Special Section on New Era of Transporter Science: Unraveling the Functional Role of Orphan Transporters—Minireview

Transporters in Regulatory Science: Notable Contributions from Dr. Giacomini in the Past Two Decades

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ABSTRACT

Transporters govern the access of molecules to cells or their exit from cells, thereby controlling the overall distribution of drugs to their intracellular site of action. Clinically relevant drug-drug interactions mediated by transporters are of increasing interest in drug development. Drug transporters, acting alone or in concert with drug metabolizing enzymes, can play an important role in modulating drug absorption, distribution, metabolism, and excretion, thus affecting the pharmacokinetics and/or pharmacodynamics of a drug. Dr. Kathy Giacomini from the University of California, San Francisco is one of the world leaders in transporters and pharmacogenetics with key contributions to transporter science. Her contributions to transporter science are noteworthy. This review paper will summarize Dr. Giacomini's key contributions and influence on transporters in regulatory science in the past two decades. Regulatory science research highlighted in this review covers various aspects of transporter science, including understanding the effect of renal impairment on transporters, transporter ontogeny, biomarkers for transporters, and interactions of excipients with transporters affecting drug absorption.

SIGNIFICANCE STATEMENT

This review paper highlights Dr. Giacomini's key contributions and influence on transporters in regulatory science in the past two decades. She has been at the cutting edge of science pertaining to drug transport, drug disposition, and regulatory science, leading to a new era of translational sciences pertaining to drug disposition and transporter biology. Her research has and will continue to bring enormous impact on gaining new knowledge in guiding drug development and inspire scientists from all sectors in the field.

Introduction

Membrane transporters are expressed in various tissues throughout the human body, controlling the movement of endogenous and exogenous substances in and out of cells at various sites in the body. More than 450 human transporters have been identified, and approximately 30 transporters are known to play a role in drug transport (Giacomini et al., 2010; Giacomini and Sugiyama, 2017). Transporters can affect a drug's pharmacokinetics by controlling absorption, distribution, and elimination processes. They can also affect a drug's pharmacodynamics by influencing its access to the site of action (Giacomini and Sugiyama, 2017). Transporters have become important as drug targets, for example, urate transporter (URAT1, *SLC22A12*) inhibitors as treatment of gout and sodium/glucose cotransporter-2 (SGLT2, *SLC5A2*) inhibitors

for treating type 2 diabetes. More recently, the US Food and Drug Administration (FDA) approved maralixibat, an ileal bile acid transporter [apical sodium–bile acid transporter (ASBT), *SLC10A2*] inhibitor, for the treatment of cholestatic pruritus in patients at least 1 year old who have Alagille syndrome, a rare disease (Shirley 2022a,b). Over the past 20 years, research activities have generated a vast amount of data on transporters.

Dr. Kathy Giacomini, from the University of California, San Francisco (UCSF), is one of the world leaders in transporters and pharmacogenetics. Her contributions to transporter research are remarkable and instrumental. She champions knowledge of transporters in drug development, regulatory science, and pharmacotherapy with a clinical focus. One author of this paper, Dr. Lei Zhang, was a graduate student in Dr. Giacomini's laboratory from 1994 to 1998 who has worked at the FDA since 2002. She continued to collaborate with Dr. Giacomini on various regulatory science projects on transporters. She witnessed Dr. Giacomini's continued impact in the transporter science field, not only in the academic institutions at the "bench" but also on the translational side to the "bedside."

ABBREVIATIONS: BCRP, breast cancer resistance protein; BCS, biopharmaceutics classification system; BE, bioequivalence; CERSI, Center of Excellence in Regulatory Science and Innovation; CKD, chronic kidney disease; CL$_{sec}$, secretory clearance; DDI, drug-drug interaction; EMA, European Medicines Agency; FDA, US Food and Drug Administration; GFR, glomerular filtration rate; GLUT, glucose transporter; INH, intact nephron hypothesis; ITC, International Transporter Consortium; MATE, multidrug and toxin extrusion protein; MCM, medical countermeasure; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; PBPK, physiologically based pharmacokinetic; P-gp, P-glycoprotein; PI, principal investigator; PK, pharmacokinetics; PMDA, Japan's Pharmaceuticals and Medical Devices Agency; RI, renal impairment; RLD, reference listed drug; SLC, solute carrier; UCSF, University of California, San Francisco.

