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Small-molecule protein tyrosine kinase inhibitors for the treatment of metastatic prostate cancer

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Abstract

The microenvironment is critical to the growth of prostate cancer (PCa) in the bone. Thus, for clinical efficacy, therapies must target tumor–microenvironment interactions. Several protein tyrosine kinases have been implicated in the development and growth of PCa bone metastasis. In this review, specific protein tyrosine kinases that regulate these complex interactions, including PDGFR, the EGFR family, c-Src, VEGFR, IGF-1R, FGFR and c-Met will be discussed, with an emphasis on why these kinases are promising therapeutic targets for metastatic PCa treatment. For each of these kinases, small-molecule inhibitors have reached clinical trials. Current results of these trials and future prospects for the use of tyrosine kinase inhibitors for the treatment of PCa bone metastases are also discussed.

Protein tyrosine kinases (PTKs) have become major targets in numerous types of solid tumors. These enzymes, which may be classified as receptor or nonreceptor kinases, are frequently mutated, overexpressed (because of gene amplification or increased translation) or increased in specific activity (due to activation or overexpression of ‘upstream’ molecules that lead to increased kinase activity). Small-molecule inhibitors, such as Gleevec, have shown remarkable success in controlling the earlier stages of chronic myelogenous leukemia, a disease ‘addicted’ to aberrant expression of the *BCR–Abl* fusion gene. Targeting Abl is highly successful prior to the very late stage of the disease (blast crisis) developing. Partly based on this paradigm and increasing knowledge of mechanisms by which PTKs are aberrantly activated, numerous small-molecule inhibitors as well as monoclonal antibodies, are now undergoing clinical trials to ‘block’ signaling from selective PTKs. In some instances, such as mutated EGFR found in a small percentage of lung cancer, and B-Raf mutations in melanoma, treatment with selective inhibitors has led to increased patient survival. Often, however, resistance arises through overexpression of a PTK not targeted by the initial treatment; for example c-Met overexpression, which often occurs in patients treated with targeted therapies to EGFR [1]. Nevertheless, our increasing knowledge of which PTKs may be ‘drivers’ of tumor progression and which contribute to resistance to both targeted therapies and chemotherapy is leading to better clinical trials that are gradually increasing survival of patients with numerous solid tumors.

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In **prostate cancer** (PCa), the roles of PTKs in progression, metastasis, and growth at the metastatic site (usually the bone) have also received considerable attention. However, there is little evidence that PCa is 'addicted' to any specific PTK. Rather, the complex interaction between microenvironment and tumor appears to be a major force in metastatic disease [2–5]. The progression of PCa in the bone is in part through the bidirectional interactions between the PCa cells and bone that leads to the vicious cycle, whereby tumor release factors affect bone remodeling, causing growth factors to be released from bone matrix and these bone-derived factors to further activate multiple tyrosine kinases in the tumor. These interactions do not mean that increased expression of specific PTKs is not important in PCa progression and metastatic growth in the bone; rather that the mechanisms by which PTK are involved in PCa progression are greatly influenced by their cognate growth factors in the microenvironment. As examples, the expression of receptor PTKs c-Met and IGF-R are increased in bone metastases, and this overexpression correlates with poor survival, discussed below [6–8], but the ligands for these receptors are also present in the bone, released by tumor/bone interactions (see later) and must be considered when small-molecule inhibitors of these enzymes are used in therapy, as these PTKs affect overlapping pathways. In addition, several PTKs affect androgen receptor (AR) signaling by phosphorylating AR [9]. Thus, the effects of inhibitors on AR must also be considered when PTK inhibitors are used in clinical trials. The following sections will describe the effects of PTK inhibitors in use in clinical trials for metastatic PCa; combination strategies with PTK inhibitors and other signaling inhibitors will also be described. **Tyrosine kinase inhibitors** (TKIs) that have already been tested clinically will be described first.

Src family kinases

The Src family kinases (SFK) comprises nine highly related nonreceptor PTKs (Src, Yes, Fyn, Lyn, Lck, Hck, Fgr, Blk and Yrk) [10]. Src, Lyn, and Fyn have all been demonstrated to play roles in PCa development and/or progression. The archetypal member, Src, was the first oncogene discovered [11], the first to demonstrate that viral oncogenes were derived from normal cellular proto-oncogenes [12] and the first to be demonstrated to have intrinsic PTK activity [13]. The structure of SFK and mechanisms of activation have been described extensively in numerous reviews [14,15]. Src family members are not directly activated by extracellular signals, but are often rapidly activated by binding to activated cellular receptors, including receptor PTKs and GPCRs, integrins and numerous inducers of stress response. As genetic and epigenetic alterations (overexpression of growth factor receptors and their ligands, and activation of integrins as examples) lead directly to Src activation during PCa progression, it is not surprising that SFK activity is increased in progressive stages of PCa [16].

