Current mouse and cell models in prostate cancer research

Xinyu Wu1, Shiaoching Gong2,3, Pradip Roy-Burman4, Peng Lee1,5,6,7 and Zoran Culig8

1Department of Pathology, New York University School of Medicine, New York, NY, USA
2Arthritis and Tissue Degeneration Program, Hospital for Special Surgery, New York, NY, USA
3Laboratory of Molecular Biology, the Rockefeller University, New York, NY, USA
4Department of Pathology, University of Southern California Keck School of Medicine, Los Angeles, CA, USA
5Department of Urology, New York University School of Medicine, New York, NY, USA
6NYU Cancer Institute, New York University School of Medicine, New York, NY, USA
7New York Harbor Healthcare System, New York, NY, USA
8Department of Urology, Innsbruck Medical University, Innsbruck, Austria

Correspondence should be addressed to P Lee or Z Culig
Emails peng.lee@nyumc.org; zoran.culig@i-med.ac.at

Abstract

Mouse models of prostate cancer (PCa) are critical for understanding the biology of PCa initiation, progression, and treatment modalities. Here, we summarize recent advances in PCa mouse models that led to new insights into specific gene functions in PCa. For example, the study of transgenic mice with TMPRSS2/ERG, an androgen-regulated fusion protein, revealed its role in developing PCa precursor lesions, prostate intraepithelial neoplasia; however, it is not sufficient for PCa development. Double deficiency of Pten and Smad4 leads to a high incidence of metastatic PCa. Targeted deletion of Pten in castration-resistant Nkx3-1-expressing cells results in rapid carcinoma formation after androgen-mediated regeneration, indicating that progenitor cells with luminal characteristics can play a role in initiation of PCa. Transgenic mice with activated oncogenes, growth factors, and steroid hormone receptors or inactivated tumor suppressors continue to provide insights into disease progression from initiation to metastasis. Further development of new PCa models with spatial and temporal regulation of candidate gene expression will probably enhance our understanding of the complex events that lead to PCa initiation and progression, thereby invoking novel strategies to combat this common disease in men.

Key Words
- androgen receptor
- oncology
- prostate

Introduction

Prostate cancer (PCa) is the most common male-specific cancer in most western countries including the United States. An important cause of morbidity and mortality in PCa is skeletal metastasis; the pathogenesis of bone metastasis is poorly understood due to the lack of relevant animal models. Androgens play crucial roles in PCa oncogenesis and progression, hence, androgen ablation therapy (surgical or medical castration) is the standard of treatment. However, most PCa cases eventually become castration-resistant PCa (CRPC), which remains the primary cause of PCa-related death. Therefore, continued generation of new PCa mouse models is necessary to enhance our understanding of PCa development and progression to metastasis.

Prostate tumor growth in xenograft models

Cell lines commonly used in xenograft models

The most commonly used cell lines for prostate xenograft models (Table 1) are LNCaP, PC3, and DU145. The LNCaP...
The PC3 cell line was originally derived from a bone metastasis of human prostatic adenocarcinoma origin (Kaighn et al. 1979). The i.v. injection of PC3 (Shervin et al. 1988, Pettaway et al. 1996) has led to the establishment of lymph node metastases. Stephenson et al. (1992) reported that orthotopic implantation of PC3 cells can also yield lymph node metastases. Some sublines from PC3 have been generated that have increased metastatic ability (Pettaway et al. 1996). 

PC-3M cells are a metastasis-derived variant of PC3. Tumors from the prostate or lymph nodes were harvested after intraprostate growth, and cells were reinjected into the prostate. This cycle was repeated three to five times to yield cell lines PC-3M-Pro4 and PC-3M-LN4. PC-3M-LN4 cells produced enhanced regional lymph node and distant organ metastasis. After i.v. or intracardiac inoculation, PC-3M-LN4 cells produced a higher...
incidence of lung metastasis and bone metastasis respectively (Pettaway et al. 1996). As PC3 is negative for AR expression, PC3-AR, a clonal PC3 cell line stably transfected with AR, has been used in various studies. The DU145 cell line, which has less metastatic potential compared with PC3 cells, was derived from a brain metastasis of human prostatic adenocarcinoma origin (Stone et al. 1978; Table 3).

