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Evolving Therapies and FAK Inhibitors for the Treatment of Cancer

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Abstract

Despite advances in medical and surgical therapy, cancer kills more than half a million people in the United States annually, and the majority of these patients succumb to metastatic disease. The traditional approach to treating systemic disease has been the use of cytotoxic chemotherapy. However, chemotherapy is rarely curative and toxicity is often dose limiting. In addition, the effects of chemotherapy are nonspecific, targeting both malignant and normal tissues. As a result, recent efforts increasingly have focused on developing agents that target specific molecules in tumor cells in order to both improve efficacy and limit toxicity. This review summarizes the history and current use of targeted molecular therapy for cancer, with a special emphasis on recently developed inhibitors of Focal Adhesion Kinase (FAK).

Keywords

Angiogenesis; carcinogenesis; focal adhesion kinase; targeted therapeutics; tyrosine kinase

INTRODUCTION

More than 550,000 people in the United States die from cancer annually, and the majority of these succumb to metastatic disease [1]. The traditional approach to treating systemic disease has been the use of cytotoxic chemotherapy. However, chemotherapy is rarely curative and toxicity is often dose limiting. Moreover, the effects of chemotherapy are nonspecific, targeting both malignant and normal tissues. As a result, recent efforts increasingly have focused on developing agents that target specific molecules in tumor cells in order to both improve efficacy and limit toxicity [2].

TYROSINE KINASE INHIBITORS

One of the first classes of molecules to be suggested as a potential target for anticancer therapy was the tyrosine kinases (TKs). As their name implies, these enzymes catalyze the phosphorylation of tyrosine kinase moieties on a variety of other signaling proteins [3]. TKs can be classified as either receptor or non-receptor kinases. Receptor tyrosine kinases (RTKs) are membrane spanning proteins that generally function in pairs. Activation induces dimerization, and dimerization then triggers a phosphorylation cascade involving the cytosolic non-receptor tyrosine kinases (Fig. 1) [3–6]. Non-receptor tyrosine kinases relay

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CONFLICT OF INTEREST

Dr. Vita Golubovskaya discloses potential conflict of interest with CureFAKtor Pharmaceuticals.

intracellular signals by additional protein phosphorylation [6]. Many processes involved in tumor progression and metastasis, including proliferation, angiogenesis, migration and cell survival, are influenced by activation of RTKs and the subsequent signal cascade [3, 5]. Moreover, mutations can alter the expression or activation of TKs and thereby lead to uncontrolled activation in cancer cells [7]. Of the fifty-eight known RTKs, approximately 30% have been found to be either mutated or unregulated in cancer [4, 7, 8]. In addition, several RTKs are known to play important roles in tumorigenesis, and have become effective therapeutic targets. For example, c-kit is unregulated in gastrointestinal stromal tumors (GISTs) and acute myelogenous leukemia (AML), HER2 is elevated in breast cancer, and RET is altered the MEN disorders [7]. These and other RTKs have long been known to play a role in cancer progression and, as such, inhibition of TKs has been at the forefront of targeted cancer therapy.

The recognition that TKs play a central role in many tumorigenic processes prompted the development of a wide variety of TK inhibitors (TKIs). These agents function by targeting the receptor or the ligand that promotes the downstream signal cascade [3]. TKIs can be classified based upon the targeted molecule or the targeted signal cascade. Increasingly, however, these agents are classified based upon molecular structure; this classification divides TKIs into the following groups: (1) monoclonal antibodies, (2) small molecule kinase inhibitors, and (3) multitargeted kinase inhibitors (Table 1).

Monoclonal Antibodies

Monoclonal antibodies were at the forefront of TKI development. The first TKI developed for cancer therapy was imatinib mesylate, designed to treat chronic myelogenous leukemia (CML). The development of this drug was based upon the observation that most patients with CML possess the t(9;22) translocation mutation (Philadelphia chromosome) that fuses the Abl tyrosine kinase to the Bcr gene on chromosome 22 [3, 9]. This mutation then results in the production of two tyrosine kinases, p190 and p210, both of which are involved in hematopoetic stem cell proliferation and inhibition of apoptosis [3]. Imatinib, therefore, was designed to block the ATP binding site on these proteins, hindering activation and downstream signaling. This prototypical TKI revolutionized the treatment of CML and, as such, laid the ground work for the development of a wide array of similar TKIs [10].

In addition to blocking ATP binding in p190 and p210, imatinib was also found to inhibit the c-kit and PDGFR tyrosine kinases. After demonstrated success in treating CML, imatinib was then tested in patients with tumors possessing mutations in c-kit and PDGFR [11]. Gastrointestinal stromal tumors (GISTs), for example, are notoriously resistant to cytotoxic chemotherapy, but are well known to express c-kit. Imatinib therapy proved to be highly successful in these unusual tumors and has significantly altered the approach to treating patients with GIST [12]. Currently, there are several clinical trials designed to test the efficacy of imatinib in other solid tumors including colorectal cancer, ovarian cancer, prostate cancer and thyroid cancer [13]. Nevertheless, despite successes with this agent, prolonged use of imatinib has resulted in the development of resistant tumors. The most common mechanism of resistance appears to involve mutations in the kinase domain of bcr-abl that then prevent binding of the drug [14]. As a result, current research is focusing on overcoming this limitation.

The epidermal growth factor receptor family of TKs has also provided a number of targets for TK inhibition. Epidermal growth factor receptor 2 (EGFR2, ErbB2), also known as the human epidermal receptor 2 (HER2) for example, can bind a wide array of growth factors, thereby inducing dimerization and stimulating downstream activation of either the RAS/MAPK, PI3 kinase/Akt/mTOR, or other signaling pathways, that promote cell proliferation and migration and inhibit apoptosis [15, 16], [15] HER2 is over expressed in many

malignancies, and between 20–30% of advanced breast cancers express this receptor [15, 17]. Trastuzumab is a humanized monoclonal antibody that inhibits activation of the HER2 receptor has been shown to affect breast cancer cells by inducing cell cycle arrest at G1 *via* up regulation and translocation of p27 from cytosol to nuclei [15, 18, 19], Trastuzumab has demonstrated efficacy against both early and late stage breast cancer, and is currently the standard of care for HER2 positive tumors [20, 21].

