The evolving biology and treatment of prostate cancer

Russel S. Taichman,1,2 Robert D. Loberg,1,3 Rohit Mehra,1,4 and Kenneth J. Pienta1,3

1University of Michigan Comprehensive Cancer Center, Ann Arbor, Michigan, USA.
2Department of Periodontics and Department of Oral Medicine, University of Michigan School of Dentistry, Ann Arbor, Michigan, USA.
3Department of Medicine, Department of Urology, and 4Department of Pathology, University of Michigan School of Medicine, Ann Arbor, Michigan, USA.

Nonstandard abbreviations used: AR, androgen receptor; BPH, benign prostatic hyperplasia; CCL, CC chemokine ligand; CXCL, CXC chemokine ligand; CXCR, CXC chemokine receptor; DHT, dihydrotestosterone; DRE, digital rectal exam; NCCN, National Comprehensive Cancer Network; PIN, prostatic intraepithelial neoplasia; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; SDF-1, stromal-derived factor–1.

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Since the effectiveness of androgen deprivation for treatment of advanced prostate cancer was first demonstrated, prevention strategies and medical therapies for prostate cancer have been based on understanding the biologic underpinnings of the disease. Prostate cancer treatment is one of the best examples of a systematic therapeutic approach to target not only the cancer cells themselves, but the microenvironment in which they are proliferating. As the population ages and prostate cancer prevalence increases, challenges remain in the diagnosis of clinically relevant prostate cancer as well as the management of the metastatic and androgen-independent metastatic disease states.

Prostate cancer accounts for 33% of all cancer diagnoses in American men (218,890 in 2007) as well as 9% of cancer deaths in men (27,050 in 2007) (1). Even though mortality has fallen by 25% over the last decade and the 5-year survival rate is approaching 100%, several challenges to decreasing the morbidity and mortality from this disease remain.

Autopsy studies have shown that at the time of death, approximately 70% of men have cancer in their prostate gland, but these cancers are most often not clinically relevant (generally referred to as latent, microscopic, or histologic). It has been estimated that 15%-30% of males over the age of 50 and as many as 80% of males over the age of 80 harbor microscopic, undiagnosed prostate cancer (2). Prostate cancer is currently diagnosed in 1 of 6 men and is treated because it is thought to be clinically relevant; however, it is fatal for only 3% of men. Prostate cancer is generally diagnosed because of an elevated prostate-specific antigen (PSA) level or abnormal digital rectal exam (DRE) (1). PSA is a protein produced by normal epithelial cells of the prostate gland as well as prostate cancer cells. It is present in small quantities in the serum of men without cancer, but is routinely elevated in the presence of prostate cancer and in other benign prostate disorders such as infection, inflammation, and benign prostatic hyperplasia (BPH). Serum PSA as a screening tool sets the upper limit of normal at 4.0 ng/ml; levels above that point identify men who should be considered for prostate biopsy. As a result of PSA screening, most cancers are now discovered while they are still localized to the gland, and overt metastatic disease at the time of diagnosis has become a relatively rare event (1, 3). Unfortunately, PSA does not distinguish which type of prostate cancer a man may have in his gland at a given time—a microscopic cancer that will never cause a problem, a clinically relevant cancer that will cause morbidity and mortality if left in place, or a cancer that is lethal and hence incurable with localized therapy because it has already metastasized to distant organs. Recent studies suggest that prostate cancer is being overdiagnosed 30%-50% of the time (i.e., finding clinically irrelevant cancers); others suggest that we may be treating 20 or more men in order to keep 1 man from dying of prostate cancer (3–7). The current challenge is to identify which men have disease that may be cured with treatment, and which men do not require treatment and therefore should not be exposed to the morbidities associated with therapy.