**Table 2** Transgenic models of PCa generated with the prostate-specific probasin promoter.

<table>
<thead>
<tr>
<th>Model</th>
<th>Invasive carcinoma</th>
<th>Metastasis</th>
<th>Purpose</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>PB-large-T/small-t (TRAMP model)</td>
<td>&gt;12 weeks</td>
<td>Lung, liver, kidney, salivary gland, lymph node, bone; exhibits neuroendocrine features</td>
<td>To study the molecular mechanism of normal prostatic cells and the factors influencing the progression to PCa</td>
<td>Greenberg et al. (1995) and Gingrich &amp; Greenberg (1996)</td>
</tr>
<tr>
<td>Lady model</td>
<td>20 weeks</td>
<td>No</td>
<td>To study the sequential mechanisms in multistep tumorigenesis</td>
<td>Kasper et al. (1998) and Masumori et al. (2001)</td>
</tr>
<tr>
<td>PBECO:RI</td>
<td>24 months</td>
<td>No</td>
<td>To study the mechanisms of early stages prostate carcinogenesis As PBECO:RI</td>
<td>Voelkel-Johnson et al. (2000)</td>
</tr>
<tr>
<td>PB-fos</td>
<td>No</td>
<td>No</td>
<td>As PBECO:RI</td>
<td>McDonnell et al. (2000)</td>
</tr>
<tr>
<td>PB-bcl2</td>
<td>No</td>
<td>No</td>
<td>To study the bcl2 effect on PCa</td>
<td>Stanbrough et al. (2001)</td>
</tr>
<tr>
<td>PB-mAR</td>
<td>One animal</td>
<td>No</td>
<td>To assess preventative hormonal therapies</td>
<td></td>
</tr>
<tr>
<td>LPB-SV40 large-T antigen line 12T-10 (Lady model)</td>
<td>6–12 months, adenocarcinoma, with neuroendocrine features</td>
<td>Lymph node, liver, lung, spleen, kidney, bone</td>
<td>As Lady model</td>
<td>Masumori et al. (2001)</td>
</tr>
<tr>
<td>PB-FGF7 (PKS)</td>
<td>No</td>
<td>No</td>
<td>To study the effect of FGF-7 signaling on interaction between the prostate epithelial – stromal</td>
<td>Foster et al. (2002)</td>
</tr>
<tr>
<td>PB-FGFR2iiib (KDNR)</td>
<td>No</td>
<td>No</td>
<td>To study the emergence of neuroendocrine phenotype in prostate glands</td>
<td>Foster et al. (2002)</td>
</tr>
<tr>
<td>PB-large-T/small-t (Rat model)</td>
<td>30–35 weeks</td>
<td>Neuroendocrine, into surrounding tissues</td>
<td>A rat model for the PCa</td>
<td>Asamoto et al. (2002)</td>
</tr>
<tr>
<td>ARR2PB-FGF8b</td>
<td>No</td>
<td>No</td>
<td>To investigate the mechanism of development and progression of prostatic hyperplasia and preneoplastic lesions</td>
<td>Song et al. (2002)</td>
</tr>
<tr>
<td>MPAKT model</td>
<td>No</td>
<td>No</td>
<td>To study the role of Akt in prostate epithelial cell transformation and in the discovery of molecular markers</td>
<td>Majumder et al. (2003)</td>
</tr>
<tr>
<td>PB-Myc-PAI (Lo-Myc model)</td>
<td>&gt;12 months</td>
<td>No</td>
<td>To study the relevance of mouse models for human disease. As PB-Myc-PAI</td>
<td>Ellwood-Yen et al. (2003)</td>
</tr>
<tr>
<td>ARR2PB-myc-PAI (Hi-Myc model)</td>
<td>&gt;6 months</td>
<td>No</td>
<td>To study the effect of Insulin-like growth factor IGF1 on PCa</td>
<td>Konno-Takahashi et al. (2003)</td>
</tr>
<tr>
<td>PB-IGF1</td>
<td>No</td>
<td>No</td>
<td>To study the function of the F-box protein SKP2 on PCa</td>
<td>Shim et al. (2003)</td>
</tr>
<tr>
<td>PB-RAS</td>
<td>No</td>
<td>No</td>
<td>To elucidate the mechanisms and potential PCa relevance of intestinal metaplasia</td>
<td>Scherl et al. (2004)</td>
</tr>
<tr>
<td>p53/His273 mutant</td>
<td>No</td>
<td>No</td>
<td>To study the relevance of multiple genes involved in progression of slow-growing prostate tumors expressing oncogenes alone to metastatic cancer</td>
<td>Elgavish et al. (2004)</td>
</tr>
<tr>
<td>ARR2PB-hepsin</td>
<td>No</td>
<td>No</td>
<td>To study the role of hepsin in metastasis of PCa</td>
<td>Klezovitch et al. (2004)</td>
</tr>
</tbody>
</table>
PC3 and DU145 cells are androgen-independent PCa cells; however, neither cell lines express AR. Since most human androgen-independent PCa maintains AR expression, efforts have been focused on developing AR-positive androgen-independent PCa cell lines. The LNCaP-abl cell line was established by Culig et al. (1999) by culturing androgen-sensitive LNCaP cells in androgen-depleted medium for 87 passages. The LNCaP-abl cells express high levels of AR and display a hypersensitive biphasic proliferative response to androgen until passage 75. Growth of LNCaP-abl xenografts in nude mice was stimulated by bicalutamide and repressed by testosterone (Culig et al. 1999). IL6 reportedly has divergent effects on the growth of the androgen-responsive cell line LNCaP. By using prolonged treatment with this cytokine a subline, LNCaP-IL6, was generated that does not show the growth-inhibitory response in spite of upregulated expression of endogenous IL6. LNCaP-IL6 cells grow more rapidly in nude mice than do their LNCaP-IL6 counterparts, which were established after serial passaging in the absence of IL6 (Steiner et al. 2003). In LNCaP-IL6 cells, there is an upregulation of cyclin-dependent kinase 2 and reduced expression of the tumor suppressors pRb and p27 (Table 4).

Thalmann et al. (1994) developed the androgen-independent subline, LNCaP C4-2. This LNCaP subline

### Table 3: Transgenic models of PCa generated with nonprobasin promoter.

<table>
<thead>
<tr>
<th>Model</th>
<th>Invasive carcinoma</th>
<th>Metastasis</th>
<th>Purpose</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>gp91-phox-SV40 large-T/small-t</td>
<td>Neuroendocrine</td>
<td>Surrounding tissues</td>
<td>To study neuroectodermal malignancies</td>
<td>Skalnik et al. (1991)</td>
</tr>
<tr>
<td>MMTV-wap</td>
<td></td>
<td></td>
<td>To study the function of the whey acidic protein in prostate</td>
<td>Hennighausen et al. (1994)</td>
</tr>
<tr>
<td>C3(1)-polyoma virus middle T</td>
<td>Yes</td>
<td>No</td>
<td>To study the role of the polyomavirus middle T gene in urogenital growth and development</td>
<td>Tehranian et al. (1996)</td>
</tr>
<tr>
<td>C3(1)-SV40 large-T/small-t</td>
<td>&gt; 28 weeks with neuroendocrine differentiation</td>
<td>No</td>
<td>To study mechanisms of the progression of invasive carcinomas from PIN precursor lesions</td>
<td>Shibata et al. (1996)</td>
</tr>
<tr>
<td>Fetal gamma globin-SV40 large-T/small-t</td>
<td>16–20 weeks, epithelial with luminal epithelial and neuroendocrine features</td>
<td>3–4 months, adrenal, lung, lymph nodes, bone, thymus, intrascapular tissue of neck and shoulders</td>
<td>To examine interactions between subtypes of prostatic epithelial cells</td>
<td>Perez-Stable et al. (1996)</td>
</tr>
<tr>
<td>MMTV-kgf</td>
<td>No</td>
<td>No</td>
<td>To study the function of kgf</td>
<td>Kitsberg and Leder (1996)</td>
</tr>
<tr>
<td>C3(1)-bcl-2</td>
<td>No</td>
<td>No</td>
<td>To study the effect of bcl2 on prostate neoplastic development</td>
<td>Zhang et al. (1997)</td>
</tr>
<tr>
<td>MT-1-rPRL</td>
<td>No</td>
<td>No</td>
<td>To study the effect of overexpressing the prolactin gene on the prostate gland</td>
<td>Wennbo et al. (1997)</td>
</tr>
<tr>
<td>Cryptdin 2-SV40 large-T/small-t</td>
<td>12 weeks</td>
<td>16 weeks, lymph nodes lung, liver, bone</td>
<td>To study the significance of neuroendocrine differentiation in PCa</td>
<td>Garabedian et al. (1998)</td>
</tr>
</tbody>
</table>