In addition, trials are underway pairing trastuzumab with more traditional chemotherapeutic agents in an attempt to both improve efficacy and to decrease toxicity [20]. The recent phase III ToGA trial has suggested that trastuzumab may be a reasonable adjunct to capecitabine and cisplatin or fluorouracil and cisplatin for patients with HER2-positive gastric or gastroesophageal junction cancer [22, 23]. Trials are also underway to test the efficacy of trastuzumab in combination with other targeted therapies. For example, trastuzumab-DM1 is a combination of the monoclonal antibody and the maytansine-derivative, DM1, a drug that interferes with microtubule formation. Pre-clinical studies demonstrate efficacy in lapatinib and trastuzumab-refractory breast cancer cells, and this combination is currently in phase II clinical trials for the treatment of breast cancer [24–27].

Another TKI that has proven useful is cetuximab, a monoclonal antibody that targets epidermal growth factor receptors [5, 28]. The history of cetuximab development is interesting. Initially, a murine monoclonal antibody (called 225) that could bind and inhibit EGFR was found to increase apoptosis and cell cycle arrest in G1 [29]. Experimental data were promising, however concern about the use of a mouse monoclonal antibody in the human population, and the potential for anti-mouse antibody response, prompted chimerization of the antibody with human IgG1 [30, 31]. The resulting chimeric antibody (C225, cetuximab) has subsequently proven to be both safe and efficacious in a number of settings [31, 32]. Cetuximab in conjunction with cytotoxic chemotherapy improves progression free survival and overall response rate in chemoresistant metastatic colorectal cancer [5, 33]. In 2004, cetuximab either in combination with irinotecan or as a single agent was approved by the FDA for the treatment of metastatic colorectal cancers that express EGFR and are refractory to irinotecan- or oxaliplatin-based therapies [5, 34, 35]. Another interesting finding with cetuximab has been the identification of KRAS mutation status as a predictor of response to therapy. As cetuximab increasingly was used to treat refractory metastatic colorectal cancer, it became clear that this agent is most effective in a subset of patients whose tumors possessed wild-type KRAS [33, 36–38]. In contrast, tumors possessing a KRAS mutation responded poorly to cetuximab [39–41]. As a result, current practice requires KRAS testing for patients under consideration for treatment with cetuximab [42, 43]. Finally, cetuximab in combination with chemotherapy has proven useful in several other malignancies, including head and neck squamous cell carcinoma, and is under investigation for use in other cancers. Additional EGFR inhibitors (panitumumab, pertuzumab) also are being studied and hold promise [43–48].

Small Molecule TKIs

The second class of TKIs includes several small molecules that inhibit activation of these enzymes. For example, Gefitinib is a small molecule inhibitor that targets the epidermal growth factor receptor 1 (EGFR1/HER1) by inhibiting autophosphorylation [27, 49, 50] Gefitinib was originally approved for the treatment of non-small cell lung cancer in 2003. However, a variety of later trials have shown mixed response [51–55]. Erolotinib, another small molecule inhibitor of EGFR autophosphorylation, has had somewhat greater success. In a large trial treating patients with advanced non-small cell lung cancer (stage IIIB or IV), erlotinib therapy prolonged progression free and overall survival, and is currently considered second line therapy for treating non-small cell lung cancer [56–59]. Erlotinib also has

proven efficacy in proved in combination with gemcitabine for treating pancreatic cancer [59].

Multitargeted Inhibitors

The third class of TKIs, multitargeted inhibitors, includes a variety of agents with varied mechanisms of action. The uniting factor among these molecules is their ability to inhibit multiple TKs, and, with hope, to overcome the development of resistance. For example, several molecules are designed to inhibit not only EGFR/HER2 activation, for example, but also downstream cell signaling molecules such as the src family of kinases, and proteins such as c-kit, HER2 and PDGFR [60]. Lapatinib is an EGFR and HER2 inhibitor that possesses extended binding time to EGFR that prolongs its inhibitory effect. This agent has been studied alone and in combination for treating breast cancer. Although efficacy as a single agent was limited, in combination with cytotoxic chemotherapy, lapatinib does improve outcome. For example, in patients with metastatic breast cancer that over express HER2, treatment with lapatinib plus capecitabine markedly improved progression free survival and overall disease progression [27]. Similarly, lapatinib and letrozole have proven useful in postmenopausal women with advanced breast cancers that over express HER2 and are hormone receptor positive [61]. Another multi-targeted TKIs, dasatinib, has demonstrated increased inhibitory activity against bcr-abl compared to imatinib *in vitro* and is currently approved for the treatment of CML in patients who have developed resistance to imatinib [10, 60, 62, 63]. Finally, additional multi-targeted agents are under development. For example, neratinib inhibits both EGFR (ErbB1), HER2 (ErbB2), and HER4 (ErbB4) [64]; clinical trials are underway [13, 65].

Several of the multitargeted TKIs are more difficult to classify because they target a variety of kinases and downstream signaling cascades. For example, some of these molecules inhibit angiogenesis by blocking the vascular endothelial growth factor receptor (VEGFR), while also inhibiting tyrosine kinases such as c-kit and HER2. Sunitinib, for example, inhibits c-kit, PDGFR-α, CSF-1 receptor, and VEGFR-1, 2 and 3 [27]. The FDA approved of its use in advanced renal cell carcinoma after it demonstrated efficacy by improving progression free survival and overall survival compared to interferon-α [66, 67]. Sunitinib also has been used successfully to treat GIST tumors that have developed resistance to imatinib, and is FDA approved for use in that setting [66, 68, 69]. Sunitinib also has been studied for treating refractory thyroid cancer [70] and metastatic breast cancer [71]. However, not unexpectedly, one consequence of targeting so many different TKs has been increased toxicity. For example, in the study treating metastatic breast cancer, dose modification was necessary in 56% of patients due to adverse effects [71]. Similarly, in a study combining sunitinib with cyclophosphomide and methotrexate, of the 15 patients studied, three developed neutropenia and five developed mucositis [27]. Another phase I dose-escalation study combining sunitinib and capecitabine in patients with solid tumors, five grade 3 adverse effects emerged: abdominal pain, mucosal inflammation, fatigue, neutropenia and hand-foot syndrome [72]. Similar side effects have been reported in other clinical trials, and one trial was terminated early because of the high incidence of neutropenia, febrile neutropenia and fatigue [27]. Interestingly, in one study of efficacy against hepatocellular carcinoma, the neutropenia and skin toxicities seemed to correlate with response to therapy, overall survival and time to tumor progression, suggesting that those toxicity may be a marker for tumor response [73].

