CHAPTER-2

Aims

&

Objectives
2.0. Aims and Objectives

2.1. Issues, Problems and Goals:

Carcinoma of cervix remains one of the greatest killers of women worldwide with approximately 529,000 new cases and more than 275,000 deaths occurring each year, out of which 134,000 new cases and 72,000 deaths are reported from India alone in 2008, making it one of the leading cancers of women in many developing countries (http://globocan.iarc.fr/factsheets/cancers/cervix/). One out of six cancer cases among women in the world is a gynecological cancer. It is the third most common cancer among women worldwide and it should not be forgotten number that it is number one cancer in the developing part of the world, with bare minimal resources to cope up with the problem. Four out of five new cases, and a similar proportion of deaths, occur in developing countries where screening programs are not well established or effective. Moreover, the global incidence of cervical cancer is on rise. Further, it is predicted that where the total annual incidence in 2002 was 493,000 cases, by the year 2020 it will become 702,500. This amounts to a 42% increase, compared to 2002. In less developed countries, there will be a 56% increase, compared to an 11% increase in more developed countries (Parkin, Bray et al. 2005; Parkin and Bray 2006).

Theoretically this major killer is preventable, owing to its long pre-invasive stage, accessibility of uterine cervix for examination by various noninvasive tests, feasibility to collect exfoliated cytology samples and also the availability of effective treatments for the premalignant phase of the disease. Although the current screening methodology (exfoliated cytology) has helped to reduce the cervical cancer incidence worldwide, cases of cervical cancer continued to occur, may be attributed to a number of reasons like low sensitivity and specificity, errors in sampling and interpretation and socio-economic issues. While cytological screening has substantially reduced cervical cancer incidence and mortality where ever it has been successfully implemented, it is limited by low single-test sensitivity and poor reproducibility for equivocal and minor abnormalities. Despite the recently introduced preventive vaccines against HPV16 and HPV18, screening needs to continue, since only about 70% of cervical cancers will be prevented. However, HPV vaccination will further reduce the efficiency of cytological screening. Therefore, new screening modalities need to be evaluated and pursued. Hence there is a need to develop
alternative strategies of high sensitivity and specificity for screening of cervical cancer in addition to finding efficient therapeutic regimes.

Therefore it is important now that we should develop better understanding about this carcinogenesis at a molecular level and translate this knowledge to develop better screening, diagnostic and therapeutic tools. Current experimental evidences have shown that both genetic and epigenetic alterations are expected to occur during all stages of cancer progression and can provide vital information on cancer progression. It has been proposed that changes in the DNA methylation status are among the most common epigenetic alterations in the development of many cancers. DNA methylation studies offer a number of advantages for studying gene expression. First, the methylation pattern in a DNA molecule is relatively stable, in contrast to RNA transcripts. Second, methylation measurements can be made with absolute reference points. Finally, changes in methylation patterns may be both qualitative and quantitative, leading to assays with high specificity and sensitivity. In addition, such assays are more general than those for individual mutations and are localized to promoter regions in contrast to mutations that can spread out in the gene. Thus methylation level determinations offer myriad oncology-related clinical applications as changes in the regulation of DNA methylation are an early signal in tumor development.

Determining the methylation levels in DNA of cells in body fluids/exfoliated cytology offers the possibility of obtaining information on gene expression through non-invasive sampling, making them valuable in population screening where the clinical follow-up of false-positives can be costly and invasive. In population screening, methylation markers can be used as a supplemental tool in risk assessment or disease detection. Such markers can enhance the specificity of existing screening methods. Identification of numerous epigenetic alterations in cervical cancer during neoplastic transformation offers new possibilities of diagnosis and treatment. Since changes in DNA methylation occur very early during the etiology of carcinogenesis, it could be used as marker for early identification of cervical cancer. Subsequently on understanding the mechanism, these could be used as targets for therapy. Thus identification of a set of genes hyper- and hypo- methylated could offer novel means of screening the (pre) neoplastic cervical cancer lesions.
The activation of oncogenes, proto-oncogenes, and transposable elements and the inactivation of tumor suppressor genes is one of the main events leading to the development and progression of all common forms of human cancer. Cancer is a multifactorial disease wherein hundreds to thousands of genes are altered simultaneously. Therefore it is important to use sensitive and high resolution genome wide technique such as microarray for screening large scale genomic alterations followed by their validation using gene specific approaches. Current experimental evidences suggest that DNA methylation patterns are likely to gain increasing importance in the management of cancer patients in the near future. This study is aimed at identifying genes which have altered methylation pattern by genome wide search using high throughput techniques like microarray followed by their validation in clinical samples to identify markers of diagnostic and prognostic significance using robust and sensitive techniques.

2.2. The Objectives of the Present Proposal:

1. Identification of epigenetically modified genes which are critical for cellular processes and that may play a role in altered cellular function in cervical cancer
2. Evaluation of their methylation pattern in normal and cervical cancer and identify nucleic acid sequences regulated by methylation
3. Establishment of their relevance using a rapid and sensitive validation technology
4. Correlate the findings by testing a panel of cervical cancer samples
5. Epigenetic therapy using inhibitory drugs

The study is expected to identify group of novel genes with abnormal methylation pattern which is of clinical significance.