### Table 4: Haplotype and knock-out mouse models of PCa.

<table>
<thead>
<tr>
<th>Model</th>
<th>Invasive carcinoma</th>
<th>Metastasis</th>
<th>Purpose</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>RARγ1−/−</td>
<td>No</td>
<td>No</td>
<td>To study neuroendocrine differentiation</td>
<td>Lohnes et al. (1993)</td>
</tr>
<tr>
<td>p27kip1−/−</td>
<td>No</td>
<td>No</td>
<td>To study the function of the whey acidic protein in prostate</td>
<td>Cordon-Cardo et al. (1998)</td>
</tr>
<tr>
<td>PTEN+/−</td>
<td>No</td>
<td>No</td>
<td>To study the role of the polyomavirus middle T gene in urogenital growth and development</td>
<td>Podsypanina et al. (1999) and Di Cristofano et al. (2001)</td>
</tr>
<tr>
<td>Nkx3.1−/−</td>
<td>No</td>
<td>No</td>
<td>To study the effect of overexpressing the prolactin gene on the prostate gland</td>
<td>Schneider et al. (2000)</td>
</tr>
<tr>
<td>Stat5a−/−</td>
<td>No</td>
<td>No</td>
<td>To study the effect of overexpressing the prolactin gene on the prostate gland</td>
<td>Nevalainen et al. (2000)</td>
</tr>
<tr>
<td>PB-Cre4 RXRαERT</td>
<td>No</td>
<td>No</td>
<td>To study the significance of neuro-endocrine differentiation in PCa</td>
<td>Huang et al. (2002)</td>
</tr>
<tr>
<td>PSA-CRE Nkx3.1ERT</td>
<td>No</td>
<td>No</td>
<td>To study the significance of neuro-endocrine differentiation in PCa</td>
<td>Abdulkadir et al. (2002)</td>
</tr>
<tr>
<td>PB-Cre4 PTENloxp/loxP</td>
<td>9 weeks</td>
<td>No</td>
<td>To study the significance of neuro-endocrine differentiation in PCa</td>
<td>Wang et al. (2003)</td>
</tr>
<tr>
<td>MMTV-Cre PTENloxp/loxP</td>
<td>3 weeks</td>
<td>No</td>
<td>To study the significance of neuro-endocrine differentiation in PCa</td>
<td>Backman et al. (2004)</td>
</tr>
<tr>
<td>Fsp1-Cre Tgfbr2ERT</td>
<td>No</td>
<td>No</td>
<td>To study the significance of neuro-endocrine differentiation in PCa</td>
<td>Bhowmick et al. (2004)</td>
</tr>
<tr>
<td>PB-CreAPClox/lox</td>
<td>7 months</td>
<td>No</td>
<td>To study the significance of neuro-endocrine differentiation in PCa</td>
<td>Bruxvoort et al. (2007)</td>
</tr>
</tbody>
</table>
was able to metastasize to bone; however, the frequency was low (2 of 20). Sublines derived from C4-2, designated as B2, B3, B4, and B5, were established and had a higher propensity to metastasize to bone and cause osteoblastic lesions (Wu et al. 1998, Thalmann et al. 2000). The LNCaP-AI cell line is an androgen-independent prostatic carcinoma derived from the androgen-dependent LNCaP-FGC cells. LNCaP-AI cells express higher level of AR compared with LNCaP cells and retain sensitivity to androgen stimulation (Lu et al. 1999).

The VCaP cell line was derived from a vertebral bone metastasis of a hormone-refractory prostate tumor. This cell line expresses high levels of PSA, prostatic acid phosphatase (PAP), cytokeratin-18, and the wild-type AR (Korenchuk et al. 2001). Loberg et al. (2006) generated androgen-independent PCa cell line by implanting VCaP cells subcutaneously and serially passaging in castrated male SCID mice.

MDA PCa 2a and MDA PCa 2b were established in 1997 from bone metastasis of an androgen-independent PCa (Navone et al. 1997). Both the MDA PCa 2a and the MDA PCa 2b cells have two mutations in the Ar gene, the T877A found in LNCaP cells and also a substitution of leucine with histidine at position 701 (L701H). This double mutation in these two cell lines leads to decreased androgen sensitivity and altered ligand specificity (Zhao et al. 1999, 2000).

CWR22 cells originated from a primary tumor and showed secretion of PSA (Wainstein et al. 1994). Relapsed androgen-independent xenografts can be established with CWR22 cells (Nagabhushan et al. 1996). Three other CWR xenografts from primary PCa, CWR21, CWR31, and CWR91 were established (Navone et al. 1998) by using sustained-release testosterone pellets in the host mice to obtain tumor growth. The patients whose primary PCa gave rise to CWR21, CWR31, and CWR22 had Stage D prostatic carcinoma with osseous metastases. After androgen withdrawal, the human primary PCa xenograft CWR22 regresses markedly, and blood PSA levels fall in the mice. A novel AR mutation characterized by in-frame tandem duplication of exon 3 that encodes the second zinc finger of the AR DNA-binding domain has been detected in the relapsed CWR22 xenograft (Tepper et al. 2002). CWR22Rv1 is derived by serial passaging of CWR xenograft with repeated tumor regression and relapse under castrated condition (Sramkoski et al. 1999). In addition to the AR mutant (H874Y), AR splice variants were initially discovered in the CWR22R xenograft line, and have since been identified in the VCaP cell line, LuCaP xenografts, the Myc-CaP genetically engineered mouse model of PCa and clinical CRPC PCa. Watson et al. (2010) found that AR splice variants are able to function independently of full-length AR (ARFL), demonstrated that several AR splice variants remain dependent on ARFL heterodimerization for nuclear translocation and transcriptional activity, and overall AR activity remains sensitive to ligand-binding-domain targeted anti-androgens (Table 5).

Other cell lines used are the LuCaP23 series, PC-82, PC-295, and PC-310 lines (van Weerden et al. 1993, Noordzij et al. 1996, Jongsm a et al. 1999, Korenchuk et al. 2001), as well as androgen-independent PC-346, PC-346C, and PC-34 lines. Two other transplantable models, LAPC-3 and LAPC-4, were isolated from different patients with advanced disease. The LAPC-3 tumor is androgen-independent, whereas LAPC-4 is androgen-responsive (Klein et al. 1997). These cells express wild-type AR.

