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Special Section on Mechanism-Based Predictive Methods in Drug Discovery and Development—Editorial

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In the current issue of Drug Metabolism and Disposition (DMD), Dr. Yuichi Sugiyama, a highly esteemed scientist in the field of pharmacology and one of the most prolific authors in DMD (Ding, 2023), is celebrated for his seminal contributions to the fields of physiologically based pharmacokinetics (PBPK) and membrane transporters in a special section authored by him and several of his former trainees, titled “Mechanism-Based Predictive Methods in Drug Discovery and Development.” Dr. Sugiyama began his career at the University of Tokyo in 1974 and was mentored by Dr. Manabu Hanano (professor) and Dr. Shoji Awazu (associate professor), where he first encountered the concept of PBPK modeling and, later, mechanism-based pharmacokinetics. He studied hepatology at UCLA from 1979 to 1981 and, after returning to the University of Tokyo, was promoted to associate professor in 1989 and professor in 1991. During his tenure at the University of Tokyo, he trained 79 Ph.D.- and 86 master-level students, and he is now active in various positions in academia and global pharmaceutical industries. After he retired from the University of Tokyo, he continued his scientific pursuits as the head of the Sugiyama Laboratory in the RIKEN Innovation Center in Yokohama and as a professor emeritus at the Innovation base of Josai International University.

Throughout his career, Dr. Sugiyama has focused on unraveling the mechanisms underlying the pharmacokinetics of drugs and developing methods for quantitative prediction of their properties. He has covered diverse research areas, including molecular biology, pharmacogenomics, molecular imaging, in silico analysis, and metabolomics. He has developed novel approaches, such as in vitro–in vivo extrapolation, to address uncertainties caused by species differences in drug transport, metabolism, and protein binding. His work on PBPKs has been pivotal for quantitative in vitro to in vivo extrapolation, especially for developing models for predicting drug clearance and the magnitude of drug–drug interactions (DDIs) in humans. Further, his studies on membrane transporters, which encompass functional and kinetic characterization, and the impact of genetic variations, have been fundamental to our understanding of the role of transporters in drug disposition. Dr. Sugiyama is the author of 720 original articles, 80 review articles, and 30 book chapters, including 104 papers published in DMD from 1984 to 2022 (Ding, 2023). Thomson-Reuters has ranked him a Highly Cited Researcher in Pharmacology and Toxicology for many years, on his works related to “Studies on Drug Transporters and the Quantitative Analysis of the Role of Drug Transporters in Drug Clearance and Tissue Distribution of Drugs.” (Mizuno et al., 2003; Nishizato et al., 2003; Shitara et al., 2006; Shitara and Sugiyama, 2006).

Dr. Sugiyama was the recipient of many awards, which include the following:
1. The American Association of Pharmaceutical Sciences Distinguished Scientist Award in 2003
2. The Pharmaceutical Sciences World Congress Research Achievement Award in 2007
3. The International Society for the Study of Xenobiotics (ISSX) Asia Pacific Scientific Achievement Award in 2008
4. The International Pharmaceutical Federation Host-Madsen Gold Medal in 2009
5. The Medal with Purple Ribbon, by the Government of Japan in 2010
6. The 2012 Bernard B. Brodie Award from the Division for Drug Metabolism and Disposition of the American Society of Pharmacology and Experimental Therapeutics (Fig. 1)
7. The Rawls–Palmer Progress in Medicine Award from the American Society of Clinical Pharmacology and Therapeutics 2014
8. The RT Williams Distinguished Scientific Achievement Award from the International Society for the ISSX in 2013

In addition to his scientific work, Dr. Sugiyama has held leadership positions in several scientific organizations. In particular, he has served as the chair of the board of Pharmaceutical Sciences of the International Pharmaceutical Federation and president of the ISSX and the Japanese Society for the Study of Xenobiotics and strongly promoted worldwide drug metabolism, disposition, and transporter research.

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Dr. Sugiyama has been utilizing PBPK models for the past 45 years to predict in vivo kinetics, including metabolic clearance, tissue uptake, excretion clearance, and DDIs. He kicks off this special section with an overview of recent research conducted at the University of Tokyo, RIKEN, and Josai International University. Over the past 20 years, Dr. Sugiyama’s primary focus has been addressing the challenges of predicting human hepatic clearance through in vitro experiments, explicitly employing the in vitro–in vivo extrapolation approach. This special section will emphasize Dr. Sugiyama’s contributions to the theoretical framework and methodology in PBPK modeling and the extended clearance concept. In addition, he will introduce a novel process called the cluster Gauss–Newton method, which represents the current state-of-the-art advancements and prospects of the previously noted objectives (Sugiyama and Aoki, 2023).

Drs. Nozaki and Izumi from Global Drug Metabolism and Pharmacokinetics, Tsukuba Research Laboratories, Eisai Co., Ltd., are long-time collaborators with Dr. Sugiyama. Dr. Nozaki is a former Ph.D. student of Dr. Sugiyama. In “Preincubation Time-Dependent, Long-Lasting Inhibition of Drug Transporters and Impact on the Prediction of Drug–Drug Interactions” (Nozaki and Izumi, 2023), Drs. Nozaki and Izumi reviewed the in vitro effects of preincubation time-dependent, long-lasting inhibition for OATP1B1 and other solute carrier transporters. Through the collaboration with Dr. Sugiyama, trans-inhibition and cis-inhibition mechanisms were identified for the preincubation effect of cyclosporine A on OATP1B1 inhibition, which provides insights on how to improve the accuracy and confidence of DDI predictions (Nozaki and Izumi, 2023).

