation is now known with slow acetylators having point mutations in the *NAT2* gene which result in the protein becoming unstable and accumulating intracellulary in regions in the cytosol known as aggresomes. Proteins in aggresomes are identified for ubiquitination and intracellular destruction. Within the Japanese population, there is a different distribution of *NAT2* alleles such that the most common allele causing slow acetylation in Caucasians is missing in the Japanese but the mechanism of slow acetylation with the commonest Japanese *NAT2* slow allele is likely to occur through the same protein destabilisation mechanism. The final point I made was in relation to autoimmunity due to treatment with sulphasalazine and mesalazine. Metabolism by gut bacteria may be important in generating immunotoxic metabolites. Azoreductase is such a metabolic enzyme where structural information is now available with an understanding of structure activity relationships. The use of bacterial enzymes as well as human enzymes for structure based drug design can be informative and may well also have a role in predicting immunotoxicity once databases which cover molecular and systems data are available in the future.

Following the scientific sessions at the Japanese Society for Immunotoxicology, we had a very interesting series of visits organized by Dr. Nakamura both to Himeji Castle and also to Nara where I was unfortunately too large to wriggle through the Buddha's nostril. Dr. Nakamura and his colleagues made sure that we were able to sample Kobe beef and local fish delicacies with confidence. Their guidance through Osaka station was masterful. I am sure that otherwise I would still be there! We are very grateful to Dr Nakamura and his students

for giving up their holiday weekend to take us to see such wonderful sights.

On 25th September, Dr Dieter and I were invited to give seminars at Shionogi & Co., Ltd. This was my first visit to a Japanese drug company and was very enlightening. It is also the first time that I have given a talk wearing slippers. Dr. Nakamura had asked me to give a talk on Drug Induced Allergy at Shionogi and I discussed work on penicillin and cephalosporin induced allergy. It is not work which I have done myself but Oxford University is well known for work in these areas in the Sir William Dunn School of Pathology. I also presented some of my own research work on development of novel anti-tubercular agents. The question session was extremely lively and gave me much food for thought. We discussed how a compound might generate an allergic reaction and how this might be predicted. We discussed that a covalent reaction between the compound, or its metabolite, and a self molecule, usually a protein was necessary in order for a chemical to act as a hapten. We discussed possible ways of identifying a covalent, as opposed to a hydrophobic, interaction between a chemical and a protein. The questions relating to animal models were outside my area of expertise but Prof. Dieter's comments were very helpful and informative. Prof. Dieter gave an extremely elegant presentation at Shionogi which again generated enthusiastic questions from the audience. I felt privileged to have been invited to give a talk. Dr. Nakamura most graciously accompanied us back to our hotel in Osaka.

On the following day my husband and I travelled to Hiroshima for the start of a short holiday travelling in Japan which was most enjoyable and allowed us to see contrasting geographical areas of Japan, each with their special blend of traditional and high-tech features. We would not have made the trip apart from the wonderful opportunity as a result of the invitation of Prof. Yoshino to speak at the Japanese Society for Immunotoxicology and at the Shionogi & Co., Ltd.. It was a great pleasure to meet and discuss with Japanese colleagues, to exchange cultural experiences and to make new friends.

Fig. 1 Himeji castle.


Fig. 2 A trip to Nara.

## JSIT and ImTOXSS Bring an International Focus on Developmental Immunotoxicity (DIT) Safety Testing

Contributed by Rodney R Dietert, PhD (Professor of Microbiology and Immunology, Cornell University, USA)

### The Scientific Visit

It was a special honor to attend and present my research in developmental immunotoxicology at the 14th Annual Meeting of the Japanese Society of Immunotoxicology held in Kobe, Japan 20-21 September, 2007. My lecture was entitled "Developmental Immunotoxicity and Critical Widows of Exposure for Children's Health". Along with Dr. Kenneth Hastings, I was privileged to represent the Immunotoxicology Section of the Society of Toxicology (U.S.) as a speaker at this important scientific

immunotoxicology meeting and to join Drs. Edith and Robert Sim as a guest at this special forum. Following this forum I had the pleasure of visiting Shionogi & Co., Ltd. for a second lecture and a discussion session on developmental immunotoxicology testing.

Dr. Kazuichi Nakamura served as the host and provided an exceptional itinerary that featured both scientific enlightenment and historical inspiration. I am particularly grateful to Dr. Nakamura for a wonderfully planned visit and for the honor to meet JSIT Executive President Dr. Motoyasu Ohsawa, Meeting President Dr. Shin Yoshino, Dr. Keiko Nohara and other members of the society. The meeting itself was filled with exceptional research and new insights on the immunotoxicity of drugs and environmental contaminants. I was particularly impressed by the new research pertaining to both mechanism and outcomes of xenobiotic-induced immune dysfunction that reached far beyond traditional concepts of immunosuppression. There were many presentations addressing dysfunction that included concern for hypersensitivity and autoimmunity. Additionally, the idea was evident that risk of immunotoxicity can include concomitant increases in hypersensitivity and/or autoimmunity along with targeted immunosuppression.

