SL05 **Pharmacogenetics for Clinical and Translational Research**

Timothy S. TRACY
College of Pharmacy, University of Kentucky

Advances in pharmacogenetics have transformed the way scientists design and develop drugs and how clinicians treat patients with drug therapy. Discoveries of genetic polymorphisms in drug metabolizing enzymes and drug transporters have led to a better understanding of inter-subject variability in rates of drug metabolism and transport and allowed for more informed dosing directed to the patient's unique genotype and phenotype. Though polymoprhisms in drug metabolizing enzymes have been known since the 1950's (N-acetyltransferase polymorphisms), it wasn't until the discovery of genetic polymorphisms in CYP2D6 and appreciating the large number of therapeutically important drugs metabolized by this enzyme, that the therapeutic importance of these genetic variations became fully appreciated and entered therapeutic decision making. A classic example of the clinical impact of these polymorphisms involving a narrow therapeutic index drug involves CYP2C9 and warfarin. Awareness and understanding of this polymorphism has allowed for more individualized warfarin dosing and reduced the incidence of adverse effects. The subsequent discovery of genetic polymorphisms in the vitamin K oxidoreductase protein where warfarin exerts its action (target protein) has allowed for even more precise dosing through the understanding of not only drug metabolizing enzyme variation, but also in variation in drug target responsiveness to the therapy. The decoding of the human genome has led to the identification of a number of new therapeutic targets toward which new drugs can be developed and targeted. For example, discovery of the HER2 protein associated with more aggressive form of breast cancer exhibits genetic variability in its expression. Development of trastuzumab (Herceptin™), which targets this protein selectively allows for dosing in patients most responsive to this therapy and patients who do not over-express this protein and would not be responsive to the therapy can receive alternative therapies. The greatest impact developing drugs that selectively affect target proteins that exhibit genetic polymorphisms has been in the area of cancer treatment, though other therapeutic targets are being researched. Through the understanding of how changes in drug metabolizing enzymes and transporters affect the pharmacokinetics of drugs and the subsequent impact on therapeutic efficacy or toxicity, clinicians have been better able to personalize dosing. Likewise, identification of previously undiscovered drug targets for which therapies can be developed for specific patient populations has led to more targeted therapies with fewer adverse effects, better efficacy and reduced exposure to drugs that are less than optimally effective.