

Pharmacogenomics Dictate Pharmacokinetics: Polymorphisms in Drug-Metabolizing Enzymes and Drug-Transporters

Debasis Mondal*, Samantha L. Gerlach,
Amrita Datta, Geetika Chakravarty and Asim B. Abdel-Mageed
*Tulane University School of Medicine
Department of Pharmacology, New Orleans, LA
USA*

1. Introduction

1.1 Drug discovery and clinical evaluation

The discovery of a drug is focused on the goal of producing a useful therapeutic agent through a process utilizing the multiple skills and expertise of basic scientists, pharmaceutical chemists, toxicologists, clinical investigators, governmental regulators and clinicians (Mager DE, 2009; Michel MC, 2009; Nagase H, 2011). Drug development and its clinical evaluation is thus a very lengthy and expensive endeavor. One has to first come up with a novel mechanism, identifying relevant target(s) and pathway(s) towards formulation of a new chemical entity (NCE) to treat a disease. Both *in vitro* and *in vivo* models that are relevant to the disease form the basis of preclinical testing and identification of lead compounds, and the development of an Investigational New Drug (IND), and ultimately the entry of only a select few into human clinical trials. Therefore, initial studies in drug developments involve the synthesis and extraction of new compounds, their biological screening and pharmacological testing, followed by small animal model testing of toxicology and safety profiles. These early pharmacokinetic (PK) measurements guide researchers to formulate effective pharmaceutical dosage, *in vivo* stability, elimination and eventually the therapeutic index of lead compound(s). In pre-clinical studies, a favorable PK outcome can lead to the FDA approval for the phase-I, -II and -III clinical evaluation process (Fasolo A, 2009). However, even after clinical approval, drugs have to be continuously monitored towards improvements in their bioavailability, therapeutic, and toxicologic differences especially in a large patient population with patient-specific variability. For example, the azathioprine and mercaptopurine intolerance in patients were found to be linked to the deficiency of a metabolic enzyme, thiopurine S-methyltransferase, and formed the genetic basis for a molecular diagnostic test to designate specific population (Yates CR, et al. 1997). Thus, before testing in humans can start, a significant body of pre-clinical data on PK must be compiled and an appropriate dose should be established to ensure human safety. Toxicology, pharmacology and pharmaceutical sciences all represent the core of pre-

* Corresponding Author

clinical drug development which is repeatedly addressed in the clinical trials and post-clinical approval phases. Each phase of drug development has to be designed to accrue the necessary information to assess the probability of success of an NCE which remains the fundamental pathway to successful clinical approval (DiazGranados N, 2008). The continually expanding knowledge base on the development of new agents and novel delivery and formulation strategies are enabling a favorable *in vivo* PK and a more efficacious drug discovery process. Advances in the understanding of multiple factors that regulate drug disposition and response in individuals are elucidating the molecular basis of ethnic and inter-individual variability in drug action (Xie HG, et al. 2001; Soldin OP, et al. 2009). Furthermore, due to their *in vivo* safety and efficacy profiles, a number of natural products have recently entered clinical trials as potent anti-inflammatory agents (Basnet P, 2011; Abdel-Tawab M, 2011), however, their role in drug-drug interaction issues is not being addressed in specific patient populations.

1.2 Importance of preclinical *in vivo* models

The use of *in vivo* models to obtain vast quantities of PK/PD data is a well-established pre-clinical approach. Before any clinical testing can be initiated in humans, it is important to compare the PK and PD properties of candidate molecules; model potential relationships among dose, concentration, efficacy, and/or toxicity in appropriate animal model systems (Sausville EA, 2006; Kennedy AJ, 2010; Miyagawa F, 2010). For a more thorough and comprehensive understanding of the experimental approaches in mouse models, please refer to 'The handbook of experimental animals' by Elsevier Academic Press (Hans H, 2004). Numerous inbred mouse models are available to delineate the efficacy of drugs in specific disease models, such as the WKY and SHR strains which are optimal for studying antihypertensive and antidiabetic agents (Kennedy AJ, 2010) and the leptin knockout mice (ob/ob) as models for obesity and insulin resistance (Lijnen HR. 2011). Several disease specific knockout and transgenic mouse models are also used, for instance, to study cardiovascular drugs (Avila MD, 2011; Xiangdong L, 2011; Zaragoza C, 2011) and autoimmune disease targeting agents (Gulinello M, 2011; Schroeder MA, 2011). Immunodeficient animals, such as nude, SCID and SCID/NOD tumor xenograft mouse models, are also important for testing and development of new chemotherapeutic drugs (Sausville EA, 2006; Khan N, 2009; Umar A, 2010; Baiocchi M, 2010). The utility of these animal models to study cancer-initiating cells which are responsible for tumor recurrence and resistance, is showing great promise towards development of more potent anti-cancer agents (Wee B, 2011).

Studies completed in laboratory animals give useful indications for drug development, and many lead compounds that show compromised potency *in vitro* can turn out to be more effective *in vivo* because of their favorable pharmacokinetics, e.g. greater absorption, better distribution and stability, etc. Studies are first initiated in small animal models, e.g. mouse, rats, rabbits, to test for acute, sub-chronic and then chronic toxicity. In acute toxicity tests, one administration of the drug or chemical is given to each animal in order to generate a safe and effective dose-response curve. Appropriate pharmacological testing in disease models are carried out to determine 50% effective dose (ED₅₀). For some anti-tumor and anti-viral agents, even IC₉₀ (90% inhibitory concentration) is incorporated in these initial studies in order to demonstrate the potency (Cummins CL, et al, 2003). Following acute administration, analytical methods are developed for determination of absorption, distribution, metabolism and excretion (ADME) of the drug. The subchronic toxicity tests

usually involve animals exposed to the drug for 60–90 days duration. Both multiple administrations and/or continuous exposure via food or water to one dose level of a chemical per animal, is carried out to measure drug accumulation and possible toxicities. Depending on the animal species being used, the chronic toxicity tests usually takes 2 to 5 years to complete and may include both multiple administrations per day or continuous exposure measures via subcutaneous or intramuscular depot. Indeed, alterations in drug elimination rates and toxic outcomes are particularly important when drugs are given repeatedly. Certain therapeutic agents tend to accumulate toxic concentrations in tissues and organs when eliminated slowly or their metabolism is compromised, drug accumulation may occur with toxic concentrations reached in important tissues and organs. Alternately, faster elimination than expected due to increased breakdown of the agent may cause sub therapeutic concentrations to be reached, thus enabling the rapid selection of drug resistance, often observed with antibiotics and antimicrobials. Therefore, a commonly employed formula for ascertaining therapeutic dose levels in both pre-clinical and clinical models is, “*Maintenance dose = Dosing amount X Dosing interval*”. Both *in vitro* and *in vivo* uptake experiments in rats have been able to predict the hepatic and renal clearance of a number of drugs, and were able to delineate drugs which are substrates for drug-metabolizing enzymes and drug-transporters (Watanabe T, et al. 2009). Several transgenic and knockout mouse models have also been used to understand the role of drug-metabolizing enzymes and drug-transporters, and in the discovery of novel inhibitors of these factors in order to increase drug efficacy *in vivo* (Salphati L. et al., 1998; Shitara Y. et al., 2002; van Waterschoot RA, 2011). Because the drug levels in plasma or tissues are often more predictive of a safe dose which can be extrapolated to humans, preclinical toxicology in animals underscores the importance of PK studies. The choice of endpoints and correct surrogate markers are very important and careful consideration must be given to the definition of therapeutic efficacy. Safety is the most important concern in clinical trials and then the emphasis is directed towards drug efficacy. In addition to examining safety and effectiveness, studies in animal models also emphasize critical aspects of drug kinetics, including proper dose determination, biotransformation, drug binding to plasma proteins, induction or inhibition of enzymes and potential interaction with other drugs (Evans W, et al. 1989; Evans W, et al. 1992). The choice of representative controls is also an essential component in PK studies in both preclinical and clinical settings. Indeed, most concurrently controlled trials are double-blind and randomized studies where both objective evidence and subjective complaints are taken into account towards a clearer representation of therapeutic value of the drugs being tested for a specific disease indication.

2. Pharmacokinetics

Cell membranes are biologic barriers that selectively inhibit passage of drug molecules. Drugs may cross cell membranes by passive diffusion, facilitated passive diffusion, active transport, or pinocytosis. Thus, drug PK is critically affected by body mass, obesity as well as age and health status of the subject. Since numerous currently used drugs may manifest toxic effects and may have long-term teratogenic effects, therapeutic drug monitoring in children has become an essential component of clinical testing as emphasized by pediatric pharmacokinetics (McLeod HL, et al. 1992). In general, drug elimination may occur through biotransformation and by the passage of molecules from the blood to the outside of the body through urines, bile or other routes. Therefore, the PK study relies on measurements of levels of the test drug in blood and

urine at various times after administration. If a drug is ineffective at the given dose, the above measurements resolve issues of efficacy vs. poor absorption or rapid elimination. All the organs except the lungs are in parallel because they are perfused by a fraction of the whole blood in each passage. Drug levels in blood achieve equilibrium with drug entry into subvascular tissues and drug levels which are excreted or metabolized. PK studies investigate the parameters which regulate therapeutic concentrations of drugs and/or its metabolites, and their movement in different parts of the body (Ritschel WA & Kearns GL. 1999). Initial studies of *in vivo* PK measurements required complex mathematical modeling of absorption (A) and distribution (D). Absorption indicates the passage of drug molecules from the administration site to the blood, and distribution indicates the passage of drug molecules from blood to the tissues. As the roles of liver and kidney in drug disposition become clearer, essential components, such as the rate of drug metabolism (M) and drug excretion (E) from the body are increasingly examined. The choice of best route of drug administration establishes the best dose regimen and determines whether dose individualization would be necessary based on patient and disease characteristics, e.g. drug elimination rates (Ritschel WA & Kearns GL. 1999). Recent findings clearly indicate that these two later parameters in ADME are also critically regulated by intracellular drug metabolizing enzymes and membrane bound drug-transporters (Wikinski, S. 2005). Flexibility in the design of studies is very desirable at this stage. Furthermore, extremely slow metabolism of certain drugs may result in their accumulation and toxicity, thus mandating changes in subsequent doses. All drugs are eventually excreted from the body, and many require bio-activation to form the active compound [Figure-1].

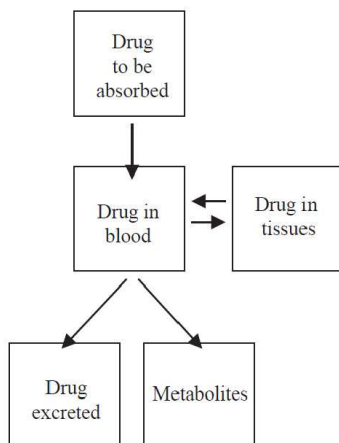


Fig. 1. *Drug absorption and disposition*. A graphic representation of drug disposition is shown where drug entry first occurs in the blood circulation and then drugs pass through tissues and organs. Blocks designate the equilibrium seen between drug absorption, distribution, metabolism and elimination (ADME) parameters.

2.1 Routes of administration

To gain a proper understanding of drug PK, first of all, it is essential to understand, compare and contrast different routes of drug administration, and acknowledge their advantages and disadvantages. Drug absorption is determined by the drug's physicochemical properties,

formulation and route of administration. Depending on the preclinical findings on ADME in animal models, administration could be either Enteral (oral, buccal/sublingual) or Parenteral [subcutaneous (SC), intramuscular (IM) or intravenous (IV)] (Evans W, et al. 1992; Ritschel WA. 1999; Hans H. 2004). Dosage forms (e.g., tablets, capsules, solutions) are formulated to be given by various routes. Regardless of the route of administration, drugs must be in solution to be absorbed. Unless given IV, a drug must cross several semipermeable cell membranes before it reaches the systemic circulation. Oral drug delivery is highly advantageous since it is convenient and cheap and patient compliance is good. Different formulations such as fast release tablets, capsules, enteric coated pills, suspensions and mixtures can be used to enhance drug uptake by intestinal epithelial lining and to facilitate drug stability in the stomach and small intestine. However, there are several disadvantages related to oral delivery, especially its inefficiency in reaching therapeutic plasma levels. Low oral bioavailability can be due to decreased stability and solubility of the drug in the gastrointestinal (GI) tract. In addition, the GI lining expresses a number of Cytochrome P450 (CYP450) enzymes and drug-efflux transporters which can suppress drug uptake and enhance metabolism.

Presystemic metabolism is a significant challenge even after intestinal uptake due to the transport of drugs to the liver via the hepatic portal vein. Examples of drugs that experience a significant 'first-pass effect' are imipramine, morphine, propranolol, buprenorphine, diazepam, midazolam, demerol, cimetidine, and lidocaine. The first pass effect and liver metabolism can be bypassed via buccal or sublingual administration which significantly increases bioavailability (Brockmeier D. 1988; Haber PS, 1996; Brown AS, 1998). In recent years, the first pass effect has also been exploited in converting an inactive form of a drug (e.g. 3-methylmorphine or Codeine) to the pharmacologically active form (morphine) by first pass metabolism (KuKanich B. 2010; Nieminen TH, 2010). However, under most circumstances, the oral drug delivery approach is inconvenient and only small doses can be accommodated. Hence, several strategies to directly infuse drugs, so that rapid plasma levels can be achieved, are SC, IM and IV delivery methods. One advantage of SC delivery is that drugs can be self-administered. Although absorption is slow via this route, it can be improved by local massage or heat. Unfortunately, this method can be painful and irritant drugs can cause local tissue damage. In contrast, IM injections can accommodate a larger volume of drug delivery, and now a number of drugs are using IM strategies to facilitate depot formation for sustained release effects. The trained personnel are required for IM injections, however, the site of injection can significantly influence systemic absorption of the drug. A quicker response is possible with IV drug delivery and large doses may be given into a peripheral vein over 1 to 2 minutes or longer by infusion. In most of the pre-clinical PK studies, this is the route of choice for drug infusion and monitoring of toxicity, especially of chemotherapeutic agents (Wong J, 2008; Serwer LP, 2011). The IV method however requires trained personnel to maintain sterility, and pyrogen testing, while the cost of preparation, transport and storage of such preparations can be expensive.

2.2 Fick's law of diffusion

Drugs diffuse across a cell membrane from a region of high concentration to one of low concentration. Diffusion rate is directly proportional to the gradient but also depends on the molecule's lipid solubility, size, degree of ionization, and the area of absorptive surface. Lipid-soluble drugs diffuse most rapidly and small molecules tend to penetrate membranes more rapidly than larger ones. Drug effectiveness using any of the above delivery approaches

ultimately requires transport across membrane barriers. In addition, membrane transporters play active roles in both drug influx and efflux and therapeutic levels in sequestered tissues. Oral drugs need efficient transport across intestinal epithelial lining and subsequently through the endothelial lining of blood capillaries. Drugs diffuse across a membrane in an attempt to equalize the drug concentration on both sides of the membrane. Fick's law was the driving force that represented a tendency for molecules to move from levels of higher concentration to lower concentration in accordance with random molecular motion. This has been attributed to the fact that the rate of diffusion across a membrane is directly proportional to the concentration gradient of a substance on either side of the membrane and is inversely related to the thickness of the membrane. Therefore, the rate of drug transport across the membrane has been described by the Fick's law of diffusion [Figure-2].

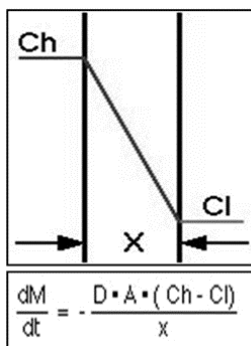


Fig. 2. Fick's law of diffusion. Molecules tend to move from a higher concentration to a lower concentration where the rate of diffusion across a membrane is directly proportional to the concentration gradient and inversely related to the thickness of the membrane. Rate of movement of Molecules per unit time = (Area)x(Permeability coefficient)x(Ch - Cl)/ Thickness.

Previously, most drugs were thought to cross biologic membranes by passive diffusion which occurs when the drug concentration on one side of the membrane is higher than on the other side. Therefore, in the past, the absorption principles for a drug molecule were primarily dependent on its aqueous diffusion, especially within large aqueous components (e.g. interstitial space, intracellular cytosol). This view of drug movement is dictated by their ability to transport drugs across epithelial and endothelial membrane tight junctions (Matsuhisa K, 2009; Furuse M. 2010). Both physiological conditions and disease status, especially inflammatory cytokines, are known to regulate drug transport from the blood to the tissues via these tight junctions (Tarbell JM. 2010; Srinivas SP. 2011). This drug absorption into tissues is also facilitated via transport through aqueous pores which allows diffusion of molecules with molecular weights up to 30 kDa. Lipid diffusibility of drugs is also an essential component in a drug's ability to be transported from one compartment to another since many lipid barriers separate tissue compartments and drug partition coefficients between aqueous and lipid environments. In addition, the ionization states of drugs have been studied to determine their PK efficacy and bioavailability. However, rapid dissolution and absorption is not always the objective. Sometimes a slower release is required, e.g. for Tolbutamide (used to lower blood sugar): a more sustained release is better, causing a more gradual reduction in blood sugar (Tassaneeyakul W, 1992; Lee CR,

2003). In addition, as mentioned earlier, the rate at which a drug dissolves is also dependent on its solubility and acid-base dissociation constants, according to the 'Henderson Hasselbalch equation, e.g. free acid or base forms of Penicillin achieve different serum levels. Also, absorption of antimicrobials can be extended by using IM injection of their less insoluble salt forms (e.g. Penicillin G). For other drugs, suspensions or solutions in nonaqueous vehicles (e.g., crystalline suspensions for insulin) are designed to delay absorption. Most drugs are weak organic acids or bases, existing in un-ionized and ionized forms in an aqueous environment. The un-ionized form is usually lipid soluble (lipophilic) and diffuses readily across cell membranes. The ionized form has low lipid solubility (hydrophilic) and high electrical resistance and thus cannot penetrate cell membranes easily. The proportion of the un-ionized form present (and thus the drug's ability to cross a membrane) is determined by the pH and the drug's pK_a (acid dissociation constant). However, whether a drug is acidic or basic, most absorption occurs in the small intestine because the surface area is larger and membranes are more permeable.

Although the surface area of the epithelial lining allows for high rate of absorption, the endothelial lining of blood vessels is relatively non-porous. For numerous diseases of the central nervous system (CNS), e.g. gliomas, AIDS dementia, epilepsy, etc., drug absorption into the brain has been a significant problem (Aragon-Ching JB, 2007; Reichel A. 2009). This is especially due to the presence of blood-brain barrier (BBB) and blood-cerebrospinal fluid (CSF) barrier (Mehdipour AR, 2009; Johanson CE, 2011). The membranes between the blood and brain have effectively no pores and prevent many polar materials (often toxic materials) from entering the brain. However, smaller lipid materials or lipid soluble materials, such as diethyl ether, halothane, can easily enter the brain. Several *in vitro* models have been developed to overcome drug inefficacies in the brain (Wilhelm I, 2011; Tóth A, 2011; Potschka H. 2010). The absorption of a drug and/or its metabolites into the kidney is also very crucial in dictating drug elimination and in suppressing accumulation of toxic levels of the drug. This is especially important since the membranes of the renal tubules and renal glomerulus are quite porous allowing non-polar and polar molecules (~ M.W. 70 kDa) to pass through and allows for rapid excretion of polar substances (drug and waste compounds) (Verbeeck RK, 2009; Hartmann B, 2010). However, lipophilic compounds or non-ionized species are reabsorbed dependent on the pH and pK_a of the drug which dictates the elimination rate and is measured in patients via creatinine clearance rates (CCR) (Kooman JP. 2009; Bogard KN, 2011; Fesler P, 2011), a parameter which will be emphasized later in this chapter in relation to drug-transporter expression in the liver and the kidney.

In contrast to passive diffusion, active transport is selective, requires energy expenditure and may involve transport against a concentration gradient. Active transport seems to be limited to drugs structurally similar to endogenous substances (e.g. ions, vitamins, sugars, amino acids). These drugs are usually absorbed from specific sites in the small intestine. As will be discussed in more detail in this chapter, we have discovered that complex mathematical modeling is necessary to determine the volume of distribution and therapeutic window for drug action. Furthermore, we now appreciate the role of special carriers present on lipid membranes that regulate drug transport into various compartments.

