



Message from the former JSIT president

Jun-ichi Sawada

(Pharmaceuticals and Medical Devices Agency)

I am delighted that Prof. Takahiko Yoshida was elected the new president at General Meeting on September 12. I wish our society's further development under the new board.

During my 6 year term, foundation of the JSIT awards, documentation of the JSIT annual business plans and reports, improvement of the JSIT website, and establishment of the cooperative framework between JSIT and SOT-ISS were performed to enhance the JSIT activities. I was very pleased that the previous annual meetings were successfully held, where very active discussion was presented. I appreciate great efforts by the board and committee members and annual meeting presidents and their staffs.

I would like to appreciate again all the JSIT (and also SOT-ISS) members for your cooperation and participation in the activities of JSIT.

Inauguration address of the new president of the JSIT

Takahiko Yoshida

(Asahikawa Medical University)

I assumed the presidents of the Japanese Society of Immunotoxicology at October 1, 2013 in the annual meeting. I will write some words of my greeting and wishes.

The Japanese Society of Immunotoxicology (JSIT) is in the 20th anniversary year. I remember when I attend the 5th International Conference on Immunopharmacology Meeting at Tampa, FL, UAS in 1991, Dr. Motoyasu Osawa talked passionately about willing to found the scientific group in Japan looks like Immunotoxicology Specialty Section (ITox-SS) of Society of Toxicology (SOT) in the USA with Dr. Michael I. Luster who become my boss in

National Institute of Environmental Sciences (NIEHS), NIH during my studying abroad. I feel it was the most recent scene. After the establishment of JSIT's former study group in 1994, JSIT had been progressing under the leadership of Dr. Hiroshi Nakura, Dr. Motoyasu Osawa and Jun-ichi Sawada. Although I feel asking for too much appointment of the JSIT on the process of firm progression, I would like to contribute my mite to continuous development of the JSIT.

Since the factors (mainly chemicals) influencing on the immune system exist around our life widely, member of JSIT has wide diversity; drug development, occupational and environmental health; and academia, businesses and public administration. Furthermore, the targets of the research have increased these days, since various healthy foods, supplementary foods and cosmetics become popular in general, and genetically-modified products and nanomaterials are introduced to our daily life. So JSIT is expected to work on the various needs of the community to achieve the security and peace of mind of people. Although immunotoxicological research techniques had been developed based on the international harmonized standard, from my perspective, recent rapid progression of immunology and molecular biology and those research techniques bring forward them into new phase. I had been studying the immunotoxicology myself from early 1980s. The immunomodulations which I observed but those mechanisms were unknown in those days became to be ascertained and newly reported in the meeting of JSIT in recent years. It makes me realize the proverb "History repeats itself" is reality even in scientific researches and "Time flees away without delay". I will hope the members of JSIT especially young researchers will fulfill people's expectations and obtain fruitful works using various research techniques.

**The 21st Annual Meeting of JSIT 2014
(Japanese Society of Immunotoxicology)**

Date:

September 11-12, 2014

Venue:

Tokushima Bunri University,
International Conference Hall,
180 Yamashiro-cho, Tokushima, Japan.

Theme:

“A Step forward in Immunotoxicological Studies”

Special lecture 1:

Dr. Marc Pallardy (Université Paris-Sud)

Special lecture 2:

Dr. Tatsuyoshi Kawamura (University of Yamanashi,
Faculty of Medicine)

Educational lecture:

Dr. Yoshiyuki Minegishi (The university of Tokushima,
Institute for Genome Research)

Symposium:

Next-generation Approach in Immunotoxicology

Workshop:

Immunotoxicology Methods

Deadline for abstract submission:

June 27, 2014

President:

Prof. Seiichiro Himeno

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20th Memorial Symposium Report

Hidekazu Fujimaki

(JSIT committee for Science and Editing)

In the 20th Anniversary of Annual Meeting of JSIT, the 20th Memorial Symposium was held with outstanding researchers in Immunotoxicology field invited from outside and inside Japan. Dr. Motoyasu Oosawa (Food and Drug Safety Center) and I acted as chairmen.