In addition to Src, two of its related family members have been implicated in PCa, Lyn and Fyn, both of which are also overexpressed in PCa. Lyn is involved in prostate development, and a peptidomimetic inhibitor of Lyn slowed tumor growth *in vivo* [17]; a result confirmed by stable transfection and expression of a Lyn shRNA [18]. Fyn affects prostate cell proliferation and chemotaxis, especially in response to HGF [19], a growth/migration factor present in the bone microenvironment.

Ectopic expression of constitutively active mutants of Src, Yes and Fyn in primary prostate cells are able to induce prostate tumors after implantation into mice [20]. Although the mutations used to activate Src have not been demonstrated in PCa, all three kinases were able to induce tumors, with Src the most potent oncogene, followed by Fyn and Lyn. Thus, considerable preclinical evidence supports the use of SFK inhibitors in PCa and especially in PCa bone metastases.

Currently, four different small-molecule SFK inhibitors have reached clinical trials: dasatinib, saracatinib, bosutinib and KX2-391 [21]. The first three of these inhibitors compete for ATP binding, whereas KX2-391 competes with Src substrate binding. Importantly, all these inhibitors have additional targets to SFKs, and their efficacy may depend, in part, on these additional targets, with potentially unexpected consequences [22]. Considerable work must be performed before an understanding of the relevance of these additional targets to the efficacy of a given SFK inhibitor, but different side effects are observed from different inhibitors, suggesting different 'off-target' effects.

Of particular interest in PCa, the major defect observed in *src*^{-/-} mouse is osteopetrosis, a thickening of bones due to defective osteoclast function [23]. Hence, it would be predicted that Src inhibitors would have bone turnover effects in humans. This prediction was borne out by studies of Hannon *et al.* who tested the Src-selective inhibitor, saracatinib (AZD0530) on bone turnover in a Phase I trial in healthy men [24]. A dose-dependent decrease in bone resorption markers C-telopeptide of type 1 collagen (serum CTX) and N-telopeptide of type 1 collagen (urinary NTX) was observed in men treated with saracatinib relative to untreated men, in accordance with the expectation from the *src*^{-/-} mouse strain. Similar effects were seen in men with bone-metastatic PCa with the SFK/Abl inhibitor, dasatinib, described below.

As described above, saracatinib was first tested in healthy men in Phase I trials. More recently, saracatinib was used in a single-agent Phase II trial conducted by the California Cancer Consortium in patients with advanced castrate-resistant PCa (CRPC) [25]. While the drug was generally well tolerated, little clinical efficacy was observed in this study. These results are not unexpected, as considerable preclinical evidence suggests combination therapy will be required for efficacy of SFK inhibitors. Additional clinical trials have used dasatinib either twice daily [26] or, more recently, once a day [27] in CRPC patients with metastasis. The studies showed similar and encouraging results in a subset of patients.

Another recent study used dasatinib in combination with docetaxel in a Phase I/II [28] was sufficiently promising to be shortly followed by a Phase III trial. A subset of patients in the Phase I/II trial had durable responses of more than three years with no rise in prostate-specific antigen (PSA) yet observed. The Phase III trial is completed at the time of writing, but has yet to be unblinded. Thus, early trials on SFK inhibitors are showing promise. Determining why some patients respond well to SFK inhibitors, whereas others fail to do so remains an important challenge in determining the best utility of these inhibitors.

EGFR signaling axis

The EGFR family comprises four structurally related members, EGFR (ERBB1 and HER1); HER2 (Neu and ERBB2); HER3 (ERBB3) and HER4 (ERBB4) [29–32]. EGFR binds a number of ligands including EGF, TGF α and amphiregulin with high affinity. Other factors demonstrated to bind EGFR with lower affinity include betacellulin, heparin-binding EGF and epiregulin. These latter factors are also known to bind HER4. Neuregulins (NRGs) also bind members of the EGFR family, with NRG1 and NRG2 binding both HER3 and HER4, whereas NRG3 and NRG4 bind only HER4. Her2 is not directly bound by a ligand, but can heterodimerize with ligand-bound EGFR, participating in signal transduction. Homo- or heterodimerization is required to stimulate the intrinsic tyrosine kinase activity of the EGFR family, with heterodimers generally more strongly propagating downstream signals [32]. Activation of the EGFR family triggers numerous signaling pathways [33] important in development, proliferation and wound healing.