Several other multitargeted TKIs are currently under investigation. Axitinib inhibits all VEGF receptors (1, 2 and 3), PDGFR-β and c-kit [27]. Clinical trials continue to investigate the use axitinib for the treatment of a variety of solid tumors including, but not limited to, renal cell carcinoma, hepatocellular carcinoma, colorectal cancer, lung cancer, and melanoma [13]. Vandetanib inhibits EGFR, the kinase domain of VEGFR2, and RET

autophosphorylation that is currently in the early stages of clinical investigation [27, 74–78]. At present, the indications for use of these agents, both alone or in combination with other drugs, is evolving and awaits the results of clinical trials.

TKIs represent some of the earliest efforts at targeted therapeutics and the development of monoclonal antibodies, small molecule inhibitors, and multitargeted TKIs has laid the ground work for the development of other biologic agents. In addition, these agents have taught us that in some cases biomarkers like KRAS mutation and EGFR overexpression can predict response. As such, TKIs were some of the first agents to be used in a truly individualized approach to cancer therapy.

ANGIOGENESIS INHIBITORS

Angiogenesis is one of the earliest events in tumor growth and is characterized by tumor microvascular formation [79]. Once a tumor grows beyond the limit of oxygen diffusion (approximately $2mm^3$), the hypoxic environment triggers the release of pro-angiogenic factors that in turn stimulate new blood vessel formation. The pro-angiogenic factors released include, vascular endothelial growth factors (VEGFA, B, C, D and E), basic fibroblast growth factor (bFGF), IL-8, placenta-like growth factors (PLGF-1 and 2), neurophilins (NRP1 and NRP2), transforming growth factors (TGF), fibroblast growth factor (FGF), and platelet derived growth factor (PDGF) [5, 79, 80]. Although all of these molecules represent potential anti-angiogenic targets, VEGF and its receptors, VEGFRs, have received the most attention. VEGFR stimulation activates intracellular PLC_ (phospholipase C-γ), PKC (protein kinase C) and the MAPK pathway, PI3 kinase, Akt/PKB (protein kinase B), NFκB, endothelial nitric oxide syntheses, and inhibits pro-apoptotic proteins, thereby inducing endothelial cell survival, proliferation and migration, and increasing vasodilation, vascular remodeling and vessel permeability [81]. In normal tissues, VEGFR2 appears to be the major inducer of angiogenesis, whereas the relatively weak signal cascade of VEGFR1 may actually decrease angiogenesis. VEGFR3 is involved in embryologic and post-natal angiogenesis and lymphangiogenesis. In cancer, VEGFR1 and 2 appear to be the receptors most involved in tumor angiogenesis [5]. Both VEGF and VEGFRs have emerged as logical targets for drugs seeking to inhibit angiogenesis [42, 79].

Bevacizumab is an anti-VEGFA antibody that has been widely studied and utilized. This agent reduces the amount of effective circulating VEGFA and thereby prevents VEGF receptor activation [42]. Clinical efficacy of this agent was first demonstrated in metastatic colorectal cancer. In this setting, bevacizumab in combination with irinotecan, 5FU and leukovorin (FOLFIRI) induced higher response rates and prolonged progression free and overall survival compared to traditional chemotherapy [82]. As a result, bevacizumab is currently utilized for both first and second line therapy in stage IV colorectal cancer [83, 84]. Nevertheless, as with most other biologic agents, subsequent experience with this drug has yielded mixed results. The BRiTE (Bevacizumab Regimens' Investigation of Treatment Effects) study, an observational cohort study of 1,953 patients with metastatic colorectal cancer from 248 United State sites between 2004 and 2005, examined the efficacy of bevacizumab combined with chemotherapy as first line treatment for metastatic colorectal cancer. At 20 months, progression free survival was observed in 22% of patients who had received bevacizumab, while disease progression was seen in 79% of the patients. In addition 66% of patients died during the study period, and 12% either withdrew from the study or were lost to follow-up [85]. Similarly, in a phase III study by Stathopoulos in 2010, median overall survival did not differ between groups that received bevacizumab with chemotherapy (irinotecan, 5FU, leukovorin) and groups who received chemotherapy alone [86]. At present, bevacizumab is widely used for treating metastatic colorectal cancer, but its ultimate utility remains to be seen.

The efficacy of bevacizumab has subsequently been tested in other tumor types, including pancreatic and hepatocellular carcinoma, renal cell carcinoma, neuroendocrine tumors, non-small cell lung cancer, and breast, brain and ovarian cancers, and, as was the case with colorectal cancer, results have been promising but mixed. [13] In non-small cell lung cancer, effects on overall survival were inconsistent, but the drug appeared to slow the progression of the disease [87]. *In vitro* data suggest efficacy in combination with docetaxal for treatment of breast and prostate cancers [88]. In combination therapy with paclitaxel for metastatic breast cancer, bevacizumab improved response rates compared to paclitaxel alone [89]. Moreover, in a Phase II study of bevacizumab with erlotinib for treating recurrent malignant glioma, progression free survival was not significantly improved in patients who received bevacizumab [90]. To date, the FDA has approved bevacizumab in combination with carboplatin and paclitaxel for the treatment of non-small cell lung cancer, and in combination with interferon for the treatment of metastatic renal cell carcinoma [84, 91, 92]. It has also been approved for use as a second-line single agent for the treatment of glioblastoma [84]. In 2008, bevacizumab was approved as first-line treatment in combination with paclitaxel for metastatic HER2 negative breast cancer [84]. However, the results of more recent analyses of several clinical trials have failed to show any survival advantage in breast cancer patients who receive bevacizumab compared to chemotherapy alone. As a result, the Oncologic Drugs Advisory Committee of the U.S. FDA has made the controversial recommendation that approval be withdrawn for first-line treatment for metastatic breast cancer [93]. The FDA is currently reviewing the data on this drug, and the decision regarding possible revocation of approval are pending [94].

