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Special Section on New Era of Transporter Science: Unraveling the Functional Role of Orphan Transporters–Editorial

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In the current issue of *Drug Metabolism and Disposition (DMD)*, Dr. Kathleen M. Giacomini, a world-renowned leader in membrane transporter biology, pharmacogenomics, and regulatory sciences, along with and several of her former trainees contribute a special section titled, "New Era of Transporter Science: Unraveling the Functional Role of Orphan Transporters." After obtaining her bachelor's degree in pharmacy from the University of Houston, Dr. Giacomini received her Ph.D. in pharmaceutics from the State University of New York at Buffalo and completed postdoctoral training at Stanford University. She has been a faculty member of University of California, San Francisco (UCSF) since 1982 and was recently named dean of the UCSF School of Pharmacy. She is a cofounder of the International Transporter Consortium, which brings together scientists from academia, industry, and regulatory agencies worldwide to advance knowledge of transporters in drug development with the goal of improving human health. She is also a co-director of the UCSF-Stanford Center of Excellence in Regulatory Science and Innovation in partnership with the US Food and Drug Administration (FDA). Dr. Giacomini is the recipient of numerous awards for her seminal work in membrane transporter genomics and the role these proteins have in drug targeting, disposition, and response. Some of her notable honors include the North American Scientific Achievement Award from the International Society for the Study of Xenobiotics, the Volwiler Research Achievement Award and Paul Dawson Biotechnology Award given by the American Association of Colleges of Pharmacy, the Rawls-Palmer Progress in Medicine Award from the American Society for Clinical Pharmacology and Therapeutics, the Bill Heller Mentor of the Year Award from the American Foundation for Pharmaceutical Education, the Bernard B. Brodie Award from the Division for Drug Metabolism and Disposition of the American Society of Pharmacology and Experimental Therapeutics (Fig. 1), and the Distinguished Pharmaceutical Scientist Award given by the American Association of Pharmaceutical Scientists.

Membrane transporters play a major role in human physiology and in drug disposition and response. In 1997, Dr. Giacomini's laboratory cloned and characterized the first human polyspecific organic cation transporter from liver (Zhang et al., 1997), which was almost simultaneously cloned in another laboratory (Gorboulev et al., 1997), and discovered that variants in the gene were associated with the disposition of and response to the antidiabetic drug metformin (Shu et al., 2007). Recently, her group unraveled the functional role of the orphan solute carrier (SLC) 22A24, an anion exchanger that preferentially transports steroid glucuronide conjugates (Yee et al., 2019).

Dr. Giacomini trained over 35 graduate students and 30 postdoctoral fellows with many of those trainees becoming national and international leaders in the pharmaceutical sciences. Dr. Sook Wah Yee was a postdoctoral fellow under Dr. Giacomini and is currently a UCSF assistant adjunct professor conducting research on transporters using metabolomic and genome-wide association methodologies. In this issue of *DMD*, Dr. Yee, along with Dr. Giacomini, contributes the comprehensive review, "Emerging Roles of the Human Solute Carrier 22 Family" (Yee and Giacomini, 2022), which summarizes the physiologic and pharmacologic roles of SLC22 family members and the impact of genetic variants in these transporters on disease and drug response. Recent studies deorphaning SLC22 family members are also discussed.

Dr. Lei Zhang obtained her Ph.D. with Dr. Giacomini and is deputy director of the Office of Research and Standards, Office of Generic Drugs at the Center for Drug Evaluation and Research, at the FDA. Dr. Zhang and her colleagues contribute the article, "Transporters in Regulatory Science: Notable Contributions from Dr. Giacomini in the Past Two Decades" (Zhang et al., 2022), which summarizes Dr. Giacomini's key contributions and influences on transporters in regulatory science through her collaborations with FDA scientists. The article highlights the founding of the International Transporter Consortium and its workshops and white papers. These white papers review transporters that are clinically important in drug absorption, action, and disposition; the emerging roles of transporters; and in vitro methods to study drug interactions involving these transporters, and provide recommendations and decision frameworks to guide clinical studies on drug-drug interactions.