The goal of PSA screening is to provide a balance between missing clinically important cancers and performing unnecessary biopsies. Unfortunately, the sensitivity of the PSA test at the cutoff value of 4 ng/ml is only approximately 20%, and this has led to the overdiagnosis and treatment of many men with microscopic cancers that may not benefit from local treatment. In addition, approximately another 20% of patients who undergo primary treatment for prostate cancer still develop metastatic disease as a result of dissemination of cancer cells outside of the prostate prior to diagnosis. If the PSA level threshold for diagnosis is lowered to less than 4 ng/ml in an effort to catch these cancers prior to metastasizing, more cancers will be discovered and treated with the intent to cure, but the sensitivity for discovering cancers that may be clinically relevant would decrease even further. Thus the PSA cutoff of 4.0 ng/ml is neither highly sensitive nor is it specific to the diagnosis of clinically relevant, truly localized, prostate cancer. To address these issues, the major medical societies such as the American Cancer Society, the American Urological Association, and the National Comprehensive Cancer Network (NCCN) are changing their suggested screening guidelines (see American Cancer Society guidelines for prostate cancer screening) (8).

Tracking a man’s PSA level for several years may be very useful in differentiating between lethal and nonlethal cancers. Findings from the Baltimore Longitudinal Aging Study determined that 10–15 years before diagnosis, the PSA levels of men who eventually died of prostate cancer were rising at an exponential rate (6). Men who had

We are on the verge of accusing 1 in 5 men of having prostate cancer.
—H. Ballentine Carter, Prouts Neck, Maine, USA, November 2, 2006
Evolving screening guidelines for prostate cancer detection: NCCN early detection screening guideline. Physicians should initiate a discussion of the risks and benefits of early prostate cancer detection and offer baseline screening with DRE and PSA beginning at age 40. PSA values are shown in ng/ml. Men with PSA less than 0.6 ng/ml at age 40 should repeat screening at age 45; if PSA is less than 0.6 ng/ml at age 45, annual screening should be considered at age 50. If initial PSA at age 40 is 0.6 ng/ml or more, or if the patient has a family history of prostate cancer (+FH) or is African American, annual screening with DRE and PSA is recommended. If subsequent PSA is less than 0.6 ng/ml, the patient can repeat screening at age 45; all others should continue with annual screening. In the annual screening group, men with PSA 2.6–4.0 ng/ml, or whose PSA velocity (PSAV) exceeds 0.35 ng/ml yr, should be considered for biopsy. Biopsy is highly recommended for any individual with PSA greater than 4.0 ng/ml and for men with positive DRE at any point in the screening process. Note that PSA velocity measurements (shown in ng/ml/yr) should be made on at least 3 consecutive specimens drawn over a period of at least 18–24 months.
agents and/or ingestion of carcinogens (16–20). As premalignant lesions progress to primary cancer, to metastatic cancer, and to androgen-independent cancer, genetic alterations continue to accumulate within the tumor cells (Figure 3) (15–27). In addition to these genetic changes, androgens act as promoters for further growth and proliferation. The androgen testosterone is bound to sex hormone–binding globulin in the circulation (Figure 4). After DHT binds to the androgen receptor (AR), the receptor dimerizes and is phosphorylated and is then transported to the nucleus, where it binds to genes with androgen response elements, a process modulated by coactivators and corepressors (28, 29). If a normal prostate epithelial cell is prevented from metabolizing testosterone, it undergoes programmed cell death (i.e., apoptosis).

Prostate carcinomas present as different grades based on a histologic pattern that is scored by the Gleason grading system (30). In this system, the most prominent histologic pattern is assigned a grade of 1–5, and the second most common pattern is assigned another grade; these 2 grades are summed and reported as the total Gleason score. The most common pattern is a Gleason 3, and was generally well tolerated. Unfortunately, when the prostate cancers were analyzed by Gleason score, there were an increased number of high-grade prostate cancers (Gleason higher than 7) found in the finasteride arm than in the placebo arm of the trial. The reasons for this remain unclear, but several possible explanations exist. (a) The higher-grade cancers may be the result of the hormone treatment inducing a more poorly differentiated phenotype. This would mimic what is seen after treatment with androgen-ablating agents in men with hormone-refractory prostate cancer. (b) There was an almost 25% reduction in gland volume in the finasteride-treated group; this volume reduction would increase the likelihood that cancer, especially higher-grade cancer, would be sampled in a biopsy procedure. (c) A potential ascertainment bias may also be involved. Because finasteride decreases the symptoms of BPH and decreases PSA increases caused by BPH, men with persistently elevated PSA levels on finasteride would have an increased probability of harboring prostate cancer compared with men with high PSA levels not on finasteride. The study demonstrated a higher sensitivity of detecting prostate cancer in the finasteride arm, and this increased sensitivity may be responsible at least in part for the increased detection of high-grade cancers in that group (40–43). Men enrolled in this trial are still being followed, and further investigation will hopefully clarify these issues. In the meantime, finasteride has not been widely adopted as a chemopreventive agent for prostate cancer. Other agents that target testosterone metabolism by inhibiting 5α-reductase, such as dutasteride, are currently in clinical trial (44).