Toxicity has also been of concern with bevacizumab. While the most common toxicities are not severe (hepatotoxicity, proteinuria, diarrhea, myelosuppression, fatigue, infection, pain, nausea/vomiting, and hypokalemia), more rare but serious problems have been observed [87, 89, 90, 95]. For example, the BRiTE study identified new onset or worsening hypertension in 22% of patients and hypertension was implicated in eight serious adverse events. Additional less common but serious adverse events included postoperative wound healing complications (4%), grade 3–4 bleeding (2.2%), arterial thromboembolic events (2%), and gastrointestinal perforation (2%). Significant postoperative wound healing complications occurred following major surgery and in patients in whom surgery was undertaken within two weeks of the last bevacizumab dose [85]. These adverse events has led to an FDA drug warning and safety labeling update concerning these adverse effects [84].

Although bevacizumab has been most widely studied, other anti-angiogenic agents are under development. For example, Aflibercept (VEGF Trap) is a molecule in which the ligand binding domains of the VEGFR1 and VEGFR2 proteins are fused with human IgG1, forming a decoy receptor that binds all VEGFs and placental growth factor [27]. While this agent appears promising in the preclinical setting, clinical safety and efficacy have not yet been proven [27].

CELL CYCLE INHIBITORS

Cell cycle perturbations are also known to play a role in cancer progression, therefore the regulators of these processes also represent viable anti cancer targets. The cell cycle is regulated by a variety of cyclins and cyclin dependent kinases (CDKs; Fig. 2), and the CDKs, in turn, are regulated by several naturally occurring inhibitors (CDKIs) that prevent CDK binding to cyclins. Progression through the cell cycle is permitted to occur when the CDKIs do not prevent CDK/cyclin interactions. For example, cyclinE/CDK2 complex formation promotes cell entry into S phase, and CyclinB/CDK1 allows mitosis to occur [96, 97]. Overall, nine CDKs have been described and these molecules interact with twenty

possible cyclins (A-T) [96]. In addition, there is evidence that CDK or cyclin production is disrupted in several malignancies, including melanoma, lung, breast and colorectal cancers [96, 98, 99].

The existence of naturally occurring CDKIs provided a logical starting point for anti-cancer drug development. For example, flavopiridol is an analogue of a naturally occurring flavinoid CDKI [100]. Flavopiridol acts on the G1 and S phases of the cell cycle *via* inhibition of CDKs 2, 4, 6, and 9, and has demonstrated early success *in vitro* by inducing arrest of cellular growth and inducing apoptosis in chronic lymphocytic leukemia and colorectal cancer cells [101, 102]. Currently, flavopiridol is useful for treating recurrent CLL, where it has been shown to induce a clinical response in patients with high-risk genomic features [103]. In addition, when given with cytosine arabinoside and mitoxantrone, flavopiridol induced complete remission in 67% of patients with AML who had poor risk features (older age, unfavorable genetic mutations, or secondary AML) [104]. Phase I trials indicate drug tolerability and phase II trials continue to test this drug's efficacy in a variety of cancers [105].

Roscovitine is a similar CDKI that inhibits cyclinE/CDK2, cyclinB/CDK1, cyclinH/CDK7, and cyclinT1/CDK9 and prevents progression through S, G2 and M phases of the cell cycle [96]. *In vitro* studies also indicate that this drug induces apoptosis by activating p53, suppressing NF-κB, and down-regulating Mcl-1 (an anti-apoptosis protein) in multiple myeloma cells [106–108]. It also inhibits mitosis by decreasing production of promoters of cell division, such as Aurora-A/B, CDC25C, polo-like kinase, and WEEL [109]. Preclinical studies have demonstrated the efficacy of this agent in a variety of cancer cell lines. A phase II clinical trial of roscovitine for the treating resistant non-small cell lung cancer has recently been completed, and phase I investigation of its clinical safety in treating any solid tumors resistant to standard treatment is underway [13].

In addition to flavopiridol and roscovitine, and increasing number of both naturally occurring and synthetic CDKIs are currently undergoing preclinical and clinical evaluation Table 2. E7070, AZD5438, SNS-032 (BMS-387032), bryostatin-1, PD 0332991, and SCH 727965 are CDKIs that are at various stages of development. Although many of these agents look promising, safety and efficacy are not yet well understood [96].

INDUCERS OF APOPTOSIS

In addition to aberrant cell cycle regulation, cancer cells often display decreased rates of apoptosis compared to non-neoplastic cells. Two major pathways are involved in this process of programmed cell death: an extrinsic pathway, mediated by death receptors such as FAS, TNF, and TRAIL, and an intrinsic pathway that is mitochondrial and apoptosome-mediated. Cancer therapies that target the inappropriate loss of control over apoptosis have been developed to induce the intrinsic and extrinsic pathways either independently or together [2].

Apoptosis inducers are generally classified based on their mechanism of action. Bortezomib, a boronic acid dipeptide, was the first pro-apoptotic agent used in cancer treatment. Bortezomib promotes apoptosis by inhibiting the 26S proteosome, thereby inhibiting degradation of a number of cellular proteins that are involved in the cell cycle, transcription, and tumor suppression [110]. Early work suggested that 26S proteosome inhibition promoted apoptosis in multiple myeloma cells, [110] and the APEX trial suggested superior efficacy of bortezomib over dexamethasone for refractory multiple myeloma [111]. Additional trials have suggested that bortezomib may augment the activity of more traditional chemotherapeutic agents. In multiple myeloma, the addition of bortezomib to melphalan and prednisone slowed time to disease progression, increased the incidence of

partial and complete response, prolonged the duration of response, and improved three year survival compared to melphalan and prednisone alone [112].