Several studies have demonstrated that EGF or TGF α can stimulate osteoclast formation, leading to bone resorption [34–36]. Because of this role in osteoclast function and bone

turnover, several inhibitors of EGFR and/or HER2/neu (both small-molecule inhibitors and monoclonal antibodies), including trastuzumab (a monoclonal antibody targeting HER2), gefitinib, also known as Iressa[®] (a small-molecule inhibitor targeting primarily EGFR), erlotinib (a small-molecule inhibitor targeting primarily EGF-R), pertuzumab (a monoclonal antibody to HER2 targeting a different epitope than trastuzumab) and lapatinib (a pan EGFR family inhibitor) have been used as single agents or in combination with chemotherapy in clinical trials in patients with CRPC [37–43]. Unfortunately, none of these trials has shown much promise [32].

The only member of the EGFR family quite frequently overexpressed in PCa is HER3 [44,45]. Inhibiting EGFR and HER2 leads to activation of HER3. Specifically, while inhibition of EGFR and HER2 decreased AR transcriptional activity, the remaining AR function was mediated by HER2/HER3 heterodimerization, not through EGFR [46]. Androgen withdrawal in androgen-dependent cell lines has also been shown to lead to increased HER3 expression [47], but inhibition of HER1 and HER2 sensitizes PCa cells to androgen withdrawal by decreasing HER3 expression [48]. Additionally, HER3 is increased in expression by inhibitors of PI3K in PCa cells, leading to upregulation of AR [49]. Biologic functions of signaling through HER3 in PCa and resistance to therapy are being rapidly elucidated. Soler *et al.* demonstrated that HER3 is required to maintain the motile and invasive phenotype of the prostate tumor cell line, DU-145 [50]. Collectively, these data suggest that HER3 may play an important role in PCa progression.

The above results suggest that pan EGFR inhibitors might hold promise in CRPC therapy. However, as discussed above, one such inhibitor, lapatinib, was ineffective in clinical trials [43]. In combination with erlotinib, the pan TKI inhibitor, MP470, inhibited growth of prostate tumor cell lines [51]. MP470 is being evaluated in Phase I clinical trials. Other pan EGFR inhibitors are in development, such as AZD8931 [52], but their effectiveness as therapies for PCa remain unknown. In light of our current knowledge, it is likely that pan HER3 inhibitors will be required to target EGFR family signaling, but their potential success will depend on use in combination therapy, especially with inhibitors affecting AR signaling.

PDGF/PDGFR signaling axis

The PDGF/PDGFR signaling axis results from complex interactions between several forms of the ligand that bind to their receptors. PDGFs are members of a family of four distinct polypeptides encoded by four different genes. The individual PDGFs are termed PDGF-A, PDGF-B, PDGF-C and PDGF-D. PDGFs function as homo- or hetero-dimers, linked through disulfide bonding. Specifically, five forms of PDGF dimers have been identified: PDGF-AA, PDGF-BB, PDGF-AB, PDGF-CC and PDGF-DD. Two PTK receptors for PDGFs have been identified: PDGFR α (activated by binding PDGF-AA, PDGF-AB, and PDGF-CC) and PDGFR β (activated by binding PDGF-BB and PDGF-DD) [53]. In addition, PDGFR α /PDGFR β form heterodimers that can be activated by binding of PDGF-BB, PDGF-AB and PDGF-CC. As with the other **receptor tyrosine kinases** discussed in this review, ligand binding leads to dimerization of the receptor. Transphosphorylation of the receptor occurs, which both activates the intrinsic tyrosine kinase activity of the receptor and leads to recruitment of signaling proteins including SFK, PI3K, and phospholipase C γ [54]. These interacting proteins induce signaling cascades that promote proliferation, survival and cell migration, although only PDGFR β /PDGFR β homodimers and PDGFR α /PDGFR β heterodimers are associated with chemotaxis of smooth muscle cells as well as fibroblasts. Crosstalk of PDGFR occurs with other signaling molecules, such as integrins [55]. Primary roles of PDGFs in adults include stimulation of wound healing [56] and regulation of interstitial fluid pressure of tissues [57,58]. Studies of genetically engineered mice have

demonstrated that PDGF is important in vessel maturation and recruitment of pericytes to blood vessels, the latter of which is a PDGFR β -dependent function [58].

