Novel Therapeutic Inhibitors of the c-Met Signaling Pathway in Cancer

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Abstract A wide variety of human malignancies exhibit sustained c-Met stimulation, overexpression, or mutation, including carcinomas of the breast, liver, lung, ovary, kidney, and thyroid. Notably, activating mutations in c-Met have been positively identified in patients with a particular hereditary form of papillary renal cancer, directly implicating c-Met in human tumorigenesis. Aberrant signaling of the c-Met signaling pathway due to dysregulation of the c-Met receptor or overexpression of its ligand, hepatocyte growth factor (HGF), has been associated with an aggressive phenotype. Extensive evidence that c-Met signaling is involved in the progression and spread of several cancers and an enhanced understanding of its role in disease have generated considerable interest in c-Met and HGF as major targets in cancer drug development. This has led to the development of a variety of c-Met pathway antagonists with potential clinical applications. The three main approaches of pathway-selective anticancer drug development have included antagonism of ligand/receptor interaction, inhibition of the tyrosine kinase catalytic activity, and blockade of the receptor/effector interaction. Several c-Met antagonists are now under clinical investigation. Preliminary clinical results of several of these agents, including both monoclonal antibodies and small-molecule tyrosine kinase inhibitors, have been encouraging. Several multitargeted therapies have also been under investigation in the clinic and have demonstrated promise, particularly with regard to tyrosine kinase inhibition.

Background

Receptor tyrosine kinases (RTKs) are key regulators of critical cellular processes such as cell growth, differentiation, neovascularization, and tissue repair. In addition to their importance in normal physiology, aberrant expression of certain RTKs has been implicated in the development and progression of many types of cancer. These RTKs have emerged as promising drug targets for cancer therapy.

The RTK c-Met is the cell surface receptor for hepatocyte growth factor (HGF), also known as scatter factor (1, 2). HGF is a 90 kD multidomain glycoprotein that is highly related to members of the plasminogen serine protease family. It is secreted as a single-chain, inactive polypeptide by mesenchymal cells and is cleaved to its active α/β heterodimer extracellular form by a number of proteases (3). The α chain NH$_2$-terminal portion contains the high-affinity c-Met receptor-binding domain, but the β chain is required to interact with the c-Met receptor for receptor activation (4). The c-Met receptor, like its ligand, is a disulfide-linked heterodimer consisting of extracellular α and β chains (Fig. 1). The α chain, heterodimerized to the amino-terminal portion of the β chain, forms the major ligand-binding site in the extracellular domain. The transmembrane domain, and the juxtamembrane region containing the receptor downmodulation c-Cbl-binding domain, is adjacent to the kinase domain and the carboxy-terminal tail that is essential for downstream signaling (5). HGF binding induces c-Met receptor homodimerization and phosphorylation of two tyrosine residues (Y1234 and Y1235) within the catalytic site, regulating kinase activity (6). The carboxy-terminal tail includes tyrosines Y1349 and Y1356, which, when phosphorylated, serve as docking sites for intracellular adaptor proteins, leading to downstream signaling (7, 8). The c-Met receptor is expressed in the epithelial cells of many organs during embryogenesis and in adulthood, including the liver, pancreas, prostate, kidney, muscle, and bone marrow.

HGF-mediated activation of c-Met results in a complex genetic program referred to as "invasive growth," consisting of a series of physiological processes, including proliferation, invasion, and angiogenesis, that occur under normal physiological conditions during embryonic development and postnatal hepatic and cardiac injury repair, and pathologically during oncogenesis (9–12). Hypoxia has been demonstrated to activate c-Met transcription and amplify HGF signaling *in vitro* and *in vivo* (13, 14). Signaling through c-Met promotes proliferation and survival through a variety of downstream effectors. Signaling for mitogenesis and growth occurs through