ETS family of transcription factors (31–34). This fusion of the 3’ end of the ETS family member to the 5’ end of TMPRSS2 leads to the overexpression of an androgen-responsive oncoprotein. The TMPRSS2-ETS fusions have been noted in over 70% of several series of hospital-based prostate cancers, suggesting that it may be one of the most common somatic molecular rearrangements in human cancer (35–37). The most common variant noted occurs via intronic deletion, resulting in the TMPRSS2-ERG 21q22.2 fusion. Evidence suggests that the TMPRSS2-ETS gene fusions first appear in late PIN lesions and are related to an invasive phenotype (35). TMPRSS2-ERG fusion prostate cancer is associated with higher tumor stage and prostate cancer–specific death as well as with specific morphologic features associated with aggressive prostate cancer: blue-tinted mucin, cribriform growth pattern, macronucleoli, intraductal tumor spread, and signet-ring features (34, 36, 37). Efforts are underway to identify these gene fusions in the urine of patients with prostate cancer to improve detection and predict prognosis (36).

Targeting steps in early prostate tumorigenesis for prevention

Men castrated at adolescence (eunuchs) lack traits attributable to male hormones and do not suffer from prostate cancer (38). This practice, while offering a potential cure for virtually all prostate cancer, has understandably not been widely accepted as a standard medical treatment and has left the scientific/medical community searching for other solutions. Because testosterone acts as a tumor promoter in at least early prostate cancer, it can be used as a target for the chemoprevention of prostate cancer.

The phase III Prostate Cancer Prevention Trial demonstrated that treatment with the 5α-reductase inhibitor finasteride for 7 years led to a 25% decrease in the incidence of prostate cancer in men over the age of 50 (39). This medication left potency intact and was generally well tolerated. Unfortunately, when the prostate cancers were analyzed by Gleason score, there were an increased number of high-grade prostate cancers (Gleason higher than 7) found in the finasteride arm than in the placebo arm of the trial. The reasons for this remain unclear, but several possible explanations exist. (a) The higher-grade cancers may be the result of the hormone treatment inducing a more poorly differentiated phenotype. This would mimic what is seen after treatment with androgen-ablating agents in men with hormone-refractory prostate cancer. (b) There was an almost 25% reduction in gland volume in the finasteride-treated group; this volume reduction would increase the likelihood that cancer, especially higher-grade cancer, would be sampled in a biopsy procedure. (c) A potential ascertainment bias may also be involved. Because finasteride decreases the symptoms of BPH and decreases PSA increases caused by BPH, men with persistently elevated PSA levels on finasteride would have an increased probability of harboring prostate cancer compared with men with high PSA levels not on finasteride. The study demonstrated a higher sensitivity of detecting prostate cancer in the finasteride arm, and this increased sensitivity may be responsible at least in part for the increased detection of high-grade cancers in that group (40–43). Men enrolled in this trial are still being followed, and further investigation will hopefully clarify these issues. In the meantime, finasteride has not been widely adopted as a chemopreventive agent for prostate cancer. Other agents that target testosterone metabolism by inhibiting 5α-reductase, such as dutasteride, are currently in clinical trial (44).
Understanding that prostate carcinogenesis occurs as a result of interactions between genes and the environment has led to the development of several other potential chemoprevention strategies that are aimed at preventing DNA damage or the proliferation of premalignant cells (Table 1) (15, 45, 46). Antioxidants, which are believed to prevent DNA damage by oxygen free radicals, are in clinical trials and include pomegranate juice, curcumin, vitamin D, vitamin E, selenium, and lycopene (45–48). The Selenium and Vitamin E Cancer Prevention Trial, a phase III randomized, placebo-controlled trial (32,400 enrolled) of selenium (200 μg/d) and/or vitamin E (400 IU/d) supplementation for a minimum of 7 years and a maximum of 12 years was initiated in 2001 to test the effectiveness of these agents to prevent prostate cancer (49).