The xenograft models, in particular LNCaP xenografts, have been of great benefit in establishing our understanding of prostate tumorigenesis, the central role of the AR and a number of common gene changes in PCa. Although not ideal, this model is still used in many preclinical and basic science applications in vitro and in vivo in many labs as a first port-of-call that might inform use of longer timeframe and more expensive transgenic model systems. LNCaP and LAPC-4 xenograft models have been used in drugs studies (Klink et al. 2013). LNCaP-LN3 orthotopic PCa xenografts were used to evaluate the response of PCa bone metastasis to anti-VEGF receptor

**Table 5**  Bigenic mouse models of PCa.

<table>
<thead>
<tr>
<th>Model</th>
<th>Invasive carcinoma</th>
<th>Metastasis</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTEN&lt;sup&gt;+/−&lt;/sup&gt;, Cdkn1b&lt;sup&gt;−/−&lt;/sup&gt;</td>
<td>&gt; 12 weeks (25% of mice) Yes</td>
<td>No Lung, lymph nodes, kidney, liver, neuroendocrine</td>
<td>Di Cristofano et al. (2001) Kwabi-Addo et al. (2001)</td>
</tr>
<tr>
<td>PTEN&lt;sup&gt;+/−&lt;/sup&gt; × TrAMP</td>
<td>&gt; 6 months</td>
<td>Rate decreased by ~50% 8 months lymph nodes, liver, lung, neuroendocrine &gt; 9 months lymph nodes</td>
<td>Kim et al. (2002) and Abate-Shen et al. (2003) Polnashed et al. (2003) Klezovitch et al. (2004) Zhong et al. (2006)</td>
</tr>
<tr>
<td>PTEN&lt;sup&gt;+/−&lt;/sup&gt; × Nkx3.1&lt;sup&gt;−/−&lt;/sup&gt;</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>TRAMP FGF2&lt;sup&gt;−/−&lt;/sup&gt; 12T-10 × MT-DNIIR</td>
<td>&gt; 6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PB-CreFgf8b × PTEN&lt;sub&gt;flow/flow&lt;/sub&gt;</td>
<td>9 months</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
(flk-1) antibody (DC101) treatment (Sweeney et al. 2002). Kochuparambil et al. (2011) found that a PC3 xenograft model produced in nude mice with simvastatin treatment exhibited reduced tumor growth associated with decreased Akt activity and reduced PSA levels.

Site of xenograft

Subcutaneous xenograft  Athymic mice lack mature T-cells, which enable cross-species ‘xenografted’ tissues, including tumor cells, to be tolerated by the immune system of the recipient animal and subcutaneous xenograft of tumor cells has been performed in most preclinical studies to date. The advantages of subcutaneous tumor models are their ease of tumor establishment, management, and reproducibility. However, there is no metastasis observed with conventional subcutaneous xenografts (Kerbel 2003).

Subrenal capsular xenograft  Renal grafting is the process of recombining PCa cells with rat urogenital sinus mesenchyme cells and then transplanting this recombiant tissue beneath the kidney capsule in an immuno-deficient mouse to assess growth and other phenotypes (Xin et al. 2003). Another purpose for renal grafting is to determine the physiological significance of genes that cannot be studied via whole-body knockouts due to embryonic lethality, for example, the Rb (Rb1)-null mouse (Hayward et al. 2003). This procedure is also used to determine the ability of putative basal-like prostate stem cells from either the normal mouse prostate or mouse PCa tissues to generate prostatic tissue and ducts (Lawson et al. 2007, Liao et al. 2010). Similarly, the model has been used to show that castration-resistant Nkx3.1 (Nkx3.1)-expressing cells (CARNs) are putative prostate luminal epithelial stem cells (Wang et al. 2009).

Orthotopic transplantation model  In the experiment where prostatic (orthotopic) transplantation of PC-3M and LNCaP cell lines were transplanted into male nude mice, lymph node metastases were observed in all mice given an injection of PC-3M cells in the prostate (Stephenson et al. 1992). Rembrink and co-workers found local growth of LNCaP cells in 7 of 10 animals, and lymph node metastasis in 4 of 10 animals. Significant serum PSA levels and strong AR expression in primary and metastatic tumor tissues were observed (Rembrink et al. 1997). Pettaway et al. (1996), using orthotopic transplantation, reported on the generation of variants of PC3 and LNCaP with an increased metastatic potential, producing tumors in lung and bone. Thalmann et al. (1994) were able to select a LNCaP subline, C4-2, with increased metastatic potential to lymph nodes and bone.

PC3-green fluorescent protein (GFP) cells were grown subcutaneously and then sectioned into small fragments and surgically implanted into the mouse prostate (Yang et al. 1999). This experiment yielded extensive bone metastasis in three out of five mice. LNCaP sublines labeled with GFP were also shown to metastasize to mouse bone (Patel et al. 2000). Castration following orthotopic implantation of xenografts from LuCaP 23.8 and LuCaP (Corey et al. 2003) yielded mice that were PSA-positive on bone marrow reverse transcriptase PCR, suggesting the presence of micrometastases after castration (Corey et al. 2003b).

Co-xenograft models  Co-xenograft models are very useful for investigating the role of two or more different factors in PCa as well as tumor microenvironment. Chung and colleagues coinoculated NbF-I (a fibroblast cell line established from the ventral prostate of Nb rats) and NbE-I (an epithelial cell line established from the ventral prostate of Nb rats) subcutaneously into either adult male syngeneic rats or athymic nude mice and induced the development of tumors that resembled carcinosarcoma on histopathological evaluation (Chung et al. 1989). Camps et al. (1990) reported that co-inoculation of tumorigenic NbF-I fibroblasts with human PC-3 prostatic carcinoma cells accelerated tumor growth and shortened tumor latency period. Gleave et al. (1991) co-inoculated LNCaP cells and various nontumorigenic fibroblasts into athymic mice to evaluate the role of tumor cell–host stromal interaction and stromal specific growth factors in PCa growth and progression. They demonstrated that fibroblasts differed in their ability to promote prostatic carcinogenesis. Craig et al. (2008) showed that co-inoculation of male athymic nude mice with PC-3 PCa cells and U937 promonocytic cells enhances tumor growth and increases tumor angiogenesis. Li et al. (2008) used stromal–epithelial co-injection xenograft to demonstrate that the expression of stromal AR inhibits PCa growth.