This review paper summarizes Dr. Giacomini's scientific contributions that have been major leaps to influence the field of transporters in regulatory science in the past two decades through collaborations with the FDA scientists. FDA defines regulatory science as "the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products" (https://www.fda.gov/science-research/science-and-research-special-topics/advancing-regulatory-science).

Formation of the International Transporter Consortium and Its Impact on Transporter Science

Drug interaction potential is recognized as an important consideration in the evaluation of a new molecular entity (NME). Evaluation of drug interactions is an integral part of drug development and regulatory review prior to market approval (Huang et al., 2007, 2008; Zhang et al., 2009a,b; Rekić et al., 2017; Yoshida et al., 2017). In the 1990s, the FDA guidance documents on drug-drug interactions (DDIs) only discussed interactions mediated via drug metabolizing enzymes. Since early 2000, the importance of transporters in DDIs has been increasingly recognized. Many significant DDIs have been attributed to transporters. For example, the withdrawal of cerivastatin in early 2000 (Charatan, 2001) was due to significant DDIs caused by the inhibition of a hepatic transporter, organic anion transporting polypeptide (OATP)1B1 (SLCO1B1), that led to increased cerivastatin drug levels (Shitara et al., 2004). The FDA started to include recommendations for transporter studies in 2006 with a particular focus on P-glycoprotein (P-gp), the most studied transporter at the time. However, knowledge on other transporters was limited then.

There was a need to build a community consensus on transporters that play an important role in DDIs and drug safety and efficacy. In 2007, the International Transporter Consortium (ITC) was established (Huang et al., 2010) (https://www.itc-transporter.org/). Dr. Giacomini was one of the cofounders and has served as the cochair of the ITC Steering Committee for more than a decade since 2007. The mission of this Consortium is "to encourage dialog in all sectors of transporter research to solidify our present understanding, challenge our current thinking, and position ourselves to better address the complex and critical issues related to transporters in drug development" (Huang et al., 2010). As a cochair of the ITC Steering Committee, she has led the scientific programming for numerous transporter workshops and symposia, including four ITC Workshops in 2008, 2012, 2017, and 2021. Dr. Giacomini effectively brings together experts from academia, industry, and regulatory agencies to gain different perspectives on transporter science and applications in clinical pharmacology. Her advocacy in assembling expert working groups to generate white papers that review current knowledge and identify key gaps in our understanding has moved the field forward and markedly influenced regulatory guidances related to transporter-mediated drug interactions. She is the lead author on the most highly cited review on membrane transporters in drug development (∼3000 citations) published after the first ITC Transporter Workshop (Giacomini et al., 2010).

Dr. Giacomini also coedited "Human Transporters"- and "Advances in Transporters"-themed issues of Clinical Pharmacology and Therapeutics (July 2013 and November 2018, respectively) after the second and third ITC Workshops in 2012 and 2017 (Giacomini and Huang, 2013; Giacomini et al., 2018), respectively. The themed issues included approximately 20 whitepapers generated from these successful workshops. These whitepapers have addressed several key questions for drug development, including which transporters are clinically important in drug absorption, action, and disposition; which transporters are having emerging roles; and which in vitro methods are suitable for studying drug interactions involving these transporters with recommendations and decision frameworks to help guide clinical drug interaction studies (Brouwer et al., 2013, 2015; Chu et al., 2013, 2018a,b; Giacomini et al., 2013; Hillgren et al., 2013; Kalvass et al., 2013; Tweedie et al., 2013; Zamek-Gliszczynski et al., 2013, 2018a,b; Lee et al., 2014; Evers et al., 2018; Guo et al., 2018; Kenna et al., 2018; Schlessinger et al., 2018; Yee et al., 2018). New research in transporters was also highlighted. Work derived from ITC in the past decade has impacted regulatory agencies worldwide on their guidance development. For example, five whitepapers were cited in the FDA's in vitro drug interaction guidance (https://www.fda.gov/media/134582/download).