It has been known for several decades that men from Asian countries have a much lower incidence of prostate cancer, and one hypothesis behind this observation is their high consumption of antioxidants in the form of naturally occurring estrogens (isoflavones) through the ingestion of soy and green tea (50). One such isoflavone, genistein, has been demonstrated to induce the expression of genes involved in defense against oxidative stress (51). In
addition, it has been demonstrated in breast and prostate cancer cells that genistein induces apoptosis and inhibits activation of cell survival genes in the NF-κB and Akt signaling pathways (50). Even though definitive evidence is lacking, many physicians recommend green tea as a preventive measure against prostate cancer.

Other strategies for prostate cancer prevention are also under investigation (Table 1). For reasons that remain unclear, prostate epithelial cells and prostate cancers have high levels of polyamines. These molecules are involved in many biochemical processes including cellular proliferation, cell cycle regulation, and protein...
As an inhibitor of ornithine decarboxylase, the rate-limiting enzyme in the polyamine synthetic pathway, α-difluoromethylornithine, is being studied as a chemoprevention agent (52). The selective estrogen receptor modulator toremifene is being investigated for its ability to inhibit the evolution of PIN to prostate cancer (53). In addition, 3,3′-diindolylmethane acts as an angiogenesis inhibitor and has been demonstrated to downregulate the androgen receptor and the AKT pathway in prostate cancer cells (54). Exisulind, an inhibitor of cGMP phosphodiesterase that induces apoptosis, has been studied extensively alone and in combination with other agents as both a preventive and a treatment for different stages of prostate cancer (55). Multiple nonsteroidal antiinflammatory drugs, including celecoxib, hold promise as chemoprevention agents for cancer, including prostate (46, 56).

### Targeting metastatic prostate cancer for treatment

Although metastatic prostate cancer remains an incurable disease at present, therapy can delay progression. The first step in treatment of metastatic disease is to block testosterone-driven proliferation of prostate cancer cells through androgen deprivation therapy with medical or surgical castration. This causes apoptosis in the majority of the prostate cancer cells and leads to a remission in the majority of patients for 18–36 months (28). During that clinical remission, cells that have escaped the requirement of testosterone to grow continue to proliferate, and a castration-independent clone (hormone refractory, androgen independent) of cells emerges as the predominant phenotype. Median survival time for men with androgen-independent disease is approximately 18–24 months (57). Current research is focused on understanding the molecular events that underlie the transition to androgen independence in order to develop new treatment strategies.

### Targeting the androgen-independent prostate cancer cell

As a prostate tumor becomes androgen independent, multiple alternative cellular pathways, some involving the AR and others bypassing it, support tumor cell growth (Figure 4) (28, 29). These

### Table 1

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exisulind</td>
<td>Inhibits cGMP phosphodiesterase (55)</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>Inhibits COX-2; increases β-catenin (56)</td>
</tr>
<tr>
<td>Genistein</td>
<td>Multiple effects including downregulation of AR, ERα, PR, EGFR, and IGF1 (50, 51)</td>
</tr>
<tr>
<td>DFMO</td>
<td>Multiple effects caused by inhibited ornithine decarboxylase (52)</td>
</tr>
<tr>
<td>Diindolylmethane</td>
<td>Inhibits angiogenesis (54)</td>
</tr>
<tr>
<td>Toremifene</td>
<td>Selective ER modulator (53)</td>
</tr>
<tr>
<td>Selenium yeast</td>
<td>Antioxidant (49)</td>
</tr>
<tr>
<td>Vitamin D analog</td>
<td>Antioxidant (45)</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Antioxidant (49)</td>
</tr>
<tr>
<td>Pomegranate</td>
<td>Antioxidant (47)</td>
</tr>
<tr>
<td>Lycopene</td>
<td>Antioxidant (48)</td>
</tr>
<tr>
<td>Curcumin</td>
<td>Antioxidant (48)</td>
</tr>
<tr>
<td>Finasteride</td>
<td>Inhibits 5α-reductase (39)</td>
</tr>
<tr>
<td>Dutasteride</td>
<td>Inhibits 5α-reductase (44)</td>
</tr>
</tbody>
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For more information, see ref. 46. ER, estrogen receptor; DFMO, α-difluoromethylornithine; PR, prostaglandin receptor; COX-2, cyclooxygenase-2.

