



June,
2016

The 5th Japanese Society of
Immunotoxicology Award
(The 2016 JSIT Award)

Effects of genetic polymorphisms on
anti-cancer drug-induced myelotoxicity

Jun-ichi Sawada
Pharmaceuticals and Medical Devices Agency

Individual or ethnic differences in drug responsiveness are well known. The genetic polymorphisms of drug-responsive molecules, including metabolic enzymes detoxifying drugs, have been extensively studied. At the National Institute of Health Sciences, we had surveyed genetic polymorphisms responsible for the adverse reactions induced by several anti-cancer drugs. In this presentation, I would like to talk about the two genes, *UGT1A1* and *CDA* for irinotecan and gemcitabine toxicities, respectively, and recent trends in this field.

Irinotecan is a prodrug generating SN-38, an active anti-cancer metabolite. SN-38 is further metabolized into an inactive metabolite, SN38G, glucuronidated SN-38, by the UDP-glucuronosyl transferase, *UGT1A1*.

Patients having defective *UGT1A1* genotypes may exhibit strong adverse reactions following administration of irinotecan. We have shown that the diplotypes, *28/*28, *6/*28, *6/*6, are causative genotypes responsible for severe adverse reactions including leukopenia. Thus, for the first time, we showed that *6, in addition to *28 was an important factor in irinotecan-induced leukopenia in Japanese patients.

The 23th Annual Meeting of JSIT 2016
(Japanese Society of Immunotoxicology)

September 5-7,2016

(9/5 Lecture open to the public, 9/6-7 Annual Meeting)

Kitakyushu International Conference Center
3-9-30 Asano, Kokurakita-ku, Kitakyushu-shi,
Fukuoka 802-0001

URL: <http://convention-a.jp/en/>

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Deadline for abstract submission: June 24(Fri), 2016

The theme for this Meeting:

“Immunotoxicology practiced in society”

《 Outline of Meeting 》

Special lecture:

Victor J. Johnson, Ph.D.

(Grants & Contracts PI / Study Director.
Burleson Research Technologies, Inc.)

Educational lecture:

Dr. Kazuyoshi Saito

(University of Occupational and Environmental Health, Japan.)

Dr. Kazuhiro Yatera

(University of Occupational and Environmental Health, Japan.)

Dr. Minoru Sato

(University of Occupational and Environmental Health, Japan.)

Symposium:

“Effect of ultra fine and fine particle on the lung and its social practice”

Dr. Kenji Mizuguchi

Dr. Yasumitsu Nishimura

Dr. Etsushi Kuroda

Dr. Hiroto Izumi

Workshop

Oral / Poster Presentation

Awards ceremony

Social gathering September 6(Tue)

Gemcitabine is a still important drug for treatment of pancreatic cancer. Gemcitabine (dFdC) is also a prodrug, activated by phosphorylation (into dFdCDP and dFdCTP). Gemcitabine is metabolized into an inactive compound dFdU by cytidine deaminase (CDA). We have found that the haplotype *3 of the CDA gene with the amino acid substitution Ala70Thr is responsible for gemcitabine-mediated toxicity. Especially, the homozygotes of *3 showed life-threatening severe reactions.

Currently, reports on a large number of drug response-related genetic polymorphisms have been accumulating. When efficacy or safety of a drug is largely affected by genetic polymorphisms, development of a so-called companion diagnostics is necessary for the prediction of such effects. For searching biomarkers to be used for companion diagnostic devices, new technologies including whole genome or epi-genome analysis are available. It is desirable that true “precision medicine” using good biomarkers are achieved.

The 5th Japanese Society of Immunotoxicology Prize for Encouragement

An Immunotoxic Perspective Regarding the Impact of Environmental Pollutants On Allergic Diseases and Lifestyle Diseases

Rie Yanagisawa

Center for Health and Environmental Risk Research,
Molecular Pathology Section

Over the past few decades, environmental factors have caused an increase in allergic diseases and lifestyle diseases. Fetuses, infants, children, and patients are considered particularly vulnerable to environmental factors. This study investigates the effects of exposure to environmental pollutants in allergic diseases and lifestyle diseases, such as obesity.