2.3 Compartmental models and important PK parameters

Compartmental analysis uses kinetic models to describe and predict the concentration-time curve. PK compartmental models are often similar to kinetic models used in other scientific

disciplines such as chemical kinetics and thermodynamics. At different times after drug administration, much information can be obtained on the passage of drug molecules between blood and tissues and on the rate of drug elimination in the urine or feces by measuring the concentrations of drugs in different body fluids or within tissues [Figure-3]. The advantage of compartmental over some non-compartmental analyses is the ability to predict the concentration at any time post drug infusion; however, the disadvantage of this complex system is the difficulty in developing the proper model and validating the proper rate constants for the ADME principles.

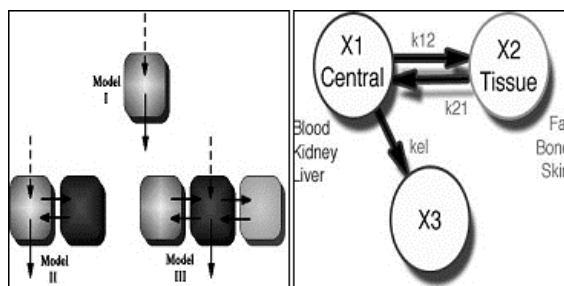


Fig. 3. *Compartment models used in drug disposition measurements.* The simplest PK compartmental model (Model-I) is the one-compartmental PK model with IV bolus administration and first-order elimination. In multicompartmental modeling, the rate constants for drug transport to-and-from the central reservoir (blood) to tissues such as fat, bone or skin (k_{12} and k_{21}) and the rate of elimination by the kidney and liver (k_{el}), are needed to be determined.

The planning, execution and analysis of the results of a PK study depends closely on the purpose of the experiment. For example some studies may be planned to get accurate estimates of drug absorption or to obtain information on the drug elimination kinetics (Evans W, et al. 1989; Evans W, et al. 1992; Ritschel WA & Kearns GL. 1999). Consequently the experimental protocols may vary considerably. Hence, to effectively plan a pharmacokinetic experiment, the following conditions should be well defined: the route of drug administration, dose regimen, which tissues to sample, sample times, analytical method, and the animal species. In clinical settings, the inclusion and exclusion criteria of subjects for observation and the population kinetics of the drug are taken into account.

Mathematical models are essential tools in PK measurements because these models aid in defining a set of parameters that describe drug disposition and the relationship of underlying biological processes. In model building, the linear compartmental models, the clearance models, and the multiexponential functions, constitute various passages of drugs through different compartments. Starting from a simple description of the drug profile in the plasma, the experimenter may gain better insight and reasonable approximations of the biological and physiological aspect of the system. The analysis of the assumptions, approximations of the model, and a comparison of the performance of different models may thus be very useful in identifying new aspects of the system and to design experiments able to deliver continuous and increasingly relevant knowledge. This chapter will only touch briefly on each of these important PK parameters to familiarize the reader with the concepts, but for detailed descriptions of these mathematical models the reader is requested to consult the following more comprehensive reviews on PK (Evans W, et al. 1992; Ritschel WA & Kearns GL. 1999).

During mathematical calculations estimate drug disposition rates, to compartmental models have been beneficial tools to understand the effects of the overall system under study. Both single and multicompartmental modeling is needed to obtain accurate measures of drug levels in tissues and possible efficacies at site of action. This is carried out following oral or IV infusion of the drug and sampling of plasma concentrations at different time points. The following parameters are determined simultaneously which include peak plasma concentrations (C_{max}), peak time to attain C_{max} (T_{max}), half-life ($t_{1/2}$), and area under the plasma concentration curve (AUC). It should be noted that each parameter of this model which deals with the rate constants, do not represent a single physical variable, but a set of variables which may not be distinguished at a given time point. The kinetic profile of a single drug in the plasma may be well summarized by the above parameters, and is depicted in the plasma concentration vs. time curves [Figure-4].

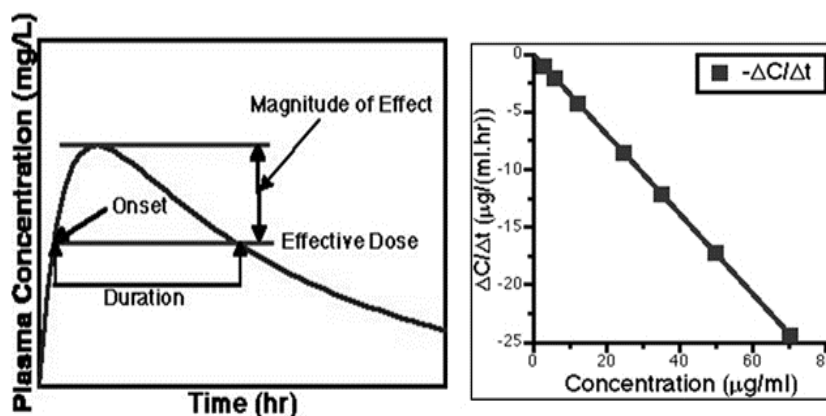


Fig. 4. The plasma concentration vs. time curve. The curve on the left illustrates plasma concentration of the drug at different times following IV introduction. The onset of drug effect, magnitude and duration of drug effect, as well as the therapeutic window for the drug can be determined from these *in vivo* measurements. The line graph on the right illustrates the rate of change in plasma concentration ($\Delta C/\Delta t$) of the drug which is dependent on the initial drug concentrations. This type of rate change analysis is helpful in determining the rates of elimination and metabolism, as well as the half-life of the drug.

The C_{max} and T_{max} may be directly obtained from experimental observations of each subject and these two parameters are closely dependent on the experimental protocol because the concentrations are always decreasing after the initial dose. The peak time corresponds to the time of infusion if the drug is infused by IV at a constant rate. However, after oral administration C_{max} and T_{max} are dependent on the extent and the rate of drug absorption, and on the disposition profile of the drug. Consequently these two parameters can characterize the properties of different formulations of the drug in the same subject. All of the initial information on C_{max} and T_{max} should be generated when presenting the design of a pharmacokinetic study.

The half life of a drug has a significant relevance in the determination of dosage of a drug. Half-life ($t_{1/2}$) is derived from a mathematical property of the monoexponential function curve

which results in elimination of half of the drug after a fixed time interval [Figure-5]. This means that the kinetic profile of many drugs is well approximated by a monoexponential function in the terminal phase and consequently it makes sense to define the half-life, or terminal half-life, in order to characterize the slope of the curve in this phase. Therefore, the drug elimination rate (K_{el}) is the sum of the rate constants due to the rate of metabolism (K_m) and the rate of excretion (K_{ex}), and it can be defined as $K_{el} = K_m + K_{ex}$. Since drug elimination is an exponential process, the time required for a twofold decrease is proportional to $\ln(2)$ or 0.693 which equals the natural logarithm of two, and $t_{1/2} = (0.693)/K_{el}$. Therefore, if C_0 is the drug concentration at time 0 and λ is dependent on the half-life of the curve, then the following relationship can be extrapolated as: $t_{1/2} = 0.693 / \lambda$. With a single compartmental model, a monoexponential function can thus be used to calculate plasma concentration at a specific time after administration. This can be written as: $c(t) = C_0 \times e^{-\lambda \cdot t}$ where $c(t)$ is the drug concentration at time t . Indeed, the terminal half-life is often used to describe decay of the drug concentration during the terminal phase.

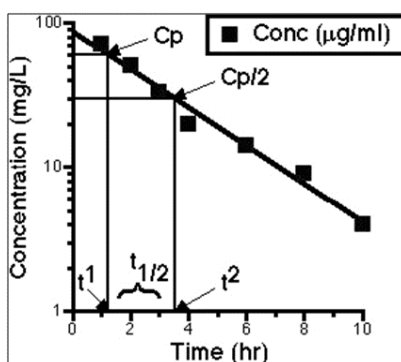


Fig. 5. The half life of drugs *in vivo*. Half life of a drug is dependent on Rate of Elimination of the drug. The semi-log plot shows plasma levels of drugs (C_p) and different time post infusion (e.g. t_1 , t_2 , etc.). It is a constant rate of decline which is independent of the starting time of drug administration.

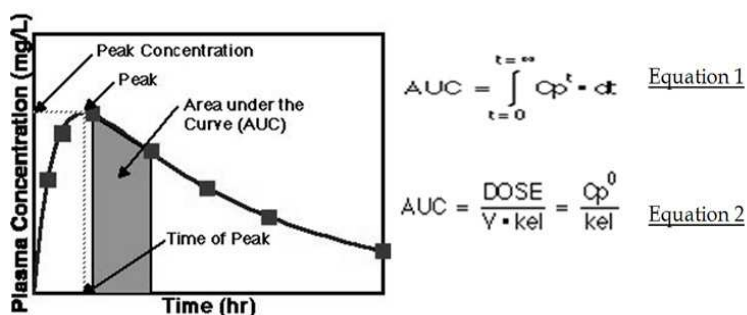


Fig. 6. The AUC analysis. The AUC is calculated by adding the different AUC-segments together. Each very narrow segment has an area of $C_p \cdot dt$. The AUC depends on the volume of distribution (V) and the rate of elimination (K_{el}). It is calculated from time 0 (administration time, C_p0) to infinity as shown in equations 1 and 2.

The extent and rate of drug absorption and distribution thus play important roles in pharmacokinetics. These parameters are usually referred to as the drug bioavailability (BA). The area under the plasma concentration curve (AUC) value is very useful for calculating the relative efficiency and BA of different drugs and possibly their metabolic products, e.g. the metabolic products of the anti-cancer agent irinotecan (Mathijssen RH, et al. 2001). The AUC is calculated by adding the AUC-segments together under the plasma concentration vs. time curve. Each very narrow segment of the curve has an area equal to plasma concentration at different time intervals (i.e. $C_p \times dt$) [Figure-6]. The AUC is calculated from time 0 (administration time) to infinity after single drug administration, and within the dose interval after multiple dose treatment. By integrating this equation that $t_{1/2} = 0.693 / \lambda$ between 0 and infinity, we can obtain the values for $AUC = C_0/\lambda$. This suggests that the area under the curve can also be computed easily from the C_0 , e and λ values. The C_0 and λ can be estimated by a non-linear regression technique or by linearizing the data using the log-transformation.

The AUC can also be used to measure both the volume of distribution (V_d) and the drug elimination process. Under very general assumptions, the AUC is closely dependent on the drug amount that enters into the systemic circulation and on the ability that the system has to eliminate the drug (clearance). Therefore, AUC can be used to measure the drug amount absorbed or the efficiency of physiological processes that characterize drug elimination. Clearance (CL), on the other hand, depends on the functionality of the eliminating organs, i.e. the kidney or the liver, therefore possible inefficiencies of these organs can have consequences on clearance, AUC and drug levels. For example, a fraction of a dose may be metabolized during the early passage through the gastrointestinal (GI) tract or through the liver after an oral dose and part of the dose may not even reach the blood due to drug malabsorption. The consequences are incomplete absorption of the drug into the systemic circulation and incomplete drug availability which may result in an ineffective treatment. Evidence that drug PK may drastically be changed due to either IV or oral administration of the anti-diabetic agent metformin, were also clearly shown in these early studies (Pentikainen PJ, 1979). From the plasma AUC and the CL, it is possible to compute the drug amount which enters into the systemic circulation in a particular subject. The following very general definitions can be given: $CL = D/AUC \times V_d$ where CL = drug amount eliminated per unit of time/drug concentration in plasma, and the volume of distribution (V_d) = drug amount in the body/drug concentration in plasma [Figure-7].

For drugs with narrow therapeutic index and significant side-effect profiles, it is common that multiple exponential terms are needed to fit the plasma concentrations after an IV bolus, and more complex mathematical modeling is carried out to more accurately determine the PK parameters. In order to get a good interpolation of the data after oral or extravascular administration, multiple exponential terms should be added to the above simple equations of PK. Although plasma drug concentrations are increasing just after oral administration and decreasing after the peak time, the predicted data may be biased when fitted by a monoexponential function, and interpolation of oral or IV profile may be obtained by adding new exponential terms with the following equation: $C_{(t)} = A_1 \times e^{-\lambda_1 t} + A_2 \times e^{-\lambda_2 t}$, which is called a biexponential function. In order to get the best fit of the experimental data and the best accuracy in the estimated parameters, a number of these exponential terms should be chosen. By taking into account the numerous compartments that the drug can be distributed to, as well as the number of rate constants necessary to ultimately determine the drug concentration remaining at a certain time, the above equation

is frequently changed to represent an integration function: $C_{(t)} = \sum A_i \times e^{-\lambda_i t}$. Following these calculations, the initial drug level and the AUC can be computed by the integrated parameters of the curve as represented by the equation: $C_0 = \sum A_i \times e \times AUC = \sum_i A_i / \lambda_i$ where C_0 is equal to 0 after oral or extravascular administration. This literally means that the terminal half-life is always represented by $0.693/\lambda_n$, where the λ_n is the lowest exponent.

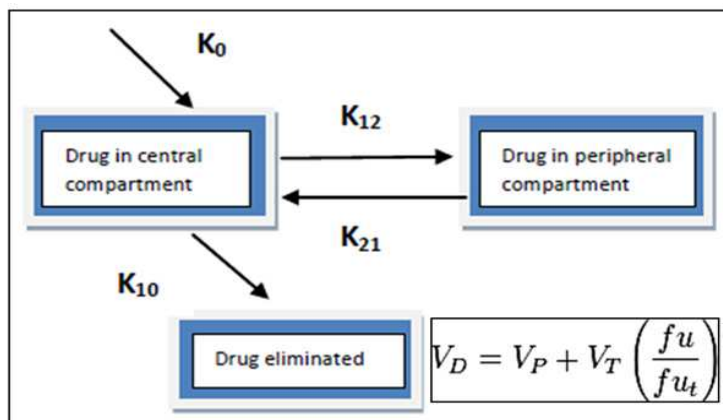


Fig. 7. *Multicompartmental Models*. Frequently, a multicompartmental model and equation are implemented where the rate constants for drug absorption and distribution are calculated. In this model, the k_0 represents initial absorption process and the processes of tissue absorption, distribution and excretion are denoted by using multiple rate constants such as k_{12} , k_{21} , and k_{10} . In this multicompartmental system, a drug appears to be dissolved in total body volume which is also referred to as the 'apparent' volume of distribution (V_D). The V_D can be used to determine how readily a drug will displace into the body tissue compartments relative to the blood, where: V_P = plasma volume; V_T = apparent tissue volume; f_u = fraction unbound in plasma and f_{u_T} = fraction unbound in tissue.

Although these multiexponential functions require complex calculations, they are needed to determine drug disposition in both preclinical and clinical settings. The importance of such rigorous calculations was recently underscored by findings that Clopidogrel, an anti-platelet drug used to treat heart attack and stroke, which had a very narrow therapeutic index and caused significant side effects in the elderly (Roden, DM. & Stein, CM. 2009), needed careful dose adjustments depending on the patient's renal clearance rates (Goteti K, 2008).

The majority of drugs currently used have approximately a biexponential profile in plasma after an intravenous bolus, but there are exceptions especially after oral administration. Indeed, very often the drug profile is not monoexponential, and the concentrations of many drugs in plasma and tissues may not decay in a linear fashion (Evan W., 1989). Highly comprehensive data on drug profiles, not only in the plasma, but also in all other tissues or fluids, and especially addressing the differences due to the routes of administration are needed. Therefore, for a given drug, a single kinetic profile may be well summarized by C_{max} , T_{max} , $t_{1/2}$ and AUC, however, with drugs having more than one profile, the mean and standard deviation of these individual parameters, may be needed to summarize the drug kinetics especially in multiple animals or in the whole population (Dreisbach AW, 2008 & 2009).

3. Drug metabolizing enzymes and drug-transporters

Until recently, when a drug exhibited poor oral bioavailability, it was generally assumed that this was due to either physicochemical problems associated with poor solubility in the GI fluids or inability to diffuse through the intestinal membrane, or alternatively, due to significant first-pass hepatic metabolism. Based on a series of cellular, animal and human studies, we now realize that both intestinal metabolic enzymes and efflux transporters, working together as a protective mechanism, may be responsible for the poor bioavailability of a number of drugs (Furuta T, 1998; Schellens JH, 2000; Luo FR, 2002). Drug metabolizing enzymes and drug-transporters critically regulate the extent of drug distribution throughout the body and the rate of drug clearance from the body (Volm M, 1991; Wacher VJ, 1995). The CYP450 enzymes are the major enzymes involved in drug metabolism and bio-activation, accounting for ~75% of the total metabolism. The CYP enzymes catalyze the oxidation of organic substances such as lipids, steroidal hormones, and xenobiotics, and they are the primary enzymes involved in drug metabolism and bioactivation (Guengerich, 2008). The first evidence of the Cyp450 system in regulating drug-interactions was observed when the effects of ketoconazole, a potent inhibitor of multiple drug-metabolizing enzymes, were shown to increase digoxin absorption and disposition in a rat model (Salphati, L. 1998). The ATP-binding cassette (ABC) transporters are a family of transmembrane proteins that harness the energy of adenosine triphosphate (ATP) hydrolysis to translocate a variety of substrates including lipids, sterols, metabolic products and drugs across extra- and intracellular membranes (Davidson et al., 2008).

PROCESS	ENZYMES	TRANSPORTERS
ABSORPTION	-	++
DISTRIBUTION	-	+++
METABOLISM	+++	+
EXCRETION	-	+++

Table 1. Both drug metabolizing enzymes and drug-transporters regulate ADME.

Over the past several decades, considerable efforts to delineate the characteristics influencing activation and regulation of these enzymes and proteins have provided a valuable foundation of data illustrating their different effects on the distribution, metabolism and clearance of drugs. Increasing evidence suggests that CYP450 enzymes and ABC transporters significantly impact drug bioavailability, and a variety of factors including age, sex, health and genetics influence their activity (Sai K, 2003; Allabi AC, 2004). The following section summarizes how the aforementioned factors may impact PK and PD to ultimately guide health care providers in making informed decisions about the type of drug, dosage and dosage scheduling for safe administration. Since all drugs are eventually excreted from the body, and many require bio-activation to form the active compound, the field of PK has begun to focus not only on drug metabolism by the CYPs, but also on the full spectrum of drug disposition, including a growing list of transporters that influence absorption, distribution and excretion [Table-1].

3.1 The CYP450 system

CYP450 enzymes are present in most tissues of the body and play important roles in hormone synthesis and breakdown (including estrogen and testosterone synthesis and metabolism), cholesterol synthesis and vitamin D metabolism (Salphati, L. 1998; Guengerich, 2008; Bjorkman S. 2005). CYP450 enzymes also function to metabolize potentially toxic compounds, including drugs and products of endogenous metabolism such as bilirubin, principally in the liver. A subset of CYP450 enzymes play important roles in the synthesis of steroid hormones (steroidogenesis) by the adrenals, gonads, and peripheral tissue: CYP11A1 (steroid 20 α -hydroxylase), CYP11B1, CYP17A1, CYP21A1 (in the adrenal cortex conducts 21-hydroxylase activity) and CYP19A all catalyze aromatization of androgens to estrogens. These enzymes belong to the superfamily of proteins containing a heme cofactor and, therefore, are hemoproteins which have been named on the basis of their cellular (cyto) location and spectrophotometric characteristics (chrome). When the reduced heme iron forms an adduct with carbon monoxide (CO), the P450 enzymes absorb light at wavelengths near 450 nm, identifiable as a characteristic Soret peak, thus the name CYP450.