The last of the PDGF family to be discovered, PDGF-D, has been implicated in malignant transformation [59], and is overexpressed in PCa, promoting angiogenesis and invasion by binding PDGFR β [60,61]. Overexpression of PDGF-D in PC3 PCa cells increased proliferation rates and invasion of these cells, and conditioned medium from PC3 cells overexpressing PDGF-D-induced tube formation in human umbilical vein endothelial cells [62], suggesting that PDGF-D promotes angiogenesis. Using the same system, this group further demonstrated that PDGF-D contributes to epidermal-to-mesenchymal transition (EMT) [63]. Thus, PDGF-D has been suggested as a novel target for PCa [59], although no specific inhibitors have yet to be developed.

In both primary PCa and bone metastases, PDGF-R is almost universally overexpressed relative to normal tissue, with very high expression in PCa bone metastases [64–66]. Using the metastatic PC3-MM2 cells implanted into the tibia of male nude mice, Uehara *et al.* demonstrated that treatment with the multikinase inhibitor, imatinib, with or without paclitaxel, decreased tumor proliferation and increased apoptosis [67]. In a second study, this group also demonstrated that intratibial implantation of PC3-MM2 cells that were multidrug resistant and insensitive to paclitaxel and imatinib *in vitro* were still sensitive to imatinib *in vivo* with or without paclitaxel, with decreased bone tumor incidence and tumor weight. PDGFR phosphorylation was inhibited in both tumor cells and endothelial cells, the latter of which underwent apoptosis, suggesting that imatinib-targeting of endothelial cells played a major role in the anti-tumor effects observed in this system, implicating the importance of targeting the microenvironment for treatment of PCa bone metastases [68], and that imatinib is important in inhibiting angiogenesis. These studies were, in part, responsible for initiating a Phase I/II study on imatinib, described below.

Small-molecule inhibitors of PDGFR have been developed and tested in clinical trials. The multi-institutional Phase II study using SU101 for the treatment of hormone-refractory PCa resulted in partial response in one of 19 patients [69]. A Phase I trial in androgen-independent PCa showed promising results based on PSA decline when imatinib mesylate was applied in combination with docetaxel [70]. A randomized study followed testing imatinib plus docetaxel versus docetaxel alone for the treatment of 144 men with progressive CRPC with bone metastases [71]. The results showed no significant difference in times to progression between the two groups of patients [71]. Another clinical trial that tested PDGFR inhibitor in neoadjuvant setting by combining imatinib therapy, docetaxel and hormone ablation in the preoperative setting in high risk localized PCa [72]. No pathological complete remissions were observed. The lack of promise from most of the clinical studies suggests that either PDGFR inhibitors are unlikely to be efficacious for the treatment of PCa or the right combinations of PDGFR inhibitors with other chemotherapy and/or signal transduction inhibitors have yet to be found.

VEGF & VEGF receptors

Angiogenesis, the growth of new from existing blood vessels, is critical for the development, growth and metastatic dissemination of tumors [73]. The search for tumor-derived factors contributing to this process led to the identification of VEGF, also known as VEGF-A, as an endothelial mitogen [74]. VEGF belongs to a family of structurally related dimeric proteins that includes VEGF-B, VEGF-C, VEGF-D and VEGF-E, as well as PlGF [75]. VEGF ligands activate angiogenic programs through binding of several receptors, including VEGF receptor (R)-1, -2, -3, and neuropilins (NRP). VEGFR-1 (Flt-1) binds VEGF, VEGF-B, and PlGF. VEGFR-2 (Flk-1/KDR) is expressed on nearly all endothelial

cells and binds VEGF, VEGF-C, VEGF-D and VEGF-E to control endothelial cell proliferation, migration and survival. Through binding to VEGF-C and VEGF-D, VEGFR-3 is thought to facilitate the outgrowth of lymphatic vessels. Additionally, NRP1/2 are co-receptors for VEGF. NRP1 binds the VEGF isoform VEGF₁₆₅ and PlGF, and NRP2 binds VEGF₁₆₅ and VEGF-C. Unlike other VEGFRs, NRPs lack intracellular signaling domains, and their specific role in angiogenesis is not fully understood [76]. Although VEGF-A binds VEGFR-1 with a higher affinity than VEGFR-2, the biological effects of VEGF-A are thought to be mediated through VEGFR-2. On ligand binding, VEGFR-2 dimerizes, resulting in kinase activation and autophosphorylation of tyrosine residues that leads to the activation of signal-transduction molecules including PI3K, Akt, Ras, Src, phospholipase C γ and MAPK [77].