After the ITC Workshops and the first ITC whitepaper, the list of transporters has expanded over time as data on clinically important transporter-mediated DDIs accumulated. The FDA's draft guidance, as released in 2012, included seven transporters for routine evaluations [i.e., efflux transporters, P-gp (ABCB1) and breast cancer resistance protein (BCRP) (ABCG2) (ATP-binding cassette (ABC) superfamily] and uptake transporters, OATP1B1 (SLCO1B1), OATP1B3 (SLCO1B3), organic anion transporter (OAT)1 (SLC22A6), OAT3 (SLC22A8), and organic cation transporter (OCT)2 (SLC22A2) (solute carrier, or SLC, superfamily)]. These transporters were selected after careful considerations of the recommendations of the ITC (Giacomini et al., 2010; Huang and Woodcock, 2010), the FDA Advisory Committee meetings in 2006 and 2010 (https://wayback.archiveit.org/7993/20170403222244/https://www.fda.gov/ohrms/dockets/ac/cder06.html#PharmScience; https://wayback.archive-it.org/7993/20170403224116/https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/ucm201700.htm), and scientific exchanges with experts in other regulatory agencies, including the European Medicines Agency (EMA) and Japan's Pharmaceuticals and Medical Devices Agency (PMDA). With regard to tissue localization, important transporters are located in the intestine (P-gp and BCRP), liver (OATP1B1, OATP1B3, P-gp, and BCRP), and the kidneys (OAT1, OAT3, OCT2, P-gp, and BCRP). After subsequent ITC workshops, based on new development in the transporter research, renal efflux transporters [i.e., multidrug and toxin extrusion proteins MATE1 (SLC47A1) and MATE2-K (SLC47A2)], were also recommended for routine evaluation as part of DDI assessments in drug development by regulatory agencies (Hillgren et al., 2013; Dong et al., 2016) (EMA DDI guideline: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-drug-interactions-revision-1_en.pdf; PMDA DDI guideline: https://www.pmda.go.jp/files/000228122.pdf; FDA in vitro DDI guidance: https://www.fda.gov/media/134582/download; FDA clinical DDI guidance: https://www.fda.gov/media/134581/download).

Between 2012 and 2020, the EMA, PMDA, and FDA have revised or finalized their drug interaction guidance documents that adopted recommendations on transporters generated from the ITC workshops and publications (FDA in vitro DDI guidance: https://www.fda.gov/media/134582/download; FDA clinical DDI guidance: https://www.fda.gov/media/134581/download; PMDA DDI guideline: https://www.pmda.go.jp/files/000228122.pdf; https://ddblog.labcorp.com/2020/06/a-comparison-of-fda-ema-pmda-regulatory-agency-guidance-for-in-vitro-drug-drug-interaction-ddi-assessments/; EMA DDI guideline: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-drug-interactions-revision-1_en.pdf). In 2022, additional transporter whitepapers will be published after the 4th ITC Transporter Workshop, held in April 2021. A Clinical Pharmacology and Therapeutics (CPT) "Transporters"-themed issue for which Dr. Giacomini serves as the coeditor will be published in September 2022 (https://www.ascpt.org/Resources/ASCPT-News/View/ArticleId/27447/Call-for-Papers-Transporters).

In current drug development, information on metabolism, transport, and drug interactions is important for the benefit/risk assessment of drug products. The international harmonization efforts on DDI evaluation are being pursued at the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). A draft ICH M12 guideline on "Drug Interaction Studies" was recently published for public consultation (https://database.ich.org/sites/default/files/M12_Step1_draft_Guideline_2022_0524.pdf). The guideline is intended to provide a consistent approach in designing, conducting, and interpreting enzyme- or transporter-medicated in vitro and clinical DDI studies during the development of a therapeutic product.

FDA Critical Path Initiatives

In addition to collaborating with the FDA to hold the first ITC Transporter Workshop in 2008 supported by the FDA Critical Path Initiative (Huang and Woodcock, 2010) (https://www.fda.gov/science-research/science-and-research-special-topics/critical-path-initiative), Dr. Giacomini further developed a research project to build a transporter database, where such a database was rare at the time and contained nonsystematic information (Table 1).

UCSF-FDA TransPortal. More than 10 years ago, although a large body of data pertaining to drug transporters was available in the literature, there were few databases that informed drug developers, regulatory agencies, and academic scientists about transporters that are important in drug absorption, action, and disposition. Recognizing the importance of a database on transporters to disseminate information timely and widely, Dr. Giacomini collaborated with the FDA to build a transporter database, the UCSF-FDA TransPortal, in 2012 (Morrissey et al., 2012). It is a useful repository of information on transporters important in the drug discovery process, supported by the FDA-led Critical Path Initiative (https://www.fda.gov/science-research/science-and-research-special-topics/critical-path-initiative). Information in the database includes transporter expression, localization, substrates, inhibitors, and drug-drug interactions.