Four lectures were as follows: “Immunotoxicology: Current Situations and future perspective” presented by Dr. Jun-ichi Sawada (Pharmaceuticals and Medical Devices Agency), “Molecular and cellular bases for chronic inflammation-associated organ fibrosis” presented by Prof. Kouji Matsushima (The Department of Molecular Preventive Medicine, Graduate School of Medicine, The University of Tokyo), “Clinical evaluation of immunotoxicity: Past and Current strategies” presented by Prof. Jacques Descotes (Poison Center and Pharmacovigilance Department, Lyon University Hospitals, Lyon, France), “Addressing Uncertainty in Immunotoxicology: Evaluating Risk for Immunomodulatory Compounds” presented by Dr. Laine Peyton Myers (US Food and Drug Administration, Silver Spring, MD, USA)

During the symposium, valuable suggestions about new aspect for Immunotoxicological techniques for validation and standardization, acceleration of Molecular integrated biology, translational Immunotoxicology between basic and clinical trials etc were received. These may be useful for the future perspectives for JSIT members. Finally, Dr. Motoyasu Oosawa summarized that regarding Immunotoxicological risk assessment and problem solving, it has still many questions to answer. However, he said that we have to develop reasonable evaluation methods and protocol based on the recent International guidance. Finally, it is better to do collaboration between clinicians, immunologists and toxicologist to promote the health standard of public and we hope to discuss the development novel approaches to Immunotoxicology evaluation in next year JSIT meeting.



Immunotoxicology: Current Situations and Future perspective.

Jun-ichi Sawada

(Pharmaceuticals and Medical Devices Agency)

At the 20th Annual Meeting of JSIT, we had the memorial symposium, where the past and current immunotoxicological researches are reviewed and future perspectives were addressed.

Currently there are the two major international guidance documents on immunotoxicity risk assessment: ICH S8 Guideline for human pharmaceuticals and the IPCS/WHO Guidance for chemicals. Although their scopes and objectives are quite different, both of them use weight-of-evidence approaches based on significant immunotoxicological concerns.

Recently, a number of novel players involved in immunomodulation have been reported. They include T cell, macrophage and dendritic cell subsets/phenotypes; pattern recognition receptors responsible for innate immunity; and nuclear receptors including AhR, PPARs, RARs, RXR, RORs and VDR. In these situations, I addressed the problems and possible solutions for immediate-type drug allergy, drug-induced autoimmunity, and intestinal immunotoxicity.

Prediction of immediate-type allergenicity

At present, no testing methods for predicting immediate-type allergenicity. A number of factors are involved in elicitation of IgE-mediated drug-specific responses, and they include Th2-prone genetic and environmental backgrounds, reactivity of the drug and its metabolites with proteins, formation of B and T cell epitopes, interactions among T, B and dendritic cells, Ig and TCR repertoires, and Ig class switching. Especially, mechanisms of hapten presentation by dendritic or B cells remain unclear. To obtain a good prediction method, these factors and mechanisms should be further elucidated.

Chemical-induced autoimmunity

A variety of chemicals are known to induce autoimmunity either specific or nonspecific for the drug. Modes of development of autoimmunity are not simple, and various factors are involved in the induction or enhancement of autoimmunity. PPAR agonists, interferons, Th17 cells, proinflammatory cytokines, and ROSs are known as autoimmunity-promoting factors. On the contrary, Treg cells and anti-inflammatory cytokines suppress the induction of autoimmunity. PLNA and autoimmunity model mice used to predict the autoimmunity-inducing or -enhancing activities are insufficient, and novel biomarkers should be developed and evaluated for prediction of autoimmunity-inducing activities of chemicals.

Intestinal immunotoxicity

In the intestinal tissues, a large variety of lymphoid and non-lymphoid cells are located and responsible for acquired and innate immunity to intestinal microbacteria and food antigens. Intestinal immunotoxicity can be defined as adverse effects on the immunological functions of intestine, e.g., IgA synthesis, blocking of infectious agents, tolerance to food allergens, control of inflammatory responses, maintenance of commensal microflora. Immunotoxicity of various chemicals to intestinal tissues may be underestimated and should be re-evaluated from the immunotoxicological points. In addition to IgA levels and histopathological examination of intestinal tissues, novel biomarkers for intestinal immunotoxicity are desired.

