Lung cancer is the leading cause of cancer related deaths worldwide. 28% of total cancer deaths are occurring due to lung cancer. About 80–90% case of human lung cancers are attributed to cigarette smoking (Risch & Plass, 2008; Meuwissen & Berns, 2005). Remaining 10-20% incidences are due to environmental or other factors. Lung cancer generation in smokers may occur due to the persistence of the multiple genetic lesions over the years (Meuwissen & Berns, 2005). Mostly the lung cancer patients are smokers, but lung cancer develops only in a minority of smokers, therefore, it is suggested that genetic, epigenetic or environmental factors are also involved in lung cancer initiation and progression (Peto et. al, 2000; Mattson et. al, 1987). Genetic or epigenetic variation, differences in carcinogen metabolism of an individual may play an essential role in the development of this environmental cancer (Schwartz et al, 2007). Major concern with lung cancer is the late diagnosis with only 7% survival rate. Only 13% of lung cancer patients survive more than 5 years (Risch & Plass, 2008).

Lung cancer lethality pertains to its late diagnosis, low clinical response or development of multiple drug resistance. However, the reasons behind it are not fully understood but may attributed to lack of non invasive detection procedures, new markers and new interventions to deal with lung cancer (Incoronato et al, 2011).

New developments in the field of early detection, prognosis and chemoprevention are needed to diagnose, and cure the cancer and/or to give better survival to a cancer patient (Herbst et al., 2008). The understanding of the complex nature of cancer genesis and the study of early molecular events of tumor development in experimental system can change the scenario of cancer prevention and control (Herbst et al., 2008; & Plass, 2008). Periodic studies of lung cancer development may be of use in elucidating the alteration in molecular pathways involved in tumor development. These pathways may serve as molecular markers or targets for cancer prevention and control.

Lung tumorigenesis and pathogenesis involved various genetic and epigenetic pathways which show a clear difference between smokers and nonsmokers (Brambilla & Gazdar, 2009). Epigenetic changes and inflammation have been shown as the earliest changes in
lung tumorigenesis. It has been shown that histologically normal and pre-neoplastic cells in smoker lung have a number of genetic and epigenetic abnormalities. This phenomenon suggests a sequential development of lung tumor from normal epithelial cells involving a multistep process in different areas of the lung (Brambilla & Gazdar, 2009; Meuwissen & Berns, 2005; Wistuba et al., 2000).

Advances in the understanding of development of lung cancer biology may prove to be helpful in customizing therapy or diagnosis by search of newer targets including specific genes and pathways. The pathways and genes which have potential impact on lung cancer development or have been investigated extensively are growth suppressive pathways (p53/Retinoblastoma/P14ARF, Serine/Threonine kinase11), growth promoting pathways (Epidermal Growth Factor Receptor/ Ras/ Phosphatidylinositol 3-Kinase), inflammatory pathways (NF-κB, Interleukine 6 (IL6), Signal transducer and activator of transcription (STAT3) etc.) apoptotic pathways (Bcl-2/Bax/Fas/FasL), DNA repair (O6-methylguanine DNA methyltransferase (MGMT), Mut L homolog 1 (MLH1) etc.), immortalization genes and epigenetic changes or gene silencing pathways (DNA methyl transferase (DNMT), Histone deacetylas (HDAC), histone methyltransferase (HMT), polycomb group proteins etc.) (Brambilla & Gazdar, 2009).

Epigenetic changes which include DNA methylation and histone modifications are important in determining cell fate and development through the regulation of gene expression. But deregulation in epigenetic change has serious consequences including development of cancer (Cavalli, 2006). Almost every type of human cancer including lung cancer have some or other epigenetic defects in terms of genomic DNA hypomethylation, promoter hyper methylation, histone modification or altered expression of epigenetic mediators (Esteller, 2008). Modification in chromatin structures and the specific gene expression by epigenetic changes could transform a cell that can develop in lung cancer. In human lung cancer, promoter DNA hypermethylation is involved in the silencing of various tumor suppressor genes (TSGs). The best studied example is the case of the cell division kinase inhibitor p16\textsuperscript{INK4a} (CDKN2A). The genes which are involved in a broad range of biological processes, their promoter DNA hypermethylation and transcriptional
silencing appears as a key event in lung carcinogenesis. The important role of hypermethylation can be envisaged in the work of Brena et al. 2007, as they have suggested near about 395 restrictions landmark genomic scanning (RLGS) fragments were hypermethylated in lung tumors. DNA methyltransferase DNMT1, DNMT3A and DNMT3B over expression has been reported in non small cell lung carcinoma (NSCLC) among smoker patients, and correlates with hypermethylation of tumor suppressor gene (Broeck et al., 2009). On the other hand involvement of global DNA hypomethylation in the progression of lung tumors has been proved in the normal part of the lung from cancer patient as compared to a normal individual (Anisowicz et al., 2008).