In PCa, several parameters associated with tumor angiogenesis have been found in correlation with Gleason score, stage, metastatic progression, and survival. For example, high microvessel density, vascular size and irregularity are associated with increased long-term risk of death [78]. Moreover, VEGF and VEGF-C have been implicated in disease progression and **bone metastasis** [79–81], VEGF-C has been linked to lymph node metastasis [82], and elevated VEGF in plasma and urine is an independent indicator of poor prognosis [83,84]. VEGF plays a critical role during bone vascularization [85,86] and formation during normal development and repair [87,88] and the bone-remodeling process that takes place in PCa skeletal metastasis [80]. Moreover, tumor cell-derived VEGF can affect the proliferation and maturation of osteoclasts, osteoblasts, and their precursors in bone. For example, osteoclast precursors express VEGFR-1, which may facilitate their homing to the site of bone resorption and osteoclastogenesis [89,90].

Most therapeutic efforts directed toward inhibiting the angiogenic processes for the treatment of PCa have focused on the VEGF pathway. Several inhibitors have been tested, including bevacizumab (a monoclonal antibody that blocks human VEGF), aflibercept or VEGF-trap (a fusion protein of the VEGFR extracellular domain and the Fc portion of IgG1), antibodies that block the VEGFR (IMC-1121b), and small-molecule inhibitors of the VEGFR tyrosine kinases, which because of structural similarity, generally inhibit other target kinases, such as the PDGF and c-Kit receptors. Several different multi-targeted TKIs with some selectivity to VEGFR have been evaluated in PCa (including sorafenib, sunitinib, cediranib and pazopanib) [91–93], with the most number of trials using sunitinib. Two Phase II studies in predominantly metastatic castration-resistant patients showed single agent activity of sunitinib [94,95], often discordant with rising PSA levels. However, a Phase I/II trial of sunitinib in combination with docetaxel demonstrated promising results [96]. An independent study of sunitinib plus androgen deprivation in newly diagnosed, nonmetastatic PCa before prostatectomy described two pathologic complete responses after only 3 months of treatment in patients with high-grade disease [97].

Available data indicate that, in PCa, sunitinib affects endothelium and bone. Similar to other types of cancer, the concentrations of several mediators of angiogenesis including VEGF, soluble VEGFR-2 and soluble VEGFR-3 are significantly modulated upon treatment, consistent with an on-target effect [94,96]. Of relevance, and consistent with osteoclast expression of VEGFR-1 and CSF-1R, both sunitinib targets, serum N-telopeptides and thus osteoclast activity decreased in patients with bone metastasis treated with sunitinib [94]. Unfortunately, the available preliminary results of a large Phase III trial of sunitinib plus prednisone versus placebo plus prednisone in metastatic CRPC patients resistant or intolerant to docetaxel demonstrated no survival advantage for the experimental arm, suggesting that sunitinib may only benefit subpopulations of PCa patients or, alternatively, that redundant mechanisms of communication between tumor cells and stroma other than VEGF need to be simultaneously inhibited [98].

The IGF/IGF-R signaling axis

Two insulin-like growth factors (IGF1 and IGF2) have been identified, as have two receptor PTKs (IGF-1R and IGF-2R) to which these growth factors bind. Both IGF1 and 2 bind to IGF1R, whereas IGF2 (but not IGF1) also binds IGF-2R [99]. IGF-1R has emerged as a target in numerous solid tumors, including PCa. IGF-1R is synthesized as a single-chain precursor, which is processed in the Golgi to yield first a heterodimer then heterotetramer (2 α and 2 β chains) linked by disulfide bonds. IGF-1R can also heterodimerize with the insulin receptor and be activated by insulin [100]. IGF-1R is implicated in proliferation and survival of many tumor types [101], and is overexpressed in PCa [102]; IGF-1R signaling has been linked to PCa risk, and one of its ligands, IGF-1, is also overexpressed in PCa bone metastases [103] where it promotes proliferation and survival of PCa cells [104–108]. Studies with monoclonal antibodies to IGF-1R have implicated this receptor as important in PCa progression in androgen-sensitive as well as resistant tumor models [109]. Five fully humanized monoclonal antibodies to IGF-1R: IMC-A12, AMG 479, MK0646 and AVE1642 have reached clinical trial, but none has been tested specifically against prostate tumors [110].