Since 2012, the database has been updated periodically with additional support from the National Institute of Environmental Health Science (NIEHS) and National Institutes of Health (NIH) involving additional principal investigators (PIs). The database's new name is UCSF-FDA TransPortal + UCSD/UCD-NIEHS TICBase (https://transportal.compbio.ucsf.edu/). The database continues to serve as a valuable online resource for research and drug development.

FDA's Centers of Excellence in Regulatory Science and Innovation Research

Dr. Giacomini has also collaborated with the FDA to advance regulatory science by applying findings from academic research to support both new drug and generic drug development and regulation (Table 1).

In 2011, the FDA established the Centers of Excellence in Regulatory Science and Innovation (CERSIs) to help achieve the FDA's mission to protect and promote public health (https://www.fda.gov/media/96457/download). The CERSI program has since grown from two to four Centers and now includes six universities and/or academic medical centers (https://www.fda.gov/science-research/advancing-regulatory-science/centers-excellence-regulatory-science-and-innovation-cersis). The CERSI program is one of the best ways for biomedical community and the public to interact with the FDA (Altman et al., 2015; Weichold, 2019). Dr. Giacomini has been an inspiring leader to promote and facilitate collaborations between academic institutions and regulatory agencies to improve the development and regulation of safe and effective therapies. Through Dr. Giacomini's leadership as the coprincipal investigator, the UCSF-Stanford CERSI was established in 2014 as the first CERSI located outside of the Washington-Baltimore metropolitan area, and it actively works with the FDA to advance regulatory science through innovative research, training, and scientific exchange (https://pharm.ucsf.edu/cersi/about).

The recent paper by Giacomini et al. (2019) has highlighted some of the research projects and outcomes of the UCSF-Stanford CERSI program. The FDA Visiting Scientist Program under the UCSF-Stanford CERSI has brought over 140 FDA scientists to UCSF and Stanford University to engage with the scientific community on the west coast and meet with UCSF/Stanford faculty members to explore opportunities for collaborative research projects (https://pharm.ucsf.edu/cersi/vsp).

TABLE 1

Regulatory science research on transporters: collaboration between Dr. Giacomini and FDA

Research	Objectives	Status	Publications and Online Links
UCSF-FDA TransPortal	To build a publicly accessible database on transporters to disseminate information on transporters (including transporter expression, localization, substrates, inhibitors, and drug-drug interactions) timely and widely	Completed	(Morrissey et al., 2012) https://transportal.compbio.ucsf.edu/
Effect of Renal Impairment on Transporters	Phase I: To understand the effect of uremic solutes on renal transporter activity (OATs and OCT2) and how renal impairment may affect renal transporter activity to help PBPK modeling for prediction Phase II: To determine whether drug administration reduces the clearance of waste solutes, resulting in their accumulation in the body and unintended side effects	Phase I: Completed Phase II: Ongoing	(Hsueh et al., 2016, 2018; Cheung et al., 2017)
Ontogeny of Transporters	To understand the ontogeny of various transporters by studying expression of transporters in children and adults from kidney and brain tissues and use PBPK modeling to support the dosing of antimicrobial agents in children	Ongoing	(Cheung et al., 2019a,b)
Identification and Validation of Biomarkers for BCRP	To validate metabolic biomarkers for BCRP both in vitro in cellular assays and in vivo through a clinical study in healthy subjects	Ongoing	https://clinicaltrials.gov/ct2/show/NCT04542382
Excipient Database	To build a databased on oral excipients used in approved drug products	Completed	(Irwin et al., 2017; Pottel et al., 2020)
In Vitro Inhibition of Excipients on Transporters	To study vitro inhibition of excipients on intestinal transporters (OATP2B1, P-gp, and BCRP)	Completed	(Zou et al., 2020a,b; Bajaj et al., 2021)
Effect of Excipients on the Oral Absorption of Fexofenadine in Humans	To assess the effect of one excipient on the bioavailability of a model drug	Ongoing	https://clinicaltrials.gov/ct2/show/NCT04534153

These research projects address the FDA's specific needs and align with the Agency's stated research priority areas (https://www.fda.gov/science-research/advancing-regulatory-science/fda-centeroffice-regulatory-science-research-priority-areas-cersi-program). To date, the UCSF-Stanford CERSI program has supported 65 collaborative research projects with the FDA, which has resulted in at least 60 scientific publications and has influenced numerous FDA guidance documents. UCSF-Stanford CERSI frequently collaborates with FDA Centers and Offices and has cosponsored scientific workshops and events; these are usually open to the public and listed on the UCSF-Stanford CERSI website (www.ucsfstanfordcersi.org). The UCSF-Stanford CERSI program also conducts training programs in regulatory science for graduate students and postdoctoral fellows at both universities; these fellows are key to some of the collaborative research projects highlighted below.