Modification of histone and DNA methylation pathways are interlinked. Histone modification adds up in the TSG silencing or oncogenes expression of by compacting or relaxing the chromatin structure (Kondo et al., 2002). Histone deacetylases, histone methyltransferase, histone acetyl transferases are histone modification enzymes. These enzymes recruited on methylated DNA bring about the addition or removal of acetyl or methyl groups on histone tail. Moreover, these modifiers have also shown to recruit DNMTs and facilitate DNA methylation. Predictive, prognostic and therapeutic values of DNA methylation, histone modification and their player enzymes have been reported in various human and experimental cancers. Various epigenetic therapies of cancer are under use or in clinical trial for treatment of cancer (Gronbeak et al., 2007; Roloff et al., 2003; Jones et al., 1998; Nan, 1997). Identifying molecular links between epigenetic changes and lung cancer may have important implications for defining individual lung cancer risk and tailoring chemoprevention therapies.

Cancer chemoprevention with natural products is an alternative approach, among existing therapies, which has potential to reduce or prevent the cancer incidences in a safe and non toxic way. Some examples of natural products are Indol-3-Carbinol, curcumin, epigallocatechin gallate, N-Acetyl-cysteine, Retinoids, salts of glucaric acid and vitamins like niacinamide (Berghe, 2012; Gerhauser, 2013; Hursting et al, 1999; Kelloff et al, 2000). A significant anticancer activity of the naturally occurring carbohydrate inositol hexaphosphate (IP6) has been reported in different tumor models. IP6 has been shown to
possess anti-angiogenic, anti-inflammatory and strong anti-oxidant property. However, the mode of action of chemopreventive potential of IP6 is not much understood (Raina et al., 2008; Vucenik et al., 2004; Gupta et al., 2003).

To understand molecular link of cancer development and their prevention an experimental system is inevitable. Animal model has been proved to be excellent for the purpose. Modeling mouse for understanding human diseases has been extensively used in the area of carcinogenesis and toxicology. Mice develop lung tumors with similar histogenic and molecular features to human adenocarcinoma, providing an excellent model for elucidating events that influence tumor development (Dutt & Wong, 2006, Meuwissen & Berns, 2005). Urethane present in fermented and roasted food and tobacco smoke has been extensively used to develop mouse lung tumors. Metabolites of urethane cause lung tumorigenesis. Tumors developed by urethane have similarity with human lung tumors in respect of mutational other genetic events (Stathopoulos et al. 2007).

There are various reports about the epigenetic modulation in tumors or in advanced cancer but how epigenetic scenario modulates during the development of lung tumor is not well known. Hence, by studying epigenetics of tumor development in experimental system we can evaluate their potential as a marker of detection, prognosis, and chemoprevention and target epigenetic events for therapeutic and prognostic use. This study is aimed to find out how epigenetic events are involved in the urethane induced mouse lung tumor development with respect to time and duration and their response to anticancer agents IP6. To accomplish the aim of this study following approved objectives were envisaged in the PhD thesis
Approved Experimental Objectives

i. To evaluate the alterations in epigenetics with respect to time and duration of lung tumor development by urethane.

ii. To study the expression of genes involved in methylation of DNA, transcription repression, repair, proliferation and inflammation during the development of urethane induced mouse lung tumor.

iii. To evaluate the chemopreventive potential of inositol hexaphosphate (IP6) and its effect on epigenetics in mouse lung tumor development.