First, we examined whether exposure to components of diesel exhaust particles (DEP) aggravates certain respiratory diseases, such as allergic airway inflammation and lipopolysaccharide (LPS)-induced acute lung injury in mice. Our findings revealed that DEP components diversely affect a variety of respiratory diseases.

Second, we established a model of mite allergen-induced atopic dermatitis-like skin lesion using NC/Nga mice and showed that diethylhexyl phthalate (DEHP) aggravates atopic dermatitis-like skin lesions at ambient concentrations. In addition, we found that maternal exposure to DEHP in the lactation period can accelerate atopic dermatitis-like skin lesions in male mouse offspring, possibly via Th2-dominant responses.

Next, we also focused the effects of exposure to environmental pollutants on the development of obesity. Imbalance between caloric intake and expenditure is considered a key reason for the present obesity epidemic. However, emerging evidence exists demonstrating that exposure to environmental pollutants is also an important contributor. Therefore, we investigated whether exposure to hexabromocyclododecane (HBCD), an additive flame-retardant, contributes to the initiation and progression of obesity and related metabolic dysfunction in mice fed a normal diet (ND) or a high-fat diet (HFD). This study demonstrates that enhanced weight gain, hyperglycemia, hyperinsulinemia, hepatic steatosis, and macrophage accumulation in adipose tissue occur in mice fed HBCD-treated HFD diet but not in mice fed HBCD-treated ND diet. These results suggest that HBCD may be associated with metabolic dysfunction via interactions with the diet.

Words from
New councilors

Greeting to becoming a new councilor

Eiko Koike

National Institute for Environmental Studies

First of all, I would like to express my sincere appreciation to the Board of Directors of Japanese Society of Immunotoxicology for accepting me as a councilor.

Environmental pollutants are thought to be critical problems for the increase in modern disease such as allergy and lifestyle-related diseases. I have investigated the effects of pollutants existing in the indoor and outdoor environment on respiratory system and immune system. Currently, I have been focusing on chemicals in consumer products, such as phthalates ubiquitously used as plasticizers and brominated flame retardants. I am doing research about these chemical-mediated disruptions of the immune cell function which contribute to the exacerbation of chronic inflammation such as allergy and lifestyle-related diseases. I am also concerned with the cross talk between cell-cell and cell-matrix adhesion to elucidate the molecular mechanisms in the aggravation of chronic inflammation induced by chemicals.



Words from
New councilors

Greetings on the occasion of becoming a
new councilor member

Akihiko Hisatomi

Drug Safety Reach Labs., Drug Discovery Research,
Astellas Pharma Inc.

I am Akihiko Hisatomi. I am a researcher at the Drug Safety Reach Labs. of Astellas Pharma Inc. I have taken office as a councilor of the Japanese Society of Immunotoxicology. I would like to express my heartfelt gratitude to the doctors and senior who recommended and accepted me as to this prestigious position.

Allow me to tell you a little about myself. After graduating from Kyushu University with a masters degree, I started my career at Fujisawa Pharmaceutical Co. Ltd., which is now known as Astellas Pharma Inc. I have long worked in safety research and in the evaluation of many drug candidate substances.

My first work in immunotoxicology was in a study entitled “Collaborative study to establish immunotoxicology evaluation procedures for pharmaceuticals” under the auspices of the Japan Pharmaceutical Manufacturers Association. At the 7th annual meeting of the JSIT, I was able to present the results for one substance in that study. Since then, I have worked on this field of research. Currently, I also work as a study director in immunotoxicity studies and in general toxicity studies.

Recently, I have developed an interest in the prediction of drug-induced interstitial pneumonia in the non-clinical field. Since drug-induced interstitial pneumonia is a serious adverse event in clinical settings, however, it is now difficult to detect potential risks of this pneumonia in non-clinical studies.

I will vigorously endeavor to contribute to the development of the JSIT, and wish to express in advance my appreciation to you for your ongoing support and encouragement.