Below are a few highlights of research projects on which we collaborate with Dr. Giacomini and other PI collaborators as part of UCSF-Stanford CERSI. Her research through CERSI is not only innovative but also practical to help address drug development challenges or regulatory questions.

Effect of Renal Impairment on Transporters. Chronic kidney disease (CKD) or renal impairment (RI) can affect the pharmacokinetics (PK) of many drugs, especially these drugs that are mainly cleared by the kidneys, leading to higher drug levels and potentially increased toxicities. Whereas reduced renal elimination as a result of reduced glomerular filtration rate (GFR) is expected in CKD, the effect of RI on active secretion of a drug is poorly understood. One of the characteristics of CKD is the accumulation of uremic solutes in the plasma. Less is known about the effects of uremic solutes on transporters that may play critical roles in PK of drugs in patients with CKD. A collaborative project was funded by CERSI in which Dr. Giacomini served as the PI to study the effect of RI on transporters. In this study, how uremic solutes may affect two major renal transporters, OAT1 and OAT3, was studied. Through in vitro screening in Dr. Giacomini's laboratory on 72 uremic solutes, 12 and 13 solutes were identified as inhibitors of OAT1 and OAT3, respectively (Hsueh et al., 2016). The intact nephron hypothesis (INH) predicts that glomerular filtration and tubular secretion would decline in parallel. However, review of clinical studies for 18 drugs that are known substrates of OAT1/OAT3 showed that the active secretion of most OAT1/OAT3 drugs deteriorated faster than the renal filtration in CKD. These data suggest that uremic solutes contribute to the decline in renal drug clearance in patients with CKD through inhibition of OAT1 and OAT3 (Hsueh et al., 2016). We assumed a factor Fx for the decrease in secretory clearance (CL_{sec}) in addition to change related to kidney physiology (measured by R_{GFR}, defined as the ratio of GFR measured in CKD patients and in subjects with normal renal function) for each CKD stage. Fx would be 1 if decrease in CL_{sec} is in parallel to decrease in GFR. It was found that the median Fx values decreased as renal function declined between CKD Stage 2 and CKD Stage 4. The median values of calculated Fx were 0.73 (0.31–1.33) and 0.41 (0.02–1.00) for CKD Stages 3 (moderate) and 4 (severe), respectively. The data suggested that reductions of glomerular filtration rate (GFR) and CL_{sec} (via tubular secretion) for these drugs were disproportional, particularly in severe CKD subjects. The reduction in CL_{sec} appeared to be greater than that of GFR in moderate and severe CKD.

The research project continued by developing physiologically based pharmacokinetic (PBPK) models for seven renally eliminated drugs that are known OAT1/OAT3 substrates: adefovir, avibactam, entecavir, famotidine, ganciclovir, oseltamivir carboxylate, and sitagliptin (Hsueh et al., 2018). Drug models verified using PK data from healthy subjects (HS) were coupled with physiologic models representing CKD that incorporated prior knowledge of effects of CKD on hepatic and renal elimination. For mild CKD, the use of INH, which assumes proportional reduction of GFR and CL_{sec}, appears sufficient. For moderate CKD, reduction in CL_{nr} (non-renal clearance) should be considered besides the INH. In addition to these two adjustments (INH and reduced CL_{nr}), a further reduction in CL_{OATs} (intrinsic clearance mediated by OATs) is required for predicting PK in severe CKD. The models reasonably described clinically observed PK changes in subjects with CKD and can be useful in quantitatively predicting secretory clearance of OAT1/OAT3 substrate drugs in CKD patients and in supporting dosing recommendations for these renally cleared drugs in CKD. The prediction factor and PBPK modeling were adopted by others to predict PK in renally impaired patients for OAT1/OAT3 substrates (Wang et al., 2021).