My lecture at the 14th JSIT meeting covered the biological basis for the increased sensitivity of the non-adult's immune system to toxic alteration by drugs and environmental chemicals. It also addressed the patterns of dysfunctional outcomes seen with DIT and the combinations of testing protocols that have proven most effective for detection of developmental immunotoxicants. Critical windows of vulnerability exist for the developing immune system and have been defined in previous review articles. These prenatal-perinatal windows constitute one-time immune maturational events that must occur without environmental disruption or result in risk of postnatal dysfunction and increased disease susceptibility.

Events such as myelomonocytic cell seeding of tissues and organs for homeoregulatory oversight, lymphoid seeding of the thymus, thymocyte positive and negative selection, generation, seeding and activation of T regulatory cells, dendritic cell maturation to promote Th1 responses, T helper cell balance, and macrophage systemic modification in response to surfactants near birth are critical developmental benchmarks that help define the postnatal immune system and its capacity. Additionally, requirements of the pregnancy itself needed for maintenance of a semi-allogeneic fetus place unique restriction on fetal immune development. This helps to define the particular susceptibilities that exist in DIT in contrast with adult-induced immunotoxicity.

In this lecture, I made an additional point concerning the spectrum of postnatal diseases influenced by DIT. Beyond the obvious immune-associated diseases such as childhood asthma, infectious disease susceptibility, risk of later life cancer and autoimmunity, a host of inflammatory-associated conditions appear linked with DIT. These include various neurobehavioral conditions such as Parkinson's disease, autism and schizophrenia as well as vascular system and reproductive dysfunction. Such expanded disease associations increase the need to detect potential developmental immunotoxicants and highlight the benefits that would arise from effective DIT screening of drugs and chemicals.

The lecture continued in identifying specific drugs and chemicals that serve as model developmental immunotoxicants. These xenobiotics disrupt specific events during one or more windows of immune vulnerability. With the DIT literature having expanded dramatically in the past five years, the breadth and range of known developmental immunotoxicants can now provide clues as to categories of likely toxicants and the specific immunotoxic risks. The significantly expanded literature also permits an evaluation regarding the nature of DIT alterations and the most predictive assays for detecting developmental immunotoxicants.

In considering specific testing assays and detection of developmental immunotoxicants, the take-home message was that function trumps structure. Dysfunction rather than major structural alterations is the most common DIT outcome. Not surprisingly, those combinations of assays that are capable of measuring across the spectrum of immune response capacities appear to be best for detecting developmental immunotoxicants. As a result, a multiple isotype (e.g. (IgM and IgG subtypes) T-dependent antibody response (TDAR) can be combined with a Th1-dependent assay such as the

cytotoxic T lymphocyte (CTL) assay or the delayed type hypersensitivity (DTH) assay for analysis of acquired immunity. Inclusion of a natural killer (NK) cell cytotoxicity assay further adds a useful measure of innate immunity. Cytokine measurements, immunohistology, and immunophenotype are helpful as associated measures but do not substitute for functional assays when it comes to DIT.

The question and answer discussion following the JSIT lecture was excellent and very thought provoking. It was such an honor to be a part of the session dealing with developmental immunotoxicology at this meeting.

My second presentation at Shionogi & Co., Ltd. followed a similar outline. However, the lecture time was slightly longer and it was possible to include additional materials concerning DIT testing. Much of the subsequent discussion focused on testing options including the range of potential developmental immunotoxicants and the benefits and limitations of various testing protocols.

## The Social Visit

A special treat for me was the opportunity to visit places of historical significance in Japan in the company of the Dr. Sim, Dr. Hastings, several graduate immunotoxicology graduate students and our host, Dr. Nakamura. Of course our social program began with the Kobe Bay cruise dinner associated with the conference. The Kobe skyline was so impressive. The knowledge that only a few years ago the city had been devastated by an earthquake made the scenery from the ship all the more spectacular. I particularly enjoyed comparing the bridge lighted at night from the water vs. its daytime appearance from shore.

Dr. Nakamura had arranged a magnificent schedule of touring that provided an opportunity to see many places I had read about but had only dreamed of seeing first hand. Himeji Castle and the Philosopher's Path with its many temples in Kyoto were among those. Himeji castle was both awe-inspiring in its grandeur and captivating through its broad spectrum of art and diverse stone work. I was particularly taken by the individual stone-cut designs with different symbols that were connected to each Shogun era. I will always remember the views from the castle's upper floors. We were even serenaded by an all-day rock concert from the adjacent park since our visit to Himeji occurred on a national holiday period. In Kyoto, I found a very small temple that held a very special contemplative opportunity for me.

Of course Nara was a highlight of the social visit. I had visited the park alone 26 years ago. But with the present tour, the students and Dr. Nakamura were able to provide wonderful additional information about the monuments that made the visit so much more inspiring. I think one never forgets the magnificent Buddha. Being from the Cornell Veterinary College, I was sure to extend my university's best regard and wishes for good health to Nara's population of sacred deer.

I returned with many wonderful photographs and memories from the conference, the visit to Shionogi & Co. Ltd. and the tours of the Osaka-Kobe area monuments. Dr. Nakamura provided the tour of a lifetime and I am so appreciative of his special hosting. It was an honor to have represented our Immunotoxicology Specialty Section at this conference and I look forward to facilitating continuing exchanges between JSIT and ImTox-SOT.

Fig. 3 Dr. Dietert and Dr. Hastings.

Fig. 4 With deer.