Genetically engineered mouse models  To generate a mouse model that can better recapitulate genetic events occurring in human PCa, many genes, including oncogenes, growth factors and growth factor receptors, steroid hormones, homeobox genes, and cell-cycle regulators, as well as pro- and anti-apoptotic genes and tumor suppressors, have been engineered to generate gain- or loss-of-function mouse models (Tables 2–5). These mouse models are powerful tools to study tumor biology,
the molecular mechanisms, and tumor progression. For example, transgenic mouse models have been designed to elucidate the series of events of progression from prostate intraepithelial neoplasia (PIN), a precursor of PCa, to carcinoma in situ, to invasive carcinoma and further progression to metastasis.

Models with viral oncogenes

**TRAMP/LADY models**  The first transgenic adenocarcinoma of the mouse prostate (TRAMP) model utilized expression of viral oncogenes in the prostate epithelium (Greenberg et al. 1995, Gingrich et al. 1997). In this model, expression of both the large and small SV40 tumor antigens (T/Tag) was regulated by the prostate-specific rat probasin promoter (PB). The hemizygous TRAMP mice develop progressive forms of PCa with distant site metastasis and exhibit various forms of disease from mild intraepithelial hyperplasia to large multinodular malignant neoplasia. TRAMP hemizygotes can exhibit PIN by 12 weeks of age and adenocarcinoma can arise by 24 weeks of age, mostly in the dorsal and lateral lobes of the prostate. This model was also the first to display castration-resistant disease. Castration of mice at 12 weeks of age did not affect primary tumor development or metastasis in the majority of TRAMP mice. Recently, it has been reported that the carcinoma developed from TRAMP mice exhibits mostly neuroendocrine phenotype (Chiaverotti et al. 2008). While TRAMP may be problematic in studies of oncogenesis, it is and can be used for treatment and prevention studies.

The LADY model is pathologically similar to the TRAMP model. The large PB promoter was used to express only the large-T antigen that led to the development of glandular hyperplasia and PIN by 10 weeks of age, followed by high-grade epithelial dysplasia and poorly undifferentiated adenocarcinoma by 20 weeks. There are several LADY model derivatives and some of them show neuroendocrine features (Kasper et al. 1998, Ishii et al. 2005). These models differ from human PCAs in two key respects: the rapid rate of disease progression and the prevalence of neuroendocrine differentiation of the tumor cells.

**Mouse model based on c-Myc oncogene overexpression**  The Myc oncogene enhances cell proliferation and amplification and/or overexpression of Myc has been detected in up to 30% of prostate tumors. Transgenic mice have been developed that express the Myc transgene at different levels depending on the different promoters in which they were integrated with (Ellwood-Yen et al. 2003). The Myc transgene controlled by the PB promoter has low level of expression (Lo-Myc) and the Myc transgene controlled by a reconstructed PB promoter, ARR2PB (androgen-responsive regions PB) (Zhang et al. 2000) has high level of expression (Hi-Myc). PIN lesions were detected at 2 weeks in the Hi-Myc mice, and by 4 weeks in the Lo-Myc mice, progressing to invasive adenocarcinoma by 3–6 months in Hi-Myc mice and by 10–12 months in Lo-Myc mice.

**Mouse models based on hormone receptors**  A transgenic model has been developed that selectively targets the expression of AR to the prostate epithelium under the control of a fragment of the rat PB promoter (Stanbrough et al. 2001). In this model, mice developed hyperplasia by 1 year of age, and mice older than 1 year developed focal areas of neoplasia resembling human HGPIN. These studies suggest a role for these receptors in early PCa progression; however, they also demonstrate the intricate nature of PCa carcinogenesis, requiring more than one gene change. While informative, long latent periods and the absence of metastases have limited the scope of these models, especially for therapy evaluation and for understanding late events in PCa progression. Niu et al. (2008) identified different roles of AR in prostate stromal and epithelial cells with the inducible (ind)-AR knockout (ARKO)-TRAMP and prostate epithelial-specific ARKO TRAMP (pes-ARKO-TRAMP) mouse models. The tumors developed in pes-ARKO-TRAMP mice were larger with a higher proliferation index compared with ARKO TRAMP tumors, where AR is lost in both epithelium and stroma.

Han et al. (2005) demonstrated that expression of an AR E231G mutant led to rapid development of metastatic PCAs with 100% penetrance while the AR-T857A mutant did not lead to tumor growth. Their study supported the hypothesis that AR is a proto-oncogene and that abrogation of the classical AR signal pathway by mutation or hormonal perturbation can facilitate the transformed state. This model not only explains the initially dramatic response observed in PCAs patients to hormone withdrawal, it also provides a paradigm for the subsequent emergence of hormone-therapy-resistant disease.

Albertelli et al. (2008) created mice bearing humanized AR genes (h/mAr) varying in polymorphic N-terminal glutamine (Q) tract length. The polyQ length is related to PCa initiation and androgen independence in distinct manner, with short 12Q developing palpable tumor faster in intact mice and later in castrated mice.
**TMPSRSS: ERG fusion gene transgenic mice**  
The genes, **TMPSRSS2**, which is regulated by the male sex-hormone androgen, and **ERG**, a potential oncogene, are located close to one another on chromosome 21. When fused, **TMPSRSS2** drives over-expression of the **ERG** gene.

**Klezovitch et al. (2008)** found that overexpression of **ERG** in prostate cell lines increased cell invasion and targeted expression of this transcript in vivo in luminal prostate epithelial cells of transgenic mice results in PIN. Other data have shown that for a transgenic mouse strain overexpressing **Erg** both PIN and invasive cancer developed only when this strain was crossed with **Pten**-deficient mice (**Tomlins et al. 2008, Carver et al. 2009**). This study showed that PCa specimens containing the **TMPSRSS2**–**ERG** rearrangement (~40%) are significantly enriched for **PTEN** loss. These data implicate **PTEN** loss and **ERG** rearrangements as associated events that act in tandem to promote PCa progression, potentially by inducing transcription of downstream checkpoint genes involved in promoting cell proliferation, senescence, and survival.