These drug metabolizing enzymes are primarily membrane-associated proteins, located either in the inner membrane of mitochondria or in the endoplasmic reticulum of cells. Often, they form part of multi-component electron transfer chains, called P450-containing systems. Each enzyme is termed an isoform since each derives from a different gene. It should be noted, however, that structural similarity of enzymes cannot be used to predict which isoforms will be responsible for a drug's metabolism. Because of the vast variety of reactions catalyzed by CYPs, the activities and properties of the many isoenzymes differ in many respects. Each CYP450 enzyme and their isozymes can metabolize multiple drugs and recognize molecules with disparate structures as their substrates. Drug interactions involving the CYP450 isoforms generally result from one of two processes, enzyme inhibition or enzyme induction. Enzyme inhibition usually involves competition with another drug for the enzyme binding site. This process usually begins with the first dose of the inhibitor and onset and offset of inhibition correlate with the half-lives of the drugs involved (Dossing M, 1983; Murray M, 1990). Enzyme induction occurs when a drug stimulates the synthesis of more enzyme protein, enhancing the enzyme's metabolizing capacity. It is somewhat difficult to predict the time course of enzyme induction because several factors, including drug half-lives and enzyme turnover, determine the time course of induction. Broadly, the CYPs are divided into two categories, i.e. Phase-I enzymes that introduce or remove functional groups in a substrate through oxidation, reduction or hydrolysis; and Phase-II enzymes that transfer moieties from a cofactor to a substrate via conjugation. According to a standardized nomenclature system adapted in 1996, the CYPs are divided into 18 families and 43 subfamilies on the basis of amino acid sequence homology (Ingelman-Sundberg M. 2004 & 2009; Nelson, DR. 2009). A schematic of recent guidelines for the nomenclature of CYP450 isoenzyme families, is provided [Figure-8].

The Phase-I CYP450 is a gene superfamily consisting of more than 57 genes coding for functional proteins, and 58 pseudogenes. The most common reaction catalyzed by the Phase-I enzymes is a monooxygenase reaction, e.g. insertion of one atom of oxygen into an organic substrate (RH) while the other oxygen atom is reduced to water: $\text{RH} + \text{O}_2 + 2\text{H}^+ + 2\text{e}^- \rightarrow \text{ROH} + \text{H}_2\text{O}$. The majority of these genes are polymorphic. Current information on genetic variants can be found at the human CYP allele home page (<http://www.imm.ki.se/CYPalleles/> and <http://www.cypalleles.ki.se/>). More than 434 different alleles of the genes encoding

xenobiotic metabolizing P450 enzymes are presented on this site. Among these, three subfamilies of CYPs, including CYP1, CYP2, and CYP3, contribute to the oxidative metabolism of more than 90% of clinically used drugs. Overall, approximately 10 of the CYP450 enzymes are responsible for the metabolism of a large number of pharmacologic agents in human beings, and six of them are considered most important: CYP3A4, CYP2D6, CYP2C19, CYP2C9, CYP1A2 and CYP2E1. CYP3A4 is the most abundantly expressed cytochrome and composes 30 to 40% of the CYP in the liver and in the small intestine. CYP2D6 is implied (at 20%) in the metabolism of active compounds and CYP2C9 coupled with CYP2C19 can metabolize at least 15% of commonly prescribed drugs (Desta Z, 2006).

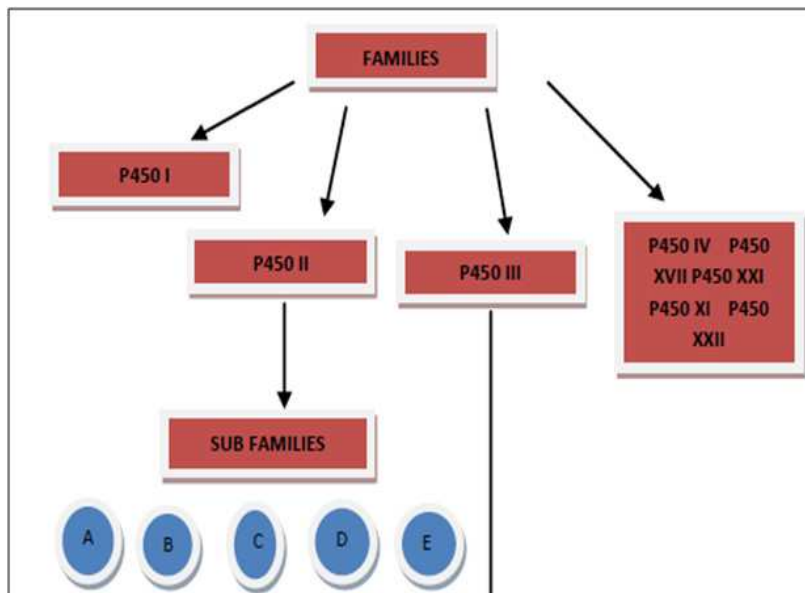


Fig. 8. CYP450 gene nomenclature. Enzymes that share at least 40% sequence homology are assigned to a family designated by an Arabic numeral, whereas those sharing at least 55% homology makeup a particular subfamily designated by a letter (A, B, C, etc.). Single members of a subfamily represent a particular enzyme and are designated by the number following the subfamily description (e.g. CYP2D6, CYP3A4). For each enzyme, the most common or “wild-type” allele is denoted as -1, and allelic variants are sequentially numbered as they are identified (i.e. -2, -3, etc.).

The most clinically important Phase-II enzymes are uridine diphosphate glucuronosyltransferase (UGT), sulfotransferase (SULT), glutathione S-transferases (GST), N-acetyltransferase (NAT) and thiopurine methyltransferase (TPMT). The human UGT superfamily is a group of conjugating enzymes that catalyze the transfer of the glucuronic acid group of uridine diphosphoglucuronic acid to the functional group (e.g. hydroxyl, carboxyl, amino, and sulfur) of a specific substrate. Glucuronidation increases the polarity of the substrates and facilitates their excretion in bile or urine. Seventeen human UGT genes have been identified thus far and are classified into two subfamilies (i.e. UGT1 and UGT2) (Nagar S, 2006). The super family of human GST catalyzes the conjugation of glutathione

(GSH) to a wide range of endogenous metabolites and xenobiotics including alkylating and free radical generating anticancer drugs (Townsend DM, 2005; Board PG. 2007). NAT2 plays an important role in the activation and/or deactivation of a large and diverse number of aromatic amine and hydrazine drugs used in the clinic, and therefore the NAT2 genotype is particularly relevant to the response to these drugs (Hein DW. 2002). TPMT is best known for its key role in the metabolism of the thiopurine drugs (e.g., 6-mercaptopurine, azathiopurine and 6-thioguanine) which are clinically used to treat cancers or as immunosuppressants (Booth RA, 2011).

3.2 The ABC and SLC transporters

Our knowledge of membrane expressed drug transporters has increased considerably in the past decade. Several transporters have been cloned and advances have been made in understanding their structure- function and characteristics (Davidson AL, 2008; Borst P, 2000; Shitara Y, 2002). Many tissues express these drug transporters such as the brain, liver, kidney and intestine; and they play an important role in defining characteristics of drug absorption, distribution and excretion of drugs. Thus, they are pivotal in affecting absorption and tissue distribution, hepatic uptake and export, as well as renal and biliary elimination of a variety of drugs. Conversely, the active transporters dictate the entry of drugs into different compartments and actively efflux drugs from intracellular compartments. Thus, drug transport via these membrane pumps could be classified as passive or active [Figure-9].

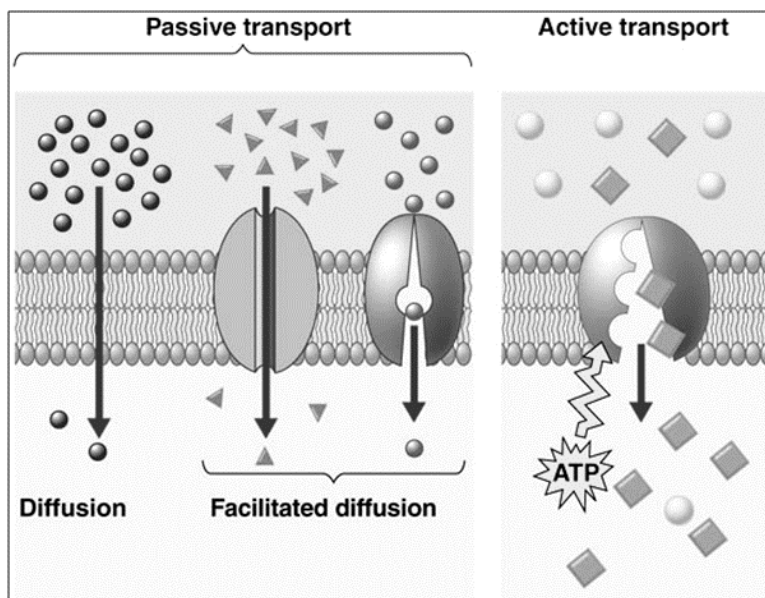


Fig. 9. Simple diffusion vs. active and passive transporters. Simple diffusion of drug across cellular membranes occur via the 'Fick's law'. However, transporters on cell membranes can both facilitate and inhibit drug transport.

URL: <http://year12biologyatmc.wikispaces.com/Active+Transport>)

A drug that moves across a membrane along its concentration gradient without expending metabolic energy is said to be transported passively. The intestinal uptake of glucose in the human body serves as a good example of passive transport (Awad WA, 2007; Durán JM, 2004). Passive transport can be divided into two sub-types. The first two involves spontaneous movement of membrane permeable substances across the membrane utilizing the laws of simple diffusion. The second type of non-energy dependent transport is facilitated diffusion where the movement of membrane impermeable substances across the membrane is aided via transporters and via co-transport of other charged ions (Dobson PD, 2008; Visentin M, 2011). Both passive and carrier-mediated drug transport processes are known to coexist in tissues and regulate drug concentrations within subvascular sites (Sugano K, 2010; Lau YY, 2007; Varghese Gupta S, 2011).

Conversely, active transport requires energy and may involve transporting the drug against their concentration gradient, involving multiple saturable carriers (Choo EF, 2000; Hinoshita E, 2000; Conrad S, 2002; Krishnamurthy P, 2006). The primary active transporters utilize adenosine triphosphate (ATP) to produce energy for transport. The transport protein itself consists of an ATPase, which hydrolyzes ATP for the required energy. However, a secondary active transport mechanism also exists where the transporter protein does not have a direct ATP coupling and utilizes the potential gradient created when ions are transported across the membrane by primary active transport, but these are mostly found in bacteria or protozoans (Boiangiu CD, 2005; Simon J, 2008). Although, a few of these active ion-pumps have been of potential importance in cancer therapeutics, e.g. proton pump inhibitors (Harguindey S, 2009). In general, drug transporters that are of clinical significance have been divided into two main classes; the solute carrier family (SLC) of passive transporters and the ATP binding cassette (ABC) family of active transporters [Table-2 & Table-3].

3.2.1 The ABC transporters

The drug-efflux function of ABC transporters enables extrusion of a wide range of substrates from the inside to the outside of a cell membrane or organelle (Jones PM, 2009; Locher KP. 2009; Degorter MK, 2011). They are known to transport lipids and sterols, ions and small molecules, drugs and large polypeptides. P-gp (ABCB1) is ubiquitously expressed in a number of important organs such as liver, intestine, lymphocytes, placenta and the brain endothelial cells. P-gp can transport mainly cationic or electrically neutral substrates as well as a broad spectrum of amphiphilic substrates. The ABCC family members confer MDR to organic anion compounds, and MRP1 is more ubiquitous than MRP-2. Interestingly, their expression can either be at the apical (AP) or on the basolateral (BL) membranes of epithelial or endothelial barriers. The ABCG2 transporter, also known as BCRP (breast cancer resistance protein) are also expressed on apical surfaces and confer resistance to Topoisomerase inhibitors and doxorubicin [Table-2].

The best characterized ABC-transporter is P-glycoprotein (also known as P-gp, MDR-1 or ABCB1) (Brinkmann U, 2001; Fromm MF. 2003; Kroetz DL, 2003). MDR-1 displays a broad substrate spectrum comprising of both neutral and cationic organic compounds. Another ABC-transporter, recently cloned from a drug resistant breast cancer line, is BCRP (a.k.a. ABCG2) and substrate specificities and tissue localization of BCRP have been found to be similar to that of MDR-1 (Jonker JW, 2000; Krishnamurthy P, 2006). BCRP is also referred to as a half transporter since it has one transmembrane domain and functions as a dimer to

transport a variety of drugs. The immunosuppressant cyclosporine-A and verapamil, a calcium channel antagonist, are competitive inhibitors of MDR-1 mediated efflux (also referred to as MDR-modulators) and have often been used in the laboratory to determine MDR-1 specific drug-efflux (Eilers M, 2008; Roy U, 2009). A newly discovered group of ABC transporters is the MDR associated proteins (MRPs) also referred to as the ABCC family of transporters (Gradhand U, 2008). MRPs are found to cotransport drugs along with glutathione (GSH) or transport GSH-drug conjugates and glucuronide-drug conjugates. Amongst the nine members of the MRP transporters family, the first five (MRP-1, MRP-2, MRP-3, MRP-4 and MRP-5) are frequently associated with the efflux of therapeutic agents. MRP-1, MRP-2 and MRP-3 transport hydrophilic anionic compounds, large molecules and peptidomimetics; however, both MRP-4 and MRP-5 transport small polar compounds such as nucleosides, cyclic nucleotides and nucleoside analogs (Schuetz JD, 1999). The overexpression of ABC transporters had been shown to result in chemotherapeutics being pumped out of cells faster than they can enter, and is an well accepted mechanism leading to the development of multidrug resistance (MDR) in cancer cells (Gottesman MM, 2002; Luqmani YA. 2005; Tiwari AK, 2011). Recent studies by us, and others, have also shown that several anti-HIV-1 drugs, especially HIV protease inhibitors (HPIs) and nucleoside analog reverse transcriptase inhibitors (NRTIs) are substrates of ABC-transporters (Choo EF, 2000; Roy U, 2009) and their expression on both lymphocytes and BBB endothelial cells (ECs) can suppress drug entry into the cellular and anatomical reservoirs of HIV-1 (Eilers M, 2008; Tarbell JM. 2010; Shen S, 2010). The polarized expression of MRPs regulates the directional transport of drugs in and out of various tissue compartments. Both P-gp and MRP1 are predominantly expressed in the human lung; thus, these transporters may be pivotal in the protection against toxic compounds.

Gene	Protein	Tissue distribution	Polarity	Representative drug substrates
ABC transporters				
ABCB1	MDR1 (P-gp)	Liver, intestine, kidney, blood-brain barrier, lymphocytes, placenta	AP	Anthracyclines, taxanes, vinca alkaloids, imatinib, etoposide, levofloxacin, erythromycin, cyclosporine, tacrolimus, digoxin, quinidine, verapamil, diltiazem, ritonavir, saquinavir, talinolol, phenytoin, cimetidine, simvastatin, morphine, hydrocortisone
ABCC1	MRP1 (GS-X)	Ubiquitous	BL	Anthracyclines, vinca alkaloids, irinotecan, SN-38, methotrexate, camptothecins, saquinavir, ritonavir, difloxacin, drug-glucuronate/-glutathione/-sulfate conjugates
ABCC2	MRP2 (cMOAT)	Liver, kidney, intestine	AP	Anthracyclines, vinca alkaloids, methotrexate, camptothecins, rifampin, pravastatin, and drug-glucuronate/-glutathione/-sulfate conjugates
ABCG2	BCRP	Liver, intestine, placenta, breast	AP	Anthracyclines, irinotecan, SN38, SN38G, imatinib, tamoxifen

Table 2. *ABC family of drug transporters*. The gene name and common protein names for the most common transporters are shown. Their tissue distribution, expression polarity (apical or basal) and representative drugs that are transported by each of the drug-efflux pumps, are shown. (Adapted from Bluth MH, 2011). URL: <http://dx.doi.org/10.2147/PGPM.S18861>

3.2.2 The SLC transporters

The solute carrier family functions by facilitative diffusion and secondary active transport (Shitara Y, 2002; Hagenbuch B, 2003; Niemi M, 2004; Lau YY, 2007; Visentin M, 2011). SLC transporters, also known as the organic anion transporter polypeptide (OATP) belong to a

large superfamily that comprises of approximately 300 SLC genes classified into 43 families. The SLC transporters transport both endogenous molecules like amino acids, sugars etc. and many exogenous drugs [Table-3]. They are located on the cell membrane as well as on the intracellular membrane of organelles. Except for SLC22A11 (OAT4) all others are expressed on basolateral membranes. They can transport a variety of small molecules and inhibitors of the SLC transporters have proved useful in the treatment of a variety of disorders, including depression, epilepsy and Parkinson's disease (Kuroda M, 2005; Gether U, 2006; Thwaites DT, 2011). Variance in the expression and function of these transporter proteins can significantly impact the PK profile of a number of drugs.

Uptake transporters belong to the SLC family while efflux transporters belong to the ABC family. Many of these drug transporter proteins contain polymorphisms which can significantly alter their function. Within the last decade more information has become available reinforcing the fact that polymorphisms which effect expression or activity of the drug transporters contribute to the variability seen in the drug disposition between individuals. A number of studies have demonstrated the importance of P-gp for drug disposition in humans (Fromm MF, et al, 2003). Chemotherapeutic drugs (e.g. paclitaxel), uricosuric agents (e.g. probenecid), and the leukotrienes (LT) receptor antagonist (e.g. MK-571), are known inhibitors of MRPs (Eilers M, 2008). A number of preclinical and clinical trials are also being carried out to discover new and more effective efflux pump inhibitors (EPIs). Initial studies showed that PSC 833, a P-gp specific EPI was able to increase the efficacy of vincristine and digoxin in rat models (Song, S. 1999). In recent years, both verapamil and cyclosporine-A analogs are showing significant promise as safe and effective EPIs (Bauer F, 2010; Kolitz JE, 2010; O'Brien MM, 2010; Patel NR, 2011).

Gene	Protein	Tissue distribution	Polarity	Representative drug substrates
SLC transporters				
OATP family				
SLC21A3	OATP1A2 (OATP-A)	Ubiquitous, with highest expression in brain and testis	BL	Rosuvastatin, methotrexate, ouabain, D-penicillamine
SLC21A6	OATP1B1 (OATP-C)	Liver	BL	Statin, pravastatin, fexofenadine, and repaglinide, rosuvastatin, ouabain, D-penicillamine, rifampin
SLC21A8	OATP1B3 (OATP8)	Liver	BL	Digoxin, rifampin, ouabain, methotrexate, D-penicillamine, rosuvastatin, cyclosporin
SLC21A9	OATP2B1 (OATP-B)	Ubiquitous	BL	Benzylicillin, rosuvastatin
OCT family				
SLC22A1	OCT1	Liver	BL	Metformin, cisplatin, oxaliplatin, imatinib, procainamide, citalopram, cimetidine, quinidine, verapamil, acyclovir
SLC22A2	OCT2	Kidney	BL	Metformin, cisplatin, oxaliplatin, imatinib, procainamide, citalopram, cimetidine, quinidine, amantadine
SLC22A3	OCT3	Brain, liver, kidney, heart, muscle, placenta, and blood vessels	BL	Cimetidine, agmatine, adefovir, catecholamines
OAT family				
SLC22A6	OAT1	Kidney, brain	BL	Methotrexate, salicylate, antiviral agents (eg. acyclovir)
SLC22A7	OAT2	Liver, kidney	BL	Methotrexate, salicylate, tetracyclines
SLC22A8	OAT3	Kidney, brain, muscle	BL	Methotrexate, antiviral agents (eg. acyclovir), cimetidine, pravastatin, salicylate
SLC22A11	OAT4	Kidney, placenta	AP	Methotrexate, cimetidine, salicylate, tetracyclines

Table 3. SLC family of drug transporters. The gene name and common protein names, tissue distribution, polarity (apical or basal) and representative drugs transported by each, are shown. (Adapted from Bluth MH, 2011).

