Breast cancer is the most frequent cancer in women and represents the second leading cause of cancer death among women after lung cancer. The biology of breast carcinoma is complex, with myriads of factors including steroid hormones and their receptors, peptide growth factors, oncogenes and tumor suppressor genes may play crucial role in its development and progression. Hence, the quest is to develop new ways to exploit the knowledge obtained by delineation of the pathways through which these genes or factors act and the basis of their varying actions in specific cell types for the benefit of cancer patients.

The tumor suppressor gene p53 is found to be altered in approximately 20-40% of all breast cancer cases depending on tumor size and stage of disease. The p53 gene is a complex gene at the centre of cellular pathways with multiple interactions involved in the responses to the cell damaging agents like radiotherapy and chemotherapy. Through regulation of cell growth and division, gene transcription, DNA repair and genomic stability, p53 behaves as a “guardian of the genome”. Aberrations of p53, including alterations in the upstream and downstream pathways (e.g. MDM-2, p21 and Bax), mutation, and modifications of protein expression and activation makes p53 a key target for anticancer therapy. The precise clinical importance of p53 in human breast cancer as a diagnostic marker, predictor of disease response or poor prognostic factor is still controversial. However, therapeutic strategies to bolster the function of normal p53 or substitute for its function where p53 is mutant are yielding in vitro, in vivo and clinical advances. Substantial progress in our understanding for breast carcinoma has been achieved while there remains much still to be understood and developed into clinically useful strategies with respect to p53 in breast cancer. Mutations in the p53 gene are the most frequent genetic lesions in breast cancer, suggesting a critical role of p53 in breast cancer development, growth and chemosensitivity. Delineation of the role that p53 may play in cell cycle and anticancer chemo sensitization, has been hampered by the lack of appropriate model. Hence, there is a continuing need for genetically matched cell systems that only differ in p53 protein status to model cellular behaviors that are frequently observed in cancers in relation to both growth and...
anticancer drug responses. This thesis deals with the development and characterization of MCF-7As53 cell line derived from breast carcinoma MCF-7 cells as an isogenic cell system differing only in p53 status. This model provides us with a valuable tool to delineate role of p53 in growth and chemosensitivity of breast cancers and also allows us more systemic approach to decipher both upstream and downstream role of p53 as well as signaling networks and pathways it regulates in cancer cells.

Apoptosis (programmed cell death) is involved in the cell death caused by anticancer drugs and the tumor suppressor p53 is believed to be of key importance in this process. Additionally, the combination therapy with multiple drugs or with multiple modalities has come up as a common practice in treatment of cancer. When anticancer agents with similar and different modes of action are combined, the outcome can be synergistic, additive or antagonistic. The combination chemotherapy may derive its efficacy partly, through coordinated regulation of specific gene products associated with apoptosis. Furthermore, characterization of molecular events that underlie susceptibility of specific tumor cells to combination chemotherapeutic regimens may lead to additional improvements in treatment strategies for cancers. The work presented in this thesis identifies the effect of recently reported anticancer antibiotic doxycycline (DOX) on cytotoxic activity of anticancer drug cyclophosphamide (CPA), and investigated the target molecules involved in cell death. DOX is potentially beneficial in bone metastasis of breast cancer cells and CPA is an important component of chemotherapeutic regimen for treatment of breast cancers. Therefore we postulated that this combination treatment might enhance antitumor effect of CPA on breast cancer cells with the elucidation of significant role played by p53 both in vitro and in vivo.

Finally, the major drawback with cancer therapy is the development of resistant cells within tumors due to their heterogeneous nature and due to inadequate drug delivery during chemotherapy. Therefore, the propagation of injury ("bystander effect") from directly damaged cells to other cells may have great implications in cancer chemotherapy. The bystander effect (BE) is a chemo and radiobiological phenomenon that has come to the force recently. It describes the ability of cells
affected by an agent to convey manifestations of damage to other cells neither directly targeted by the agent nor necessarily susceptible to it per se. The general advantage of the bystander cell killing phenomenon is the large therapeutic index that can be achieved. However, the implication of chemotherapeutic stress induced bystander cell death has been least investigated regimen in cancer biology. It is now widely admitted that breast carcinoma is a genetically and clinically heterogeneous disease. Moreover, chemotherapeutic drugs can induce apoptosis and upregulate death ligands or their receptors which may subsequently play a significant role in death signal amplification via bystander effect in a mixed population of cells. In the present study, we developed an original in vitro model dedicated to the exploration of bystander cytotoxicity induced during breast carcinoma chemotherapy. We, for the first time demonstrated that MCF-EGFP target cells die when cocultured with MDA-MB-231 effector cells that were pretreated with 5-FU. This phenomenon is both drug and cell type specific and is dependent on membrane bound death receptor/death ligand, Fas/FasL system.

Our study contains detailed investigations on the role of tumor suppressor p53 in the growth of breast cancer cells and chemotherapy induced apoptosis in these cells both in vitro and in vivo. In addition, it not only includes the strategies to enhance therapeutic potential of specific anticancer drugs in breast cancer chemotherapy but also describes the potential implications of chemotherapeutic drugs induced bystander cell killing.