**Mouse models based on growth factors and growth factor receptors**  
A transgenic mouse model of activated **HER2/Neu (Erbb2)** receptor, a member of the epidermal growth factor receptor (EGFR) family, driven by the mouse probasin gene promoter has been developed (**Li et al. 2006**). These mice develop prostatic atypical hyperplasia followed by PIN and invasive carcinoma; immunostaining of which indicates that the tumors are not neuroendocrine in origin. Microarray- and immunophenotyping-based expression profiling of these tumors has revealed altered expression of several novel genes (>50) together with increased expression of **EGFR**, **Erbb3**, and phosphorylated AR (**Li et al. 2006**).

Fibroblast growth factor, 8-isoform b (**FGF8b**) showed high expression in human clinical sex-organ-related cancers including hormone-refractory PCa. Transgenic mice overexpressing **FGF8b** under the control of the **ARR2-PB** promoter developed multifocal epithelial hyperplasia followed by high-grade PIN, but this did not lead to local invasion or metastases (**Song et al. 2002**). Transgenic mice overexpressing **FGF7** under the control of **PB** promoter develop prostate epithelial hyperplasia after 12 months of age, which does not progress to invasive carcinoma (**Foster et al. 2002**). Similar results have been obtained when **FGF** receptors are targeted; transgenic mice overexpressing **FGFR1** under the control of **ARR2-PB** promoter develop various grades of PIN (**Song et al. 2002, Freeman et al. 2003**), and other studies also demonstrated that **FGFR1** is the most important **FGF** receptor in promotion of prostate carcinogenesis (**Acevedo et al. 2007**).

Transgenic models based on **FGFR2iib**, transforming growth factor receptor β (TGFβ), **IGF1**, keratinocyte, and **EGF**s have also been developed.

**Knockout mouse models based on tumor suppressor genes**  
Tumor suppressor genes are frequently mutated or lost in human cancer. A number of transgenic models have been generated by altering tumor suppressor genes.

**Mice with p53 (Trp53) mutation**  
Modification of p53 expression in PCa has been performed either by mutation or by loss of one copy of the **p53** gene. **Elgavish et al.** used a gene encoding a mutant **p53**, placed under the control of the rat **PB** to study the role of **p53** mutations in PCa. The resulting transgenic mice exhibited HGPIN lesions (grades III–IV) by 52 weeks of age together with reduced apoptotic potential (**Elgavish et al. 2004**).

**Loss of function of the retinoblastoma protein (pRB) mice**  
The retinoblastoma tumor suppressor gene, **Rb**, located at 13q has also been associated with PCa, and its mutations can be early events in PCa. A transgenic mouse with a conditional deletion of **Rb** gene specifically in prostate epithelial cells was generated. Inactivation of pRB family proteins (Rb/p107/p110) in prostate epithelium can induce epithelial proliferation and apoptosis and is sufficient to produce PIN, adenocarcinomas develop in all mice with no evidence of neuroendocrine tumors (**Hill et al. 2005**).

**Pten-deficient mice**  
**PTEN** is a key tumor suppressor, and its loss has been linked to many cancers, including a strong correlation with PCa. Indeed, loss of function in phosphatase and tensin homologue deleted from chromosome 10 (PTEN) is found in about 35% of primary PCa and 63% of metastatic tissues. **Pten** knockout mouse was created by generating a null mutation in the **Pten** gene and showed that **Pten** inactivation enhanced the ability of embryonic stem cells to generate tumors in nude and syngeneic mice (**Di Cristofano et al. 1998**).

**Wang et al. (2003)** generated the murine **PTEN** PCa model which recapitulates the disease progression seen in humans: initiation of PCa with PIN, followed by progression to invasive adenocarcinoma, and subsequent
metastasis (Trotman et al. 2003) generated a hypomorphic \textit{Pten} mouse mutant series with decreasing PTEN activity: \textit{Pten}^{hy/+} > \textit{Pten}^{+/−} > \textit{Pten}^{hy−} > \textit{Pten} prostate conditional knockout (\textit{Ptenpc}) mutants. They found that the extent of \textit{Pten} inactivation in a dose-dependent fashion determines PCa progression, its incidence, latency, and biology. The dose of PTEN affects key downstream targets such as \textit{Akt}, \textit{p27Kip1} (\textit{Cdkn1b}), \textit{Mtor}, and \textit{Foxo3}.

**Nkx3.1 knockout mice** Nkx3.1 is a prostate tumor suppressor gene which is essential for normal prostate function and epithelial proliferation. Mutations of Nkx3.1 are found in 60–80% of prostate tumors. Nkx3.1 knockout mice (conventional and conditional) display epithelial hyperplasia and PIN with increasing age. Neoplastic properties are associated with homozygous deletion, but mutants fail to develop invasive carcinoma (Abate-Shen et al. 2000). This mouse line provides a model for studying early stage disease (Abdulkadir et al. 2002).

**Transgenic mice with multiple genetic mutations**

Targeted deletion of \textit{Rb} showed that the conditional loss of even a single allele of this gene in the prostate epithelial cells causes focal hyperplasia, providing a model for studies of early stage PCa (Maddison et al. 2004). In addition, tissue recombination with \textit{Rb} has revealed that the deletion of this gene may predispose prostate epithelial cells to carcinogenesis (Wang et al. 2000). Interestingly, in contrast to the conditional silencing of either \textit{p53} or \textit{Rb}, the synergistic inactivation of both genes results in invasive carcinomas (Zhou et al. 2006). These mice developed highly metastatic tumors that are resistant to androgen ablation and share several molecular features seen in advanced-stage human PCa. Zhong et al. (2006) generated a new combinatorial mouse model which harbors the \textit{Fgf8b} transgene and haploinsufficiency in PTEN, both in a prostate-epithelium-specific manner. In this model, prostatic adenocarcinoma can be yielded with readily detectable lymph node metastases, whereas single models with each of the defects were shown earlier to progress generally only up to PIN. This study indicated that the cooperation between \textit{Fgf8b} activation and PTEN deficiency is linked to acquisition of additional genetic alterations for the progression of the lesions to primary adenocarcinoma and a complete loss of PTEN function is required for the development of invasive cancer. These studies have reaffirmed the importance of multiple gene changes in the progression of PCa.

**PCa metastasis models**

According to recent literature, about 20–40% of PCa patients with follow-up will experience PSA recurrence after prostatectomy and 30% of these biochemically recurrent cases will develop overt metastasis (Antonarakis et al. 2012). The metastasis of PCa to bone is the most significant cause of morbidity and mortality in this disease (Logothetis & Lin 2005). Subcutaneous PCa xenografts do not yield metastatic lesions, therefore various other models have been developed to study PCa metastasis.