URL: <http://dx.doi.org/10.2147/PGPM.S18861>

4. Pharmacogenomics

Even using the same medications, different patients respond in different ways. Defining the changes seen in drug efficacy and toxicity are of crucial significance since PK measurements alone cannot explain such variability (Kuehl P, 2001; Evans WE, 1999; Kroetz DL, 2003; Lai Y, 2011). The inpatient variability and large population differences suggest that genetic inheritance may be a critical determinant of the therapeutic responses to drugs which are substrates for ABC-transporters and CYP450 enzymes (Ameyaw MM, 2001; Dorne JL, 2002; Evans WE, 2001). Although we know many nongenetic (or epigenetic) factors influence the effects of medications, including age, organ function, concomitant therapy, drug interactions and the nature of the disease, there are now numerous examples of cases in which inter-individual differences in drug response are attributed to sequence variants in genes encoding drug-metabolizing enzymes and drug transporters. Moreover, recent findings demonstrate that genetic differences in both drug metabolizing enzymes and drug transporters ultimately regulate the individualistic differences in drug PK (Evans WE, 2003; Staatz CE, 2010). Because most drug effects are determined by the interplay of several gene products that influence the PK and PD of medications, including inherited differences in drug targets (receptors) and drug disposition (metabolizing enzymes and transporters), the genetic characteristics in different patient populations, as well as within individuals, have become increasingly important in regulating PK. This new field of Medicine is now known as pharmacogenomics (PG).

A gene is considered to be polymorphic when the frequency of a variant allele in a specific population is at least 1% (Sachidanandam R, 2001). More than 1.4 million single-nucleotide polymorphisms (SNPs) were identified in the initial sequencing of the human genome, with over 60,000 of them in the coding region of genes (www.ncbi.nlm.nih.gov/SNP/GeneGt.cgi?geneID=5243). Some of these SNPs have already been associated with substantial changes in the metabolism or effects of medications and some are now being used to predict clinical response. The burgeoning field of PG uses these genome-wide approaches to elucidate the inherited differences between persons and their drug responses (Lamba JK, 2002; MacPhee IA, 2005; Tamura A, 2007a ; Song IS, 2008; Staatz CE, 2010a). It has been suggested that 20 to 95 % of the variability in drug disposition and effect can be attributed to genetics; therefore, considerable efforts to investigate the genetic factors influencing drug response via PG studies hold the promise of personalized medical care in the future. Such an approach focuses on drugs and drug combinations that are optimized to each individual's unique genetic makeup (Tamura A, 2007b; Staatz CE, 2010b). Mutations play a clear role in the functioning of the majority of the body's organs (lung, liver, brain, etc.) in which CYP and ABC transporter expression may regulate drug distribution and clearance. For example, mutations in the ABC transporter, cystic fibrosis transmembrane conductance regulator (CFTR) is responsible for the development of the lung disorder cystic fibrosis, while the cause of Tangier disease, a high cholesterol-related condition, is attributed to mutations in ABCA1 (van der Deen et al., 2005). Other studies provide evidence that genetic polymorphisms exert an effect on interethnic variation and frequency of CYP and multi-drug resistance gene (MDR1) alleles among Orientals, Caucasians and Africans (Iida A, 2002; Lai et al., 2011). Furthermore, interpatient variability in drug response and toxicity to standard doses of the most commonly prescribed chemotherapeutic agents is often explained, in part, by genetic polymorphisms in genes encoding CYP enzymes and ABC transporters. Single nucleotide polymorphisms (SNPs)

account for 80% of all sequence variations residing in genes and these sequence variations can result in a multitude of adverse drug reactions (Lee et al, 2010). We may be able to facilitate personalized clinical treatment of pain and opioid addiction by understanding the PK and PD of methadone. Methadone, a P-gp substrate primarily metabolized by CYP3A4 and CYP2B6, has a narrow therapeutic index and large interpatient variability. Genetic polymorphisms in genes coding for the methadone-metabolizing enzymes and P-gp contribute to the interindividual variability of methadone kinetics and methadone blood concentrations (Li et al., 2008). Ensuing discussion illustrates the relevance of cancer pharmacogenomic studies in optimizing chemotherapeutic response by enhancing the efficacy and safety of some select chemotherapy drugs.

4.1 Polymorphisms in the CYP-450 genes

Polymorphisms within the CYP genes include gene deletions, missense mutations, deleterious mutations creating splicing defects or premature stop codon and gene duplications, which can result in abolished, reduced, normal or enhanced enzyme activity (Ball SE, 1999; Lamba JK, 2002; Daly AK. 2006; Bluth MH, 2011) [Table 4]. A number of studies have shown interindividual variability and tissue specificity in the expression of cytochrome P450 gene expression (Koch I, et al, 2002). As a result, patients can be classified into four phenotypes based on the level of a CYP enzyme activity: poor metabolizer (abolished activity), intermediate metabolizer (reduced activity), extensive metabolizer (normal activity), and ultrarapid metabolizer (enhanced activity). Substantial evidence suggests that genetic polymorphisms within the CYP genes have significant impact on drug disposition and/or response. The lack of functional CYP3A5 may not be readily evident, because many medications metabolized by CYP3A5 are also metabolized by the universally expressed CYP3A4. For medications that are equally metabolized by both enzymes, the net rate of metabolism is the sum of that due to CYP3A4 and that due to CYP3A5; the existence of this dual pathway partially obscures the clinical effects of genetic polymorphism of CYP3A5 but contributes to the large range of total CYP3A activity in humans. Notably, the most pharmacologically and clinically relevant CYP polymorphisms are found in *CYP2D6*, *CYP2C9*, and *CYP2C19* genes (Ingelman-Sundburg M. 2004; Bluth MH, 2011). Of the Food and Drug Administration (FDA)-approved drug labels referring to human genomic biomarkers, 62% pertain to polymorphisms in the CYP enzymes, with *CYP2D6* (35%), *CYP2C19* (17%), and *CYP2C9* (7%) being the most common [Table-2]. The genetic basis of CYP3A5 deficiency is predominantly a SNP in intron 3 that creates a cryptic splice site causing 131 nucleotides of the intronic sequence to be inserted into the RNA, introducing a termination codon that prematurely truncates the CYP3A5 protein. Although it is now possible to determine which patients express both functional enzymes (i.e., CYP3A4 and CYP3A5), the clinical importance of these variants for the many drugs metabolized by CYP3A remains unclear. Differences in the *CYP450* genotypes may contribute to the inter-ethnic variations in the disposition and response of substrate drugs (Burk O, 2002; Rettie AE, 2005; Lim HS, 2007). However, pharmacogenetic testing for drug metabolizing enzymes is not yet frequently implemented in the clinic practice (Gardiner SJ, 2005).

The most common functional polymorphisms occurring in few of the major human CYP genes, along with allele frequencies and functional effects, are provided in Table-4. CYP1 genes are mainly expressed in extrahepatic tissues and have been linked to bioactivation of a variety of carcinogens. Multiple SNPs in CYP1 increase their functional activity by inducing

gene expression or protein stability and have been linked to ethnic differences in PK (McIlwain CC, 2006). The CYP1A1 polymorphism, CYP1A1*2C is associated with increased lung cancer risk in African Americans. Their role in estrogen activation has also linked several CYP1A1 genotypes to increased risk of prostate, breast and ovarian cancers.

Common allelic variants	Polymorphism/substitution	Allele frequency (%) ^a			Functional effect ^b
		Caucasian	Asian	African	
CYP1A1					
CYP1A1*2A	3698T>C(Mspl)	6.6–19.0	33–54	22–28	↑ Inducibility
CYP1A1*2B	1462V; 3698T>C(Mspl)	–	–	–	↑ Inducibility
CYP1A1*2C	1462V	2.2–8.9	28–31	0.0–2.7	↑ Activity
CYP1A1*3	3204T>C	0	0	7.6–14.0	Normal
CYP1A1*4	T461N	2.0–5.7	–	–	Normal
CYP1A2					
CYP1A2*1C	–3860G>A				↓ Inducibility
CYP1A2*1F	–163C>A	33	68		↑ Inducibility
CYP1A2*1K	Haplotype (–63C>A, –739T>G, –729C>T)	0.5			↓ Inducibility ↓ Activity
CYP2A6					
CYP2A6*1 × 2	Gene duplication	1.7		0.4	↑ Activity
CYP2A6*2	L160H	1–3		<1	↓ Activity
CYP2A6*4	Gene deletion	0.5–1.0	7–22	15–20	Abolished activity
CYP2B6					
CYP2B6*4	K262R	5			↑ Activity
CYP2B6*5	R487C	11–14	1		↓ Expression
CYP2B6*6	Q172H; K262R	16–26	16		↑ Activity
CYP2B6*7	Q172H; K262R; R487C	13	0		↑ Activity
CYP2C8					
CYP2C8*2	I269F	0.4		18	↓ Activity
CYP2C8*3	R139K; K399R	13	0	2	↓ Activity
CYP2C8*4	I264M	7.5			↓ Activity
CYP2C9					
CYP2C9*2	R144C	13–22	0	3	↓ Activity
CYP2C9*3	I359L	3–16	3	1.3	↓ Activity
CYP2C9*5	D360E	0	2	0	↓ Activity

Table 4. (Continued)

CYP2C19					
<i>CYP2C19*2</i>	Splicing defect; I331V	15	30	17	Abolished activity
<i>CYP2C19*3</i>	W212X; I331V	0.04	5	0.4	Abolished activity
<i>CYP2C19*17</i>	I331V	18	4		↑ Transcription
CYP2D6					
<i>CYP2D6*3</i>	Frameshift	1–2	<1		Abolished activity (PM)
<i>CYP2D6*4</i>	Splicing defect	20–25	1	6–7	Abolished activity (PM)
<i>CYP2D6*5</i>	Gene deletion	4–6	4–6	4–6	Abolished activity (PM)
<i>CYP2D6*10</i>	P34S; S486T	<2	50	3–9	↓ Activity (IM)
<i>CYP2D6*17</i>	T107I; R296C; S486T	<1		20–34	↓ Activity (IM)
<i>CYP2D6*41</i>	R296C; splicing defect; S486T	1.3	2	5.8	↓ Activity (IM)
<i>CYP2D6*1</i> × <i>N</i> , <i>N</i> ≥ 2	Gene duplication				↑ Activity (UM)
<i>CYP2D6*2</i> × <i>N</i> , <i>N</i> ≥ 2	Gene duplication				↑ Activity (UM)
CYP3A4					
<i>CYP3A4*1B</i>	5' flanking region	2–9	0	35–67	Altered expression
<i>CYP3A4*2</i>	S222P	2.7–4.5	0	0	Substrate-dependent altered activity
<i>CYP3A4*3</i>	M445T	1.1			↓ Activity
<i>CYP3A4*17</i>	F189S	2.1			↓ Activity
<i>CYP3A4*18</i>	L293P	0		1	↑ Activity
CYP3A5					
<i>CYP3A5*3</i>	Splicing defect	90	75	50	Abolished activity
<i>CYP3A5*6</i>	Splicing defect	0	0	7.5	Severely ↓ activity
<i>CYP3A5*7</i>	346Frameshift	0	0	8	Severely ↓ activity
CYP3A7					
<i>CYP3A7*1C</i>	Promoter	3		6	↑ Expression
<i>CYP3A7*2</i>	T409R	8	28	62	↑ Activity

Table 4. Most common functional polymorphisms in major human CYP genes (adapted from Bluth MH, 2011).

DOI: <http://dx.doi.org/10.2147/PGPM.S18861>

Since both CYP1A2 and CYP2A6 can convert nicotine to cotinine, polymorphisms in these enzymes are associated with nicotine addiction and tobacco-related cancers. The CYP2B6 polymorphisms may affect the PK and therapeutic outcome of anti-HIV agents such as efavirenz and nevirapine. Indeed, the CYP2B6 variant, Q172H is linked to increased breakdown of these anti-HIV drugs in different minority population (Musana AK, 2005). The CYP2C9 accounts for ~20% of total hepatic CYP contents, and the CYP2C9*2 (R144C) and CYP2C9*3 (I359L) variants may affect PK of numerous important pharmaceutical agents such as warfarin, celecoxib, ibuprofen, phenytoin, etc. (Rettie AE, 2005). Interestingly, the CYP2C8*3 (R139K; K39R) is associated with lower activity and

decreased clearance of both R- and S-ibuprofen, and polymorphisms in CYP2C19 effect the response of several classes of drugs, including proton pump inhibitors and barbiturates. Although CYP2D6 is involved in the metabolism of ~25% of all drugs, SNPs in this gene is mostly due to changes in activity rather than induction in gene expression. The CYP2D6 genotypes exhibit large interethnic differences and are of significant importance for the dosing of many drugs, including tricyclic antidepressants, antiarrhythmics, neuroleptics, analgesics, antiemetics, and anticancer drugs. CYP3A4 has the highest abundance in the human liver (~40%) and metabolizes over 50% of all currently used drugs. Genetic polymorphisms in CYP3A4 appear to be more prevalent in Caucasians, but a direct clinical association has not been established. The clinical relevance of CYP3A5 polymorphisms are demonstrated by changes in PK of immunosuppressive drugs such as tacrolimus.

4.2 Polymorphisms in drug-transporters

Within the SLC superfamily, genetic variance in organic anion-transporting polypeptides (OATPs) have been most well characterized (Kameyama Y, 2005; Xu G, 2005; Song IS, 2008; Franke RM, 2009). The OATPs are expressed in many tissues like liver, gut and BBB. OATP1B1 is one of the major uptake transporters expressed in hepatocytes and transports drugs like rifampin and statins etc. This protein is encoded by *SLCO1B1*, several allelic variants of which have been characterized and resulted in decreased transporter activity. Another example is OATP-C, which is a liver-specific transporter involved in the hepatocellular uptake of a variety of clinically important drugs. A number of functionally relevant SNPs have been reported in OATP (Xu G, 2005). In *in vitro* experiments several variants showed reduced uptake of the OATP-C substrates estradiol, estrone sulfate and E2-17- β G (Kameyama Y, 2005). Also, OATP-C variants were found to have reduced cell membrane expression compared with the wild-type transporter, especially under inflammatory conditions (Le Vee M, 2008). These studies have implicated SLC and OATP transporters in drug disposition as well as in normal physiological functions such as hormonal signaling.

Polymorphisms within the ABC transporter super family have been well classified and SNPs within *ABCB1* or *MDR-1* gene (coding for P-gp) serves as an excellent example (Hoffmeyer S, 2000; Tanabe M, 2001; Brinkmann U, 2001; Ieiri I, 2004). P-gp genes have a wide range of substrates including anti cancer agents, antiarrhythmics and immunosuppressive drugs (Drescher S, 2002; Hulot JS, 2005; Elens L, 2007; Thervet E, 2008). P-gp expression is widely distributed, liver, the intestines both small and large, and the blood brain barrier (BBB) endothelial cells. In addition, polymorphisms in both MRP (ABCCs) and BCRP (ABCG) are expected to affect the pharmacokinetics of several drugs, however, a clear pattern of increase or decrease has not yet been decipherable (Tamura A, 2006a & 2006b). Large inter-individual variability in P-gp expression, almost two to eight folds, has been observed in healthy volunteers, leading to significant differences in the bioavailability of P-gp substrate drugs within a population. Individual variations in the expression of ABC transporters may give rise to a change in the bioavailability of a particular drug and may thus lead to a need for change in dosing. Increasing evidences demonstrate that both genotypic and phenotypic polymorphisms may affect membrane transporters and that this may well be the cause for variability of a drugs PK profile and toxicity in different ethnic groups [Table-5].

Allele variants	Polymorphism/substitution	Allele frequency (%) ^a			Allele variant	Polymorphism/substitution	Allele frequency (%) ^a		
		Caucasian	Asian	African			Caucasian	Asian	African
ABCB1				OATP					
1236C>T	Silent	34-42	60-72	15-21	SLCO1A2 (OATP1A2)				
2677G>T	A893S	38-47	32-62	15/ND	38T>C	13T	11.1	0	2.1
/A	/T	/1-10	/3-22		516A>C	E172D	5.3	0	2.1
3435C>T	Silent	48-59	37-66	10-27	833A	N278del	0	0	0.6
ABCB1*13	1236C>T/2677G>T/3435C>T haplotype	23-42	28-56	4.5-8.7	SLCO1B1 (OATP1B1)				
ABCC1				SLCO1B3 (OATP1B3)					
128G>C	C43S		1		217T>C	F73L	2	0	0
1299G>T	R433S	1.4			388A>G	N130D	30	54	74
2012G>T	G671V	2.8			463C>A	P155T	16	0	2
ABCC2				SLCO1B1 (OATP1B1)					
1271A>G	R412G				521T>C	V174A	14	0.7	2
1249G>A	V417I	22-26	13-19	14	1463G>C	G488A	0		9
3563T>A	V1188E	4-7	1		2000A>G	E667G	2		34
4544G>A	C1515Y	4-9			SLCO1B3 (OATP1B3)				
ABCG2				SLCO1B1 (OATP1B1)					
34G>A	V12M	2-10	15-18	4-6	334T>G	S112A	74		
376C>T	Q126stop	0	0.9-1.7	0	699G>A	M233I	71		
421C>A	Q141K	9-14	27-35	1-5	1564G>T	G522C	1.9		
				OCT					
				SLC22A1 (OCT1)					
				41C>T					
				S14F					
				0					
				0					
				3.1					
				480C>G					
				G160L					
				0.65					
				8.6-13.0					
				0.5					
				1022C>T					
				P341L					
				0					
				16					
				8.2					
				1201G>A					
				G401S					
				1.1					
				0					
				0.7					
				1222A>G					
				M408V					
				60					
				74-81					
				74					
				1256delATG					
				M420del					
				18					
				0					
				2.9					

Table 5. Most common functional polymorphisms in major ABC and SLC transporters (adapted from Bluth MH, 2011).

DOI: <http://dx.doi.org/10.2147/PGPM.S18861>

Although our knowledge of polymorphisms in ABC and SLC transporters and their clinical association to different drug PK is just developing, the most common functional polymorphisms occurring in some of the major transporter genes, along with allele frequencies and functional effects, are provided in Table-5. Sequence diversity and haplotype structure in the human ABCB1 (MDR1, multidrug resistance transporter) gene were previously documented (Kroetz DL, 2003; Pauli-Magnus C, 2004; Wang J, 2006; Kimchi-Sarfaty C, 2007; Elens L, 2007). Numerous functional implications of these genetic polymorphisms in P-gp have also been clearly seen. Several SNPs in the ABCB1 gene, e.g. 1236C>T and 3435C>T are silent polymorphisms occurring outside of the coding region, and do not change the expression of P-gp (Hitzl M, 2001 & 2004). However, these SNPs change protein translation and substrate specificities. It has also been shown to affect its mRNA, may reduce heteronuclear RNA (hnRNA) processing and translation of the protein. Interestingly, these two SNPs have been shown to correlate with ethnic differences in drug disposition (Wang D, 2005). The ABCB1*13 genotype has also been shown to affect

inhibition by some of the efflux-pump modulators. Several genetic polymorphisms in the *ABCC1* gene are associated with doxorubicin-induced cardiotoxicity (Wojnowski L, 2005). These SNPs were found to be associated with reduced intestinal expression of P-gp, along with increased oral bioavailability of digoxin. Several of the *ABCC* genes, which code for the MRP transporters, are known to affect both drug-efflux and apical to basal drug transport (Fellay J, 2002). Several *ABCC1* SNPs have been associated with anthracycline-induced cardiotoxicity. The *ABCC2* associated SNPs can alter their expression and localization within the cells. Also, several of them, e.g. 3563T>A (V1188E) and 4544G>A (C1515Y), have also been associated with anthracycline-induced cardiotoxicity. Several *ABCG2* genetic variants, which code for the BCRP transporter, are also found to change transporter activities and have been associated with MDR tumors. Interestingly, unlike *ABCB1* (P-gp), a clear clinical correlation with race has not been established with any of these other ABC-transporters.

Less emphasis has been placed on changes in passive diffusion due to polymorphisms in the *SLC* genes. Although numerous polymorphisms have been identified and code for altered protein such as *SLCO1A2*, *SLCO1B1*, *CLCO1B3*, etc, most of them have been shown to suppress facilitated diffusion of their substrates and some of these may also affect substrate specificities. However, due to the lack of correlative studies with these SNPs occurring in different OATP transporters, we know very little about their ultimate effects on drug disposition. Also, less is known about the role of polymorphisms in the phase-II enzymes, such as the *UGT* family members (Guillemette C. 2003; Han JY, 2006; Lo HW, 2007). Genetic variations in *UGT* genes alter the function or expression of the protein, and potentially modify the glucuronidation capacity of the enzyme. Furthermore, SNPs have been identified in most of the human *SULT* genes (Glatt H, 2004) which are associated with altered enzymatic activity and have the potential to influence therapeutic response. Two human *NAT* genes, *NAT1* and *NAT2*, carry functional polymorphisms that influence the enzyme activity (Hein DW. 2002; Walker K, 2009) and bioactivation (via O-acetylation) of aromatic and heterocyclic amine carcinogens. Patients who inherit defective *TPMT* alleles are at significantly increased risk for thiopurine-induced toxicity (e.g. myelosuppression) (Peregud-Pogorzelski J, 2010; Ben Salem C, 2010). Indeed, clinical diagnostic tests are now available for the detection of the SNPs in human *TPMT* gene that lead to decreased or abolished enzyme activity (Nguyen CM, 2011).