### Table 2

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Target</th>
<th>Sample agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate cancer cell</td>
<td>Aberrant growth factor receptor activation</td>
<td>EGFR: gefitinib (66); PDGF: imatinib (70); IGF1R: A12 (71); receptor tyrosine kinase: BAY 43-9006 (69); IL-6: CNT0328 (68)</td>
</tr>
<tr>
<td></td>
<td>Bcl-2</td>
<td>AT101 (73)</td>
</tr>
<tr>
<td></td>
<td>Microtubules</td>
<td>Ixabepolone halichondrin (79–81)</td>
</tr>
<tr>
<td></td>
<td>DNA replication</td>
<td>Satraplatin (77)</td>
</tr>
<tr>
<td></td>
<td>Histone deacetylase</td>
<td>Vorinostat (78)</td>
</tr>
<tr>
<td></td>
<td>Proteasome</td>
<td>Bortezomib (64)</td>
</tr>
<tr>
<td></td>
<td>Hsp90</td>
<td>17-AAG (60)</td>
</tr>
<tr>
<td></td>
<td>Clusterin</td>
<td>OGX-011 (76)</td>
</tr>
<tr>
<td></td>
<td>mTOR</td>
<td>Rapamycin analogs (75)</td>
</tr>
<tr>
<td></td>
<td>? Proliferation</td>
<td>Calcitriol, DN-101 (82)</td>
</tr>
<tr>
<td>Osteoblast</td>
<td>Endothelin-1 receptor</td>
<td>Zoledronic acid, samarium, strontium (100–102)</td>
</tr>
<tr>
<td>Osteoclast</td>
<td>Pyrophosphate</td>
<td>Denosumab (103)</td>
</tr>
<tr>
<td></td>
<td>RANKL</td>
<td>Dasatinib (104, 105)</td>
</tr>
<tr>
<td></td>
<td>SRC</td>
<td>SRC inhibitors; denosumab (103)</td>
</tr>
<tr>
<td>Endothelial cell</td>
<td>VEGF</td>
<td>Bevacizumab, VEGF-TRAP (108, 112)</td>
</tr>
<tr>
<td></td>
<td>VEGFR</td>
<td>Sunitinib, vatalanib, sorafenib (109–112)</td>
</tr>
<tr>
<td></td>
<td>αvβ3 Integrin</td>
<td>TAE 226, VEGFR-TRAP (108, 112)</td>
</tr>
<tr>
<td></td>
<td>Permeability</td>
<td>Cilengitide (114)</td>
</tr>
<tr>
<td></td>
<td>Macrophages</td>
<td>Dimethylxanthenone (113)</td>
</tr>
<tr>
<td>Immunologic activation</td>
<td>Macrophages</td>
<td>CNT0888 (97)</td>
</tr>
<tr>
<td></td>
<td>T cells (CTLA-4)</td>
<td>MDX-010 (119)</td>
</tr>
<tr>
<td></td>
<td>Dendritic cells</td>
<td>Sipuleucel-T (117); GVAX (118)</td>
</tr>
<tr>
<td></td>
<td>Cell antigens</td>
<td>MUC-1 antibodies (120), PSMA (J591 conjugates) (121, 122)</td>
</tr>
</tbody>
</table>

CTLA-4, CTL-associated antigen–4; Hsp, heat shock protein; mTOR, mammalian target of rapamycin; MUC-1, Mucin 1; RANKL, receptor activator of NF-κB ligand.
alternative pathways include: (a) amplification of the AR with associated hypersensitivity to lower levels of DHT; (b) broadening of the specificity of the AR to other hormone molecules (receptor promiscuity); (c) activation of the AR through phosphorylation by nonhormone kinases (outlaw pathways); (d) activation of growth through pathways that are independent of the AR (bypass pathways); and (e) repopulation of the tumor through androgen-independent stem/progenitor cells.