Several small-molecule inhibitors of IGF-1R have been developed and are in various stages of preclinical and clinical trials. INSM-18 (nordihydroguaiaretic acid) has been tested in a Phase I/II clinical trial for patients with relapsed PCa [111]. While the drug was well tolerated, only one patient from the 11 evaluated on this trial had a decrease in PSA of more than 50%. A Phase II study on this agent for patients with nonmetastatic hormone-sensitive PCa was stopped early due to no significant PSA decline [112]. Another IGF-1R inhibitor in clinical trial is BMS754807 (with six trials in progress). Safety and tolerability have been established in a recent dose-escalation Phase I trial of BMS-754807 [201], where the maximal tolerated dose had not been reached at the time of this writing [113]. This small-molecule inhibitor has not yet been used specifically in patients with advanced PCa, although preclinical evidence [Dayyani F, Gallick GE, Unpublished Data] suggests it may be promising in combination with Src family inhibition.

c-Met & HGF

c-Met is a surface receptor with intrinsic PTK activity that is expressed mainly in epithelial cells [114]. The receptor is composed of a disulfidelinked heterodimer consisting of a transmembrane β -chain and an extracellular α chain. The structure of c-Met has been extensively described [115,116]. c-Met has only one ligand, HGF, also described as scatter factor. HGF belongs to the plasminogen subfamily of S1 peptidases, although HGF itself lacks protease activity [117]. HGF expression is generally restricted to cells of mesenchymal origin [114,118]. Active HGF results from secretion of an inactive pro-HGF precursor that is subsequently cleaved into an active form consisting of a disulfide linked active α -chain and β -chain molecule [119]. Physiologically, the HGF/c-Met signaling axis regulates critical steps of embryogenesis as well as tissue repair in adult life, promoting cellular proliferation, differentiation, migration and neovascularization. Aberrant activation of the c-Met/HGF pathway in tumor cells enhances their survival, proliferation, invasive growth capabilities and promotes EMT [120].

A number of lines of evidence demonstrate that the c-Met-mediated signaling pathway is important in PCa progression including local invasion, bone metastasis and castration resistance. c-Met expression is significantly upregulated in the majority of PCa cell lines with highest expression in the more invasive cell lines, and in these *in vitro* models c-Met contributes both to proliferation and invasion [121]. Additionally, in PCa cell lines, c-Met

expression is inversely correlated with AR expression and PSA production, with less differentiated cell lines expressing higher levels of c-Met [122,123].

In the prostate, c-Met is primarily expressed by the epithelial compartment and HGF by prostate stromal cells [124], indicating a paracrine mechanism of c-Met activation. In prostate tumor tissues, immunohistochemical studies have shown that c-Met expression is increased in primary tumors relative to normal prostate tissue, with further increases observed in bone metastases [7,125]. Both HGF and c-Met are found in the urine of PCa patients, and levels are significantly elevated in patients with metastatic disease compared with patients with localized disease [123,126]. Thus, the c-Met/HGF signaling pathway is important in tumor–microenvironment interactions, regulating PCa invasive and metastatic growth.

The above studies demonstrate that c-Met is an attractive target for therapeutic intervention of PCa growth and progression. Several strategies have been proposed to interfere with HGF/c-Met signaling including small-molecule TKIs that inhibit c-Met kinase activity and monoclonal antibodies to both HGF ligand and c-Met receptor. Discussion of the latter is beyond the scope of this review.

Several small-molecule inhibitors that target c-Met have been developed, although none are selective to c-Met alone. These TKIs to c-Met have rapidly reached clinical trial and for most, incomplete information is available as to their eventual success. Below, we describe some of the inhibitors in clinical trial.

BMS-777607 is a potent, ATP-competitive c-Met inhibitor. Recent *in vitro* data showed that BMS-777607 inhibits scattering, migration and invasion of prostate tumor cells in doses less or equal to 1 μ M. At much higher doses, proliferation is also affected [127]. These data suggest that inhibition of c-Met is more important to invasion and metastasis, rather than local growth of PCa. BMS-77607 is currently undergoing Phase I and II trials in patients with advanced PCa [127,202]. PF-2341066 is another ATP-competitive c-Met inhibitor with additional potent activity against anaplastic lymphoma kinase [128]. PF-2341066 showed a moderate antiproliferative activity against AR positive and negative PCa cell lines, with drug responsiveness inversely associated with AR levels [128]. In preclinical mouse studies, PF-2341066 suppressed the growth of AR positive, androgen-independent prostate cells and showed a synergistic activity with castration therapy against AR positive castration-resistant PCa cells. These studies suggest that PF-2341066 (and perhaps other c-Met inhibitors), are likely to have synergistic activity with androgen-deprivation treatment. PF-2341066 has reached Phase I clinical trial [203]. Foretinib/GSK 1363089 is a multi-targeted TKI whose targets include c-Met, Ron, AXL, VEGFR2 and PDGFR [129]. Although Foretinib has been tested in several solid tumors in Phase I and Phase II studies, no specific studies have focused on PCa [130]. ARQ-197 is a more selective, but less potent TKI that in contrast with other c-Met inhibitors in development, is a non-adenosine triphosphate competitive inhibitor. In preclinical studies, ARQ-197 showed antitumor activity in numerous cell types, including PC3 prostate tumor cells [131]. In PC3 tumors grown in immunocompromised mice, ARQ-197 led to dose-dependent effects on growth inhibition of PC3-derived tumors in immunocompromised mice. These, and other preclinical studies, led to Phase I and II clinical trials in patients with solid tumors who failed first-line treatment. Preliminary results demonstrated anti-tumor activity, as well as inhibition of other signaling enzymes that can be activated by the HGF/c-Met signaling axis, including FAK [132]. The possible efficacy of ARQ-197 on PCa bone metastases has yet to be evaluated.

