C. Statement of research achievements, if any, on which any award has already been received by the applicant along with citation (not to exceed 2000words)

Prof. Mandal has made excellent contribution to identify specific genes and their biological significance in cancer Biology. He has cloned a naturally occurring short form of Metastasis Associated 1 with ER-binding motif which stimulates malignant phenotypes. Oestrogen receptor (ER) is a good prognostic marker for the treatment of breast cancers. Upregulation of metastatic tumour antigen 1 (MTA1) is associated with the invasiveness and metastatic potential of several human cancers and acts as a co-repressor of nuclear ER-. Here we identify a naturally occurring short form of MTA1 (MTA1s) that contains a previously unknown sequence of 33 amino acids with an ER-binding motif, Leu-Arg-Ile-Leu-Leu (LRILL). MTA1s localizes in the cytoplasm, sequesters ER in the cytoplasm, and enhances non-genomic responses of ER. Deleting the LRILL motif in MTA1s abolishes its co-repressor function and its interaction with ER, and restores nuclear localization of ER. Dysregulation of human epidermal growth factor receptor-2 in breast cancer cells enhances the expression of MTA1s and the cytoplasmic sequestration of ER. Expression of MTA1s in breast cancer cells prevents ligand-induced nuclear translocation of ER and stimulates malignant phenotypes. MTA1s expression is increased in human breast tumours with no or low nuclear ER. The regulation of the cellular localization of ER by MTA1s represents a mechanism for redirecting nuclear receptor signaling by nuclear exclusion. This work has been published in Nature (Ref: Nature, 2001, 418(6898):654-657, in press News several times in Houston, USA. Citation of this paper is 428 as per Google scholar.

He also established a direct link between telomerase activity and cancer progression through the cell cycle. Apoptosis is a physiological mechanism of cell death that plays an important role in the regulation of tissue homeostasis. The regulation of apoptosis is a complex process and involves a number of gene products including the survival factor Bcl-2, which has been found to be frequently deregulated in human cancers. In addition to deregulation of apoptosis, the process of neoplasia is also believed to be driven by the activation of telomerase, a ribonucleoprotein complex that adds telomeric repeats (hexanucleotide 5′-TTAGGG-3′) to the ends of replicating chromosomes. Activation of telomerase has been detected in a vast majority of human cancer cells. Although recent studies have demonstrated the wide occurrence of telomerase activation and Bcl-2 deregulation in human cancer cells, it remains unclear whether there is any linkage between the deregulation of Bcl-2 and telomerase activity in cancer cells. In the studies presented here, we report that the stable overexpression of Bcl-2 in human cancer

cells with low Bcl-2 expression was accompanied by increased levels of telomerase activity. In addition, using an IL-2-dependent cytotoxic T-cell line, CTLL-2, we demonstrated that IL-2 deprivation (8 h), which is known to down-regulate Bcl-2 expression, also resulted in concurrent inhibition of telomerase activity in the absence of any detectable apoptosis and accumulation of cells in the G0/G1phase of the cell cycle. Re-exposure of IL-2-deprived CTLL-2 cells to the recombinant IL-2 led to the up-regulation of both Bcl-2 expression and telomerase activity. Taken together, these findings establish a close linkage between the modulation of telomerase activity by survival factor Bcl-2, and provide a model to study regulation of telomerase activity by an anti-apoptotic pathway that is widely deregulated in cancer cells. Those works are published in Proc Natl Acad Sci USA (1997) 93(12):6091-6095, Citation Index- 404 and J Biol Chem (1997(272(22):14183-14187), Citation-264.

He also documented that the incorporation of an anti-EGFR plus VEGFR strategy with chemotherapy could be more effective in treating patients. Celecoxib has shown potential anticancer activity against most carcinomas, especially in patients with familial adenomatous polyposis and precancerous disease of the colon. However, serious side effects of celecoxib restrict its generalized use for cancer therapy. In order to resolve these issues and develop an alternative strategy/preliminary approach, chitosan modified hydroxyapatite nanocarriers-mediated celecoxib delivery represents a viable strategy. Dr Mandal has characterized the nanoparticle for morphology, particle size, zeta potential, crystalinity, functional group analysis, entrapment efficiency, drug release and hemocompatibility. The effects of celecoxib-loaded nanoparticles on colon cancer cell proliferation, morphology, cytoskeleton, cellular uptake and apoptosis were analyzed in vitro. Further, they have evaluated the antiproliferative, apoptotic and tumor inhibitory efficacy of celecoxib-loaded nanocarriers in a nude mouse human xenograft model. Nanoparticles exhibited small, narrow hydrodynamic size distributions, hemocompatibility, high entrapment efficiencies and sustained release profiles. In vitro studies showed significant antiproliferation, apoptosis and time-dependent cytoplasmic uptake of celecoxib-loaded Hap-Cht nanoparticles in HCT 15 and HT 29 colon cancer cells. Additional in vivo studies demonstrated significantly greater inhibition of tumor growth following treatment with this modified nanoparticle system. This study indicates a promising, effective and safe means of using celecoxib, and potentially other therapeutic agents for colon cancer therapy. This work has been published in Biomaterials 32(15): 3794-3806, Citation-202.

