The Food and Drug Administration's (FDA's)
2015 ORSI Science Symposium
April 27, 2015
SPEAKER ABSTRACTS AND BIOGRAPHIES

Session 1: Centers for Excellence in Regulatory Science and Innovation (CERSIs) Presentations – 8:35-11:30 AM

University of California-San Francisco/Stanford University CERSI

CERSI	**University of California-San Francisco (UCSF)-Stanford University**
Speaker	**Kathy M. Giacomini, PhD**
Title and Location	**Professor and Co-Director** **UCSF-Stanford CERSI** **Department of Bioengineering and Therapeutic Sciences** **University of California, San Francisco, CA**
Biography	**Dr. Kathy Giacomini received her Ph.D. in Pharmaceutics from the State University of New York at Buffalo and completed a post-doctoral fellowship at Stanford University. Dr. Giacomini is considered a leader in the field of pharmacogenomics of membrane transporters. She led the discovery of coding region variants of about 50 membrane transporters that play a role in drug response in ethnically diverse populations. Dr. Giacomini and her group functionally characterized over 100 transporter variants in cells, discovering both gain of function and loss of function variants that may lead to variation in drug response. She has received numerous awards for her research including the Dawson Award of the American Association of Colleges of Pharmacy; the Research Achievement Award in Drug Metabolism from the American Association of Pharmaceutical Scientists and the Rawls Palmer Award from the American Society for Clinical Pharmacology and Therapeutics. She is an elected member of the National Institute of Medicine.**
Presentation Title	**Renal Impairment in New Drug Development**
Presentation Abstract	**Organic anion-transporting polypeptide 1B1 (OATP1B1) and organic anion-transporting polypeptide 1B3 (OATP1B3) are two major hepatic transporters which play important roles in drug elimination. This presentation details our investigation on whether uremic toxins, which accumulate in renal impairment, inhibit the activities of these two transporters. At around 100x free uremic concentration, creatinine, indoxyl sulfate, and p-cresyl sulfate resulted in OATP1B1 inhibition rates of 38%, 53%, and 31%, respectively. Incubation with homocysteine and indoxyl sulfate resulted in OATP1B3 79% and 33% inhibition, respectively. IC50 of indoxyl sulfate was 2232±61uM for OATP1B1 and 1077±67uM for OATP1B3. Homocysteine inhibited OATP1B3 at an IC50 of 1108±53uM. In conclusion, we have identified several uremic toxins that inhibit OATP1B1 and OATP1B3. Notably, indoxyl sulfate is a mutual inhibitor of OATP1B1 and OATP1B3, and homocysteine potently inhibits OATP1B3. Furthermore, treatment with a cocktail of uremic toxins displayed an increased inhibitory effect. These results suggest that the accumulation of uremic toxins observed in renal impairment functions to inhibits the activity of OATP1B1/1B3, which leads to altered pharmacokinetics for certain drugs as observed clinically.**