Molecular and cellular bases for chronic inflammation-associated organ fibrosis

Kouji Matsushima

(The Department of Molecular Preventive Medicine,
Graduate School of Medicine, The University of Tokyo,
7-3-1, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan)

Organ fibrosis is an intractable, progressive condition that arises in multi-factorial chronic inflammatory diseases in which excessive deposition of extracellular matrix (ECM) severely impairs tissue architecture and

function, eventually resulting in organ failure. The cellular origin and molecular bases for the accumulation of Col I-producing fibroblasts and myofibroblasts, which are responsible for the excessive deposition of ECM during the fibrotic processes remain elusive. After brief introduction on the current understanding of the cellular origin of myofibroblasts, I will present our recent study on the dynamics of fibroblasts in murine experimental lung fibrosis models.

Clinical evaluation of immunotoxicity: past and current strategies

Jacques Descotes

(Poison Center and Pharmacovigilance Department,
Lyon University Hospitals, and Claude Bernard University,
Lyon, France (e-mail: descotes@me.com))

The adverse clinical consequences of immunotoxic effects (immunosuppression, immunostimulation, hypersensitivity and autoimmunity) are fairly well established thanks to the knowledge gained from major immunotoxic events occurring during the past 3 decades. However, clinical immunotoxicology has long been overlooked. In the 1980s, 2 publications recommended rather similar tiered strategies to test humans potentially exposed to immunotoxicants. Basic tests were recommended to screen for immunological changes, then more specific tests only in those humans with abnormal results, and finally elaborated or research tests selected case by case. The inclusion of clinical monitoring during clinical trials is expanding, although still often restricted to drug candidates with expected effects on the immune system. No regulatory document has been published to help design clinical monitoring. Current strategies are reminiscent of early strategies. The most commonly used endpoints include blood cell counts, standard clinical chemistry, and lymphocyte subset immunophenotyping. Immunization studies with vaccines or neoantigens are the leading assays, which may also include skin testing to KLH, lymphocyte function assays, and cytokine production. The clinical relevance of the generated data is still a matter of debate. Efforts to better standardize and validate endpoints and assays currently used in clinical

monitoring as well as novel biomarkers of immunotoxicity are urgently needed. Translational immunotoxicology could also help improve the immune safety evaluation of drug candidates.

Addressing Uncertainty in Immunotoxicology: Evaluating Risk for Immunomodulatory Compounds

Laine Peyton Myers

(Senior Pharmacology/Toxicology Reviewer,
US Food and Drug Administration
Silver Spring, MD)

Immunotoxicology in risk assessment has made great advancements since the first guidelines for immunotoxicology risk assessment in the 1970s/1980s. Unfortunately, many of the tools currently in use for immunotoxicology risk assessment are more immunosuppression-based and are silent or vague on how to assess immunostimulatory or immunomodulatory compounds. One exception would be hypersensitivity. However, even with a rodent model, there are limitations to detect moderate to mild sensitizers. Current guidances (both a 2002 US FDA guidance and the ICH S8 guideline) do not address much substance outside of immunosuppression. Granted, a few concepts are discussed, but the guidances are mostly silent on a good model for immunostimulation or immunomodulation. Unfortunately, it is not the guidances that are at fault, but of a lack of the basic science to translate nonclinical risk assessment to the clinic. Simply put, we currently lack good nonclinical models for detecting immunomodulatory and immunostimulatory compounds that can translate to clinical risk assessment. There is a need to identify the current state of the science for assessing risk assessment models for immunomodulatory effects, a need to identify research gaps, and a plan for updating the current guidances. This hole in our immunotoxicology risk assessment could be an opportunity for cooperation between regulators, industry, and academia to help mitigate risks of immunomodulatory and immunostimulatory compounds in humans.

Report on the joint symposium at the annual meeting of Japan Toxicology Society

Takemi Otsuki

(Department of Hygiene, Kawasaki Medical School)

To celebrate the 20th anniversary of Japanese Society of Immunotoxicology (JSIT), we had memorial lecture and symposium on the 19th and 20th annual meetings which were held at the Jikei University School of Medicine, Tokyo and Yoyogi Campus of the Tokai University, Tokyo, respectively.

