7. SUMMARY AND CONCLUSION

Gastric cancer has a moderate prevalence in India compared with other Asian countries like China and Japan, but the mortality rate of this disease is comparatively higher in almost all countries. The etiological discrepancies and clinical manifestations make this disease quite different from other type of cancers. In general, carcinogenesis is through various genomic events including somatic mutations, epigenetic alterations and post-transcriptional regulations. These changes could either inactivate tumor suppressors or activate oncogenes. These changes could facilitate inhibition of tumor suppression rather than activation of oncogenes by classical somatic mutation model of cancer. Hence, it is essential to identify these changes for better understanding the development of gastric carcinogenesis.

Long non-coding RNAs are transcripts that lack protein coding abilities. These class of non-coding RNAs are major constituents of the highly evolved genomes including human and found to be associated with various biological processes involved in normal development and cancer. The biological role of IncRNAs is diverse where the majority of the IncRNAs can interact with DNA, RNA and proteins and are associated with maintenance of genome integrity and chromatin modifications. Apart from these functions, IncRNAs have been found to be serving as miRNA sponges which might influence the translation of by allowing the escape of mRNA targets from miRNA mediated regulation. IncRNAs able to sponge miRNAs are known as competing endogenous RNAs (ceRNA).These CeRNAs harbour microRNA response elements which can attract and sponge the miRNAs and leave their downstream target mRNA free from post-transcriptional regulation.

This research study was designed to identify a few IncRNAs that could acts as ceRNAs in gastric cancer and also to find out the interactive network among them. This study used thirty five gastric cancer samples with matching normal tissues for the expression profiling of IncRNAs, miRNAs and mRNAs by Taqman probe based relative quantitation methods. The expression levels of these different RNA species showed a remarkable interaction when they were analysed with statistical and bio-informatic tools. Further the integrated analysis of IncRNA, mRNA and common targeting miRNAs yielded a specific ceRNA network which suggested that
IncRNAs namely H19, Linc-RoR, GAS5, PTENP1, TUG1 and MALAT1 could potentially act as competing endogenous RNAs that can sponge and regulate the biological role of has-miR-145, has-miR-148a and has-miR-21. This interactions were further evaluated by analysing the expression level of KLF4, DNMT1, EGFR and AGO4.

The IncRNAs identified in this study are involved in many critical events like genomic imprinting, stemness and reprogramming, growth arrest, proliferation, tumor suppression, and invasion. In addition to that, higher level of miR-145, miR-21 and low level of miR-148a was observed in the study samples. The downregulation of miR-148a could be advantageous to gastric cancer development since it is a well-established tumor suppressor that regulate H19 and DNMT1. The genes evaluated in the study are basically involved in many key processes like transcriptional activation, DNA methylation, cell-cell communication, RNA processing.

The IncRNA members of the ceRNA network identified in the study are found to be active partners of P53 mediated transcriptional regulatory network. Classically it is well established that p53 mutations are less frequent in Indian cancers. In this study, it observed that there was H19 upregulation which could be connected with p53 inactivation. This strongly suggests upregulated H19 may play a critical role in Indian gastric cancer patients. Also, the identified ceRNA network is organised with handful of IncRNAs which can participate in other cellular events hence they can be used as prognostic and diagnostic markers for gastric cancer patients of Indian origin. Identification of other important IncRNA players could lead to understand the molecular complexity of gastric cancer and better management of the disease.