**Intracardiac injection**

Intracardiac injection of PCa cells has been a method used to produce skeletal metastases in animals, using Mat-LyLu, PC3M, LNCaP C4-2, and PC3 cell lines for injection (Rabbani et al. 1998, Wu et al. 1998, Shukeir et al. 2004). Injected cells via this method are subject to high blood flow and also circumvent the pulmonary clearance of cells compared with the tail vein injection models. LNCaP C4-2 cells showed the highest metastatic capability in SCID/bg mice. Retroperitoneal and mediastinal lymph node metastases were noted in three out of seven animals, whereas two of seven animals developed osteoblastic spine metastases. Intracardiac injection of LNCaP C4-2 in athymic hosts produced spinal metastases in one of five animals at 8–12 weeks postinjection; PC-3 injected intracardially also metastasized to the bone but yielded osteolytic responses. Metastases to the spine and long bones have been observed using this method, however, the disadvantage of this method is widespread metastasis to soft tissues in a pattern uncharacteristic of PCa.

**Intratibial and intrafemoral injections**

It is very difficult to establish a mouse model that spontaneously metastasizes to bone, therefore direct injection methods were used to study PCa cell–bone interactions and potential new therapies (Soos et al. 1996, 1997, Corey et al. 2003a). In some cases, these models have been incorrectly referred to as metastasis models, although they are more precisely studies of tumor cell growth in bone. Intratibial injections were first used to compare PCa cell lines’ relative ability to invade and grow in bone (Fisher et al. 2002). Femurs are larger than tibias and in cavity size, so intrafemoral injections can also be used as metastasis models. Fizazi et al. (2003) injected human MDA-PCa 2b cells into femurs of SCID mice to study the mechanism of these
cells forming osteoblastic lesions in bone. Intrabone injections represent an important model for the elucidation of the importance of genetic pathways and other factors in PCa metastasis to bone. Intratibial and intrafemoral injections provide a platform for studying bone microenvironment and bone–tumor crosstalk.

**Intraprostatic injection**

Intraprostatic injection in immunocompromised mice also provides a useful PCa metastasis model. Sato et al. (1997) injected LNCaP cells intraprostatically in SCID and athymic nude mice and found that primary tumor incidence after intraprostatic injection was 89% (39 of 44) and 60% respectively. In ten SCID mice with primary tumors, followed for 12 weeks, retroperitoneal or mediastinal lymph node metastases were found in 100% of mice, and microscopic pulmonary metastases were identified in 40%. Intraprostatic injection provides a useful animal model to investigate mechanisms of metastasis and to evaluate therapies targeted toward inhibiting the metastatic cascade. Other sites for tumor implantation leading to metastasis include i.p. injection (Bae et al. 1994).

**Transgenic mouse models for metastasis**

A few transgenic mouse models have been established to study PCa metastasis. Mice carrying mutant N-cadherin that lacks the extracellular domain expressed specifically in the prostatic epithelium have been crossed with the TRAMP model, and the bigenic offspring exhibited significantly faster progression to metastatic disease, as well as a marked increase in the rate of metastatic PCa to bone (Winter et al. 2003). Further studies indicated that the mouse background can influence the development of bone metastasis (Hotte et al. 2002, Wang et al. 2003).

Modifications of the mouse prostate reconstitution (MPR) model have produced bone metastases at a rate of 50–90% (Shaker et al. 2000). MPRs were produced by injection of either heterozygous (+/−) or nullizygous (−/−) p53-mutant fetal prostatic epithelial cells with the recombinant retrovirus Zipras/Myc 9. Thompson et al. (1995) used this model to create prostate tissue in which ras and Myc were overexpressed in cells homozygous or heterozygous for p53 deletions. Prostatic cancer was found in 100% of the heterozygous and homozygous p53 mutant MPRs with metastatic deposits in 95% of the mice. The pattern of metastasis was remarkably similar to that in human PCa with gross metastatic deposits in the lung, lymph nodes, bone, and liver of many animals. The limitations in studying bone metastases in metastatic CR PCa has been reviewed by Sturge et al. (2011).

SMADs are a class of proteins that function as central effectors of the TGFβ superfamily (Derynick et al. 1998). Smad4 was originally identified as a candidate tumor-suppressor gene that was somatically deleted/mutated/inactivated in many pancreatic or colorectal tumors (Takaku et al. 1998, Dai et al. 1999). Smad4Lox/− allele has been developed by Bardeesy et al. (2006). Ding et al. (2011) used the conditional Smad4Lox strain to study the role of SMAD4 in PCa. They found that the functional relevance of SMAD4 was further supported by emergence of invasive, metastatic, and lethal PCa with 100% penetrance upon genetic deletion of Smad4 in the Pten-null mouse prostate. Pathological and molecular analyses, as well as transcriptomic knowledge-based pathway profiling of emerging tumors, identified cell proliferation and invasion as two cardinal tumor biological features in the metastatic Smad4/Pten-null PCa model. This model-informed progression analysis, together with genetic, functional, and translational studies, establishes SMAD4 as a key regulator of PCa progression in mice and humans.

**PCa mouse models for stem cell studies**

Stem cells can divide and differentiate into diverse specialized cell types and can self-renew to produce more stem cells. In the prostate, basal, secretory luminal, and neuroendocrine cells are potential targets for cancer initiation (Taylor et al. 2010). PCa tumors contain a subpopulation of cancer stem cells (CSCs; Tang et al. 2007). There is increasing evidence that cell markers such as stem cell antigen-1 (Sca-1), a laminin receptor a6 integrin (CD49f), CD133 (prominin), CD44 and CD117 (c-kit, stem cell factor receptor) can be used to enrich for stem cells of the mouse prostate (Lawson et al. 2005, Leong et al. 2008). A single mouse prostate stem cell defined by a Sca-1+ CD133+ CD44+ CD117+ phenotype and implanted under the renal capsule can generate secretion-producing prostatic ducts consisting of basal, luminal, and neuroendocrine cells (Leong et al. 2008).

It was reported that introduction of constitutively active AKT in Sca-1-enriched murine prostate epithelial cells resulted in the initiation of prostate tumorigenesis. Moreover, the neoplasms that develop in the Rb−/−p53−/− knockout mouse model express Sca-1 and arise in the proximal region of the gland (Zhou et al. 2007). First, multiple lines of evidence demonstrate initiation of PCa from luminal (and possibly intermediate) cells, based on targeted gene disruption by Cre-recombinase under the...
control of the probasin (either probasin or ARRs/probasin) or PSA promoters that show luminal-cell-oriented expression. Second, multiple genetic targets involved, such as Pten (Ma et al. 2005), myc (Ellwood-Yen et al. 2003), and Nkx3.1 (Iwata et al. 2010), result in tumorigenesis under luminal-specific expression.