In addition with these special events, we had special collaborating symposium with the Japanese Society of Toxicology (JSOT) in the 40th annual meeting of JSOT held on June 17 to 19, 2013 at the Makuhari Messe International Convention Complex, Chiba, Japan, hosted by Prof. Ueno K, who had been the president of the 18th Annual Meeting of the JSIT. This collaborating symposium entitled "Recent progress in immunotoxicology" chaired by Dr. Sawada J (president of the JSIT) and Prof. Otsuki (secretary of the SJSIT) was consisted with five presentations as showing below.

- 1) Nano-safety science from the view point of immunotoxicology, presented by Dr. Yoshioka Y and Tsustumi Y.
- 2) Environmental pollutants and allergy, presented by Prof. Takano H.
- 3) Molecular mechanisms of the effects of environmental chemicals on differentiation and proliferation of immune cells, presented by Dr. Nohara K.
- 4) Immunotoxicological aspects of asbestos and relation with pathophysiology, presented by Prof. Otsuki T.
- 5) Overview of the WHO/IPCS harmonized guidance for immunotoxicity risk assessment for chemicals, presented by Dr. Teshima R.

During three hours symposium, approximately 300 audiences were listened all lectures with enthusiasm and heated discussions were yielded. Since this decade, immunotoxicological special sessions had not been presented in annual meetings of JSOT, most of audiences enjoyed and had much interest to this symposium.

That day when the symposium was held was big windy day to cause the delay of Keiyo JR line unusually for Japanese railroad time schedule. However, to blow this heavy weather up, all the speakers provided intensive

talks with high scientific findings and deep and wonderful discussions were made with audiences.

Since this symposium was evaluated as great opportunity for both JSIT and JSOT, the next president of annual meeting of JSOT, Dr. Nakamura K, who is the board member and chair of international committee in JSIT, is now planning to have another collaborating symposium in the 41st Annual Meeting of JSOT, July 2-4, 2014, at Kobe Convention Center, Hyogo, Japan, with several immunotoxicological researchers in the next generation. It will be titled "The innovative next generation quest by immunotoxicological researchers (tentative title)".

We should say to all the young investigators in JSIT, the future of immunotoxicological researches are now on your hands! See you 2014, at the 21st annual meeting of JSIT in Tokushima as well as Kobe in the 41st annual meeting of JSOT.

The Outstanding Researcher Award in annual convention

Enhancing effects of isoflavones on IL-17 gene expression

Hiroyuki Kojima¹, Ryuta Muromoto²,
Miki Takahashi², Shinji Takeuchi¹,
Tadashi Matsuda²

(¹Hokkaido Institute of Public Health, Sapporo, Japan,
²Graduate School of Pharmaceutical Sciences,
Hokkaido University, Sapporo, Japan)

T helper 17 (Th17) cells, which produce interleukin 17 (IL-17) and other pro-inflammatory cytokines, were recently identified as a novel Th subset and play important roles in host defense against bacterial and fungal infections as well as in a wide variety of autoimmune diseases, including psoriasis and rheumatoid arthritis^{1,2}. In Th17 cells, the transcription of IL-17 is mediated by Th17-specific transcriptional regulators of the retinoic acid receptor-related orphan receptors α (ROR α) and γ (ROR γ)³. In our previous study, we found that several azole-type fungicides have ROR α and/or ROR γ inverse agonistic activity, and inhibit IL-17A mRNA expression in mouse T lymphoma (EL4) cells⁴. In this

study, we show that the treatment of T cells with plant-derived isoflavones resulted in enhanced IL-17A mRNA expression and protein production, the mechanisms of which involved the activation of ROR γ and signal transducers and activators of transcription 3 (STAT3).

The results are as follows.

1. Isoflavones, among the various phytochemicals tested, showed ROR γ agonistic activity in the ROR γ -mediated reporter gene assay.
2. Treatment of EL4 cells or murine splenocytes with isoflavones enhanced IL-17A mRNA expression and IL-17A production in the RT-PCR and flow cytometric analysis, respectively.
3. An isoflavone, biochanin A (BA), enhanced the interaction between ROR γ and steroid receptor coactivator-1 (SRC-1), which can bind to ROR γ and potentiate its transcriptional activity, in a co-immunoprecipitation experiment using HeLa cells.
4. BA enhanced STAT3 phosphorylation in the Western blot analysis using anti-P STAT3, and also enhanced ROR γ mRNA expression in the EL4 cells.
5. BA failed to induce IL-17 mRNA expression in the ROR γ -knockdown EL4 cells and STAT3-knockdown EL4 cells.

