Prostate cancer is the second most common adenocarcinoma amongst men whereas BPH is the non-malignant overgrowth of the prostate gland. Androgen and androgen receptor signaling pathways are known to be the key players of these two proliferative diseases of the prostate gland. There is thus great necessity to understand the interplay of genes in the androgen receptor pathway and thereby identify specific genes that may eventually serve as cancer biomarkers.

TaqMan® gene expression array was used to narrow down our search for differentially expressed genes between BPH and cancer tissue samples. Differentially expressed genes were subsequently selected for the construction and hypothesis testing of a probable signaling pathway. Significant over expression of an immunophilin molecule FKBP4 was identified in prostate cancer. FKBP4 gene expression was validated in a larger patient sample size with the help of qRT-PCR and western blot analysis. Protein localization was analyzed by immunohistochemistry in patient tissue samples. The localization and expression of FKBP4 were also examined with the help of western blot and immunocytochemistry in both androgen-responsive LNCaP and androgen-independent PC3 cell lines. In addition, c-Myc was also found to be overexpressed in cancer samples and prompted us to investigate its role in the expression of FKBP4. It was found from siRNA-based knock down of c-Myc and ChIP assay that FKBP4 transcription was directly influenced by the c-Myc gene. As a downstream component, the expression of FGF8 was also high in PCa compared to BPH tissues, and down regulated after c-Myc silencing.

Cell cycle regulatory proteins like CyclinD1, CDK4 and SMAD3 showed over expression in prostate cancer samples. Concomitantly, p21 was found to be down regulated in cancer samples. Phosphoisomers of SMAD3 protein were also investigated in prostate cancer and linker phosphorylated SMAD3 was found to be highly overexpressed in prostate cancer in contrast to carboxy terminal phosphorylated SMAD3. Two different SNPs pertaining to AR (rs6125) and FKBP4 (rs10047621) were also investigated in order to find out if any genetic association with prostate cancer. Taken together, our study establishes, for the first time, a relationship between FKBP4, c-Myc, AR and FGF8 genes in prostate cancer.