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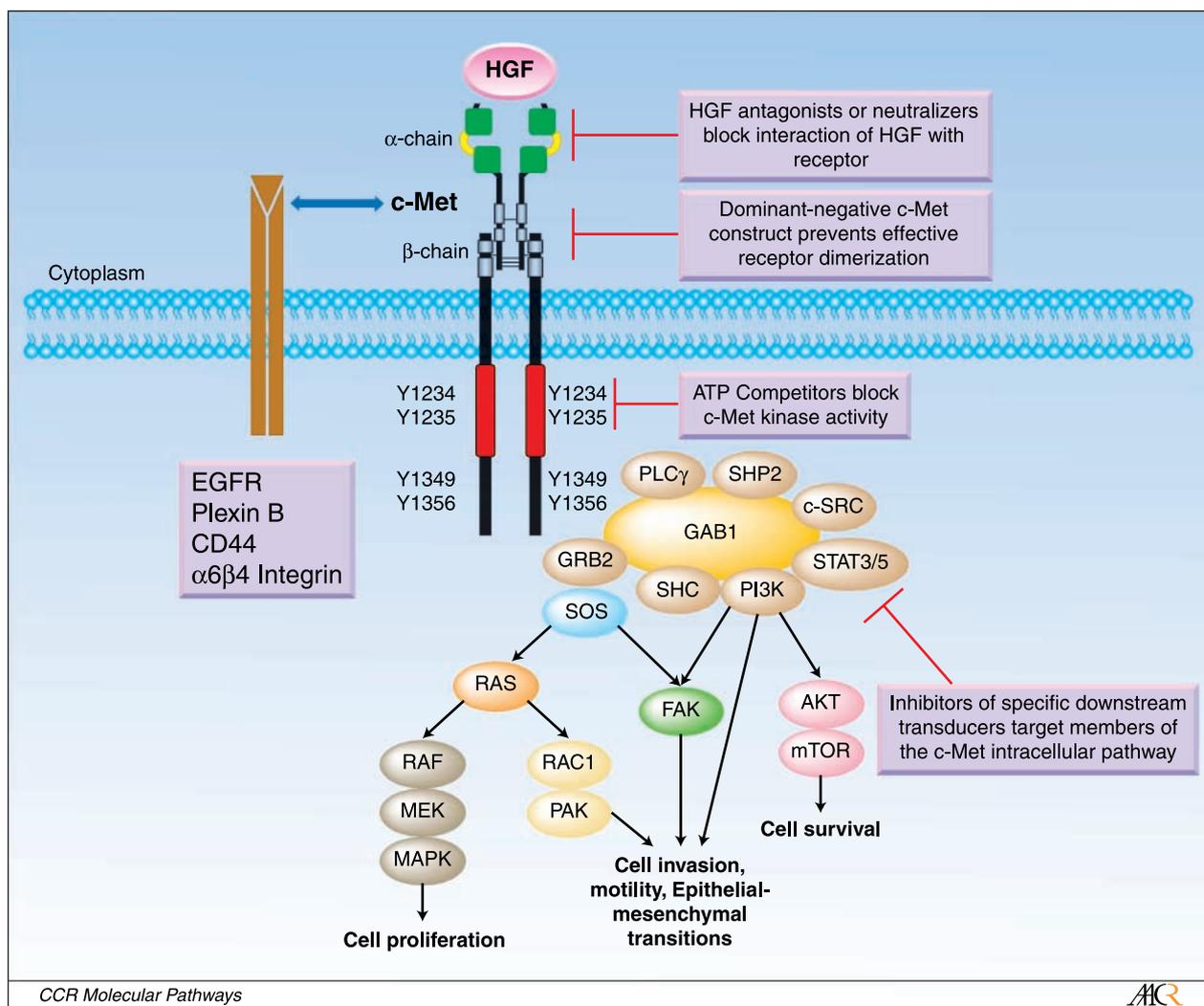
Fig. 1. Major signaling pathways activated through c-Met, interactions between c-Met and other membrane receptors, and c-Met signaling inhibition strategies. HGF binding results in c-Met autophosphorylation of tyrosines Y1234 and Y1235 within the activation loop of the kinase domain and subsequent phosphorylation of tyrosines Y1349 and Y1356 near the -COOH terminus. Important adapter proteins and direct kinase substrates activated downstream in the c-Met pathway include growth factor receptor-bound protein 2 (GRB2), Grb2-associated adaptor protein 1 (GAB1), phosphatidylinositol 3-kinase (PI3K), son of sevenless (SOS), rat sarcoma oncogene homolog (RAS), mitogen-activated protein kinase (MAPK), signal transducer and activator of transcription 3/5 (STAT 3/5), SRC, SRC homology protein tyrosine phosphatase 2 (SHP2), SRC homology domain c-terminal adaptor homolog (SHC), phospholipase c-γ (PLC), Ras-related C3 botulinum toxin substrate 1 (RAC1), p21-activated kinase (PAK), focal adhesion kinase (FAK), AKT, and mammalian target of rapamycin (mTOR). Crosstalk between c-Met and various membrane protein partners, including the epidermal growth factor receptor (EGFR), the plexin B family, $\alpha6\beta4$ integrin, and CD44, results in additional signaling response modulation.