The above findings reiterate the fact that both genotypic and phenotypic polymorphisms may affect variability in drug disposition. Further studies of the polymorphisms in human drug-metabolizing enzymes and drug-transporters would shed more light on the subject of pharmacogenomics, and could be used in selecting drugs and dosages according to genetic and specific individual markers in order to individualize drug therapy. Just as for CYP450's, the possibility of defining patient populations and even individual patients on the basis of drug transporter polymorphisms may improve drug safety and efficacy in the future. Positron emission tomography (PET) may serve as a very useful tool in determining the *in vivo* effects of transporters and their polymorphisms (Martínez-Villaseñor D, 2006; Cantore M, 2011). Also in the future it would be valuable to establish a correlation between genotype and phenotype and then assess the effects of polymorphisms on drug transporter expression and function and in turn, effects on drug disposition.

5. Pharmacogenomics: A potent tool for maximizing chemotherapeutic response

5.1 Genetic variations in TPMT may be used to predict toxicity to 6-Mercaptopurine

Thiopurine methyltransferase (TPMT) catalyzes the S-methylation of 6-MP to form inactive metabolites. Genetic variations in the *TPMT* gene have profound effects on the bioavailability and toxicity of 6-MP. It has been demonstrated that about 1 in 300 individuals inherit TPMT deficiency as an autosomal recessive trait. Patients who carry *TPMT* polymorphisms are at risk for severe hematologic toxicities when treated with 6-MP because these polymorphisms lead to a decrease in the rate of 6-MP metabolism (Evans WE, 1991; Lennard L, 1993). Currently, TPMT testing is being used for dose optimization in children with ALL before 6-MP therapy is initiated.

5.2 Genetic variations in UGT1A1: The basis of inter-patient variability with Irinotecan therapy

Irinotecan (Camptosar®; Pfizer Pharmaceuticals; New York, NY, <http://www.pfizer.com>) has potent antitumor activity against a wide range of tumors, and it is one of the most commonly prescribed chemotherapy agents. However, dose-limiting toxicities of irinotecan interfere with optimal utilization of this important drug. Once consumed the drug requires metabolic activation by carboxylesterase to form the active metabolite 7-ethyl-10-hydroxycamptothecin (SN-38), which in turn inhibits topoisomerase-I. SN-38 is further detoxified via formation of SN-38 glucuronide (SN38G) (Gupta E, 1994). Toxicity of irinotecan has been associated with increased levels of SN-38. Clinical pharmacogenetics of irinotecan is mainly focused on polymorphisms in UDP-glucuronosyltransferase 1A1 (UGT1A1), the enzyme responsible for glucuronidation of SN-38 to the less toxic, inactive metabolite SN38G (Iyer L, 1998 & 1999). Variations in UGT1A1 activity most commonly arise from polymorphisms in the *UGT1A1* promoter region that contains several repeating TA elements. The presence of seven TA repeats (referred to as *UGT1A1*28*), instead of the wild-type number of six, results in reduced UGT1A1 expression and activity (Beutler E, 1998). Clinical trials are ongoing to address the impact of dose on irinotecan safety in patients with different *UGT1A1*28* genotypes (McLeod HL, 2004).

5.3 CYP2D6 allele activity affects clinical outcome of patients treated with tamoxifen

One in eight women above seventy develops breast cancer each year in the United States. Approximately 70 percent of them have estrogen receptor-positive cancer. Many of these women are prescribed tamoxifen following surgical treatment. Tamoxifen is an anti-estrogen drug that prevents relapse of cancer in 50% of patients and reduces the mortality rate by one-third in women with early breast cancer. However, there is a large group of women who do not respond to tamoxifen. CYP2D6 encodes for an enzyme involved in the metabolism of up to 25 percent of all drugs. The enzyme is present in different forms in different people and some lack it entirely. Tamoxifen is a "pro-drug," meaning that it is relatively inactive until the liver recruits the CYP2D6 enzyme and converts it into active molecules. The key role of CYP2D6 in catalyzing the conversion of tamoxifen to its abundant active metabolite endoxifen has been shown to directly affect the clinical outcome of patients treated with tamoxifen. This is because the functional alleles of CYP2D6 in some individuals result in abolished, decreased, normal, or ultrarapid CYP2D6 enzyme activity. Women with nonfunctional and reduced-function *CYP2D6* alleles appear to have

significantly lower circulating endoxifen concentrations than those with wild-type *CYP2D6*. It has also been shown that use of *CYP2D6* inhibitors such as SSRIs and SNRIs has a negative impact on the efficacy of tamoxifen. Together, these studies support the notion that low *CYP2D6* activity, caused by genetic polymorphisms or drug interactions, leads to low levels of the active tamoxifen metabolite (Jin Y, 2005; Lim HS, 2007; Hoskins JM, 2009). The effect of *CYP2D6* activity on tamoxifen pharmacokinetics also translates into an effect on clinical outcome. Despite conflicting data in some instance, the majority of retrospective studies suggest that the presence of nonfunctional or reduced-function alleles of *CYP2D6* is associated with worse outcome of patients receiving tamoxifen. A recent large retrospective analysis of 1325 patients with early-stage breast cancer treated with adjuvant tamoxifen suggests that compared with extensive metabolizer, those with decreased *CYP2D6* activity (heterozygous extensive/intermediate and poor metabolizers) have significantly increased risk of recurrence as well as worse event-free survival and disease-free survival (Schroth W, 2009). In addition, *CYP2D6* genotype has also been shown to influence the efficacy of tamoxifen as a chemopreventive agent, whereby tamoxifen-treated women with poor metabolizer phenotype was associated with a significantly higher incidence of breast cancer compared with controls (Higgins MJ, 2010). Findings from these studies support a role for the *CYP2D6* genotype in the activation of tamoxifen and likelihood of therapeutic benefit from testing for *CYP2D6* genotype.

6. Consequences of epigenetic factors on PG and PK

Genetic polymorphisms exhibited by many of the Phase-I and Phase-II drug-metabolizing enzymes as well as both passive and active drug-transporters, can alter drug distribution, drug metabolism and drug-drug interactions and are of great clinical relevance. However, a number of other factors may also contribute to the variation in polymorphism activity, including; (1) environmental factors, (2) age, sex and ethnicity of the patient, (3) physiological status, and (4) disease state. Therefore, in addition to genetic variations, changes in *CYP450* enzyme functions and ABC and SLC transporter activities are responsible for the occurrence of adverse effects or lack of therapeutic efficacy of drugs in many cases.

6.1 Drug-drug interactions regulate drug disposition

Many coadministered drugs can increase or decrease the activity of various *CYP* isozymes, by either inducing the biosynthesis of an isozyme (enzyme induction) or by directly inhibiting the activity of the *CYP* (enzyme inhibition). If one drug inhibits the *CYP*-mediated metabolism of another drug, the second drug may accumulate within the body to toxic levels. Hence, these drug interactions may necessitate either dosage adjustments or choosing drugs that do not interact with the *CYP* system (Anglicheau D, 2003). Such drug interactions are especially important to take into account when using drugs of vital importance to the patient. Drugs with important side-effects and drugs with small therapeutic windows may be subject to an altered plasma concentration due to altered drug metabolism. A classical example includes anti-epileptic drugs (Li XQ, 2004; Li Y, 2008). *CYP450* enzyme induction can occur following repeated administration of antibiotics such as Rifampin (Zhang HX, 2009). Numerous immunosuppressive drugs such as cyclosporine-A and FK-506, used in organ transplantation, show potent drug interactions and are important in pharmacogenetics (Thervet E, et al, 2008). Certain drugs can cause *CYP* enzyme inhibition

by either binding to the cytochrome component or act to competitively inhibit drug metabolism. The histamine (H₂) receptor antagonist, Cimetidine (Tagamet) and the antifungal agent, Ketoconazole (Nizoral) are known to be potent inhibitors of multiple CYPs. Several antibiotics can cause catalytic inactivation of CYPs as well. The Macrolide antibiotics (e.g. erythromycin), which are themselves metabolized by CYPs are known to complex with the cytochrome heme-iron, producing a complex that is catalytically inactive. In addition, Chloramphenicols which are also substrates of CYPs have been shown to inactivate these enzymes by their direct inactivation. It is expected that poor metabolizers would have higher concentrations of a drug that is inactivated by that enzyme pathway and therefore require a lower dose to avoid adverse reactions, whereas ultrarapid metabolizers would require a higher dose to achieve therapeutically effective drug concentrations. The opposite pattern of reactions is expected for a drug that undergoes metabolic activation. Both tobacco use and drugs of abuse, as well as dietary factors can impact CYP450 enzymes and ABC transporters, expression and function. One of the most documented relationships between disease and transporter expression is the association between the overexpression of ABC transporters and the concomitant increased efflux of chemotherapeutic drugs such as vinca-alkaloids, epipodophyllotoxins, and anthracyclines.

6.2 Social and dietary factors regulate drug disposition

Increasing evidence supports the assertion that one mechanism behind clinically significant herb-drug and food-drug interactions is interference at the level of ABC transporters and CYP enzymes (Zhang W, 2005; Marchetti et al., 2011). Naturally occurring compounds may also induce or inhibit CYP activity. For instance, grapefruit, orange, and pimento juices inhibit CYP3A4 and P-gp function, which impacts metabolism and increases drug bioavailability, and, thus, the strong possibility of overdosing. Approximately 10% of all admissions in general hospitals are the result of inappropriate administration of drugs or combinations of drugs that can cause severe to lethal drug-drug or herb-drug interactions. Grapefruit Juice, regularly used as a digestive and diuretic agent, is also known to be a potent inhibitor of CYPs (Bailey DG, 1998). The drugs most susceptible to pharmacokinetic interactions with citrus juices are those with a narrow therapeutic index and a reported affect by P-gp or CYP enzymes; thus, physicians and patients should be cognizant of these clinically significant food-drug interactions when prescribing or following drug treatment (Marchetti et al., 2011). The principle compounds in these Citrus fruits, furanocoumarins and flavonoids, cause interactions with over 50% of the most commonly prescribed drugs in major drug classes such as antiallergics, antibiotics, anxiolytics, calcium channel blockers and HIV protease inhibitors (Cuciureanu M, 2010; Kakar SM, 2004; Pillai et al., 2009). In contrast, although regular consumption of these citrus juices may decrease the therapeutically efficacious dose required, co-administration with drugs such as astemizole, terfenadine, or verapamil may severely increase drug plasma levels and result in toxicity or fatality (Bailey et al., 1998; Pillai et al., 2009).

Several other dietary components and supplements influence drug bioavailability. For example, Watercress is also a known inhibitor of CYP2E1, which may result in altered drug metabolism for individuals on certain medications (e.g., chlorzoxazone) (van Erp NP, 2005). St. John's Wort (SJW), a common herbal remedy and antidepressant, can induce CYP3A4, and also inhibit multiple CYP enzymes such as CYP1A1, CYP1B1 and CYP2D6 (Schwarz UI, 2007; Lei HP, 2010; Lau WC, 2011). Clinical studies demonstrated that coadministration of SJW significantly reduced plasma concentrations of drugs including oral contraceptives, warfarin,

verapamil and fexofenadine which was associated with both failures of therapies and under treatment (Marchetti et al., 2011). Coadministration of SJW and the HIV protease inhibitor, indinavir, or the cardiac glycoside, digoxin increased intestinal P-gp expression and produced significantly lower plasma area under the concentration-time curves. Chronic administration of SJW and cyclosporine-A significantly reduced plasma levels of cyclosporine-A, and increased acute organ rejection in transplanted patients. Curcumin, curcuminoids and catechins from green tea reduce P-gp expression *in vitro* and reports indicate that piperine, ginsenosides, capsaicin, resveratrol and silymarin inhibit *in vitro* P-gp activity.

Socially used factors such as tobacco and alcohol activate receptors that modulate P-gp and CYP expression. A genetic polymorphism in the regulatory sequences of human CYP2E1 has been associated with increased liver toxicity following ethanol consumption, especially in obese individuals (McCarver DG, 1998). Tobacco smoking also induces CYP1A2 and changes the bioavailability of numerous CYP1A2 substrates such as clozapine and olanzapine (Bartsch H, 2000). Significantly greater non-small cell lung cancer tumors were P-gp positive in smokers compared to non-smokers (V olm et al., 1991). Although it remains unclear if P-gp expression levels definitively play a defensive role towards tobacco-derived agents, there is a correlation between current smoking and resistance to the anthracycline drug doxorubicin. Therefore, significant amount of current literature verifies that drug bioavailability can be modulated by components in foods and herbs that regulate drug-metabolizing enzymes and drug-transporters. Hence, dietary components and herbal supplements has important clinical implications, especially in those individuals containing specific augmenting or suppressing polymorphisms in their CYP450 enzymes and/or ABC-transporters.

6.3 Drug disposition: Effects age, sex and ethnicity

Aging is characterized, in part, by alterations in all stages of pharmacokinetic processes (absorption, distribution, metabolism, and excretion), several of which can affect the safety/efficacy profile of a variety of drugs (McLeod HL, 1992; Aronoff GR, 1999; Bjorkman S. 2006; Corsonello A, 2010). The elderly population is more sensitive to bleeding complications arising from warfarin administration which may be attributed to variations in CYP2C9 function. In addition, elderly patients are especially susceptible to adverse drug reactions due to comorbidity, use of multiple pharmaceuticals, and age-related changes in PK (Burk O, 2002; Anglicheau D, 2003). Specific CYPs are inhibited by numerous drugs commonly prescribed to elderly patients, a fact that may help explain significant pharmacological interactions. For instance, the distribution of drugs acting on the CNS can be significantly affected by the changes of BBB permeability which occurs with aging. Several drugs are effluxed via the activity of cerebrovascular P-gp at the BBB; therefore, age-related regression in P-gp function could increase drug levels in the CNS (Corsonello et al., 2010). The CYP450-mediated hepatic drug clearance in neonates, infants and children were found to differ significantly from adults and was a predictor of drug response (Bjorkman S. 2006). The hepatic clearance of drugs in older patients can be reduced more than 40%, some of which may be attributed to alteration in CYP enzyme activity. Although some studies suggest that CYP-mediated activity and enzyme affinity for their substrates are not altered during the aging process, clinically relevant changes in drug-metabolizing enzyme expression have been observed. For instance, a clear age-related decline (20%) in the metabolism of CYP2D6 substrates has been demonstrated (Corsonello et al. 2010; Dorne et al., 2002; O'Connell et al., 2006). Selective serotonin reuptake inhibitors (SSRIs) can inhibit

CYP2D6 activity and therefore reduce the efficiency of drugs that need to be activated by CYP2D6 when coadministered, such as tamoxifen and codeine. The antiplatelet drug clopidogrel is prescribed to prevent stroke and heart attack and it requires CYP2C19 for activation. Omeprazole, a drug used to treat gastroesophageal reflux disease, is both a substrate and an inhibitor of CYP2C19. As a result, individuals with reduced CYP2C19-mediated activity will suffer from impaired clopidogrel bioactivation and enhanced accumulation of omeprazole (Furuta et al., 1998; Li et al., 2004; Roden et al., 2009).

The predominant enzymes involved in phase I hepatic drug metabolism are CYPs, several of which show clear sex-related differences and impact drug clearance (Soldin OP, 2009). Individuals exhibit great variation in biotransformation and although most 'sex-dependent' differences are eliminated with correction for height, as well as weight, composition, and surface area of the body, sex-dependent differences in biotransformation of a few drugs such as nicotine, aspirin, heparin, flurazepam, and chlordiazepoxide have been demonstrated. For instance, the activity of enzymes CYP1A and CYP2E1 is higher in men, while a higher activity of CYP2D6 and CYP3A4 enzymes have been observed in women (O'Connell MB, 2006). A series of physiological changes that are known to affect drug plasma concentrations occur during gestation and pregnancy, one of which causes significant changes in CYP enzyme activity. To date, the PK data amassed pertaining to menopause-related intestinal and hepatic CYP3A4 activity found no significant differences in biotransformation and drug clearance in pre- and postmenopausal women. Sex-related and pregnancy-related changes in drug metabolism and elimination may guide changes in dosage regimen or therapeutic monitoring to reduce possible toxicity and increase drug efficacy (Soldin and Mattison, 2009).

Race related changes in the CYP enzyme and ABC transporter activation and regulation may alter drug accumulation and contribute to the increasing occurrence of adverse drug reactions in elderly patients. Pharmacodynamic differences between races can be associated with changes in drug transporters, and both differences in baseline performance and sensitivity to treatment is attributed to drug efflux from tissues. For instance, some drugs may penetrate the CNS more readily with advancing age thereby increasing their bioavailability. The variation in frequency of SNPs for MDR1 in different racial/ethnic populations has been previously documented. Allelic frequency can differ among these groups (Kim RB, 2001; McLeod H. 2002; Hesselink DA, 2004). The incidence of C/T and C/C genotypes at position 3435 has been found to be much higher in African than in Caucasian or Asian populations (Wang D, 2005; Wang J, 2006). One crucial factor regulating drug levels in African Americans is P-gp function since decreases in P-gp expression has been linked to increased drug serum concentrations and extended drug residence time within the brain (Tirona RG, 2001). While only 26% of Caucasians and 34% of Japanese were homozygous for the C allele, 83% of Ghanaians and 61% of African Americans were homozygous for the C allele (Xie XG, 2001). Certain common allelic variants of CYP3A4 were found to be highly prevalent in different minority populations (Lamba JK, 2002a & 2002b Koch I, 2002). Population distribution and effects on drug metabolism of a genetic variant in the promoter region of CYP3A4 were also previously documented (Ball SE, 1999; Schaeffeler E, 2001). In fact, the functional decline in P-gp may play a role in the increased sensitivity to selected benzodiazepines such as flurazepam reported in patients with specific P-gp SNPs. Therefore, individualized prescriptions for patients should incorporate knowledge from basic pharmacology, race or ethnicity, clinical practice and pharmacosurveillance (Sim SC, 2005; Corsonello et al., 2010). Therefore, age, sex and race related changes in the CYP

enzyme and ABC transporter activation and regulation may alter drug accumulation and contribute to the increasing occurrence of adverse drug reactions.

6.4 Patient health status dictate drug disposition

The most noteworthy condition which alter drug bioavailability in patients is chronic renal failure (CRF) which has been shown to significantly reduce renal clearance of drugs which are predominantly metabolized by the liver and intestine (Bjorkman S, 2006). Patients with CRF exhibit decreased volume of distribution for a variety of drugs due to reduced renal and skeletal muscle mass and decreased tissue binding. In both preclinical and clinical studies, drug transporters such as P-gp and CYPs are affected. In fact, CRF causes a 40 to 85 % downregulation of hepatic and intestinal CYPs with high levels of hormones, cytokines, and uremic toxins also reducing CYP activity. The alteration in these enzymes and proteins affects drug bioavailability and increases the risk for adverse drug reactions (Dreisbach and Lertora 2008; Dreisbach 2009). In transplant patients on cyclosporine-A or tacrolimus, studies have shown changes in both CYP3A4 and P-glycoprotein activity in healthy controls and patients (Lemahieu WP, 2004). In addition to the condition or disease alone regulating enzyme activity and transporter expression, consideration should be applied during treatment for patients on multiple medications (van der Deen M, 2005). P-gp can regulate drug uptake in the CNS and is expressed constitutively in endothelial cells that form the BBB. The expression, however, can be activated or inhibited by other compounds or modified under pathological conditions. For instance, antipsychotics, antiepileptics, or antidepressants that are P-gp substrates can interact at the P-gp level and may be responsible for some documented cases of drug resistance. An induction of P-gp expression decreases psychotropic drug uptake in the central nervous system, which ultimately reduces drug efficacy (Wikinski, 2005). While the health of a patients during treatment may be primarily shaped by their disease and drug disposition, social factors will also influence treatment outcome and should be taken into account during therapeutic decisions.