Amplification of the AR is common in androgen-dependent disease and is likely secondary to either gene amplification as a result of mutation or through selective pressure of the androgen-depleted environment, causing the death of cells with fewer ARs and the clonal expansion of cells with more ARs (58, 59). Potential methods to target continued activation of ARs include the development of better antiandrogens that competitively bind the AR, inhibiting AR dimerization by blocking the dissociation of AR from the heat shock protein Hsp90 using geldanamycin (17-AAG), altering proteasome degradation of AR, and inhibiting cofactor binding to the AR (Table 2 and Figure 4, pathways i and ii) (60–64).

The phosphorylation and subsequent outlaw activation of the AR by deregulated growth factors and their downstream signal transduction kinase pathways, including IGF, keratinocyte growth factor, PDGF, EGF, and IL-6, are being targeted in clinical trials using antibodies or small-molecule kinase inhibitors (Table 2 and Figure 4, pathway iii; refs. 65–71).

Androgen-independent prostate cancer cells have been demonstrated to frequently upregulate antiapoptotic molecules including Bcl-2, allowing them to bypass their need for androgens for cell growth and survival (Table 2 and Figure 4, pathway iv) (72–74). Anti-Bcl-2 agents include AT101, which binds to the BH3 domain of Bcl-2 (73).

Inactivation of the tumor-suppressor gene PTEN with subsequent activation of Akt is also a frequent event in androgen-independent prostate cancer cells, and this is being targeted through the inhibition of mammalian target of rapamycin (75). The cytoprotective gene Clusterin has been silenced using antisense oligonucleotide OGX-011 and is the subject of ongoing phase II clinical trials (76).

Multiple agents are under clinical development for androgen-independent prostate cancer that inhibit cancer cell proliferation.
Antimicrotubule agents including ixabepilone and halichon with chromatin unfolding and subsequent gene activation (78). Therapy (Figure 4, pathway v) (14). A small population of cells that ongoing clinical trials (82).

Suberoylanilide hydroxamic acid (vorinostat), which interferes within prostate tumors and is thought to be composed of prostate cancer stem or progenitor cells (14). Although prostate-specific agents have not been identified, multiple therapeutics are being developed for clinical investigation, including inhibitors of Hedgehog, Notch, and Bim1, developmental genes that have been identified as activated in multiple stem populations (83, 84).

**Targeting therapy to bone metastases**

Bone metastases are the major cause of morbidity, and ultimately mortality, for men with metastatic prostate cancer (85, 86). The interaction of prostate cancer cells with the bone microenvironment has been described as a vicious cycle in which prostate cancer cells interact with both osteoclasts and osteoblasts in a complex interplay resulting in osteoblastic metastases (Figure 5) (85–87). Prior to the establishment of this vicious cycle, data suggest that the presence of the primary tumor can have positive and negative effects on the successful migration and growth of cancer cells at distant sites. Primary tumors appear to act in an endocrine fashion to alter the marrow environment and prime it for the arrival of metastatic cells by creating a premetastatic niche (88). Factors such as hypoxia and inflammation promote the release of factors resulting in the mobilization of bone marrow–derived endothelial progenitor cells and hematopoietic progenitor cells that circulate to distant sites and dictate the localization of metastatic spread of the tumor cells (88–91). Alternatively, primary tumors can also produce growth-inhibitory cytokines such as angiostatin, which suppress the growth of metastases (92, 93).

Prostate cancer cells that successfully metastasize to bone marrow hijack several properties exhibited by normal host cells that traffic through the circulation and bone marrow. For example, prostate cancer cells mimic hematopoietic stem/progenitor cells by upregulating the expression of stromal-derived factor–1 (SDF-1; also known as CXC chemokine ligand 12 [CXCL12], receptor CXCR4, which results in chemoattraction to the SDF-1 secreted by the osteoblasts (94, 95) (Figure 6). Moreover, SDF-1 signaling through CXCR4 triggers the adhesion of prostate cancers to bone marrow endothelial cells and osteoblasts by activating CD164 and αvβ3 integrins (94–96). Similarly, prostate cancer cells mimic monocytes by responding to CC chemokine ligand 2 (CCL2; also known as monocyte chemoattractant protein–1) secreted by bone marrow endothelial cells (97). In conjunction with prostate cancer cells using the chemokines of hematopoietic cells for homing and traffic to the marrow, it appears that the cancer cells also target the adhesive-localization molecules used by hematopoietic cells. One such molecule is annexin II. Blocking annexin II binding prevents stem cell engraftment and prostate cancer homing to the marrow (98). A key implication of these data is that soluble and insoluble factors produced in the marrow play a crucial role in the osteotropism of prostate cancer to bone (87, 99).