Interleukin-6 (IL-6) signaling network has been implicated in oncogenic transformations making it attractive target for the discovery of novel cancer therapeutics. In this study, potent antiproliferative and apoptotic effect of diacerein were observed against breast cancer. In vitro apoptosis was induced by this drug in breast cancer cells as verified by increased sub-G1 population, LIVE/DEAD assay, cell cytotoxicity and presence of terminal deoxynucleotidyl transferase dept. nick end labeling (TUNEL)-positive cells, as well as downregulation of antiapoptotic proteins Bcl-2 and Bcl-xL and upregulation of apoptotic protein Bax. In addition, apoptosis induction was found to be caspase dependent. Further molecular investigations indicated that diacerein instigated apoptosis was associated with inhibition of IL-6/IL-6R autocrine signaling axis. Suppression of STAT3, MAPK and Akt pathways were also observed as a consequence of diacerein-mediated upstream inhibition of IL-6/IL-6R. Fluorescence study and western blot analysis revealed cytosolic accumulation of STAT3 in diacerein-treated cells. The docking study showed diacerein/IL-6R interaction that was further validated by competitive binding assay and isothermal titration calorimetry. Most interestingly, it was found that diacerein considerably suppressed tumor growth in MDA-MB-231 xenograft model. The in vivo antitumor effect was correlated with decreased proliferation (Ki-67), increased apoptosis (TUNEL) and inhibition of IL-6/IL-6R-mediated STAT3, MAPK and Akt pathway in tumor remnants. Taken together, diacerein offered a novel blueprint for cancer therapy by hampering IL-6/IL-6R/STAT3/MAPK/Akt network. This work is published in Oncogene, 2015, 28; 35(30):3965-75, Citation- 30

Prof Mandal has studied the efficacy of GW627368X, a selective EP4 prostanoid receptor antagonist in treatment of cervical cancer in vitro and in vivo and elucidated its mechanism of action. I have also conducted a preclinical safety assessment of GW627368X treatment in mice sarcoma model. I utilized a combination treatment modality of EP4 receptor antagonism and photothermal therapy using gold nanoprticles. I designed multifunctional, drug loaded gold nanorod cored polymeric micelles allowing targeted drug delivery and photothermal activity simultaneously and elucidated the molecular mechanism of photothermal therapy induced cell death in cancer. All those works have been published in Biochim Biophys Acta. 2016 Oct 6. pii: S0304-4165(16)30378-6., Citation 36 and Cell Death and Disease 2016 Mar 24; 7:e2154., Citation -15. He also has shown that Lumefantrine, an antimalarial drug, reverses radiation and temozolomide resistance in glioblastoma. (Proc Natl Acad Sci U S A. 2020 Jun 2;117(22):12324-12331)

Dr Mandal's group has several patents, a) A process for the purification of a new motility-promoting protein from buffalo serum: A slaughter house waste by G.C. Majumder, M. Mandal and S. Banerjee. Patent No 185383; Issue Date: August 3, 2001; Filing Date: March 17, 1997. b) Anti-Bacterial Hydrogel Composition and Application Thereof: Filed (Ref : 708/KOL/2013), c)System for cytoreduction of circulating cancer cells from blood and a method thereof: P. Chhatrala, S Paridha and M Mandal, 686/KOL/2015, One US patent entitled: A process for the purification of a new motility-promoting protein from buffalo serum: A slaughterhouse waste by G.C. Majumder, M. Mandal and S. Banerjee.US Patent No 6613737; Issue Date: September 2, 2003; Filing Date: March 10, 1998, Another patent in Japan entitled: A process for the purification of a new motility-promoting protein from buffalo serum: A slaughterhouse waste by G.C. Majumder, M. Mandal and S. Banerjee. Japan Patent No 3251545; Issue Date: November16, 2001; Filing Date: March 6, 1998. Currently, Dr Mandal, along with a team of oncologist, physicist and engineers are trying to determine the changes of molecular, bio-physical and bio-electrical properties in cancer during the transformation from benign to malignant form as well as acquiring chemo resistance. Publication on high impact factor journals indicates the importance of his work.

Due to his significant contribution in cancer Biology area Dr Mandal received several Felloships and awards like, FNA, FASc, FNASc, FAScT, FRSB, J C Bose National Fellow, SS Katiyar Award by Indian Science Congress in 2018, Basanti Devi Award by ICMR in 2018, Subha Mukherjee Memorial award in 2013 by Physiological Society of India. He also elected as Fellow of West Bengal Science Academy in 2013 (WAST). He also serves as editorial Board members of several journals like, Scientific Report, PLos One, Journal of Biomedical Engineering. He is also invited as a reviewer of various reputed journals like, Oncogene, Cancer Letters, BBRC, BBA, International Journal of Biological Macromolecules, Computers in Biology and Medicine, Molecular Cancer Therapy, Cancer Research, Nanomedicine etc. He is also regularly invited as speaker due to his significant contribution by different International and National conference like American Cancer Research Association, Indian Cancer Research Association, Physiological Society of India, etc.