These results suggest that bioactive plant-derived isoflavones can modulate Th17 differentiation through mediation of STAT3- and ROR γ -induced IL-17 gene expression. Isoflavones have been shown to have highly estrogenic activity via estrogen receptors α and β . However, it is not known whether these compounds affect other nuclear receptors. In this study, we provided evidence for the first time that isoflavones have ROR γ agonistic activity and increase IL-17 mRNA expression and IL-17 production.

The Best Young Presenter Award

The inflammatory relative mRNA expressions of Chemokine in splenic macrophages from rats exposed to MWCNT by whole-body inhalation for 13 weeks.

Takamasa Kido

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

I am very happy and honored to be the best Young presenter Award at the 20th Annual Meeting of JSIT 2013. I would like to sincerely thank you for the committee.

In this study, the inflammatory relative mRNA expressions of inflammatory cytokines and chemokine in splenic macrophages and T-lymphocytes from rats exposed to MWCNT by whole-body inhalation for 13 weeks. Multi-walled carbon nanotubes (MWCNT) form almost nano-sized fibers. The toxic mechanism of fibrous MWCNT may be closely related to the immune system, which is affected by fibrous materials with mechanical strength. The objective of this study was to obtain information to help better explain immunotoxic mechanisms of MWCNT *in situ*. Using whole-body inhalation, male and female rats were exposed to MWCNT at 0, 0.2, 1, or 5 mg/m³ for 13 wks. Thereafter, spleens were removed from the rats. The mRNA samples were extracted from isolated activated splenic macrophages and T-lymphocytes. Real-time PCR was performed to assess the mRNA expression of *TNF α* , *IL-1 β* , *IL-6*, *IL-10*, *MCP-1*, and *MIP-1 α* genes in the macrophages, while T-lymphocytes were examined for expression of *IL-2* and *TGF- β ₁* mRNA. Relative expression of *IL-1 β* mRNA in the cells from female rats exposed to 5 mg MWCNT/m³ was significantly higher than that in control rat cells. For *IL-6* and *IL-10*, cells from rats in the 0.2 and 5 mg MWCNT/m³ had significantly higher levels of their mRNA expression than did cells from controls. Expression of *IL-1 β* , *IL-6*, and *TNF α* genes in cells from male rats in all three exposure groups were higher than in control rat cells. The expression of *MIP-1 α* in the female 5-mg group was significantly higher than that in the cells of rats in the control and 1-mg group. Only for *IL-2* was

expression apparently reduced, i.e., cells from male and female rats in all three MWCNT groups had significantly lower mRNA expression values than control rat cells. These data indicate that systemic inflammation would likely occur in rats (or maybe other hosts) exposed to MWCNT via inhalation due to increases in expressions of key inflammatory cytokines in splenic macrophages to which MWCNT were distributed. Moreover, decreases in *IL-2* expression in T-lymphocytes may be critical to any potential reductions in anti-tumor responses that have been noted by others in MWCNT-exposed hosts.

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. Scott W. Burchiel from UNM HSC College of Pharmacy, USA, Dr. Jacques Descotes from Lyon University Hospital, France and Dr. Laine Peyton Myers from US Food and Drug Administration, USA. Let's go to hear their voices. What do you feel and get from those?

Scott W. Burchiel, Ph.D.

Professor & DeSantis Chair of Pharmacogenomics
Dept of Pharmaceutical Sciences, Senior Associate Dean
UNM HSC College of Pharmacy, Albuquerque, NM

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

I was impressed with the quality of the science being pursued in Japan and the excellent research facilities that I saw at universities and elsewhere. Japanese scientists have a rich history in the development of agents such as FK-506 and now in new product development and environmental health studies. I was impressed with the critical mass of clinicians and basic scientists interested in the field of immunotoxicology.