Similarly, Dr. Giacomini's laboratory evaluated the effect of uremic solutes on the organic cation transporter OCT2, which plays a key role in the renal secretion of many basic drugs (Cheung et al., 2017). Of 72 uremic solutes screened, seven were identified as OCT2 inhibitors: creatinine, dimethylamine, malondialdehyde, trimethylamine, homocysteine, indoxyl-β-d-glucuronide, and glutathione disulfide. All except creatinine were novel OCT2 inhibitors, and three were considered potentially clinically relevant (creatinine, dimethylamine, and indoxyl-β-d-glucuronide). However, for six drugs (dexpramipexole, lamivudine, metformin, pilsicainide, sepantronium bromide, and tiotropium) that are known OCT2 substrates, both secretory clearance and glomerular filtration rate declined in parallel with the progression of CKD from Stages 2 to 4, suggesting that selective effects of uremic solutes on net tubular secretion of organic cations do not occur. This was as opposed to what was observed for drugs that are OAT substrates described above (Hsueh et al., 2016).

This research shed lights on understanding how renal impairment may impact drugs that are eliminated by major renal transporters (OATs and OCT2).

Currently, the project entered a new phase of research to determine whether drug administration reduces the clearance of waste solutes, resulting in their accumulation in the body and unintended side effects. The hypothesis is that the administration of drugs cleared by the kidney impairs the clearance of endogenous uremic solutes and thereby has the potential to increase plasma levels of these solutes and worsen uremic symptoms.

Ontogeny of Transporters. Medical countermeasures (MCMs) are FDA-regulated drugs, biologics, and devices that may be used in the event of a potential public health emergency from terrorism or emerging disease. The MCM initiative (MCMi) is an FDA-wide initiative to coordinate MCM development, preparedness, and response (https://www.fda.gov/emergency-preparedness-and-response/counterterrorism-and-emerging-threats/medical-countermeasures-initiative-mcmi). Medical countermeasures may require dosing pediatric patients, including neonates and infants, with antimicrobial agents; however, much is unknown about appropriate dosing in pediatrics. Many antimicrobial agents are substrates of transporters. PK differences between children and adults could be attributed to differences in the expression and activity of transporters between children and adults, but little is known about drug transporter activity in children. It was shown that developmental patterns in humans for individual transporters are different (Brouwer et al., 2015). Understanding the ontogeny of various transporters can help support the dosing of antimicrobial agents such as oseltamivir in children.

In collaboration with the FDA, Dr. Giacomini first characterized the developmental changes in the expression levels of renal transporters by determining transporter mRNA levels of 11 renal transporters and protein abundance of nine transporters using liquid chromatography tandem mass spectrometry selective reaction monitoring (Cheung et al., 2019a). Human postmortem frozen renal cortical tissues (preterm newborns to adults) were used for the study. This was the first study to

comprehensively determine the ontogeny of human renal transporters via mRNA expression analysis and quantitative proteomics in tissues representing a large span of ages. The collaborative study revealed that the expression of most of the transporters characterized in the study increased with age during the earliest developmental periods (<2 years old) and that maturation pattern was transporter dependent. Namely, P-gp, urate transporter 1 (URAT1), OAT1, OAT3, and OCT2 protein abundance levels were significantly lower in term newborn and infants than in the older age groups, whereas no difference in protein abundance levels was found among age groups for BCRP, MATE1, MATE2-K, and glucose transporter 2 (GLUT2). The finding that renal drug transporters exhibited different rates and patterns of maturation suggests that renal handling of substrates may change with age (Cheung et al., 2019a).

The development of physiologically based pharmacokinetic models to optimally predict doses of antimicrobials for use in pediatric patients is continuing with data obtained from the transporter ontogeny study. This collaborative work has greatly improved the understanding of the interplay between developmental physiology and drug disposition. Such efforts will help to address the remaining knowledge gaps to enhance the application of PBPK modeling in drug development for children (Cheung et al., 2019b).

The project has recently been expanded to collect data on the developmental changes in the protein expression levels of drug transporters in the blood-brain barrier to provide information for predicting drug dosing in children, especially drugs with targets in the brain (ongoing work).

All of these projects are critical for optimizing clinical study design and the success of the development of drugs that are used as medical countermeasures for children, which are inherently challenging because of ethical and logistical issues. The results generated could help build the FDA's preparedness for rapid response to health emergencies as well as adopt this data into medical use to help guide dosing for the pediatric population.