XL-184 (cabozatinib) is a potent, ATP competitive inhibitor with selectivity to c-Met and VEGFR-2 [133]. Cabozatinib is also active at higher IC50s against other RTKs including

RET, KIT, FLT3 and TIE2. Preclinical evaluation of cabozatinib showed promising antiproliferative and anti-angiogenic properties. Because of the roles of c-Met signaling in bone metastases described above, cabozatinib has been tested as a single agent in a Phase II clinical trial in patients with metastatic CRPC [133,134]. Early results have been exciting. Interim analyses from the clinical trial have shown that 86% of patients with documented bone disease at baseline experienced complete or partial response on bone scans 6 weeks after treatment initiation. Treatment with cabozatinib also led to diminished bone pain in 64% of the patients. As would be expected for an agent that targets a signaling axis important to both tumor cells and their microenvironment, reduction in bone markers including uNTx and serum alkaline phosphatase was observed in approximately 50% of the patients [134]. Although the results are promising, correlation with other markers of disease response is needed to confirm the current observations and drug efficacy in tumor epithelial compartment, and it seems likely the efficacy of XL-184 is due, in part, to inhibition of both c-Met and VEGF-R2. While it is still too early to completely evaluate the results of the trials described above, given the exciting result achieved thus far, trials with c-Met inhibitors are now being rapidly accelerated and are likely to enter the panoply of clinically useful agents that affect tumor–microenvironment interactions in PCa treatment.

The FGF/FGFR signaling axis

FGFs and their receptors (FGFRs) comprise a subfamily of receptor PTKs involved in diverse cellular and developmental processes including proliferation, apoptosis, migration, EMT and angiogenesis [135]. There are 18 different soluble FGF ligands that bind to four transmembrane receptors (FGFR1–4). The FGF receptors have a high degree of sequence homology. Like other receptor tyrosine kinases, the structure of FGFRs includes an extracellular domain that binds FGF ligands, a transmembrane domain, and an intracellular tyrosine kinase domain [136]. Binding of FGFs to FGFRs leads to receptor dimerization, activation, and initiation of an intracellular signaling cascade that triggers key downstream pathways, including Ras/MAPK, PI3K/Akt and STAT. Activated FGFRs recruit FRS2, an adapter protein that binds to the juxtamembrane portion of each receptor and acts as a critical regulatory ‘node’ for subsequent signaling events through its interactions with other adaptor proteins [137].

Within normal tissue microenvironments, FGFs are produced and secreted by stromal cells, while FGFRs are expressed on epithelial cells [138]. FGF/FGFR signaling influences complex epithelial–stromal interactions involved during development, including organogenesis of the prostate gland. For example, FGF10 production in the mesenchyme and FGFR2b expression on epithelial cells are essential for prostate formation in rodent models [139,140]. Conversely, experimentally induced overexpression of FGF10 in prostate stroma or FGFR1 in the prostate epithelium produces prostate adenocarcinoma [141,142]. Reflecting its biologic importance, FGF/FGFR signaling is normally tightly regulated, with low basal activity that is transiently induced and/or repressed by a series of feedback loops.

There is increasing evidence that constitutive activation of the FGF/FGFR axis contributes to human PCa progression [143]. In comparison to normal prostate epithelium, PCa epithelial cells aberrantly overexpress FGF ligands and FGFR1. For example, FGF9 is overexpressed in approximately 40% of primary prostate tumors and in 100% of bone metastases when compared with normal prostate glands [144]. Within bone, PCa cells expressing both FGFs and FGFRs create an autocrine/paracrine feedback loop that subverts normal bone homeostasis in favor of osteoblastic bone formation. Collectively, these results suggest that the FGF/FGFR signaling axis contributes to PCa progression and support the development of treatment strategies that target this important epithelial–stromal interacting

pathway. These treatment strategies include monoclonal antibodies against FGFs and FGFRs, FGF 'ligand' traps, and small-molecule TKIs targeting FGFRs [145,146].