Suberoylanilide hydroxamic acid (SAHA) is another inducer of apoptosis that inhibits histone deacetylase [113]. SAHA and other histone deacetylase inhibitors down regulate TNF_ receptor-1 expression and activation of NF-κB, thereby inhibiting tumorigenesis [114]. SAHA has been shown to be both safe and efficacious for treating cutaneous T cell lymphoma, and this agent is currently approved for use in patients who have failed previous treatment (third line therapy) [115]. Additional clinical investigations are underway, including a phase III trial of SAHA use against advanced mesothelioma [116].

The TRAIL1 and TRAIL 2 pathways also have been suggested to be promising pro-apoptotic targets. TRAILR1 and TRAILR2 are believed to be involved in apoptosis *via* FADD and caspase-8 and/or -10 recruitment, and/or by activation of other signaling pathways involving NF-κB, MAPK, PI3 kinase and Akt. Mapatumumab (HGS-ETR1) and lexatumumab (HGS-ETR2) are 2 monoclonal antibodies that agonistically bind the TRAILR1 and TRAILR2 receptors, respectively [117]. The role of mapatumumab and lexatumumab in combination with other agents has been supported by the observation of a synergistic effect with either antibody and cisplatin or bortezomib in non-small cell lung cancer cells and malignant mesothelioma cells, or with radiotherapy in colorectal cancer cells [118–120]. Clinical trials are underway for both mapatumumab and lexatumumab [13].

The promising results with bortezomib, SAHA, and TRAIL inhibitors has prompted the development of a variety of other pro- apoptotic agents that are currently under investigation (Table 3). TLK286 is a modified glutathione analogue that is metabolized by glutathione S transferase (GST) in the tumor cell cytosol, yielding a molecule that is toxic to the cell. Because GST is over expressed in many resistant tumor cells, TLK286 may be an ideal therapeutic option in these refractory tumors [121, 122]. Preliminary data suggest that TLK286 has little efficacy as a single agent, but combination with other agents may be useful [123–128]. FTI R115777 is a methyl quinolone farnesyl transferase inhibitor (FTI) that induces apoptosis by yet another mechanism. FTI R115777 is thought to induce cell death by disrupting the mitochondrial membrane and inducing caspase-9 activation [129]. 7AAG is a inhibitor of heat shock protein HSP90, a molecule that is frequently over expressed in tumor cells [130]. This agent has been thoroughly studied *in vitro* and *in vivo*, and affects a variety of cancer cell types by inducing apoptosis, decreasing growth, potentiating the effects of known chemotherapeutic drugs, and sensitizing tumors to radiotherapy [131]. Clinical safety and efficacy await the completion of clinical trials.

FAK INHIBITORS

Focal adhesion kinase (FAK) is a nonreceptor tyrosine kinase that increasingly has been implicated in cancer progression, and as such, appears to be a valuable target for anti-cancer agents. FAK is a 125kDa protein that was identified at adhesion sites between cells and the extracellular environment. It is encoded by a gene located on chromosome 8 and houses three domains, the amino-N-terminal domain, the central catalytic domain and the carboxy-C-terminal domain. FAK activation relies upon autophosphorylation of the unique Y-397 site that is found in the N-terminal domain. Y-397 has a number of interesting properties. This region binds a number of signaling proteins such as src, PI-3 kinase, and Grb-7. It also binds EGFR, VEGFR, and p53 and other molecules that are critical for carcinogenesis [132]. The interaction between Y-397 and p53 is particularly intriguing. It is well known that p53 is mutated in many cancers; interestingly, p53 can inhibit FAK expression, and FAK can inhibit p53 expression. In breast cancer cells, p53 mutation is highly correlated with FAK over expression [133]. FAK also activates proteins that promote cell motility and

migration, invasion, survival, angiogenesis, lymphangiogenesis, and proliferation, such as paxillin and talin [132]. (Fig. 3). From a clinical standpoint, FAK is upregulated in several types of cancer including ovarian, thyroid, head and neck, lung, kidney, brain, hepatocellular, pancreatic, colorectal, breast [134, 135], cervical [135], and prostate [136] cancers, as well as melanoma, neuroblastoma, osteosarcoma, and sarcoma [137, 138]. The potential role of FAK activation cancer growth and progression has led to the development of several therapeutic agents targeting this molecule [132] (Table 4).

With FAK as a potential target for anti-cancer therapy, the initial attempts at inhibition focused upon down-regulation of FAK expression. Initial studies demonstrated that silencing FAK by transfection with dominant negative C-terminal FAK-CD decreased adhesion, colonization, and *in vivo* tumor growth by breast cancer cells [139]. Similarly, transfection with FAK-silenced RNA (FAK-siRNA) increased rounding, decreased growth and decreased *in vivo* tumorigenesis [139]. An attempt to increase the anti-tumorigenic affect of FAK inhibition next focused on the combined inhibition of FAK and its downstream effector src. Inhibition of src with PP2 in combination with adenoviral FAK-CD resulted in increased apoptosis compared to either molecule alone [140]. These initial experiments proved that inhibition of FAK expression could decrease cellular functions associated with cancer growth and progression, providing scientific rationale for further development of FAK inhibitors.

Based upon the observed interaction between FAK and p53, another approach involved activation of p53 (therefore decreasing FAK) or elimination of p53-deficient cells. This indirect approach involved the introduction of retroviruses that express p53 into rapidly dividing p53-deficient cells. For example, AD5CMV-p53 is an adenoviral vector encoding p53 that was shown to replenish p53 in p53 deficient tumor cells. This approach inhibited lung cancer cell growth both *in vitro* and *in vivo* [141]. Clinical phase I and II trials have subsequently demonstrated that this agent is both safe and effective against esophageal squamous cell carcinoma [142, 143]. Nevertheless, concern about the safety of a viral vector and about the logistics of production and storage persist [144].