7. Drug efflux-drug metabolism alliance

There is considerable overlap in the substrate selectivity and tissue localization of specific groups of CYP450 enzymes and ABC transporters (Benet LZ, 2001 & 2004). Common substrates, inhibitors and inducers for CYP3A and P-gp clearly implicate that both common regulatory mechanisms and cross-talk between this CYP iso-enzyme and drug-efflux pump can ultimately regulate drug disposition. Interestingly, in CYP3A4-transfected Caco-2 cells the expression of several efflux transporters, e.g. P-gp, MRP1, and MRP2 were upregulated, especially after stimulation of cells with either the protein kinase-A (PKA) inducer sodium butyrate or the protein kinase-C (PKC) inducer phorbol ester 12-O-tetradecanoylphorbol-13-acetate (PMA) (Cummins, CL, 2001 & 2002). In an *in vivo* intestinal perfusion model, these investigators had also shown modulation of intestinal CYP3A metabolism by P-gp (Cummins, CL, 2003). This has led to the hypothesis that both drug-transporter and drug-metabolizing enzymes act as a coordinated barrier against xenobiotic agents. Several animal studies using *mdr1a* (-/-) knockout mice have demonstrated P-gp's importance in limiting drug absorption and decreasing bioavailability. Human clinical studies investigating the importance of intestinal CYP3A and P-gp through inhibition or induction of these proteins have provided further evidence of this interaction. Recent *in vitro* studies using CYP3A4-expressing Caco-2 cells reveal that the role of P-gp in the intestine not only limits parent drug absorption, but also increases the access of drug to metabolism by CYP3A through repeated cycles of absorption

and efflux. These early findings suggested a biochemical link or coregulation of the drug-efflux and drug-metabolism functions in cells (Benet LZ, 2001; Cummins CL, 2002). A number of recent studies further corroborate this dynamic interplay between different ABC-transporters and different Cyp450 enzymes (Lam JL, 2006; Lee NH, 2010). These studies, carried out in cellular systems, isolated organ, whole animal and human studies, have elucidated the importance of these interacting processes. The importance of this phenomenon with respect to the intestine and the liver, characterizing inhibition and induction of apical and basolateral transporters and how drug metabolism can change independent of any change in the metabolic enzymes, has been effectively shown.

8. Conclusions

As alluded to in the previous section, drug-drug interactions, environmental and physiological factors significantly contribute to inter-individual variability in drug PK. However, these differences are not sufficient to explain the significant heterogeneity associated with patient responses to therapeutic agents and their narrow therapeutic indices. Continued investigation and adaptation of PG with respect to understanding PK should provide improved benefit to therapeutic efficacy versus side-effect profiles of many drugs currently available. Studies are being translated to clinical practice via molecular diagnostics (genotyping) and identifying relevant inherited variations that may better predict patient response to chemotherapy. Among these, nucleotide repeats, insertions, deletions, and SNPs, which can alter the amino acid sequence of the encoded proteins, RNA splicing and gene transcription particularly in drug-metabolizing enzymes and drug transporters have been actively explored with regard to functional changes in phenotype (altered expression levels and/or activity of the encoded proteins) and their contribution to variable drug response. Recent studies also indicate that information on combination of polymorphisms that are inherited together (haplotype analysis) can often result in better correlation with phenotypes than with individual polymorphisms. The potential is enormous for PG to yield a powerful set of molecular diagnostic methods that will become routine tools with which clinicians will select medications and drug doses for individual patients. Gene-expression profiling and proteomic studies are evolving strategies for identifying genes that may influence drug response. Thus, patient oriented PG will provide a very unique approach towards increasing the therapeutic efficacies of numerous anti-cancer, anti-viral as well as anti-diabetic drugs. Furthermore, an effective re-evaluation of new drug design toward the generation of specific therapies focused on drugs that are not critically affected by the Cyp450 enzymes and the drug-transporter biology may eventually lead to personalized and individualized medicine. However, there are a number of issues which must be considered before developing strategies that target these inherited determinants of drug effects. One formidable challenge would be the fact that these inherited components are often polygenic and a complex interplay between genetic and epigenetic factors may ultimately dictate drug disposition. Therefore, the limitations of the current PG approaches will be the lack of complete knowledge and understanding of the complex mechanisms of drug distribution and drug-drug interactions. Another very important hurdle in correctly delineating the pharmacogenetic traits that regulate individualistic differences is the need for well characterized *in vivo* models. Studies in transgenic and knockout animals are proving highly efficacious in this respect, but only accounts for monogenic traits. Patient populations, with race, gender and ethnicity specified, who have been uniformly treated and systematically evaluated for drug action and toxicities, will be highly instrumental in making it possible to quantify the role of

different CYP450 enzymes and ABC-transporters, objectively. The marked population heterogeneity has deterred a clear understanding of the effects of specific genotypes and their importance in determining efficacy. The effects of a medication for one population or disease may not as effective for another population; therefore, PG relations must be validated for each therapeutic indication and in different racial and ethnic groups, which will indeed be a daunting task. However, since genotyping methods are improving rapidly, it will be possible to test for thousands of polymorphisms which determine patient responses. In a clinical setting, it should be easy to collect patient samples and carry out a panel of genotypes and test for those which are important determinants of drug disposition. With the advent of new computer programming and new softwares to delineate pathways and interactions, it will be possible to simplify the complexities of the alliances between drug metabolizers and drug transporters. We believe that in the near future, genotyping results will be of great clinical value only if they are interpreted according to the patient's diagnosis. An effective and safe treatment option can then be recommended by the physician.

9. Acknowledgements

We would like to thank Mrs. Nancy Busija (MA, CCC-SLP) for critical reading and editing of the chapter. Time allotted to this chapter was supported by funds from Tulane University Medical Center (TUMC) and Tulane Cancer Center (TCC) given to Dr. Mondal.

10. References

- Abdel-Tawab M, Werz O, Schubert-Zsilavec M. *Boswellia serrata*: an overall assessment of in vitro, preclinical, pharmacokinetic and clinical data. *Clin Pharmacokinet*. 2011 Jun 1;50(6):349-69. Review.
- Allabi AC, Gala JL, Horsmans Y, et al. Functional impact of CYP2C9*5, CYP2C9*6, CYP2C9*8, and CYP2C9*11 in vivo among black Africans. *Clin Pharmacol Ther*. 2004;76:113-118.
- Ameyaw MM, Regateiro F, Li T, et al. MDR1 pharmacogenetics: frequency of the C3435T mutation in exon 26 is significantly influenced by ethnicity. *Pharmacogenetics* 2001;11:217-21.
- Anglicheau D, Flamant M, Schlageter MH, et al. Pharmacokinetic interaction between corticosteroids and tacrolimus after renal transplantation. *Nephrol Dial Transplant* 2003; 18 (11): 2409-14
- Aragon-Ching JB, Zujewski JA. CNS metastasis: an old problem in a new guise. *Clin Cancer Res*. 2007 Mar 15;13(6):1644-7. Review.
- Aronoff GR, Berns JS, Brier ME, et al. *Drug Prescribing in Renal Failure: Dosing Guidelines for Adults*. 4th ed. Philadelphia, PA: ACP-ASIM; 1999.
- Avila MD, Morgan JP, Yan X. Genetically modified mouse models used for studying the role of the AT2 receptor in cardiac hypertrophy and heart failure. *J Biomed Biotechnol*. 2011;2011:141039. Epub 2011 Apr 27. Review.
- Awad WA, Aschenbach JR, Setyabudi FM, Razzazi-Fazeli E, Böhm J, Zentek J. In vitro effects of deoxynivalenol on small intestinal D-glucose uptake and absorption of deoxynivalenol across the isolated jejunal epithelium of laying hens. *Poult Sci*. 2007 Jan;86(1):15-20.
- Bailey DG, Malcolm J, Arnold O., & Spence JD. Grapefruit-juice drug interactions. *British Journal of Clinical Pharmacology*.1998. 46, 2, pp. 101 - 110.

- Baiocchi M, Biffoni M, Ricci-Vitiani L, Pillozzi E, De Maria R. New models for cancer research: human cancer stem cell xenografts. *Curr Opin Pharmacol*. 2010 Aug;10(4):380-4. Epub 2010 Jun 17. Review.
- Ball SE, Scatina J, Kao J, et al. Population distribution and effects on drug metabolism of a genetic variant in the 50 promoter region of CYP3A4. *Clin Pharmacol Ther* 1999; 66 (3): 288-94
- Bartsch H, Nair U, Risch A, Rojas M, Wikman H, Alexandrov K. Genetic polymorphisms of CYP genes, alone or in combination, as a risk modifier of tobacco-related cancers. *Cancer Epidemiol Biomarkers Prev*. 2000;9:3-28.
- Basnet P, Skalko-Basnet N. Curcumin: an anti-inflammatory molecule from a curry spice on the path to cancer treatment. *Molecules*. 2011 Jun 3;16(6):4567-98. Review.
- Bauer F, Kuntner C, Bankstahl JP, Wanek T, Bankstahl M, Stanek J, Mairinger S, Dörner B, Löscher W, Müller M, Erker T, Langer O. Synthesis and in vivo evaluation of [¹¹C]tariquidar, a positron emission tomography radiotracer based on a third-generation P-glycoprotein inhibitor. *Bioorg Med Chem*. 2010 Aug 1;18(15):5489-97.
- Ben Salem C, Ben Salah L, Belajouza C, Bouraoui K. Azathioprine-induced severe cholestatic hepatitis in patient carrying TPMT*3C polymorphism. *Pharm World Sci*. 2010 Dec;32(6):701-3.
- Benet LZ, Cummins CL, Wu C-Y. Unmasking the dynamic interplay between efflux transporters and metabolic enzymes *Int. J. Pharm.* 2004, 277, 3- 9
- Benet LZ, Cummins CL. The drug efflux-metabolism alliance: biochemical aspects. *Adv Drug Deliv Rev* 2001; 50 Suppl. 1: S3-11
- Benet LZ. The drug transporter-metabolism alliance: uncovering and defining the interplay. *Mol Pharm*. 2009 Nov-Dec;6(6):1631-43. Review.
- Beutler E, Gelbart T, Demina A. Racial variability in the UDP-glucuronosyltransferase 1 (*UGT1A1*) promoter: a balanced polymorphism for regulation of bilirubin metabolism? *Proc Natl Acad Sci USA* 1998;95:8170-8174.
- Bjorkman S. Prediction of cytochrome p450-mediated hepatic drug clearance in neonates, infants and children: how accurate are available scaling methods? *Clin Pharmacokinet* 2006; 45 (1): 1-11
- Bluth MH, Li J. Pharmacogenomics of drug metabolizing enzymes and transporters: implications for cancer therapy *Pharmacogenomics and Personalized Medicine*. 2011;4: 11 - 33
- Board PG. The use of glutathione transferase-knockout mice as pharmacological and toxicological models. *Expert Opin Drug Metab Toxicol*. 2007 Jun;3(3):421-33.Review.
- Bogard KN, Peterson NT, Plumb TJ, Erwin MW, Fuller PD, Olsen KM. Antibiotic dosing during sustained low-efficiency dialysis: special considerations in adult critically ill patients. *Crit Care Med*. 2011 Mar;39(3):560-70. Review.
- Boiangiu CD, Jayamani E, Brügel D, Herrmann G, Kim J, Forzi L, Hedderich R, Vgenopoulou I, Pierik AJ, Steuber J, Buckel W. Sodium ion pumps and hydrogen production in glutamate fermenting anaerobic bacteria. *J Mol Microbiol Biotechnol*. 2005;10(2-4):105-19. Review.
- Booth RA, Ansari MT, Loit E, Tricco AC, Weeks L, Doucette S, Skidmore B, Sears M, Sy R, Karsh J. Assessment of thiopurine S-methyltransferase activity in patients prescribed thiopurines: a systematic review. *Ann Intern Med*. 2011 Jun 21;154(12):814-23, W-295-8. Review.
- Borst P, Evers R, Kool M, Wijnholds J. A family of drug transporters: the multidrug resistance-associated proteins. *J Natl Cancer Inst* 2000;92:1295-302.

- Brinkmann U, Roots I, Eichelbaum M. Pharmacogenetics of the human drug transporter gene MDR1: impact of polymorphisms on pharmacotherapy. *Drug Discov Today* 2001;6:835-9.
- Brockmeier D. Estimating reduced availability due to first pass elimination from relative total clearance and renal clearance. *Eur J Clin Pharmacol.* 1988;35(4):397-400.
- Brown AS, James OF. Omeprazole, ranitidine, and cimetidine have no effect on peak blood ethanol concentrations, first pass metabolism or area under the time-ethanol curve under 'real-life' drinking conditions. *Aliment Pharmacol Ther.* 1998 Feb;12(2):141-5.
- Burk O, Tegude H, Koch I, et al. Molecular mechanisms of polymorphic CYP3A7 expression in adult human liver and intestine. *J Biol Chem* 2002;277 (27): 24280-8
- Cantore M, Capparelli E, Berardi F, Perrone R, Colabufo NA. Clinical Pharmacokinetic and Metabolism of PET Radiotracers for Imaging P-glycoprotein in Chemoresistant Tumor of Colorectal Cancer. *Curr Drug Metab.* 2011 Jul 25. [Epub ahead of print].
- Cascorbi I, Haenisch S. Pharmacogenetics of ATP-binding cassette transporters and clinical implications. *Methods Mol Biol.* 2010;596:95-121.
- Choo EF, Leake B, Wandel C, et al. Pharmacological inhibition of P-glycoprotein transport enhances the distribution of HIV-1 protease inhibitors into brain and testes. *Drug Metab Dispos* 2000;28:655-60.
- Conrad S, Kauffmann HM, Ito K, et al. A naturally occurring mutation in MRP1 results in a selective decrease in organic anion transport and in increased doxorubicin resistance. *Pharmacogenetics.* 2002;12: 321-330.
- Corsonello A, Pedone C, & Antonelli Incalzi R. Age-related pharmacokinetic and pharmacodynamic changes and related risk of adverse drug reactions. *Current Medicinal Chemistry.* 2010.17, 6, pp. 571 - 584.
- Cuciureanu M, Vlase L, Muntean D, Varlan I, & Cuciureanu R. Grapefruit juice – drug interactions: importance for pharmacotherapy. *Revista medico-chirurgicala a Societatii de Medici si Naturalisti din Iasi.* 2010. 114, 3, pp. 885 - 891.
- Cummins CL, Jacobsen W, Benet LZ. Unmasking the dynamic interplay between intestinal P-glycoprotein and CYP3A4. *J Pharmacol Exp Ther* 2002; 300 (3): 1036-45
- Cummins CL, Mangravite LM, Benet LZ. Characterizing the expression of CYP3A4 and efflux transporters (P-gp, MRP1, and MRP2) in CYP3A4-transfected Caco-2 cells after induction with sodium butyrate and the phorbol ester 12-O-tetradecanoylphorbol-13-acetate Pharm. Res. 2001, 18, 1102- 1109
- Cummins CL, Salphati L, Reid MJ, Benet LZ. In vivo modulation of intestinal CYP3A metabolism by P-glycoprotein: studies using the rat single-pass intestinal perfusion model *J. Pharmacol. Exp. Ther.* 2003, 305, 306- 314
- Daly AK. Significance of the minor cytochrome P450 3A isoforms. *Clin Pharmacokinet* 2006; 45 (1): 13-31
- Davidson AL, Dassa EO, & Chen J. Structure, function, and evolution of bacterial ATP-binding cassette systems. *Microbiology and Molecular Biology Reviews*, 2008. 72, 2, pp. 317 - 364.
- Degorter MK, Xia CQ, Yang JJ, Kim RB. Drug Transporters in Drug Efficacy and Toxicity. *Annu Rev Pharmacol Toxicol.* 2011 Jan 17. [Epub ahead of print]
- Desta Z, Ward BA, Soukhova NV, et al. Comprehensive evaluation of tamoxifen sequential biotransformation by the human cytochrome P450 system in vitro: prominent roles for CYP3A and CYP2D6. *J Pharmacol Exp Ther.* 2004;310:1062-1075.
- DiazGranados N, Zarate CA Jr. A review of the preclinical and clinical evidence for protein kinase C as a target for drug development for bipolar disorder. *Curr Psychiatry Rep.* 2008 Dec;10(6):510-9. Review.

- Dobson PD, Kell DB. Carrier-mediated cellular uptake of pharmaceutical drugs: an exception or the rule? *Nat Rev Drug Discov.* 2008 Mar;7(3):205-20. Review.
- Dorne JL, Walton K, Slob W, & Renwich AG. Human variability in polymorphic CYP2D6 metabolism: is the kinetic default uncertainty factor adequate? *Food and Chemical Toxicology.*2002. 40, pp. 1633 – 1656.
- Dossing M, Pilsgaard H, Rasmussen B, Poulsen HE. Time course of phenobarbital and cimetidine mediated changes in hepatic drug metabolism. *Eur J Clin Pharmacol* 1983;25:215-22.
- Dreisbach AW, & Lertora JJ. The effect of chronic renal failure on drug metabolism and transport. *Expert Opinion on Drug Metabolism and Toxicology.*2008. 4, 8, pp. 1065 – 1074.
- Dreisbach AW. The influence of chronic renal failure on drug metabolism and transport. *Clinical Pharmacology and Therapeutics.*2009. 86, 5, pp. 553 – 556.
- Drescher S, Schaeffeler E, Hitzl M, et al. MDR1 gene polymorphisms and disposition of the P-glycoprotein substrate fexofenadine. *Br J Clin Pharmacol* 2002; 53 (5): 526-34
- Durán JM, Cano M, Peral MJ, Ilundáin AA. D-mannose transport and metabolism in isolated enterocytes. *Glycobiology.* 2004 Jun;14(6):495-500. Epub 2004 Mar 19.
- Eilers M, Roy U, Mondal D. MRP (ABCC) transporters-mediated efflux of anti-HIV drugs, saquinavir and zidovudine, from human endothelial cells. *Exp Biol Med* (Maywood). 2008 Sep;233(9):1149-60.
- Elens L, Capron A, Kerckhove VV, et al. 1199G>A and 2677G>T/A polymorphisms of ABCB1 independently affect tacrolimus concentration in hepatic tissue after liver transplantation. *Pharmacogenet Genomics* 2007; 17 (10): 873-83
- Evans W, Schentag J, Jusko J (editors): *Applied Pharmacokinetics* (3rd edition). San Francisco, CA. Applied Therapeutics, 1992.
- Evans WE, Horner M, Chu YQ et al. Altered mercaptopurine metabolism, toxic effects, and dosage requirement in a thiopurine methyltransferase-deficient child with acute lymphocytic leukemia. *J Pediatr* 1991;119:985-989.
- Evans WE, Johnson JA. Pharmacogenomics: the inherited basis for interindividual differences in drug response. *Annu Rev Genomics Hum Genet* 2001;2:9-39.
- Evans WE, McLeod HL. Pharmacogenomics: drug disposition, drug targets, and side effects. *N Engl J Med* 2003; 348 (6): 538-49
- Evans WE, Relling MV. Clinical pharmacokinetics-pharmacodynamics of anticancer drugs. *Clin Pharmacokinet.* 1989 Jun;16(6):327-36. Review.
- Evans WE, Relling MV. Pharmacogenomics: translating functional genomics into rational therapeutics. *Science* 1999;286:487-91.
- Fasolo A, Sessa C. Translational research in phase I trials. *Clin Transl Oncol.* 2009 Sep;11(9):580-8. Review.
- Fellay J, Marzolini C, Meaden ER, et al. Response to antiretroviral treatment in HIV-1-infected individuals with allelic variants of the multidrug resistance transporter 1: a pharmacogenetics study. *Lancet* 2002;359: 30-6.
- Fesler P, Mimran A. Estimation of glomerular filtration rate: what are the pitfalls? *Curr Hypertens Rep.* 2011 Apr;13(2):116-21. Review.
- Franke RM, Scherkenbach LA, Sparreboom A. Pharmacogenetics of the organic anion transporting polypeptide 1A2. *Pharmacogenomics.* 2009;10:339-344.
- Fromm MF. Importance of P-glycoprotein for drug disposition in humans. *Eur J Clin Invest* 2003; 33 Suppl. 2: 6-9
- Furuse M. Molecular basis of the core structure of tight junctions. *Cold Spring Harb Perspect Biol.* 2010 Jan;2(1):a002907. Review.

