Chapter 5

CONCLUSION
Variable response to the drugs by the patients is of a major concern in the cure rates of various diseases. The variability of a drug response can lead to therapeutic failure or adverse effects of drugs in individuals or subpopulations of patients. Inter-individual variability in drug response can be attributed to genetic polymorphism in genes encoding different drug-metabolizing enzymes (DMEs), drug transporters and enzymes involved in DNA biosynthesis and repair. Mutation in a gene coding for a drug-metabolizing enzyme can cause enzyme variants with high, low or no activity. As a result of inter-individual variation patients develop adverse drug reactions; patients do not respond to drug at the given dose or respond positively to the drug administered in same dose. Unfortunately, prospective identification of those patients who are most likely to benefit from a specific therapy is not routinely possible for many diseases and medications. Thus Physicians have to optimize a dosage regimen for an individual patient by a trial-and-error method. This blind approach can lead to adverse drug reactions in some patients and in turn affects drug efficacy. Pharmacogenetics can help in assessing drug response by determining an individual’s risk of developing an adverse drug reaction, predicting pharmacological variability and thereby preventing adverse drug reactions. Genetic polymorphisms explain why a small proportion of the population may be at higher risk of drug inefficacy or toxicity.

The study was conducted with the aim to investigate the genetic polymorphisms in Indian population and effect of these polymorphisms on drug response (efficacy and toxicity) in diseased population. The study was executed by exploring genetic polymorphism in DME with special reference to Phase 1 enzymes (CYP2C19 and CYP2C9) in Maharashtrian population. These polymorphisms were short listed because of their ever increasing pharmacogenetic relevance and at the same time not much data is available on these polymorphisms in Maharashtrian population. The present study evaluated the allelic and genotype pattern of CYP2C19 and CYP2C9 in healthy Maharashtrian subjects. Meta-analysis was carried out to compare the allele and genotype frequencies with other Indian populations and populations from other continents. Our findings confirm the existence of interethnic differences in CYP2C19 allele and genotype frequencies and CYP2C9*2 mutant allele. Significant heterogeneity in frequencies of CYP2C19 alleles and genotypes were also seen within Indian subpopulations but not for CYP2C9. 19.4% of our study population possesses the poor metabolizer genotype makes it essential to evaluate the effect of various CYP2C19 substrates in Maharashtrians. Further studies are required to assess the clinical significance of those differences for treatment outcome and optimal
dosage of drugs metabolized by these polymorphic enzymes. It is of potential clinical importance to be able to identify individuals who have altered pharmacokinetics for CYP2C19/CYP2C9 substrates so that appropriate dosage strategies for these drugs can be adopted, and adverse drug reactions can be avoided.

This thesis work tried to unravel a newer concept of Ayugenomics: traditional medicine to modern pharmacogenomics. The field of pharmacogenomics and the concept of “Personalized Medicine” are new to the field of modern medical science. However, there is a long-standing tradition regarding this concept of “personalized medicine” in the Ayurveda (Indian Traditional System of Medicine). In this work we have attempted to find out whether Ayurveda Prakriti type and CYP2C19 gene polymorphism associated with the metabolic variability. Our results demonstrate a probable genomic basis for metabolic differences attributed by Prakriti in humans. Thus, the integration of Prakriti concept of Ayurveda with genomics nomenclatured as Ayugenomics is worth exploring to unravel many challenges in genomics, therapeutics and personalized medicine.

To examine the effect of genetic polymorphisms on drug response in diseased population; we have considered RA as an example of a complex, chronic disease phenotype. MTX was selected for the present study because of its wide utility as DMARD, low cost and experience in its use. The major drawbacks of MTX therapy are the large interpatient variability in clinical response and the unpredictable appearance of a large spectrum of side-effects. This significant variability in MTX response, together with the presence of effective, but expensive, alternative therapies, has led to approaches to identify predictive markers for drug response (efficacy and toxicity) prior to the initiation of MTX therapy. There are no useful and reliable clinical or molecular markers of response to therapy available to date. Hence pharmacogenetic testing may help to optimize the therapy. To the best of our knowledge, this is the first report on pharmacogenetics of MTX in Indians (Asian) RA patients covering 12 polymorphisms along with pharmacokinetics studies. Thus our findings revealed no association of any of the studied SNPs in 9 genes of folate-MTX metabolic pathway and MTX efficacy. Pharmacokinetic studies do show some trends and associations with genetic polymorphisms, ADR but need to be further validated. Our observations propose that a toxicogenetic index can provide a means of profiling patients who develop side effects to MTX and may be useful in establishing the likelihood of occurrence of side effects to MTX and may therefore help in reducing drug monitoring cost in turn maximizing the benefit-risk ratio of the drug. However,
prospective studies with large no of patients will be necessary to reveal the predictive value of this pharmacogenomic biomarker.