Biomarkers for Breast Cancer Resistance Protein. Endogenous biomarkers for transporters may be used as probes to study transporter functions in clinical studies. The knowledge on transporter biomarkers is emerging (Chu et al., 2018b). Biomarkers such as coproporphyrin I (CP I) and CP III for OATP1B1/1B3, creatinine, N^1-methylnicotinamide (NMN), or N(1)-methyladenosine (m(1) A) for OCT2 and MATEs were identified and being evaluated for DDI assessment in drug development (Lai et al., 2016; Chu et al., 2018b; Müller et al., 2018; Miyake et al., 2019, 2021; Mochizuki et al., 2021). Biomarkers for assessing the inhibition of P-gp or BCRP have not been identified, likely due to the limited involvement of intestinal P-gp and BCRP in the oral absorption of endogenous compounds. In addition, it is difficult to dissect the relative contributions of intestinal, hepatic, and renal P-gp and BCRP to altered systemic exposure of endogenous biomarkers (Chu et al., 2018b).

BCRP is a membrane transporter that plays an important role in DDIs (Lee et al., 2015; Chen et al., 2020). During drug development, clinical studies to evaluate potential transporter-mediated DDIs are often recommended. Usually, these clinical studies are triggered based on in vitro inhibition studies (Giacomini et al., 2010; Giacomini and Sugiyama, 2017) (FDA in vitro DDI guidance: https://www.fda.gov/media/134582/download). Generally speaking, in vitro cellular studies are reasonable predictors for clinical DDIs; however, they can still result in false positive and false negative predictions. Biomarkers could supplement in vitro cellular studies, reducing false positive and false negative predictions as well as the resources needed for clinical studies. There is currently no validated biomarker for BCRP. Dr. Giacomini proposed research to identity BCRP biomarkers using metabolomic data and to validate biomarkers in a clinical study. She serves as the PI for an ongoing project titled "Identification and Validation of Biomarkers for Breast Cancer Resistance Protein (BCRP)" supported by CERSI. Dr. Giacomini's group identified metabolites discovered from genome-wide association studies as novel substrates of BCRP (ongoing work). The current CERSI project is aimed to validate these metabolic biomarkers for BCRP both in vitro in cellular assays (e.g., inside-out membrane vesicles) and in vivo through a focused clinical study in healthy subjects (ClinicalTrials.gov, NCT04542382). If a biomarker(s) can be validated by this study, it will meet an unmet need for improving the BCRP-related DDI evaluation.

The COVID-19 pandemic has disrupted the conduct of the planned clinical study. Dr. Giacomini is driven by science, wanting to contribute her transporter biology knowledge to COVID-19 drugs. Her laboratory determined the potencies of the known drugs used during the COVID-19 pandemic to assess the potential of these drugs to inhibit 11 important drug transporters (Yee et al., 2021). They discovered that one of the drugs, sildenafil, for the treatment of associated pulmonary hypertension in patients with COVID-19, met the cutoff criteria based on in vitro inhibition data to inhibit BCRP in vivo. Her team then used real-world data from electronic health records and showed that patients on sildenafil significantly showed higher levels of uric acid, a well known substrate of BCRP and readily reported in electronic health records (Yee et al., 2021).

Effect of Excipients on Transporters. In addition to transporter research in regulatory science to support new drug development for a better dosing recommendation in specific patient populations (e.g., renal impairment patients or pediatrics), Dr. Giacomini also collaborates with the FDA to aid the development of generic drugs to enhance competition and drug access. Transporters in the intestine play an important role in drug absorption and thus affect drug bioavailability. Her transporter research on how excipients interact with intestinal transporters can help expand biopharmaceutics classification system (BCS)-based waivers and understand what factors may impact bioequivalence (BE) of different formulations.

Oral drug products contain both the active ingredient and excipients. Excipients or "inactive ingredients," which are often considered inert, are added to drug products to increase their stability and cohesiveness of the dosage form. Excipients can serve multiple purposes. For generic drug approval, the generic drug must be shown to be bioequivalent to the innovator's brand-name product or reference listed drug (RLD). Oral generic drug products can generally contain different excipients or different quantities of excipients from the innovator product. The formulation design considering excipient effect is very important for generic drug development to ensure BE and therapeutic equivalence of a generic product and its brand name counterpart.