- Furuta T, Ohashi K, Kamata T, Takashima M, Kosuge K, Kawakaki T, Hanai H, Kubota T, Ishizaki T, & Kaneko E. Effect of genetic differences in omeprazole metabolism on cure rates for *Helicobacter pylori* infection and peptic ulcer. *Annals of Internal Medicine*.1998. 129, pp. 1027 - 1030.
- Gardiner SJ, Begg EJ. Pharmacogenetic testing for drug metabolizing enzymes: is it happening in practice? *Pharmacogenet Genomics*. 2005;15:365-369.
- Gether U, Andersen PH, Larsson OM, Schousboe A. Neurotransmitter transporters: molecular function of important drug targets. *Trends Pharmacol Sci*. 2006 Jul;27(7):375-83.
- Glatt H, Meinel W. Pharmacogenetics of soluble sulfotransferases (SULTs). *Naunyn Schmiedebergs Arch Pharmacol*. 2004;369: 55-68.
- Goteti K, Brassil PJ, Good SS, Garner CE. Estimation of human drug clearance using multiexponential techniques. *J Clin Pharmacol*. 2008 Oct;48(10):1226-36. Epub 2008 Jun 16.
- Gottesman MM, Fojo T, Bates SE. Multidrug resistance in cancer: role of ATP-dependent transporters. *Nat Rev Cancer*. 2002;2:48-58.
- Gradhand U, Kim RB. Pharmacogenomics of MRP transporters (ABCC1-5) and BCRP (ABCG2). *Drug Metab Rev*. 2008;40:317-354.
- Guengerich FP. Cytochrome p450 and chemical toxicology. *Chemical Research in Toxicology*.2008. 21, 1, pp. 70 - 83.
- Guillemette C. Pharmacogenomics of human UDP-glucuronosyltransferase enzymes. *Pharmacogenomics J*. 2003;3(3):136-158.
- Gulinello M, Putterman C. The MRL/lpr mouse strain as a model for neuropsychiatric systemic lupus erythematosus. *J Biomed Biotechnol*.2011;2011:207504. Epub 2011 Feb 10. Review.
- Gupta E, Lestingi TM, Mick R et al. Metabolic fate of irinotecan in humans: correlation of glucuronidation with diarrhea. *Cancer Res* 1994;54:3723-3725.
- Haber PS, Gentry RT, Mak KM, Mirmiran-Yazdy SA, Greenstein RJ, Lieber CS. Metabolism of alcohol by human gastric cells: relation to first-pass metabolism. *Gastroenterology*. 1996 Oct;111(4):863-70.
- Hagenbuch B, Meier PJ. The superfamily of organic anion transporting polypeptides. *Biochim. Biophys. Acta* 2003, 1609, 1- 18
- Han JY, Lim HS, Shin ES, et al. Comprehensive analysis of UGT1A polymorphisms predictive for pharmacokinetics and treatment outcome in patients with non-small-cell lung cancer treated with irinotecan and cisplatin. *J Clin Oncol*. 2006;24:2237-2244.
- Hans H. (Editor). "The laboratory mouse". The handbook of experimental animals. Elsevier Academic Press. 2004
- Harguindey S, Arranz JL, Wahl ML, Orive G, Reshkin SJ. Proton transport inhibitors as potentially selective anticancer drugs. *Anticancer Res*. 2009 Jun;29(6):2127-36. Review.
- Hartmann B, Czock D, Keller F. Drug therapy in patients with chronic renal failure. *Dtsch Arztebl Int*. 2010 Sep;107(37):647-55; quiz 655-6. Epub 2010 Sep 17. Review.
- Hein DW. Molecular genetics and function of NAT1 and NAT2: role in aromatic amine metabolism and carcinogenesis. *Mutat Res*. 2002; 506-507:65-77.
- Hesselink DA, van Gelder T, van Schaik RH, et al. Population pharmacokinetics of cyclosporine in kidney and heart transplant recipients and the influence of ethnicity and genetic polymorphisms in the MDR-1, CYP3A4, and CYP3A5 genes. *Clin Pharmacol Ther* 2004; 76 (6): 545-56
- Higgins MJ, Stearns V. CYP2D6 polymorphisms and tamoxifen metabolism: clinical relevance. *Curr Oncol Rep*. 2010;12:7-15.

- Hinoshita E, Uchiumi T, Taguchi K, et al. Increased expression of an ATP-binding cassette superfamily transporter, multidrug resistance protein 2, in human colorectal carcinomas. *Clin Cancer Res.* 2000;6:2401-2407.
- Hitzl M, Drescher S, van der Kuip H, et al. The C3435T mutation in the human MDR1 gene is associated with altered efflux of the P-glycoprotein substrate rhodamine 123 from CD56+ natural killer cells. *Pharmacogenetics* 2001; 11 (4): 293-8
- Hitzl M, Schaeffeler E, Hocher B, et al. Variable expression of P-glycoprotein in the human placenta and its association with mutations of the multidrug resistance 1 gene (MDR1, ABCB1). *Pharmacogenetics* 2004; 14 (5): 309-18
- Hoffmeyer S, Burk O, von Richter O, et al. Functional polymorphisms of the human multidrug-resistance gene: multiple sequence variations and correlation of one allele with P-glycoprotein expression and activity in vivo. *Proc Natl Acad Sci U S A* 2000;97:3473-8.
- Hoskins JM, Carey LA, McLeod HL. CYP2D6 and tamoxifen: DNA matters in breast cancer. *Nat Rev Cancer.* 2009;9:576-586.
- Hulot JS, Villard E, Maguy A, et al. A mutation in the drug transporter gene ABCC2 associated with impaired methotrexate elimination. *Pharmacogenet Genomics.* 2005;15:277-285.
- Ieiri I, Takane H, Otsubo K. The MDR1 (ABCB1) gene polymorphism and its clinical implications. *Clin Pharmacokinet.* 2004;43:553-576.
- Iida A, Saito S, Sekine A, et al. Catalog of 605 single-nucleotide polymorphisms (SNPs) among 13 genes encoding human ATP-binding cassette transporters: ABCA4, ABCA7, ABCA8, ABCD1, ABCD3, ABCD4, ABCE1, ABCF1, ABCG1, ABCG2, ABCG4, ABCG5, and ABCG8. *J Hum Genet.* 2002;47:285-310.
- Ingelman-Sundberg M. Human Cytochrome P450 (CYP) Allele Nomenclature Committee [online]. URL: <http://www.cypalleles.ki.se/>[2009]
- Ingelman-Sundberg M. Pharmacogenetics of cytochrome P450 and its applications in drug therapy: the past, the present and future. *Trends Pharmacol Sci.* 2004;25:193-200.
- Iyer L, Hall D, Das S et al. Phenotype-genotype correlation of in vitro SN-38 (active metabolite of irinotecan) and bilirubin glucuronidation in human liver tissue with *UGT1A1* promoter polymorphism. *Clin Pharmacol Ther* 1999;65:576-582
- Iyer L, King CD, Whittington PF et al. Genetic predisposition to the metabolism of irinotecan (CPT-11). Role of uridine diphosphate glucuronosyltransferase isoform 1A1 in the glucuronidation of its active metabolite (SN-38) in human liver microsomes. *J Clin Invest* 1998;101:847-854.
- Jin Y, Desta Z, Stearns V, et al. CYP2D6 genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. *J Natl Cancer Inst.* 2005;97:30-39.
- Johanson CE, Stopa EG, McMillan PN. The blood-cerebrospinal fluid barrier: structure and functional significance. *Methods Mol Biol.* 2011;686:101-31. Review.
- Jones PM, O'Mara ML, George AM. ABC transporters: a riddle wrapped in a mystery inside an enigma. *Trends Biochem Sci.* 2009 Oct;34(10):520-31..
- Jonker JW, Smit JW, Brinkhuis RF, et al. Role of breast cancer resistance protein in the bioavailability and fetal penetration of topotecan. *J Natl Cancer Inst.* 2000;92:1651-1656.
- Kakar SM, Paine MF, Stewart PW, & Watkins PB. "6',7'-Dihydroxybergamottin contributes to the grapefruit juice effect. *Clinical Pharmacology and Therapeutics.*2004. 75, 6, pp. 569 - 579.
- Kameyama Y, Yamashita K, Kobayashi K, et al. Functional characterization of SLCO1B1 (OATP-C) variants, SLCO1B1*5, SLCO1B1*15 and SLCO1B1*15+C1007G, by using

- transient expression systems of HeLa and HEK293 cells. *Pharmacogenet Genomics*. 2005;15:513–522.
- Kennedy AJ, Ellacott KL, King VL, Hasty AH. Mouse models of the metabolic syndrome. *Dis Model Mech*. 2010 Mar-Apr;3(3-4):156–66. Review.
- Khan N, Adhami VM, Mukhtar H. Review: green tea polyphenols in chemoprevention of prostate cancer: preclinical and clinical studies. *Nutr Cancer*. 2009;61(6):836–41. Review.
- Kim RB, Leake BF, Choo EF, et al. Identification of functionally variant MDR1 alleles among European Americans and African Americans. *Clin Pharmacol Ther* 2001; 70 (2): 189–99
- Kimchi-Sarfaty C, Oh JM, Kim IW, et al. A “silent” polymorphism in the MDR1 gene changes substrate specificity. *Science* 2007; 315 (5811): 525–8
- Kolitz JE, George SL, Marcucci G, Vij R, Powell BL, Allen SL, DeAngelo DJ, Shea TC, Stock W, Baer MR, Hars V, Maharry K, Hoke E, Vardiman JW, Bloomfield CD, Larson RA; Cancer and Leukemia Group B. P-glycoprotein inhibition using valsopodar (PSC-833) does not improve outcomes for patients younger than age 60 years with newly diagnosed acute myeloid leukemia: Cancer and Leukemia Group B study 19808. *Blood*. 2010 Sep 2;116(9):1413–21..
- Kooman JP. Estimation of renal function in patients with chronic kidney disease. *J Magn Reson Imaging*. 2009 Dec;30(6):1341–6. Review.
- Krishnamurthy P, Schuetz JD. Role of ABCG2/BCRP in biology and medicine. *Annu Rev Pharmacol Toxicol*. 2006;46:381–410.
- Kroetz DL, Pauli-Magnus C, Hodges LM, et al. Sequence diversity and haplotype structure in the human ABCB1 (MDR1, multidrug resistance transporter) gene. *Pharmacogenetics* 2003; 13 (8): 481–94
- Kuehl P, Zhang J, Lin Y, et al. Sequence diversity in CYP3A promoters and characterization of the genetic basis of polymorphic CYP3A5 expression. *Nat Genet*. 2001;27:383–391.
- Kukanich B. Pharmacokinetics of acetaminophen, codeine, and the codeine metabolites morphine and codeine-6-glucuronide in healthy Greyhound dogs. *J Vet Pharmacol Ther*. 2010 Feb;33(1):15–21.
- Kuroda M, Kusuhara H, Endou H, Sugiyama Y. Rapid elimination of cefaclor from the cerebrospinal fluid is mediated by a benzylpenicillin-sensitive mechanism distinct from organic anion transporter 3. *J Pharmacol Exp Ther*. 2005 Aug;314(2):855–61.
- Lai Y, Zhang J, Wang YX, Wang XD, Li JL, Zeng YJ & Huang M. CYP3A5*3 and MCR-1 C3435T single nucleotide polymorphisms in six Chinese ethnic groups. *Pharmazie*, 2011. 66, 2, pp. 136 – 140.
- Lam JL, Okochi H, Huang Y, Benet LZ. In vitro and in vivo correlation of hepatic transporter effects on erythromycin metabolism: characterizing the importance of transporter-enzyme interplay *Drug Metab. Dispos*. 2006, 34, 1336– 1344
- Lamba JK, Lin YS, Schuetz EG, et al. Genetic contribution to variable human CYP3A-mediated metabolism. *Adv Drug Deliv Rev* 2002; 54 (10): 1271–94 (b).
- Lamba JK, Lin YS, Thummel K, et al. Common allelic variants of cytochrome P4503A4 and their prevalence in different populations. *Pharmacogenetics* 2002; 12 (2): 121–32 (a).
- Lau WC, Welch TD, Shields T, Rubenfire M, Tantry US, Gurbel PA. The effect of St John's Wort on the pharmacodynamic response of clopidogrel in hyporesponsive volunteers and patients: increased platelet inhibition by enhancement of CYP3A4 metabolic activity. *J Cardiovasc Pharmacol*. 2011 Jan;57(1):86–93.
- Lau YY, Huang Y, Frassetto L, Benet LZ. Effect of OATP1B transporter inhibition on the pharmacokinetics of atorvastatin in healthy volunteers *Clin. Pharmacol. Ther*. 2007, 81, 194– 204

- Le Vee M, Gripon P, Stieger B, Fardel O. Down-regulation of organic anion transporter expression in human hepatocytes exposed to the proinflammatory cytokine interleukin 1beta. *Drug Metab Dispos.* 2008 Feb;36(2):217-22.
- Lee CR, Pieper JA, Frye RF, Hinderliter AL, Blaisdell JA, Goldstein JA. Tolbutamide, flurbiprofen, and losartan as probes of CYP2C9 activity in humans. *J Clin Pharmacol.* 2003 Jan;43(1):84-91.
- Lee NH. Pharmacogenetics of drug metabolizing enzymes and transporters: effects on pharmacokinetics and Pharmacodynamics of anticancer agents. *Anticancer Agents in Medicinal Chemistry.* 2010. 10, 8, pp. 583 - 592.
- Lei HP, Yu XY, Xie HT, Li HH, Fan L, Dai LL, Chen Y, Zhou HH. Effect of St. John's wort supplementation on the pharmacokinetics of bupropion in healthy male Chinese volunteers. *Xenobiotica.* 2010 Apr;40(4):275-81.
- Lemahieu WP, Maes BD, Verbeke K, et al. CYP3A4 and P-glycoprotein activity in healthy controls and transplant patients on cyclosporin vs tacrolimus vs sirolimus. *Am J Transplant* 2004; 4 (9): 1514-22
- Lennard L, Gibson BE, Nicole T et al. Congenital thiopurine methyltransferase deficiency and 6-mercaptopurine toxicity during treatment for acute lymphoblastic leukaemia. *Arch Dis Child* 1993;69:577-579.
- Li XQ, Andersson TB, Ahlstrom M, & Weidolf L. Comparison of inhibitory effects of the proton pump-inhibiting drugs omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole on human cytochrome P450 activities. *Drug Metabolism and Disposition.* 2004. 32, pp. 821 - 827.
- Li Y, Kantelip JP, Gerritsen-van Schieveen P, & Davani P. Interindividual variability of methadone response: Impact of genetic polymorphism. *Molecular Diagnosis and Therapy.* 2008. 12, 2, pp. 109 - 124.
- Lijnen HR. Murine models of obesity and hormonal therapy. *Thromb Res.* 2011 Feb;127 Suppl 3:S17-20. Review.
- Lim HS, Ju Lee H, Seok Lee K, et al. Clinical implications of CYP2D6 genotypes predictive of tamoxifen pharmacokinetics in metastatic breast cancer. *J Clin Oncol.* 2007;25:3837-3845.
- Lo HW, Ali-Osman F. Genetic polymorphism and function of glutathione S-transferases in tumor drug resistance. *Curr Opin Pharmacol.* 2007;7:367-374.
- Locher KP. Review. Structure and mechanism of ATP-binding cassette transporters. *Philos Trans R Soc Lond B Biol Sci.* 2009 Jan 27;364(1514):239-45. Review.
- Luo FR, Paranjpe PV, Guo A, et al. Intestinal transport of irinotecan in Caco-2 cells and MDCK II cells overexpressing efflux transporters Pgp, cMOAT, and MRP1. *Drug Metab Dispos.* 2002;30:763-770.
- Luqmani YA. Mechanisms of drug resistance in cancer chemotherapy. *Med Princ Pract.* 2005;14 Suppl 1:35-48. Review.
- MacPhee IA, Fredericks S, Holt DW. Does pharmacogenetics have the potential to allow the individualisation of immunosuppressive drug dosing in organ transplantation? *Expert Opin Pharmacother* 2005; 6 (15):2593-605
- Mager DE, Woo S, Jusko WJ. Scaling pharmacodynamics from in vitro and preclinical animal studies to humans. *Drug Metab Pharmacokinet.* 2009;24(1):16-24. Review.
- Marchetti, S., Mazzanti, R., Beijnen, JH., & Schellens, JHM. (2007). Concise Review: Clinical relevance of drug-drug and herb-drug interactions mediated by ABC transporter ABCB1 (MDR1, P-glycoprotein). *The Oncologist*, 12, 927 - 941.
- Martínez-Villaseñor D, Gerson-Cwilich R. [PET/CT tomography. Usefulness in oncology]. *Cir Cir.* 2006 Jul-Aug;74(4):295-304. Review.

