Establishment of a Panel of Prostate Patient-Derived Xenograft (PDX) Models and Evaluation of Anti-Androgen Therapy

Jason Davies1, Anthony Oakden1, Chira Roberts1, Jane Wrigley1, Jason King1, Anne Collins2, Wubin Qian2, Likun Zhang2, Bin Fan3, Davy Ouyang2, Jie Caï3, Bryan Miller3, Rajendra Kumar3, Yinfei Yin1

1Crown Bioscience UK Ltd., Loughborough, UK; 2University of York, York, UK; 3Crown Bioscience Inc., Beijing, China

INTRODUCTION

Prostate cancer is one of the most common cancer types worldwide with limited treatment options and poor prognosis. Surgery, chemotherapies such as docetaxel (Taxotere®), and targeted therapies such as abiraterone (Zygipta®) and enzalutamide (Xtandi®) are the options available for prostate cancer patients, but they all have their limitations. The development of new prostate cancer therapies has been slow due to the lack of preclinical models that adequately represent the spectrum of benign, latent, aggressive, and metastatic forms of the human disease. Patient-derived xenograft (PDX) models have been reported to be more clinically relevant than cell lines, but the generation of prostate cancer PDX models has always been challenging.

Here we report on the establishment and validation of a panel of prostate PDX models and their utilization in preclinical studies which will help prostate cancer research.

METHODS

Primary prostate cancer samples obtained from patients in the UK undergoing radical prostatectomy were collected with ethical consent; primary sample details are summarized in Table 1. Primary tissue samples were disaggregated, and implanted subcutaneously into the left flank of male Rag2/−/γc−/− mice (The Jackson Laboratory) to generate PDX models. Subcutaneous tumor growth was evaluated and monitored by electronic calipers.

Once established in Rag2/−/γc−/− mice, tumors were expanded into JAX NSG™ mice (NOD.Cg-PrkdcscidIl2rgtm1WjlSzJ; The Jackson Laboratory) with a 1:5 passage ratio. Tissue fragments (~100mm³) were implanted subcutaneously into the left flank of each mouse, and the wound sealed with skin closure clips. Mice were terminated when tumors reached a mean diameter of 12mm, and tissue samples were collected for hematoxylin and eosin (H&E) staining, RNA sequencing, and immunohistochemistry (IHC). RNA sequencing confirmed both PR6511 and PR6512 have high KLK3 (PSA) expression. PR6511 also has a TMPRSS-ERG fusion.

Following expansion and tissue banking, PDX were tested for sensitivity to docetaxel (Taxotere®), abiraterone, bicalutamide, and enzalutamide in vivo in male NSG mice bearing tumors. Tumors were sampled pre and post dosing as well as blood samples collected for downstream analysis.

RESULTS

Table 1. Primary prostate tissue and patient information

<table>
<thead>
<tr>
<th>Model</th>
<th>Tissue Collection Date</th>
<th>Patient Age</th>
<th>Staging (T, N, M)</th>
<th>Treatments Administered</th>
<th>Treatment Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR6511</td>
<td>2014</td>
<td>67</td>
<td>M(b1)</td>
<td>HT, CT</td>
<td>CRPC</td>
</tr>
<tr>
<td>PR6512</td>
<td>2012</td>
<td>78</td>
<td>G4-S, T4, n1</td>
<td>HT</td>
<td>CRPC</td>
</tr>
<tr>
<td>PR6513</td>
<td>2014</td>
<td>69</td>
<td>G8, M(b1)</td>
<td>HT</td>
<td>HR</td>
</tr>
<tr>
<td>PR6514</td>
<td>2011</td>
<td>71</td>
<td>G8, T2b</td>
<td>HT, RT</td>
<td>HR</td>
</tr>
</tbody>
</table>

Fig. 1. Tissue structure of PDX models. H&E staining was used to assess tumor/stroma structure of original patient samples and PDX samples. Patient-derived xenografts were found to recapitulate the structures seen in the original patient samples

Fig. 2. Immunohistochemistry (IHC) analysis of castrate resistant prostate cancer (CRPC) PDX samples. Expression of prostate specific markers and basal cell layer markers was assessed using IHC

Fig. 3. Response to docetaxel in PR6511 and PR6512 patient-derived xenografts. PR6511 or PR6512 were implanted subcutaneously into mice. Once tumors had established, mice were treated with docetaxel (5mg/kg, administered intravenously once weekly). A significant reduction in tumor volume was observed in response to docetaxel treatment of the PR6511 model (p<0.0001, two-way ANOVA)

Fig. 4. Response to enzalutamide and abiraterone in PR6511 and PR6512 patient-derived xenografts. Subcutaneous tumors were established in mice with PR6511 and PR6512. Mice were treated with enzalutamide (30mg/kg, oral administration daily) or abiraterone (75mg/kg, oral administration daily). No significant response was observed for either anti-androgen therapy (assessed using two-way ANOVA)

Fig. 5. Response to bicalutamide in PR6513 patient-derived xenografts. Mice with subcutaneous PR6513 tumors were treated with bicalutamide (5mg/kg, oral administration daily). Tumor volume and mouse body weight were monitored for the duration of the study

SUMMARY

- We have established and characterized a panel of prostate cancer PDX models, which provide unique and clinically relevant models for preclinical drug evaluation
- All PDX models retained the structure of the original patient specimens, providing a more predictive alternative to cell line derived xenografts
- CRPC PDX retained androgen receptor and PSA expression levels as well as other markers of prostate cancer
- Response to docetaxel was observed in one CRPC PDX model (PR6511); however, no response to anti-androgen therapies was observed in the models tested