Dr. Joanne Wang was one of Dr. Giacomini's Ph.D. students and is currently a professor of pharmaceutics at the University of Washington and an affiliate investigator at the Fred Hutchinson Cancer Research Center. Dr. Wang and her colleagues contribute to this *DMD* issue the article, "Clinical Applications and the Roles of Transporters in Disposition, Tumor Targeting, and Tissue Toxicity of Meta-Iodobenzylguanidine" (mIBG) (Lopez Quinones et al., 2022). The article reviews the

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ABBREVIATIONS: DMD, Drug Metabolism and Disposition; FDA, US Food and Drug Administration; mIBG, meta-Iodobenzylguanidine; SLC, solute carrier; UCSF, University of California, San Francisco.

Fig. 1. Dr. Kathleen M. Giacomini was the recipient of the Bernard B. Brodie Award in Drug Metabolism and Disposition, given by the Division for Drug Metabolism and Disposition of the American Society for Pharmacology and Experimental Therapeutics in 2020. Photos are reproduced with permission from Dr. Kathy Giacomini.

differential roles of norepinephrine transporters, organic cation transporters, and multidrug and toxin extrusion transporters in mIBG disposition; its response and toxicity; and clinical applications of mIBG in neuroendocrine cancers. Understanding the molecular mechanisms governing mIBG transport in cancer and normal cells can optimize the clinical use of mIBG as a radiopharmaceutical in cancer diagnosis and treatment while minimizing toxicity in normal tissues.

Dr. Ligong Chen received postdoctoral training in Dr. Giacomini's laboratory after receiving a Ph.D. from the University of California, Berkeley. He is currently a principal investigator in pharmacology and toxicology of the School of Pharmaceutical Science at Tsinghua University, China. His research focuses on investigating various transporters' roles in human diseases and molecular mechanisms of drug toxicity. Dr. Chen and his colleagues contribute a review article on "Amino Acid Solute Carrier Transporters in Inflammation and Autoimmunity" (Sheng et al., 2022). The article summarizes the link between SLC amino acid transporters and inflammation and immune responses; specifically, SLC1 and SLC7 family members. The authors detail the importance of glutamate transporters SLC1A1, SLC1A2, and SLC1A3, which are mainly expressed in the brain, where they help prevent glutamate excitotoxicity and can potentially serve as novel therapeutic targets.

Dr. Yan Shu completed his Ph.D. under Dr. Giacomini's mentorship and is an associate professor of pharmaceutical sciences at the University of Maryland School of Pharmacy. Dr. Shu's research is focused on genetic mechanisms of drug response and the role of membrane transporters in pharmacokinetics and clinical drug response. In this special section, Dr. Shu and his colleagues contribute a review article on "Transcriptional Regulation of Solute Carrier Drug Transporters" (Zhou and Shu, 2022). The article describes the mechanisms underlying the transcription of SLC drug transporters that are clinically important in drug absorption, metabolism, distribution, and excretion. Revealing these epigenetic and nuclear receptor–mediated transcriptional regulation mechanisms of SLC drug transporters can help us understand their pharmacokinetics and pharmacodynamics, ultimately improving drug therapeutic effectiveness while minimizing drug toxicity.

Dr. Micheline Piquette-Miller received her postdoctoral training under the guidance of Dr. Giacomini after completing a pharmacy degree and Ph.D. in pharmacokinetics at the University of Alberta. She is currently a professor within the Leslie Dan Faculty of Pharmacy at the University of Toronto. Her research is primarily focused on the mechanisms involved in the pathophysiological regulation of drug transport proteins and how they impact drug disposition. In this special section, Dr. Piquette-Miller and her colleagues contribute a paper on the "Impact of Inflammation and Infection on the Expression of Amino Acid Transporters in the Placenta" (McColl et al., 2022). The article summarizes studies that investigate the impact of inflammation on placental amino acid transporter expression, identify questions that remain unanswered, and propose future areas of research to advance the field. The authors emphasize that inflammation-mediated changes in expression of amino acid transporters in the placenta may have implications for fetal outcomes, warranting further studies to investigate the underlying mechanisms and implications of these changes.

There are 465 SLC genes encoding membrane proteins that can be clustered together into 65 distinct families based on sequence homology. Many of these members are known to play key roles in pharmacokinetics and drug disposition; however, there remain many SLC proteins in the superfamily with no known substrate or function (orphans). The efforts by Dr. Giacomini and her trainees to deorphan some of these membrane transporters have demonstrated that common variants

in the transporters are associated with differences in drug response and have potential clinical implications. The cutting-edge research conducted by Dr. Giacomini and her trainees pertaining to drug transport, disposition, and regulatory science will ultimately improve drug design in developing effective treatments for human diseases.

Yurong Lai and Xiao-bo Zhong
Editors

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