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

My career has represented an interesting balance

between the development of biotechnology products and public health implications for environmental agents such as polycyclic aromatic hydrocarbons (PAHs) and arsenic. We were one of the first groups to develop murine monoclonal antibodies for tumor imaging, human monoclonal antibodies for cancer therapy, and bone marrow growth factors (GM-CSF and IL-3) for bone marrow transplants. We are now excited about understanding individual genetic risk factors for immunosuppression by environmental agents and we are embarking on whole genome sequencing studies.

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

We are pursuing the combined immunotoxic interactions between arsenic and PAHs in human peripheral blood T cells. We have found differential sensitivity in donors for T cell suppression and we are interested in exploring toxicogenomic differences between these individuals. We are currently conducting epidemiology studies in Bangladesh to examine chronic arsenic drinking water exposure and possible immune suppression. I have also been working with the U.S. FDA and the National Center for Toxicologic Research as chair of their Science Advisory Board. I have longstanding interest in the development of policies for immunotoxicity assessment in the U.S. and globally. I am also serving as the Editor-In-Chief of Toxicology and Applied Pharmacology (TAAP) and I invite Japanese scientists to submit their best work to TAAP for publication.

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

I think that we need to understand the genetic factors that influence immunotoxicity. Just as we now understand some of the genetic factors associated with drug, chemical, and food allergies we need to understand those genetic factors that cause different groups and individuals to differ in their sensitivity to chemical immunosuppression and increased risk of infectious disease and cancer.

Q5. Any other comments

I would like to thank the organizers for the wonderful opportunity to visit Japan, which was in fact my first

visit. I would also like to see more joint meeting between U.S. and Japanese immunotoxicology scientists.

Jacques Descotes, M.D., Pharm.D., Ph.D.

Lyon University Hospital

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

This was my fourth trip to Japan. From a nonprofessional point of view, I was very much impressed by the skytree tower. I think this tower is likely to become Tokyo's hallmark as widely known as the Eiffel Tower in Paris. From a professional point of view, I was very much impressed by the number of participants to this meeting of JSIT. I would not expect such a meeting in Europe could attract as many people even though there are approximately 3 times more inhabitants in the European Union than Japan. I would not even mention France where nobody would imagine to organize such a meeting due to the extremely low number of expected participants.

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

There is not one very exciting thing in my career, but two. The first exciting thing is that I can still be excited by immunotoxicology after 35 years of activity in this area. The second thing is that I could be successful in maintaining a similar level of expertise in preclinical and clinical immunotoxicology over the years.

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

My main activity regarding immunotoxicology nowadays is education. The word education can be taken from three perspectives. One is teaching and I do a lot of immunotoxicology teaching (I also plan to start an international e-learning course on immunotoxicology next year). The second one is writing books. I wrote quite a few books on immunotoxicology in the past and I am writing a new textbook on immunotoxicology due to be available freely as an ebook. The last one is consultancy. For me, consultancy most often means explaining to people who request advice, how they should understand immunotoxicity data they have generated and how they

could proceed further in immunotoxicity evaluation and drug development. These advices are thus very close to teaching even though the context is obviously different.

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

In contrast to people who claim that development of omics or in vitro techniques will be the hallmark of immunotoxicology in the 21st century, I think that the most valuable breakthrough in the coming years would be to develop translational immunotoxicology. For me, translational does not mean transposing fundamental research methods to the clinical setting, but instead to design, standardize and validate assays and biomarkers that can be used in preclinical toxicity studies as well as clinical monitoring during clinical trials. This would allow investigating the same parameters in animals and humans using very close conditions and thus improving our understanding and prediction of the immune safety of drug candidates.

Q5. Any other comments

I enjoyed the few days I spent in Tokyo very much, and I hope to be able to come to Japan one again before I retire.

Laine Peyton Myers, Ph.D.

US Food and Drug Administration

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

Experiencing the new Tokyo Tower was an amazing event. I was not prepared to experience the amazing extent and size of Tokyo. It is an amazing city with a wonderful history. The tower is a wonderful addition to experience Tokyo in a way unlike any other.

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

The most exciting event in my career to-date would be being part of the review team to approve an entirely new set of drugs for Hepatitis C. I joined the Antiviral division at the FDA after most of the major classes of HIV drugs were developed. However, HCV treatment was still in its infancy. Prior to the direct acting antivirals (some