Concluding Remarks
Benign Prostatic Hyperplasia (BPH) and Prostate Cancer (CaP) are both late onset diseases that affect majority of the elderly male population. Although there are many similarities in the molecular pathogenesis of these two proliferative diseases, BPH cannot conclusively be claimed to be first stage in the molecular pathogenesis of prostate cancer.

The androgen receptor is a key player of these two diseases and has been the focus of this study. In order to evaluate genes that are known to regulate or be regulated by the AR itself, genes expressed differentially between BPH and prostate cancer were evaluated. The present study provides some novel insights in the field of prostate cancer research that can be summarized as follows:

i. From the TaqMan® based array, we have found that most of the genes related to AR pathway was up regulated in cancer than BPH and a vast majority of the over expressed genes were found to belong to the androgen biosynthetic pathway (androgen metabolic process: ID:GO:0008209, steroid biosynthetic process: ID:GO:0006694, androgen biosynthetic process: ID:GO:0006702 and estrogen biosynthetic process :ID:GO:0006703). When the genes were narrowed down with the help of STRING and GO analysis, FKBP4 gene emerged as an important candidate gene, which is differentially expressed between BPH and cancer.

ii. FKBP52 (FKBP4 gene) expression was found to be over expressed in prostate cancer when screened in a larger number of randomly obtained patient samples. In addition, sub-cellular localization of FKBP52 inside the cell was not influenced by androgen.

iii. Cell proliferation regulatory genes: cyclin D1, CDK4 and c-Myc were found to be over expressed in prostate cancer whereas p21 was found to be down regulated in prostate cancer. Interestingly, we found Smad3 to be over expressed in prostate cancer tissues, which is quite contradictory to the conventional thought.

iv. Our study is the first to evaluate the above finding and demonstrate that Smad3 linker phosphoform (pSmad3L) is over expressed in CaP, in contrast to the carboxy terminal phosphorylated form pSmad3C, which may contribute to cancer.

v. We found that the expression of c-Myc and FKBP4 is positively correlated. Our study first proposed that c-Myc may be a transcriptional co-regulator of the FKBP4 gene,
and silencing c-Myc expression not only reduced FKBP4 expression but also decreased FGF8 expression in prostate cancer cell lines.

vi. Population based morphometric analysis of BPH tissues identified a separate trend in the parameters that is unique for Indian BPH patients and differs from both Chinese and American populations.

vii. Population based association study showed that an established SNP (G1733A) polymorphism is very rare in Eastern Indian population. Another SNP from FKBP4 gene (rs10047621) was first studied for Eastern Indian population and found show weak positive association with serum PSA level in cancer patients.

Overall, this study has attempted to evaluate differentially expressed genes which may serve as potential biomarkers in the progress of prostate carcinogenesis. The study has also established for the first time an intricate relationship between FKBP4, Fgf8 and c-Myc, along with the androgen receptor, in prostate cancer.

**Future avenues of work:**

Prostate cancer is an androgen receptor (AR)-dependent malignancy. Hormone therapy is, therefore, the primary line of systemic treatment. Despite initial disease regression, tumors inevitably recur and progress to an advanced castration-resistant state, a major feature of which is bone metastasis. Androgen receptor is a hormone-dependent transcription factor that requires proper association with multimeric chaperones and co-chaperones (Cano et al., 2015; De Leon et al., 2011) complexes to attain a functional conformation. Up-regulation of AR cofactors and chaperones that overcome low hormone conditions to maintain basal AR activity has been postulated as one of the major mechanisms of therapy relapse. Of these co-chaperones, FKBP4 represent potential therapeutic target due to its narrow functional specificity which includes glucocorticoid (GR), progesterone (PR) and most importantly androgen (AR) receptors, and is the pivotal gene in both androgen dependent and independent progression of prostate cancer. Our study, unequivocally demonstrates that FKBP4 gene expression can be used to differentiate between BPH and cancer tissue samples. Furthermore, it indicates FKBP4 to be a target for chemotherapy of prostate cancer in future given its more specific function in human physiology. FKBP4 knockout mice (Cheung-Flynn et al., 2005) displayed phenotype related to androgen insensitivity suggesting its more specific function with minimal off-target effects.
Evidences already show that clinically approved drugs, such as FK506, can target FKBP4 with much efficacy in prostate cancer (Khemlina et al., 2015; Ratajczak. 2015; Ischia et al., 2013; Liang et al., 2014; Stope et al., 2012). However, how the proline-rich FK1 catalytic domain of FKBP4 protein can be specifically targeted to obliterate any AR-FKBP4 association is a matter of extensive research.