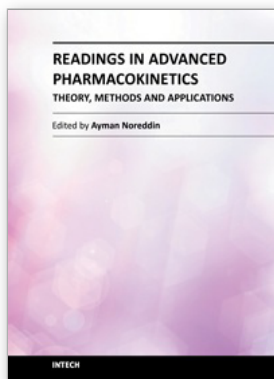
- Mathijssen RH, van Alphen RJ, Verweij J, et al. Clinical pharmacokinetics and metabolism of irinotecan (CPT-11). *Clin Cancer Res*. 2001;7:2182-2194.
- Matsuhisa K, Kondoh M, Takahashi A, Yagi K. Tight junction modulator and drug delivery. *Expert Opin Drug Deliv*. 2009 May;6(5):509-15.
- McCarver DG, Byun R, Hines RN, Hichme M, Wegenek W. A genetic polymorphism in the regulatory sequences of human CYP2E1: association with increased chlorzoxazone hydroxylation in the presence of obesity and ethanol intake. *Toxicol Appl Pharmacol*. 1998;152:276-281.
- McIlwain CC, Townsend DM, Tew KD. Glutathione S-transferase polymorphisms: cancer incidence and therapy. *Oncogene*. 2006;25: 1639-1648.
- McLeod H. Pharmacokinetic differences between ethnic groups. *Lancet* 2002;359:78.
- McLeod HL, Evans WE. Pediatric pharmacokinetics and therapeutic drug monitoring. *Pediatr Rev*. 1992 Nov;13(11):413-21. Review.
- McLeod HL, Watters JW. Irinotecan pharmacogenetics: is it time to intervene? *J Clin Oncol* 2004;22:1356-1359
- McLeod HL, Yu J. Cancer pharmacogenomics: SNPs, chips, and the individual patient. *Cancer Invest*. 2003;21(4):630-40. Review.
- Mehdipour AR, Hamidi M. Brain drug targeting: a computational approach for overcoming blood-brain barrier. *Drug Discov Today*. 2009 Nov;14(21-22):1030-6. Epub 2009 Jul 30. Review.
- Michel MC, Chapple CR. Basic mechanisms of urgency: preclinical and clinical evidence. *Eur Urol*. 2009 Aug;56(2):298-307. Epub 2009 May 26. Review.
- Miyagawa F, Gutermuth J, Zhang H, Katz SI. The use of mouse models to better understand mechanisms of autoimmunity and tolerance. *J Autoimmun*. 2010 Nov;35(3):192-8. Epub 2010 Jul 23. Review.
- Murray M, Reidy GF. Selectivity in the inhibition of mammalian cytochromes P-450 by chemical agents. *Pharmacol Rev* 1990;42:85-101.
- Musana AK, Wilke RA. Gene based drug prescribing: Clinical implications of the cytochrome P450 genes. *Wisconsin Medical J*. 2005;104:61-66.
- Nagar S, Rimmel RP. Uridine diphosphoglucuronosyltransferase pharmacogenetics and cancer. *Oncogene*. 2006;25:1659-1672.
- Nagasubramanian R, Innocenti F, Ratain MJ. Pharmacogenetics in cancer treatment. *Annu Rev Med*. 2003;54:437-52. Epub 2001 Dec 3. Review.
- Nelson, DR. The Cytochrome P450 Homepage. *Human Genomics*. 2009. 4, 59-65. URL: <http://drnelson.uthsc.edu/CytochromeP450.html>
- Nguyen CM, Mendes MA, Ma JD. Thiopurine methyltransferase (TPMT) genotyping to predict myelosuppression risk. *PLoS Curr*. 2011 May 15;3:RRN1236.
- Niemi M, Schaeffeler E, Lang T, et al. High plasma pravastatin concentrations are associated with single nucleotide polymorphisms and haplotypes of organic anion transporting polypeptide-C (OATP-C, SLCO1B1). *Pharmacogenetics* 2004; 14 (7): 429-40
- Nieminen TH, Hagelberg NM, Saari TI, Neuvonen M, Neuvonen PJ, Laine K, Olkkola KT. Grapefruit juice enhances the exposure to oral oxycodone. *Basic Clin Pharmacol Toxicol*. 2010 Oct;107(4):782-8.
- O'Connell MB, Frye RF, Matzke GR, St Peter JV, Willhite LA, Welch MR, Kowal P, & LaValleur J. Effect of conjugated equine estrogens on oxidative metabolism in middle-aged and elderly postmenopausal women. *Journal of Clinical Pharmacology*. 2006. 46, pp. 1299 - 1307.
- O'Brien MM, Lacayo NJ, Lum BL, Kshirsagar S, Buck S, Ravindranath Y, Bernstein M, Weinstein H, Chang MN, Arceci RJ, Sikic BI, Dahl GV. Phase I study of valsopodar

- (PSC-833) with mitoxantrone and etoposide in refractory and relapsed pediatric acute leukemia: a report from the Children's Oncology Group. *Pediatr Blood Cancer*. 2010 May;54(5):694-702.
- Patel NR, Rathi A, Mongayt D, Torchilin VP. Reversal of multidrug resistance by co-delivery of tariquidar (XR9576) and paclitaxel using long-circulating liposomes. *Int J Pharm*. 2011 Sep 15;416(1):296-9. Epub 2011 Jun 15.
- Peregud-Pogorzelski J, Tetera-Rudnicka E, Kurzawski M, Brodkiewicz A, Adrianowska N, Mlynarski W, Januszkiewicz D, Drozdziak M. Thiopurine S-methyltransferase (TPMT) polymorphisms in children with acute lymphoblastic leukemia, and the need for reduction or cessation of 6-mercaptopurine doses during maintenance therapy: the Polish multicenter analysis. *Pediatr Blood Cancer*. 2011 Oct;57(4):578-82. doi: 10.1002/pbc.23013.
- Pillai U, Muzaffar J, Sen S, & Yancey A. Grapefruit juice and verapamil: a toxic cocktail. *Southern Medical Journal*. 2009. 102, 3, pp. 308 - 309.
- Potschka H. Targeting regulation of ABC efflux transporters in brain diseases: a novel therapeutic approach. *Pharmacol Ther*. 2010 Jan;125(1):118-27. Epub 2009 Nov 5. Review.
- Reichel A. Addressing central nervous system (CNS) penetration in drug discovery: basics and implications of the evolving new concept. *Chem Biodivers*. 2009 Nov;6(11):2030-49. Review.
- Rettie AE, Jones JP. Clinical and toxicological relevance of CYP2C9: drug-drug interactions and pharmacogenetics. *Annu Rev Pharmacol Toxicol*. 2005;45:477-494.
- Richardson RM, Larson PS, Bankiewicz KS. Gene and cell delivery to the degenerated striatum: status of preclinical efforts in primate models. *Neurosurgery*. 2008 Oct;63(4):629-442; discussion 642-4. Review.
- Ritschel WA & Kearns GL: *Handbook of Basic Pharmacokinetics*, 5th edition. Washington, DC. APhA, 1999.
- Roden DM, & Stein CM. Clopidogrel and the concept of high-risk pharmacokinetics. *Circulation*. 2009. 119, pp. 2127 - 2130.
- Roy U, Chakravarty G, Honer Zu Bentrup K, Mondal D. Montelukast is a potent and durable inhibitor of multidrug resistance protein 2-mediated efflux of taxol and saquinavir. *Biol Pharm Bull*. 2009 Dec;32(12):2002-9.
- Sachidanandam R, Weissman D, Schmidt SC, et al. A map of human genome sequence variation containing 1.42 million single nucleotide polymorphisms. *Nature* 2001;409:928-33.
- Sai K, Kaniwa N, Itoda M, et al. Haplotype analysis of ABCB1/MDR1 blocks in a Japanese population reveals genotype-dependent renal clearance of irinotecan. *Pharmacogenetics*. 2003;13:741-757.
- Salphati, L.; Benet, L. Z. Effects of ketoconazole on digoxin absorption and disposition in rat *Pharmacology* 1998, 56, 308- 313
- Sausville EA, Burger AM. Contributions of human tumor xenografts to anticancer drug development. *Cancer Res*. 2006 Apr 1;66(7):3351-4, discussion 3354. Review.
- Savage DB. Mouse models of inherited lipodystrophy. *Dis Model Mech*. 2009 Nov-Dec;2(11-12):554-62. Review.
- Schaeffeler E, Eichelbaum M, Brinkmann U, et al. Frequency of C3435T polymorphism of MDR1 gene in African people. *Lancet* 2001;358:383-4.
- Schellens JH, Maliepaard M, Scheper RJ, et al. Transport of topoisomerase I inhibitors by the breast cancer resistance protein. Potential clinical implications. *Ann NY Acad Sci*. 2000;922:188-194.

- Schroeder MA, DiPersio JF. Mouse models of graft-versus-host disease: advances and limitations. *Dis Model Mech*. 2011 May;4(3):318-33. Review.
- Schroth W, Goetz MP, Hamann U, et al. Association between CYP2D6 polymorphisms and outcomes among women with early stage breast cancer treated with tamoxifen. *JAMA*. 2009;302:1429-1436.
- Schuetz JD, Connelly MC, Sun D, et al. MRP4: a previously unidentified factor in resistance to nucleoside-based antiviral drugs. *Nat Med* 1999;5:1048-51.
- Schwarz UI, Hanso H, Oertel R, Miehle S, Kuhlisch E, Glaeser H, Hitzl M, Dresser GK, Kim RB, Kirch W. Induction of intestinal P-glycoprotein by St John's wort reduces the oral bioavailability of talinolol. *Clin Pharmacol Ther*. 2007 May;81(5):669-78.
- Serwer LP, Noble CO, Michaud K, Drummond DC, Kirpotin DB, Ozawa T, Prados MD, Park JW, James CD. Investigation of intravenous delivery of nanoliposomal topotecan for activity against orthotopic glioblastoma xenografts. *Neuro Oncol*. 2011 Sep 27. [Epub ahead of print]
- Shen S, Zhang W. ABC transporters and drug efflux at the blood-brain barrier. *Rev Neurosci*. 2010;21(1):29-53. Review.
- Shitara Y, Sugiyama D, Kusuhara H, Kato Y, Abe T, Meier PJ, Itoh T, Sugiyama Y. Comparative inhibitory effects of different compounds on rat oatpl (slc21a1)- and Oatp2 (Slc21a5)-mediated transport *Pharm. Res*. 2002, 19, 147- 153
- Sim SC, Edwards RJ, Boobis AR, et al. CYP3A7 protein expression is high in a fraction of adult human livers and partially associated with the CYP3A7*1C allele. *Pharmacogenet Genomics* 2005; 15 (9): 625-31
- Simon J, van Spanning RJ, Richardson DJ. The organisation of proton motive and non-proton motive redox loops in prokaryotic respiratory systems. *Biochim Biophys Acta*. 2008 Dec;1777(12):1480-90.
- Soldin OP, & Mattison DR. Sex differences in pharmacokinetics and pharmacodynamics. *Clinical Pharmacokinetics*. 2009. 48, 3, pp. 143 - 157.
- Song IS, Shin HJ, Shim EJ, et al. Genetic variants of the organic cation transporter 2 influence the disposition of metformin. *Clin Pharmacol Ther*. 2008;84:559-562.
- Song S, Suzuki H, Kawai R, Sugiyama Y. Effect of PSC 833, a P-glycoprotein modulator, on the disposition of vincristine and digoxin in rats *Drug Metab. Dispos*. 1999, 27, 689- 694
- Srinivas SP. Cell signaling in regulation of the barrier integrity of the corneal endothelium. *Exp Eye Res*. 2011 Sep 24. [Epub ahead of print].
- Staatz CE, Goodman LK, & Tett SE. Effect of CYP31 and ABCB1 single nucleotide polymorphisms on the pharmacokinetics and pharmacodynamics of calcineurin inhibitors: Part I. *Clinical Pharmacokinetics*, 2010. 49, 3, pp. 141 -171.(a)
- Staatz CE, Goodman LK, Tett SE. Effect of CYP3A and ABCB1 single nucleotide polymorphisms on the pharmacokinetics and pharmacodynamics of calcineurin inhibitors: Part II. *Clin Pharmacokinet* 2010;49 (4): 207-21. (b)
- Sugano K, Kansy M, Artursson P, Avdeef A, Bendels S, Di L, Ecker GF, Faller B, Fischer H, Gerebtzoff G, Lennernaes H, Senner F. Coexistence of passive and carrier-mediated processes in drug transport. *Nat Rev Drug Discov*. 2010 Aug;9(8):597-614. Review.
- Tamura A, Wakabayashi K, Onishi Y, et al. Re-evaluation and functional classification of non-synonymous single nucleotide polymorphisms of the human ATP-binding cassette transporter ABCG2. *Cancer Sci*. 2007;98:231-239.(a)
- Tamura A, Watanabe M, Saito H, et al. Functional validation of the genetic polymorphisms of human ATP-binding cassette (ABC) transporter ABCG2: identification of alleles that are defective in porphyrin transport. *Mol Pharmacol*. 2006;70:287-296.(b)

- Tanabe M, Ieiri I, Nagata N, et al. Expression of P-glycoprotein in human placenta: relation to genetic polymorphism of the multidrug resistance (MDR)-1 gene. *J Pharmacol Exp Ther* 2001; 297 (3): 1137-43
- Tarbell JM. Shear stress and the endothelial transport barrier. *Cardiovasc Res.* 2010 Jul 15;87(2):320-30. Epub 2010 Jun 12. Review.
- Tassaneeyakul W, Veronese ME, Birkett DJ, Doecke CJ, McManus ME, Sansom LN, Miners JO. Co-regulation of phenytoin and tolbutamide metabolism in humans. *Br J Clin Pharmacol.* 1992 Dec;34(6):494-8.
- Thervet E, Anglicheau D, Legendre C, et al. Role of pharmacogenetics of immunosuppressive drugs in organ transplantation. *Ther Drug Monit* 2008;30 (2): 143-50
- Thwaites DT, Anderson CM. The SLC36 family of proton-coupled amino acid transporters and their potential role in drug transport. *Br J Pharmacol.* 2011 Apr 18. doi: 10.1111/j.1476-5381.2011.01438.x. [Epub ahead of print]
- Tirona RG, Leake BF, Merino G, et al. Polymorphisms in OATP-C: identification of multiple allelic variants associated with altered transport activity among European- and African-Americans. *J Biol Chem.*2001;276:35669–35675.
- Tiwari AK, Sodani K, Dai CL, Ashby CR Jr, Chen ZS. Revisiting the ABCs of multidrug resistance in cancer chemotherapy. *Curr Pharm Biotechnol.* 2011 Apr;12(4):570-94. Review.
- Tóth A, Veszelka S, Nakagawa S, Niwa M, Deli MA. Patented in vitro blood-brain barrier models in CNS drug discovery. *Recent Pat CNS Drug Discov.* 2011 May 1;6(2):107-18. Review.
- Townsend DM, Findlay VL, Tew KD. Glutathione S-transferases as regulators of kinase pathways and anticancer drug targets. *Methods Enzymol.* 2005;401:287-307.Review.
- Umar A, Della'Zanna G, Lubet R. Further thoughts on preclinical animal models for cancer prevention: when is it best to start treatment? What are potential histopathologic endpoints? *Semin Oncol.* 2010 Aug;37(4):339-44. Review.
- US National Center for Biotechnology Information. Single nucleotide polymorphism [online]. Available from: www.ncbi.nlm.nih.gov/SNP/GeneGt.cgi?geneID=5243 [Accessed 2009 Feb 23]
- van der Deen, M., de Vries, EGE., Timens, W., Scheper, RJ., Timmer-Bosscha, H., & Postma, DS. (2005). ATP-binding cassette (ABC) transporters in normal and pathological lung. *Respiratory Research*, 6, 1, pp. 59 - 75.
- van Erp NP, Baker SD, Zhao M, et al. Effect of milk thistle (*Silybum marianum*) on the pharmacokinetics of irinotecan. *Clin Cancer Res.* 2005;11:7800–7806.
- van Waterschoot RA, Schinkel AH. A critical analysis of the interplay between cytochrome P450 3A and P-glycoprotein: recent insights from knockout and transgenic mice. *Pharmacol Rev.* 2011 Jun;63(2):390-410. Epub 2011 Apr 13. Review.
- Varghese Gupta S, Gupta D, Sun J, Dahan A, Tsume Y, Hilfinger J, Lee KD, Amidon GL. Enhancing the Intestinal Membrane Permeability of Zanamivir: A Carrier Mediated Prodrug Approach. *Mol Pharm.* 2011 Sep 22. [Epub ahead of print]
- Verbeeck RK, Musuamba FT. Pharmacokinetics and dosage adjustment in patients with renal dysfunction. *Eur J Clin Pharmacol.* 2009 Aug;65(8):757-73. Epub 2009 Jun 20. Review.
- Visentin M, Chang MH, Romero MF, Zhao R, Goldman ID. Substrate- and pH-specific antifolate transport mediated by OATP2B1-SLCO2B1. *Mol Pharmacol.* 2011 Oct 21. [Epub ahead of print]
- Volm M, Mattern J, & Samsel B. Overexpression of P-glycoprotein and glutathione S-transferase-pi in resistant non-small cell lung carcinomas of smokers. *British Journal of Cancer.*1991. 64, 700 - 704.

- Wacher VJ, Wu CY, Benet LZ. Overlapping substrate specificities and tissue distribution of cytochrome P450 3A and P-glycoprotein: implications for drug delivery and activity in cancer chemotherapy. *Mol Carcinog.* 1995;13:129-134.
- Walker K, Ginsberg G, Hattis D, Johns DO, Guyton KZ, Sonawane B. Genetic polymorphism in N-Acetyltransferase (NAT): Population distribution of NAT1 and NAT2 activity. *J Toxicol Environ Health B Crit Rev.* 2009;12(5-6):440-72. Review.
- Wang D, Johnson AD, Papp AC, et al. Multidrug resistance polypeptide 1 (MDR1, ABCB1) variant 3435C>T affects mRNA stability. *Pharmacogenet Genomics* 2005; 15 (10): 693-704
- Wang J, Sonnerborg A, Rane A, et al. Identification of a novel specific CYP2B6 allele in Africans causing impaired metabolism of the HIV drug efavirenz. *Pharmacogenet Genomics.* 2006;16:191-198.
- Watanabe, T.; Maeda, K.; Kondo, T.; Nakayama, H.; Horita, S.; Kusuhara, H.; Sugiyama, Y. Prediction of the hepatic and renal clearance of transporter substrates in rats using in vitro uptake experiments *Drug Metab. Dispos.* 2009, 37, 1471- 1479
- Wee B, Charles N, Holland EC. Animal models to study cancer-initiating cells from glioblastoma. *Front Biosci.* 2011 Jun 1;17:2243-58. Review.
- Wikinski, S. Pharmacokinetic mechanisms underlying resistance in psychopharmacological treatment. The role of P-glycoprotein. *Vertex.* 2005. 16, 64, pp. 438 - 441.
- Wilhelm I, Fazakas C, Krizbai IA. In vitro models of the blood-brain barrier. *Acta Neurobiol Exp (Wars).* 2011;71(1):113-28. Review.
- Wojnowski L, Kulle B, Schirmer M, et al. NAD(P)H oxidase and multidrug resistance protein genetic polymorphisms are associated with doxorubicin-induced cardiotoxicity. *Circulation.* 2005;112:3754-3762.
- Wong J, Brugger A, Khare A, Chaubal M, Papadopoulos P, Rabinow B, Kipp J, Ning J. Suspensions for intravenous (IV) injection: a review of development, preclinical and clinical aspects. *Adv Drug Deliv Rev.* 2008 May 22;60(8):939-54. Epub 2008 Feb 7. Review.
- Xiangdong L, Yuanwu L, Hua Z, Liming R, Qiuyan L, Ning L. Animal models for the atherosclerosis research: a review. *Protein Cell.* 2011 Mar;2(3):189-201. Epub 2011 Apr 6. Review.
- Xie HG, Kim RB, Wood AJ, et al. Molecular basis of ethnic differences in drug disposition and response. *Annu Rev Pharmacol Toxicol.* 2001;41:815-850.
- Xu G, Bhatnagar V, Wen G, et al. Analyses of coding region polymorphisms in apical and basolateral human organic anion transporter (OAT) genes [OAT1 (NKT), OAT2, OAT3, OAT4, URAT (RST)]. *Kidney Int.* 2005;68:1491-1499.
- Yates CR, Krynetski EY, Loennechen T, et al. Molecular diagnosis of thiopurine S-methyltransferase deficiency: genetic basis for azathioprine and mercaptopurine intolerance. *Ann Intern Med* 1997;126:608-14.
- Zaragoza C, Gomez-Guerrero C, Martin-Ventura JL, Blanco-Colio L, Lavin B, Mallavia B, Tarin C, Mas S, Ortiz A, Egido J. Animal models of cardiovascular diseases. *J Biomed Biotechnol.* 2011;2011:497841. Epub 2011 Feb 16. Review.
- Zhang HX, Huang Y, Frassetto LA, Benet LZ. Elucidating rifampin's inducing and inhibiting effects on glyburide pharmacokinetics and blood glucose in healthy volunteers: unmasking the differential effects of enzyme induction and transporter inhibition for a drug and its primary metabolite *Clin. Pharmacol. Ther.* 2009, 85, 78- 85.
- Zhang W, Han Y, Lim SL, & Lim LY. Dietary regulation of P-gp function and expression. *Expert Opinion in Drug Metabolism and Toxicology.* 2009. 5, 7, pp. 789 - 801.



Readings in Advanced Pharmacokinetics - Theory, Methods and Applications

Edited by Dr. Ayman Noreddin

ISBN 978-953-51-0533-6

Hard cover, 378 pages

Publisher InTech

Published online 20, April, 2012

Published in print edition April, 2012

This book, "Readings in Advanced Pharmacokinetics - Theory, Methods and Applications", covers up to date information and practical topics related to the study of drug pharmacokinetics in humans and in animals. The book is designed to offer scientists, clinicians and researchers a choice to logically build their knowledge in pharmacokinetics from basic concepts to advanced applications. This book is organized into two sections. The first section discusses advanced theories that include a wide range of topics; from bioequivalence studies, pharmacogenomics in relation to pharmacokinetics, computer based simulation concepts to drug interactions of herbal medicines and veterinary pharmacokinetics. The second section advances theory to practice offering several examples of methods and applications in advanced pharmacokinetics.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Debasis Mondal, Samantha L. Gerlach, Amrita Datta, Geetika Chakravarty and Asim B. Abdel-Mageed (2012). Pharmacogenomics Dictate Pharmacokinetics: Polymorphisms in Drug-Metabolizing Enzymes and Drug-Transporters, Readings in Advanced Pharmacokinetics - Theory, Methods and Applications, Dr. Ayman Noreddin (Ed.), ISBN: 978-953-51-0533-6, InTech, Available from: <http://www.intechopen.com/books/readings-in-advanced-pharmacokinetics-theory-methods-and-applications/pharmacogenomics-dictate-pharmacokinetics-polymorphisms-in-drug-metabolizing-enzymes-and-drug-transp>

INTECH

open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.