Several CERSI research projects were conducted by Dr. Giacomini's laboratory to understand how excipients may affect the efficacy and safety of the drug product, including the inhibition of intestinal transporters. They determined whether excipients could inhibit intestinal uptake (OATP2B1) (Zou et al., 2020b) or efflux (P-gp and BCRP) transporters (Zou et al., 2020a; Bajaj et al., 2021) and the relevant potencies of inhibition through in vitro screening. This research aimed to understand which excipients may potentially interfere with intestinal drug transporters and which may not, an area that has not been studied before. Through in vitro inhibition studies, it was found that some excipients can inhibit these transporters at clinically relevant concentrations, indicating that certain excipients may impact oral drug absorption via intestinal transporters (Zou et al., 2020a,b; Bajaj et al., 2021). Taking OATP2B1, a key intestinal influx transporter, as an example, 24 potent OATP2B1 inhibitors were identified out of 136 unique oral excipients screened for in vitro inhibition of OATP2B1. These inhibitors were characterized by higher molecular weight and hydrophobicity compared with poor or noninhibitors. Among OATP2B1 inhibitors, several of them were dyes, including eight azo (R-N=N-R') dyes (Zou et al., 2020b) (FY2020 GDUFA Science and Research Report: https://www.fda.gov/media/146749/download#page=94). They further conducted PK studies in mice and confirmed that FD&C Red No. 40, a common azo

dye excipient and a potent inhibitor of OATP2B1, decreased the plasma level of the OATP2B1 substrate fexofenadine, potentially through inhibition of OATP2B1 in vivo (Zou et al., 2020b). Another interesting finding from the study was that gut microbiomes can metabolize these azo dyes to metabolites that are less potent to OATP2B1, thus reversing the inhibition effect (Zou et al., 2020b).

The BCS-based biowaiver approach is intended to reduce the need for in vivo BE studies (ICH M9 BCS guidance: https://www.fda.gov/media/148472/download). It can provide a surrogate for in vivo BE if an assumption of equivalence in in vivo performance can be justified by satisfactory in vitro data (e.g., solubility intestinal permeability, dissolution). The scientific data collected from this research by understanding what excipients may impact drug absorption by interacting with transporters would help inform guidances on recommending a BCS-based biowaiver approach for developing generic drugs. This work will help provide a solid scientific foundation for expansion of BCS class III (high solubility, low permeability) waivers for generic drugs beyond products that are formulated to be Q1/Q2 to the RLD [i.e., qualitatively (Q1) the same and quantitatively (Q2) similar to the corresponding RLD product] (FY2018 GDUFA Science and Research Report: https://www.fda.gov/media/130625/download).

Additionally, through CERSI research, Dr. Brian Shoichet, a co-PI at UCSF, created an open access online excipients database on approved excipients known as CERSI Excipients Browser (https://excipients.ucsf.bkslab.org/), with over 3100 excipients, 639 of which have specific molecular structure (curated) and using chemoinformatic in silico methods to screen excipients against over 20,000 possible molecular targets (Irwin et al., 2017; Pottel et al., 2020). This Excipient Browser provides chemical information on molecular excipients along with comprehensive information detailing their uses in medical products. There was an enormous need for such a resource and the database is highly used by formulation scientists. Through computational and in vitro testing, they identified that some excipients may bind to biologic targets in vitro, although the majority remain "inert" (Pottel et al., 2020). The in vivo implication of this finding remains to be understood.

The Effect of Excipients on the Oral Absorption of Fexofenadine in Humans. After in vitro studies to screen possible excipients that may inhibit the intestinal influx transporter OATP2B1, a clinical study is planned to understand if excipients may interfere with drug absorption after oral administration via interactions with OATP2B1, thereby reducing drug levels in human body (FY2021 GDUFA Science and Research Report: https://www.fda.gov/media/156481/download#page=86). Fexofenadine, a BCS class III drug and an OATP2B1 substrate, is being used as a model drug in this proof-of-concept study (ClinicalTrials.gov, NCT04534153). Sodium lauryl sulfate, an excipient found to be a clinically relevant OATP2B1 inhibitor (inhibition constant $K_i = 1.98$ μM), will be studied at two different levels. The results will identify what range of sodium lauryl sulfate may be used without likely inhibition of OATP2B1-mediated absorption of BCS class III drugs. The research outcomes will shed light on formulation design to optimally formulate drugs without including excipients that may interfere with drug absorption.

Summary

In summary, Dr. Giacomini has been at the cutting edge of science pertaining to drug transport, drug disposition, and regulatory science, leading to a new era of drug disposition and membrane transporter biology and function and translational sciences. Her research has and will continue to bring enormous impact on the safe and effective use of drugs and in guiding drug development.

Disclaimer

The article reflects the views of the authors and should not be construed to represent the views or policies of the FDA.

Authorship Contributions

Wrote or contributed to the writing of the manuscript: Zhang, Liu, Huang, Lionberger.

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