We recently initiated a clinical trial exploring the therapy potential of TKI258 (Novartis), a novel TKI with high specific activity against FGF receptor kinases [204]. In this study, men with CRPC and biopsy-proven bone marrow involvement are receiving therapy with TKI258. Preliminary results suggest clinical activity, with some patients demonstrating reductions in pain, improvements in bone scans, and responses in lymphadenopathy [Corn P *et al.* Unpublished Data]. Using molecular and pathologic techniques, bone marrow biopsies collected pretherapy and at 8 weeks after initiating treatment will be analyzed for evidence of TKI258-mediated modulation of FGF signaling in both the epithelial and stromal compartments. Results from this study will provide the foundation to develop candidate predictive markers and rational combinations based on targeted inhibition of the FGF/FGFR pathway.

Emerging targets

Ack 1 is a large (~143 kDa) **nonreceptor tyrosine kinase** containing a SAM domain, an SH3 domain, a CRIB domain, tyrosine kinase domain, a proline-rich domain near its C-terminus, and a ubiquitin binding domain. Ack 1 is recruited to the nucleus by several receptor PTKs, and after phosphorylation can translocate to the nucleus [147]. Ack 1 may be involved in nongenomic AR signaling. Ack-1 phosphorylates AR at tyr-267 and 363 within the AR transactivation domain, resulting in AR recruitment to AR responsive elements, leading to expression of AR regulated genes in the absence of androgen [148,149]. Expression of tyrosine phosphorylated (activated) Ack 1 in prostate tumors increases tyrosine-phosphorylated AR at 267. Thus, targeting Ack1 may be a strategy to suppress androgen-independent AR signaling.

Future perspective

Some promising results have been achieved by targeting PTKs that affect prostate tumor/microenvironment interactions. However, all the inhibitors discussed elicit responses only in a subset of patients. As of yet, we do not understand why some patients respond to specific TKIs and others do not. Thus, a challenge in designing appropriate clinical studies with molecular targeting agents is the identification of biomarkers that would predict which subset of patients would respond to a given targeted therapy. Appropriate biomarkers for monitoring PCa progression on any therapeutic regimen are also needed. Were these tools in hand, selection of patients likely to respond to given molecular targeting agents and the evaluation of the outcomes for a given drug would greatly improve.

PTKs have overlapping functions [33] and multiple tyrosine kinases are frequently activated in PCa bone metastasis. This precludes the success of targeting individual kinases in most patients. It is also likely that prolonged treatment with a TKI will result in activation of nontargeted kinases regulating compensatory pathways that render the tumor resistant to the initial target. Numerous examples of treatment with TKIs leading to activating nontargeted kinases with overlapping functions have been observed in other tumors. Development of markers that would be early predictors of treatment failure would allow earlier use of other targeted inhibitors that may overcome this problem. Finally, some TKIs may work best in the early stage of the metastatic process before there is too much tumor burden in the bone. Further biologic and clinical studies are necessary to clarify these issues. However, it is likely that small-molecule TKIs will play an important role in treatment of PCa metastases in the foreseeable future.

Executive summary

- Prostate cancer (PCa) metastasis is a heterogenous disease. Multiple tyrosine kinases are overexpressed and they are activated by the cognate ligands in the microenvironment.
- Tyrosine kinase inhibitors with some selectivity to Src, EGFR, PDGFR, IGFR, FGFR, VEGFR and c-Met have been developed and tested in clinical trials.
- EGFR inhibitors have shown little promise in clinical trials, potentially due to redundancy in signaling through EGFR family.
- The Src inhibitors dasatinib has completed Phase III trials with promising results in a subset of patients in Phase I/II trials in metastatic PCa.
- Inhibitors for IGFR, FGFR and c-Met are being tested clinically. Early studies in c-Met inhibitors showed promising results in a subset of patients with bone metastases.
- Due to innate and acquired resistance to tyrosine kinase inhibitors, the majority of patients with PCa metastasis are unlikely to benefit from inhibitors of individual tyrosine kinases. Therefore, combinations of small-molecule tyrosine kinase inhibitors will play an important role in the treatment of PCa metastases in the foreseeable future.

Key Terms

Prostate cancer	A form of cancer that develops in the prostate.
Tyrosine kinase inhibitors	Compounds that inhibit tyrosine kinase activity.
Receptor tyrosine kinase	Growth factor or hormone receptor that possesses tyrosine kinase activity.
Bone metastasis	Primary tumor invasion to bone.
Nonreceptor tyrosine kinase	Non-receptor protein that possesses tyrosine kinase activity.

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