In the past few years, significant progress has been made in identifying and characterizing specific endogenous substrates of organic anion-transporting polypeptide 1B (OATP1B1). These substances are promising biomarkers for evaluating clinical DDIs mediated by OATP1B. Dr. Xiaoyan Chu, who obtained her Ph.D. with Dr. Sugiyama, is a director and senior principal scientist at Merck and Co. Inc. Dr. Chu and her colleagues contributed an article on “Evaluation of the Selectivity of Several OATP1B Biomarkers Using Relative Activity Factor Method” (Chan et al., 2023). The authors evaluated the predictivity for several OATP1B1 biomarkers. They developed a new RAF method to determine the contribution of hepatic up-take transporters quantitatively. This can facilitate the mechanistic interpretation and modeling of biomarker data and the selection of appropriate biomarkers for DDI evaluation (Chan et al., 2023).

Dr. Hiroyuki Kusuhara, a former student of Dr. Sugiyama, has collaborated with him for over 20 years since starting his career as an assistant professor in Dr. Sugiyama’s laboratory. After Dr. Sugiyama’s retirement, Dr. Kusuhara became a professor at the Graduate School of Pharmaceutical Sciences, the University of Tokyo, where he continued his research on drug transporters. Dr. Kusuhara and his colleagues have contributed a review article titled “Progress in the Quantitative Assessment of Transporter-Mediated DDIs Using Endogenous Substrates in Clinical Studies” to the special section (Mochizuki and Kusuhara, 2023). The report provides a comprehensive overview of endogenous biomarkers for drug transporters in the liver and kidney. These biomarkers play a crucial role in assessing changes in drug transporter activities during clinical studies, leading to more accurate predictions of DDIs (Mochizuki and Kusuhara, 2023).

Dr. Kiyomi Ito is a professor and director at the Research Institute of Pharmaceutical Sciences, Musashino University. She worked as an assistant professor in Prof. Sugiyama’s laboratory at the University of Tokyo from 1996 to 1997. Dr. Ito and her colleagues contributed an article titled "Quantitative Consideration of Clinical Increases in Serum Creatinine Caused by Renal Transporter Inhibition" (Nakada et al., 2023). The review article explores cases of serum creatinine increase. It demonstrates that renal transporter inhibitors can elevate serum creatinine levels surpassing the thresholds used for acute kidney injury criteria. This research highlights the possibility of employing mechanistic approaches to aid decision-making in clinical development, particularly in distinguishing between acute kidney injury and creatinine–drug interactions (Nakada et al., 2023).

Dr. Yukio Kato, a former Ph.D. student of Dr. Sugiyama, is a professor of molecular pharmacotherapeutics at Kanazawa University and serves as the dean of the Faculty of Pharmacy. Dr. Kato and Dr. Hiroshi Arakawa contributed an article...
titled “Emerging Roles of Uremic Toxins and Inflammatory Cytokines in the Alteration of Hepatic Drug Disposition in Patients with Kidney Dysfunction” (Arakawa and Kato, 2023). This article comprehensively summarizes the changes in renal and hepatic pharmacokinetics and potential underlying mechanisms in kidney dysfunction conditions such as chronic kidney disease and acute kidney injury. Patients with kidney dysfunction exhibit distinct pharmacokinetic profiles compared with individuals with normal kidney function. Elevated plasma levels of uremic toxins and inflammatory cytokines observed during kidney disease can influence drug-metabolizing enzymes’ activities, expression levels, and transporters in the liver and kidneys (Arakawa and Kato, 2023).

Dr. Kazuya Maeda obtained his B.S., M.S., and Ph.D. degrees under Dr. Sugiyama’s supervision. He then continued working with Dr. Sugiyama as an assistant professor until Dr. Sugiyama retired from the University of Tokyo (2002–2012). Currently, Dr. Maeda holds the position of a full professor in the Laboratory of Pharmacuetics at the School of Pharmacy, Kitasato University. In this special section, Dr. Maeda contributes the review article “Quantitative Prediction of Intestinal Absorption of Drugs from In Vitro Study: Utilization of Differentiated Intestinal Epithelial Cells Derived from Intestinal Stem Cells at Crypts” (Maeda, 2023). The article highlights the limitations of traditional approaches in predicting intestinal drug absorption in humans. It emphasizes the advantages of novel experimental systems, mainly differentiated cells derived from intestinal stem cells at crypts (Maeda, 2023). It is worth noting that Dr. Maeda, along with Dr. Kiyomi Ito, Dr. Akihiro Hisaka, and others, played a significant role in the development of the DDI guidance at the Pharmaceuticals and Medical Devices Agency.

Finally, Dr. Sugiyama, Dr. Wooin Lee, and colleagues from the College of Pharmacy and Research Institute of Pharmaceutical Sciences, Seoul National University, co-authored the article “Predicting In Vivo Target Occupancy (TO) Profiles via PBPK-TO Modeling of Warfarin Pharmacokinetics in Blood: Importance of Low Dose Data and Prediction of Stereoselective Target Interactions.” In this article, a PBPK model incorporating target-mediated drug disposition was developed for warfarin, a drug known for its high-affinity binding to its target. This PBPK-TO modeling approach provides insights into TO prediction for drugs with high target affinity and limited distribution volume (Lee et al., 2023).

The research contributions of Dr. Sugiyama and his trainees have been fundamental in shaping our understanding of the critical roles drug transporters play in drug disposition and in making remarkable strides in predicting drug clearance. Their works are profoundly impactful by advancing the PBPK field, paving the way for improved drug development strategies and offering valuable tools and knowledge for optimizing drug therapy and minimizing potential adverse drug interactions in clinical practice.

References


Maeda K (2023) Quantitative prediction of intestinal absorption of drugs from in vitro study; utilization of differentiated intestinal epithelial cells derived from intestinal stem cells at crypts. Drug Metab Dispos 51:1136–1144.


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