Choi et al. (2012) showed that prostate luminal cells are more responsive to Pten-null-induced mitogenic signaling. However, basal cells are resistant to direct transformation. Loss of PTEN activity induces the capability of basal cells to differentiate into transformation-competent luminal cells. Their study suggests that deregulation of epithelial differentiation is a critical step for the initiation of PCa of basal cell origin.

Targeted inactivation of Pten tumor suppressor gene with PSA-Cre recombinase (Ma et al. 2005), overexpression of human c-MYC under the control of Probasin and ARrPB (Ellwood-Yen et al. 2003) and overexpression of human MYC under the control of Nkx3.1 promoter (Iwata et al. 2010), all result in tumorigenesis under luminal-specific expression. Several recent reports have also shown that progenitor cells with luminal characteristics can initiate PCa. Targeted deletion of Pten in CARNs results in rapid formation of carcinoma after androgen-mediated regeneration (Wang et al. 2009). These data indicate that luminal cells, including the CARNs as luminal stem cells, represent a potential PCa cell of origin. Alternatively, prostate-specific conditional deletion of Pten by a probasin-Cre has been shown to result in a basal cell expansion compared with luminal cells, suggesting that disease in these mice is propagated by basal cells (Wang et al. 2006). More recently, it was found that cells expressing the basal cell-specific marker p63 could initiate PCa after deletion of Pten (Mulholland et al. 2009, Liao et al. 2010). Another group also showed that the basal fraction is an efficient target population for PCa initiation in response to multiple oncogenic events including activation of the PI3K pathway, enhanced AR signaling, and increased expression of the ETS family transcription factor ERG (Lawson et al. 2010). In addition, lentiviral overexpression of ERG1 in Lin Sca-1 CD49Fhi cells resulted in a PIN phenotype, while coactivation of Akt and AR signaling resulted in adenocarcinoma (Wang & Shen 2011). Lentiviral overexpression of activated Akt and ERG in CD49FhiTrop2hi cells resulted in high-grade PIN, and coexpression of these two genes together with AR resulted in adenocarcinoma with strong resemblance to clinical PCa (Goldstein et al. 2011).

Kim et al. (2009, 2012) showed that in the prostates of mice with concurrent homozygous deletion of Pten and focal c-MYC activation, cells were of higher grade and proliferated faster than single mutant (Pten-null) cells within the same glands. The p53 pathway was activated in Pten-deficient prostate cells and tissues, but c-MYC expression shifted the p53 response from senescence to apoptosis by repressing the p53 target gene p21Cip1 (Cdkn1a).

The CSCs can be purified by taking advantage of surface markers and fluorescence-activated cell sorting techniques. The CSC properties of these cell populations were primarily demonstrated by colony-forming assays and tumor regeneration in vivo transplantsations in immunodeficient mice. Human PCa stem cells sorted with CD133+ , CD44+ , and αβ1-integrinhi display high proliferative potential in colony-forming assays, as well as the ability to differentiate into a luminal phenotype in culture (Collins et al. 2005). These cells have the capacity of colony formation and tumor initiation following s.c. injection. Other investigations have demonstrated tumor formation from subpopulations of human prostate cell lines using renal grafting assays (Gu et al. 2007). Pten deletion of one allele leads to the development of high-grade prostate intra-cellular neoplasia (Podosypalina et al. 1999). In the conditional Pten deletion mouse line, Pten is lost in prostate epithelium (Wang et al. 2003). Loss of both alleles in prostate epithelium results in adenocarcinoma beginning at 9 weeks of age and invasive PCa that metastasizes primarily to lymph nodes subsequently (Wang et al. 2003). Flow-sorted Lin Sca-1 CD49Fhi cells from the Pten null mouse model have capacity to form tumor-like spheroids in vitro and gave rise to carcinoma lesions in the resulting grafts (Mulholland et al. 2009). Using a similar approach but by further enriching for the CSC subpopulation from tumors in the conditional Pten deletion model, Liao et al. (2010) showed that a minor population of epithelial cells possess self-renewal and spheroid-forming abilities along with multipotentiality for differentiation in vitro and the ability to form tumor-like granular structures in renal grafts. Moreover, the study of Liao et al. (2010) identifies that the stem cell activity of the CSCs could be positively influenced by the presence of the cancer-associated fibroblasts relative to the normal prostate fibroblasts, implying a role in a major compartment of the tumor progression of primary or recurrent PCa.

Goldstein et al. (2010) showed that basal cells from primary benign human prostate tissue can initiate PCa in immunodeficient mice. The cooperative effects of AKT, ERG, and AR in basal cells recapitulated the histological and molecular features of human PCa, with loss of basal cells and expansion of luminal cells expressing PSA and alpha-methylacyl-CoA racemase.
Epilogue

Mouse models are playing an important role in the efforts to elucidate the genetic, biochemical, and biological parameters that may distinguish between the primary androgen-dependent growth phase of PCa and the CRPC form of the disease. Important clues on the factors that are associated with PCa metastasis and the characteristics of cancer stem/progenitor cells are also being derived from models that await further validation and correlation to human PCa. Multiple immunocompetent mouse models with spontaneous PCa serve as assets in the investigation of disease mechanisms and potential novel therapies. The critical question that remains to be asked is why mouse PCa cells, irrespective of the nature or combination of genetic mutations either fail to- or turn inefficient in forming skeletal lesions in the host animals of the corresponding spontaneous tumor model. It seems that mouse bones, as compared with human bones, are not significantly permissive to the homing or growth of PCa cells. The underlying differences may relate to the nature of the species or to the sets of genetic mutations introduced to date in the spontaneous models. Perhaps, critical genetic aberrations in the tumorigenic cells that propel bone metastasis in man remain to be identified. The diversity, both within the tissue and between individuals, of PCa, it is very reasonable that there is no single model that recapitulates all features of PCa from initiation to progression including metastasis to bone, a clinically most significant attribute of human PCa. Therefore, further refinements of currently available models and/or development of new PCa models with novel technology to overcome the limitations of current models will be necessary to study the biology of PCa, metastasis, and new therapies.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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