CONCLUSION
CONCLUSION AND FUTURE SCOPE

Pharmacogenomics is the science dealing with the concept of personalized medicine. This line of genomics is extremely important in life saving therapies such as in cancer. Many fatalities and chemotherapy failure can be prevented by application of pharmacogenomics. The science of pharmacogenomics is very vast as multiple factors can influence the outcome of any therapy. These include the transport channels, drug metabolizing enzymes and various other associated factors.

Our study aimed at documenting the frequency of major slow metabolizer alleles for DMEs which are majorly involved in metabolism of pyrimidine analogues 5-FU and gemcitabine in healthy adult Indian population. For the DPD enzyme involved in metabolism of 5-FU, the frequency of the exon 14 skipping mutation was detected to be just 0.004 and hence can be concluded to be a mutation in the adult Indian population. No variant allele for the CDA*3 haplotype was detected in our study. Although the frequency of drug associated toxicity for 5-FU and gemcitabine therapy in the India population is ~10% (grade 2-3), the IVS14+1G>A in DPYD and the 208G>A in CDA may not be a responsible factor in Indians. Hence, gene sequencing analysis of both CDA and DPYD was performed.

For the DPYD gene, two slow metabolizer alleles were detected, viz. the 2194G>A and 2656C>T at frequency of 0.13 and 0.01, respectively. Six novel variations were documented for the first time in the adult Indian population. The intronic variation 234-123G>C associated with border line toxicity was detected at frequency of 0.01 in our study. The global frequencies for these slow metabolizer variations are much lower as compared to the Indian population suggesting these to be candidate SNPs for drug associated toxicity in the Indian population.

In case of the CDA gene, the 79A>C variation was detected at a frequency of 0.14. Conflicting results exist with respect to the effect of the CDA*2 haplotype on the CDA enzyme activity. Different population studies have recorded different results. However, a recent study by Abraham et al. (2012) has demonstrated the significance of the 79A>C variations associated with Ara-C toxicity in the Indian population.
Conclusion and future scope

Since the frequency of this variant was detected to be very high at 0.14 in our study, considering this SNP as a biomarker for determining efficiency of treatment with gemcitabine or Ara-C is very important. Another candidate gene which is being studied worldwide as an influencing factor for determining outcome of therapy with gemcitabine is dCK. Variations in nucleoside transporter have also been documented to be responsible for pharmacogenetics of gemcitabine.

Further in-depth analysis needs to be done in patients treated with gemcitabine and 5-FU who experienced severe toxicity on therapy to determine the exact causative factor. Since novel variations have been detected both in *DPYD* and *CDA*, their exact effect on the enzyme activity can be determined. Large scale case-control studies can be carried out to phenotypically determine the level of DPD and CDA enzymes to determine the average level of enzyme for the Indian population.

In case of *NAT2*, the frequencies of slow acetylators have been detected to be very high. Numerous case-control studies have already been done in the Indian population to detect the association between susceptibility to different solid tumours and different haplotypes of *NAT2*. TB is endemic in India, and treatment with INH is widely done in our country. Hence assessing *NAT2* acetylator status prior to treatment is very important and the need of the hour in India.