References
Differential Gene Expression Analysis and Genetic Association Studies In Benign and Malignant Prostate Tissues

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70. Galigniana MD, Radanyi C, Renoir JM, Housley PR, Pratt WB. (2001) Evidence that the peptidylprolyl isomerase domain of the hsp90-binding immunophilin FKBP52 is involved in both dynein interaction and glucocorticoid receptor movement to the nucleus. J. Biol. Chem. 276:14884–14889
Differential Gene Expression Analysis and Genetic Association Studies In Benign and Malignant Prostate Tissues

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Differential Gene Expression Analysis and Genetic Association Studies In Benign and Malignant Prostate Tissues


List of Corrections according to the comments of Second Examiner vide letter no: 4466/Ph.D.(Sc.), Dated: 07. Jul. 2015

- **Name of the Candidate:** Ankur Bhowal
- **Title of the Thesis:** Differential Gene Expression Analysis and Genetic Association Studies In Benign and Malignant Prostate Tissues
- **Registration No:** 1845 Ph.D. (Sc) Proceed/2009, Dated: 22.5.2009

**Point 1**

*a) Incorporation of recent Literature survey in the thesis.*

In view of the above concern of the reviewer, **nineteen** numbers of references from articles published during the last five years have been included.

**Newly added recent references:**


Corresponding page and line numbers are as follows:

<table>
<thead>
<tr>
<th>Newly added References</th>
<th>Page Number</th>
<th>Line Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cano et al., 2015</td>
<td>95</td>
<td>24</td>
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<tr>
<td>Corn et al., 2013</td>
<td>82</td>
<td>05</td>
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<tr>
<td>Corona et al., 2014</td>
<td>09</td>
<td>16</td>
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<tr>
<td>Ischia et al., 2014</td>
<td>96</td>
<td>03</td>
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<td>Izumi et al., 2013</td>
<td>11</td>
<td>28</td>
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<tr>
<td>Khemlina et al., 2015</td>
<td>96</td>
<td>03</td>
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<tr>
<td>Liu et al., 2015</td>
<td>82</td>
<td>05</td>
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<td>Miah et al., 2014</td>
<td>21</td>
<td>30</td>
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<tr>
<td>Ratajczak et al., 2015</td>
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<td>Ratajczak 2015</td>
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<td>Schweizer et al., 2015</td>
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<td>Schweizer and Yu 2015</td>
<td>23</td>
<td>13</td>
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<td>Singh et al., 2015</td>
<td>24</td>
<td>10</td>
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<td>Sobol et al., 2015</td>
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<td>Stope et al., 2012</td>
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<tr>
<td>Jarvis et al., 2014</td>
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</table>

In addition following section has been incorporated in the introduction considering its huge impact in future treatment regimes in management of prostate cancer (Page 23-24).

**Recent trends in prostate cancer treatment**

Recently it has been resolved that persistent activation of the androgen receptor (AR) signaling often causes the development of castration-resistant prostate cancer (CRPC) or AIPC (Schweizer
and Yu, 2015). In a pilot study (Schweizer et al., 2015), it has been demonstrated that in some castration resistant prostate cancer (CRPC) patients, drug-resistance could be reversed by administrating cycles of androgens to achieve supra-physiological concentrations of testosterone which promotes CRPC cell death. This treatment (Bipolar Androgen Therapy or BAT) procedure, though in its early stage is showing rays of hope for men who have developed resistance to primary castration therapy and secondary androgen deprivation therapies (ADTs). Also in recent years, in a placebo-controlled Phase II trial of men with minimally symptomatic, chemotherapy-naive metastatic castration-resistant prostate cancer, PROSTVAC immunotherapy showed adequate tolerance and resulted in 44% reduction in death (Singh et al., 2015). Though these immunotherapeutic drugs showed improvement in survival, no measurable change in disease state was recorded leading to significant controversy (Sobol et al., 2015).

\textit{b) Incorporation of ‘year of publication’ in two mentioned references in the thesis.}

I deeply apologize for this unintended error. In the modified version the year of reference has been incorporated in the reference no 120 (Page 104) & 153 (Page 105).


\textbf{(Please note: Due to incorporation of additional references, the serial numbers have changed.)}
Point 2

a) Incorporation of ‘future avenues of work’ in the ‘Concluding Remarks’ section in the thesis (Page 95)

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.