While the mechanisms that result in osteoblastic metastases rather than the osteolytic metastases found in most cancers that spread to bone remain obscure, the recognition that metastatic lesions are complex systems involving a supporting framework of multiple host cells has allowed the development of several strategies that target these complex tumor cell–microenvironment interactions as well as the signal transduction pathways of other cells important to the development of metastases (Table 2 and Figure 5). The most successful of these strategies to date has been the use of the bisphosphonate zoledronate in patients with androgen-independent prostate cancer (100). Bisphosphonates, as analogs of pyrophosphate, inhibit osteoclast maturation and function.

**Figure 6**

Prostate cancer mimicry of HSC/progenitor cell homing mechanisms. The metastatic process of prostate cancer cells (PCa cells) is functionally similar to the migrational, or homing, behavior of HSCs to the bone marrow. Numerous molecules have been implicated in regulating HSC homing, participating as both chemottractants and regulators of cell growth. Endothelial cell–derived factors such as CCL2 act as chemottractants and growth factors for HSCs. Tumor-associated macrophages, and prostate cancer cells. Osteoblasts produce the chemokine SDF-1 (CXCL12), which further guides both HSCs and prostate cancer cells into the marrow through their expression of the CXCL12 receptor CXCR4. Both HSCs and prostate cancer cells use the cell surface protein annexin II (Anxa2) on both endothelial cells (not shown) and osteoblasts as a dock/lock mechanism into the bone microenvironment. Conceptually, prostate cancer cells act as parasites of the HSC niche by coopting HSC chemokinases and attachment sites to initiate a cascade of events that result in the osteoblastic metastases observed in prostate cancer patients.

by interfering with DNA replication or mitosis. A phase III trial of satraplatin, an oral platinum that inhibits replication through the formation of DNA adducts, has demonstrated activity as a second line chemotherapy for patients with androgen-independent disease (77). The increased understanding of the relationship between DNA and chromatin structural proteins has led to the development of histone deacetylase inhibitors such as suberoylanilide hydroxamic acid (vorinostat), which interferes with chromatin unfolding and subsequent gene activation (78). Antimicrotubule agents including ixabepilone and halichondrin are also under active study (79–81). Vitamin D acts as an antiproliferative agent through a variety of poorly characterized mechanisms, and high-dose calcitriol, DN-101, has demonstrated activity in androgen-independent disease and is the subject of ongoing clinical trials (82).

Another potential mechanism for survival in the androgen-depleted environment is the presence of prostate cancer stem cells that continually regenerate a heterogeneous tumor cell population that is observed in androgen-independent patients despite therapy (Figure 4, pathway v) (14). A small population of cells that are CD44+/αvβ3+CD133+ and do not express AR has been identified within prostate tumors and is thought to be composed of prostate cancer stem or progenitor cells (14). Although prostate-specific agents have not been identified, multiple therapeutics are being developed for clinical investigation, including inhibitors of Hedgehog, Notch, and Bim1, developmental genes that have been identified as activated in multiple stem populations (83, 84).
Another approach under active investigation is the interruption of macrophages induced by CCL2 is the subject of a planned clinical trial with an anti-CCL2 antibody, CNTO888 (Table 2) (97). Sipulin and proliferation of prostate cancer tumor by tumor-associated pain control in the majority of patients with osseous metastases. Dimethylxanthenone acts as a vascular disrupting agent by increasing cell permeability (113). Another strategy uses EMD 121974 (cilengitide), the inner salt of a cyclized pentapeptide containing the amino acid sequence RGD, which blocks the integrin-1 inhibitors that bind to the VEGFRs or with kinase inhibitors (Table 2). (115, 116). The infiltration of strategies (Table 2 and Figure 5) the inner salt of a cyclized pentapeptide containing the amino acid sequence RGD, which blocks the integrin-1 inhibitors that bind to the VEGFRs or with kinase inhibitors (Table 2) (97). 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