Concerns about the reliability of gene transfection and the safety of a viral vector have lead to a third approach to FAK inhibition. A variety of small molecule inhibitors have been developed with the goal of specifically blocking FAK kinase activity. The earliest small molecule inhibitor of FAK, TAE226, blocks the ATP binding site and inhibits FAK phosphorylation at both Y397 and Y861, a site that is involved with VEGF signaling. This molecule showed promise in preclinical *in vitro* and *in vivo* trials, and most recently, was found to inhibit angiogenesis in models of human colon cancer [145]. The experimental success of TAE then led to the development of additional small molecule inhibitors. Like TAE226, PF-562,271 blocks the ATP binding site of FAK and of Pyk2 (protein-rich tyrosine kinase 2), another nonreceptor tyrosine kinase known to bind and activate src [146, 147]. PF-562,271 inhibited *in vivo* breast cancer cell growth and metastasis in a murine model, and decreased the *in vivo* growth of prostate cancer cells and *in vitro* growth of lung cancer cells [146, 148–150]. It also has exhibited synergy with sunitinib in the inhibition of hepatocellular tumor growth *in vivo* [151]. Phase I clinical trials employing PF-562,271 for treating prostate, pancreatic, and head and neck cancers, have recently been completed. Another inhibitor, PF-573,228, works similarly and has been found to inhibit breast cancer cell migration [148]. Interestingly, this agent in combination with tamoxifen decreased proliferation in ER positive breast cancer cells [152]. Other FAK inhibitors include PF-04554878, which is currently in Phase I clinical trials for the treatment of advanced non-hematologic malignancies, and GSK2256098 which has completed Phase I trials [13].

Additional small molecule inhibitors of FAK have taken advantage of other mechanisms of blocking FAK activation. PND-1186, for example, is thought to inhibit ATP activity by substituting a pyridine ring for the pyramidine ring found in other ATP-binding FAK inhibitors [153, 154]. Early studies show that this molecule increases breast cancer cell apoptosis, inhibits *in vivo* breast cancer cell growth and metastasis, and inhibits ascites and peritoneal seeding in models of ovarian cancer [153, 155].

Although the early FAK inhibitors have shown significant promise in anti-tumorigenic activity, the nonspecific nature of the ATP binding in both FAK and in other tyrosine kinases in particular has raised concerns about potential toxicity. A solution, therefore, would be to target a site that is highly specific to FAK. The Y397 site appears to offer just such an opportunity. Recently, several small molecule inhibitors that directly target the Y397 autophosphorylation site have been developed [156]. One such molecule, 1,2,4,5-benzenetetraamine tetrahydrochloride (Y15), binds specifically to the Y397 site, does not affect ATP binding or Pyk-2, and effectively inhibits FAK activation. *In vitro*, Y15 increased detachment and inhibited adhesion of breast cancer cells and inhibited tumorigenesis *in vivo* [156]. Additional studies have demonstrated the efficacy of Y15 in inhibiting pancreatic and neuroblastoma tumor growth *in vivo* [157–159]. In addition, when combined with gemcitabine, these two agents demonstrated synergy in inhibiting pancreatic cancer cell growth [159].

CONCLUSION

Despite decades of experience with cytotoxic chemotherapy, no agent or combination of agents has yet to cure cancer. As the biologic underpinnings of carcinogenesis are better understood, targeting molecular therapeutics to those molecules and pathways that promote cancer growth has become an increasingly attractive adjunct. Beginning with TKIs, an increasing number of biologic agents have shown promise both in the laboratory and in clinical trials. Angiogenesis inhibitors have been widely studied and are included in multidrug regimens for treating a number of malignancies. Cell cycle inhibitors and inducers of apoptosis increasingly are showing promise. Finally, inhibition of FAK, especially by small molecule inhibitors such as Y15, may prove to be both efficacious and, with hope, nontoxic. Going forward, both cancer research and cancer therapy will no doubt rely heavily on these exciting molecular targets and their inhibitors.

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ABBREVIATIONS

CDK	Cyclin dependent kinase
EGFR	Epidermal growth factor receptor
FAK	Focal adhesion kinase
RTK	Receptor tyrosine kinase
TKI	TK inhibitor
TK	Tyrosine kinase
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

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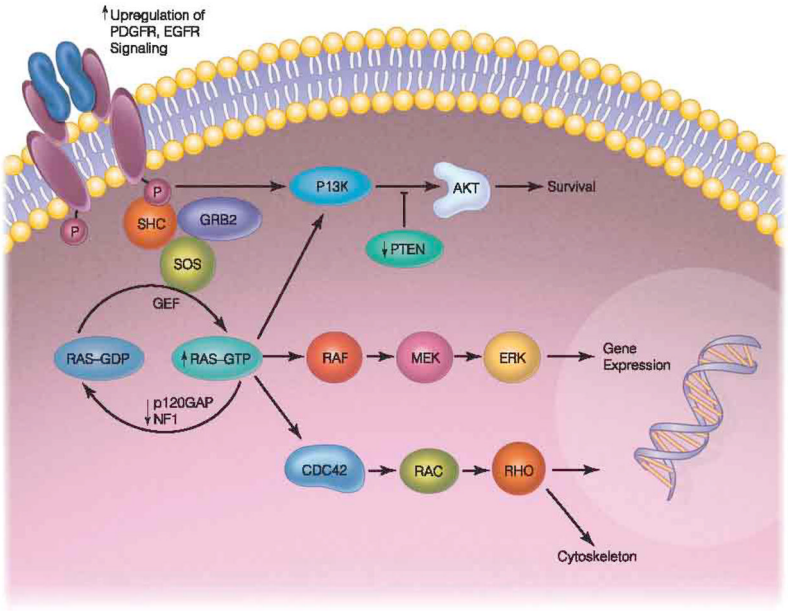

Fig. 1.

Activation of an RTK induces dimerization and downstream phosphorylation of non-receptor tyrosine kinases. Major signaling cascades include the RAS/RAF/MAPK pathway, MEK pathway, and the PI3kinase/AKT pathway.

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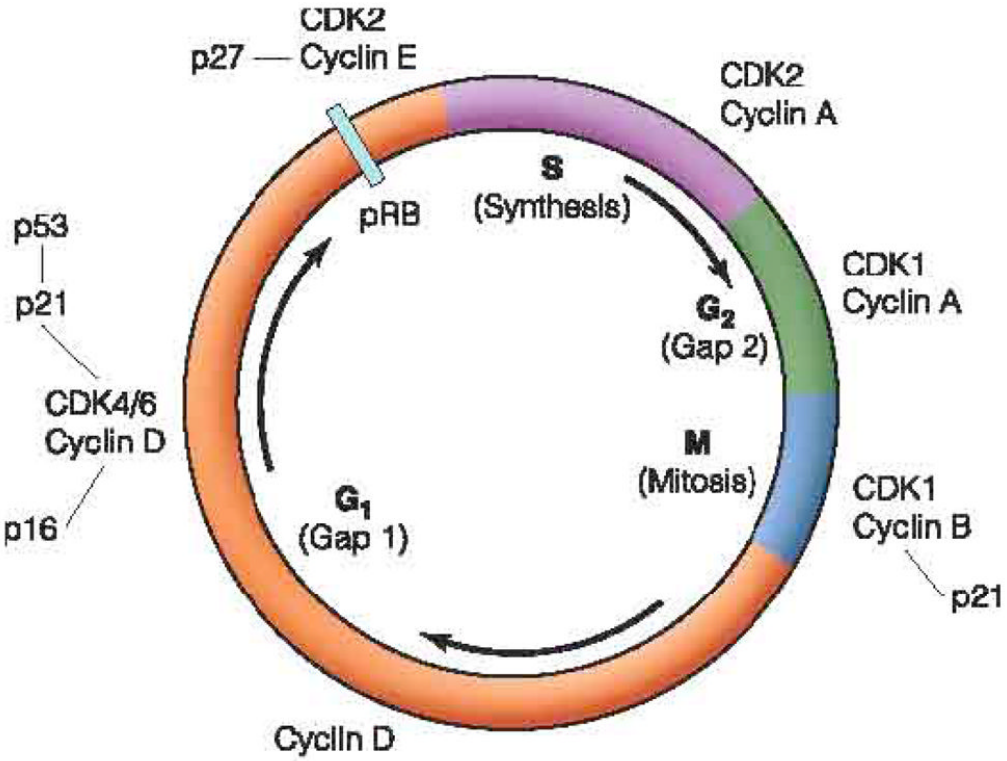

Fig. 2.

Progression through each phase of the cell cycle is regulated by cyclin/CDK interactions. (Copyright of Renaic, with kind permission of Renaic Corporation and Sysmex Corporation.)

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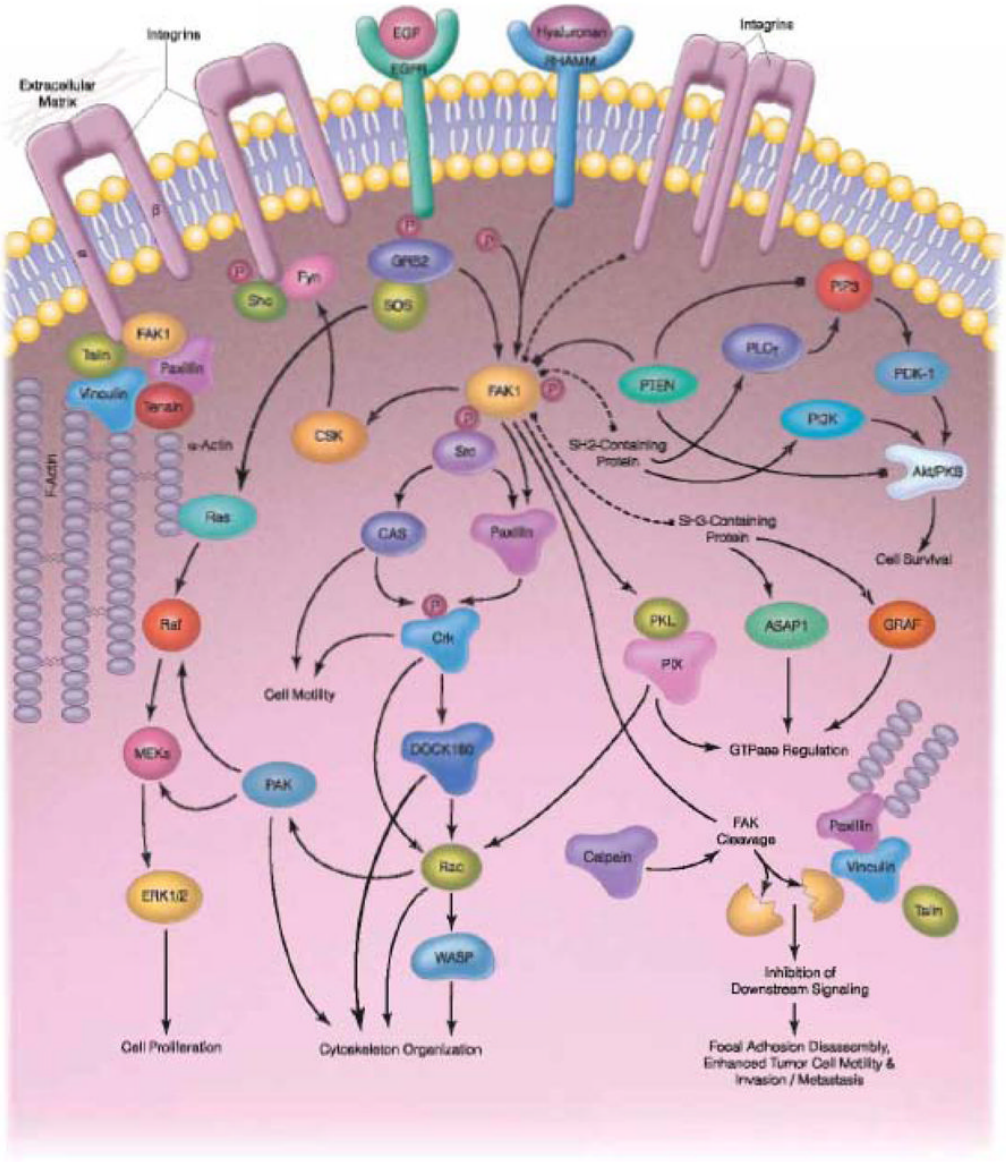

Fig. 3.

FAK plays a key role in a signaling cascade that can lead to some of the tumorigenic properties of cancer cells. FAK activation induces cell proliferation, motility, survival, invasion and metastasis.

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Table 1

Tyrosine Kinase Inhibitors [2]

Monoclonal Antibodies	**Imitinib**
	Trastuzumab
	Cetuximab
	Panitumumab
Small Molecule Inhibitors	Gefitinib
	Erlotinib
Multitargeted Inhibitors	Lapatinib
	Dasatinib
	Sunitinib
	Ax+itinib
	Vandetanib

Table 2

Cell Cycle Inhibitors [2]

Cell Cycle Inhibitor	Mechanism of Action	Effects	Clinical Trials*
flavopiridol	Inhibits CDK 2, 4, 6, 9	G1/S arrest	Phase I/II (hematologic and several solid tumors)
Roscovitine	Inhibits cyclinE/CDK2, cyclinB/CDK1, cyclinH/CDK7, cyclinT1/CDK9; p53 activation, NF-κB, decreases Mcl-1	S/G2/M arrest	Phase I/II (solid tumors)
E7070	Inhibits CDK2, cyclin E	G1/S progression	Phase I/II (several solid tumors, melanoma)
SNS-032	Inhibits CDK 2, 7, 9, VEGF	Inhibits progression and transcription, angiogenesis	Phase I (advanced B-cell lymphomas, several solid tumors)
bryostatin-1	Affects protein kinase C, CDK2; induces p21	Cell cycle modulation	Phase I/II (combination therapy for hematologic and several solid tumors)
AZD5438	Inhibits CDK1, 2, 9	Affects all phases of cell cycle	Trials terminated dues to safety concerns

* www.clinicaltrials.gov; www.cancer.gov

Table 3

Inducers of Apoptosis [2]

Inducers of Apoptosis	Mechanism of Action	Effects	Clinical Trials*
bortezomib	Inhibits 26S proteosome	Decreased degradation of cell cycle and transcription proteins	FDA approved as first-line treatment of multiple myeloma, and as second line treatment of mantle cell lymphoma.
suberoylanilide hydroxamic acid (SAHA)	Inhibits histone deacetylase	Suppress tumorigenic gene expression	FDA approved as third-line treatment of cutaneous T cell lymphoma; Phase III (advanced mesothelioma)
TLK286	Formation of a toxic metabolite	Induces apoptosis	Phase III (refractory gynecologic malignancies), combination therapy
ONYX015	Adenovirus; invades and replicates in p53 mutated cells, inactivates p53 gene	Lyses p53 mutated tumor cells	Phase I/II (combination therapy for solid tumors).
FTI-R115777	Blocks farnesylation of Ras, disrupts mitochondrial membrane, induces caspase-9 activation	Inhibit cell growth and induce apoptosis	Phase III (colorectal cancer and AML; no significant improvement in progression frees survival or overall survival, respectively). Phase I/II (pediatric leukemias, glioma)
17AAG	Inhibits HSP90	Inhibit cell motility and invasion	Phase I/II (multiple myeloma)
mapatumumab	TRAILR1 agonist	Inhibit TRAIL ligand binding and apoptotic signal cascade	Phase I/II (several solid tumors)
lexatumumab	TRAILR2 agonist		

* www.clinicaltrials.gov; www.cancer.gov

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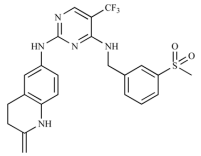
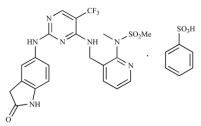
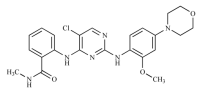
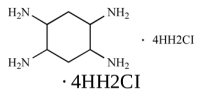
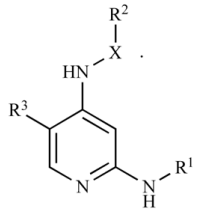
Table 4

FAK Inhibitors

Inhibitor Name	Chemical Name	Structure	
PF 573,228 (PF-228)	6-(4-(3-(methylsulfonyl) benzylamino)-5-(trifluoromethyl)pyrimidin-2-ylamino)-3, 4-dihydro quinolin-2(1*H*)-one		Pfizer
PF562, 271-26 (PF-271)	N-Methyl-N-(3-{[2-(2-oxo-2,3-dihydro-1H-indol-5-ylamino)-5-trifluoromethyl-pyrimidin-4-ylamino]-methyl}-pyridin-2-yl)-methanesulfonamide		Pfizer
NVP-226	(2-[5-Chloro-2-[2-methoxy-4-(4-morpholinyl)phenylamino] pyrimidin-4-ylamino]-N-methylbenzamide		Novartis
Y15[*]	1,2,4,5-Benzenetetraamine tetrahydrochloride	 · 4HH2CI	
PND-1186[**]	2,4-diamino-pyridine-based; X=bond or (C1-C3)alkyl comprising 0–1 heteroatom selected from the group consisting of N, O, S(O) and S(O)2, the (C1-C3)alkyl is substituted with 0–1 hydroxy, halo, (C1-C3)alkoxy, (C1-C3)alkylamino or (C1-C3)2dialkylamino groups. R1 and R2 are 5–12 membered Mono-, bi- or polycyclic, aromatic or partially aromatic rings. R3 is a trifluoromethyl, halo, nitro or cyano; salt, tautomer, solvate, hydrate, or aprodrug.		

[*] Reported by Golubovskaya *et al*., *J. Med. Chem*, V 51, p7405–7416, 2008, ref. in (15).

[**] Reported by Tanjoni *et al*., *Cancer Biol. Ther*., 2010, V 15, 2010, ref in (17).