the RAS-MAPK signaling pathway and plays an essential role in morphogenesis, the epithelial-to-mesenchymal transition that results from loss of intracellular adhesion via cadherins, focal adhesion kinase, and integrins, with change in cell shape (11). Activation of the HGF/c-Met axis prevents apoptosis through activation of phosphatidylinositol-3-kinase (PI3 kinase) and subsequent Akt activation (15–17). Crosstalk through the PI3 kinase-Akt pathway and the RAS-MAPK pathway has been implicated to promote survival (18, 19). Crosstalk between c-Met and the epidermal growth factor receptor (EGFR) has also been implicated in several biological systems (Fig. 1) (ref. 20). c-Met is also known to interact with other membrane proteins on the surface of the cell (13), including the laminin receptor $\alpha6\beta4$ integrin, the semaphorin receptors of the plexin B family, and the v6 splice variant of the hyaluronan receptor CD44 (13, 21). Crosstalk between c-Met and membrane partners assists in modulating the activation of c-Met and allows for

the integration of signals present in the extracellular environment (22).

In tumor cells, c-Met activation causes the triggering of a diverse series of signaling cascades resulting in cell growth, proliferation, invasion, and protection from apoptosis (3, 23). Data from cellular and animal tumor models suggest that the underlying biological mechanisms for tumorgenicity of c-Met are typically achieved in three different ways: (a) with the establishment of HGF/c-Met autocrine loops; (b) via c-Met or HGF overexpression; and (c) in the presence of kinase-activating mutations in the *c-Met* receptor coding sequence (3, 24–26). Overexpression of HGF and c-Met is indicative of the increased aggressiveness of tumors and poor prognostic signs in cancer patients (11).[4] HGF/c-Met signaling induces

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[4] Hepatocyte growth factor/scatter factor, Met and cancer references. Last Revised: 9/16/2008 [Available from: http://www.vai.org/met/].

tumor angiogenesis by inducing proliferation and migration in endothelial cells; by inducing expression of vascular endothelial growth factor (VEGF), a key proangiogenic factor; as well as by dramatically downregulating thrombospondin 1 (TSP-1), a negative regulator of angiogenesis (27, 28).

HGF and c-Met expression have been observed in tumor biopsies of most solid tumors, and c-Met signaling has been documented in a wide range of human malignancies, including bladder, breast, cervical, colorectal, gastric, head and neck, liver, lung, ovarian, pancreatic, prostrate, renal, and thyroid cancers, as well as in various sarcomas, hematopoietic malignancies, and melanoma (3, 29, 30).[4] Most notably, activating mutations in the tyrosine kinase domain of c-Met have been positively identified in patients with a hereditary form of papillary renal cancer, directly implicating c-Met in human tumorigenesis (26, 31). Amplification of c-Met has been implicated in the development of acquired resistance to erlotinib and gefitinib chemotherapies in non-small-cell lung cancer (NSCLC) patients (32–34).

Important Recent Work

Several recent advances in the field of HGF/c-Met signaling have occurred, further elucidating the role of c-Met in normal cellular function and oncogenesis.

- Silencing the endogenous *Met* proto-oncogene has been shown to result in lack of tumor growth, regression of established metastases, and decreased generation of new metastases, indicating the importance of persistent *Met* expression in the early phases of cancer progression (35).
- c-Met has been shown to be a sensor of adverse micro-environmental conditions (such as hypoxia) and drives cell invasion and metastasis through the transcriptional activation of a set of genes that control blood coagulation (11).
- The c-Met receptor and VEGF receptor (VEGFR) have been found to cooperate to promote tumor survival, and c-Met has additional roles in tumor angiogenesis, as an independent angiogenic factor and one that may interact with the angiogenic proliferation and survival signals promoted through VEGF and other angiogenic proteins. Hypoxia increases hypoxia-inducible factor (HIF)-1α, which subsequently increases HGF expression in tumor and surrounding normal interstitial cells with an increase in *Met* expression in endothelial and tumor cells. HGF/c-Met signaling increases VEGF levels in tumor and VEGFR2 on endothelial cells (36, 37). Increased HGF/c-Met signaling decreases thrombospondin 1 (TSP-1), the major endogenous inhibitor of angiogenesis (27). The increased HGF/c-Met signaling cooperates with VEGF signaling to increase the expression level of VEGF-regulated genes, as well as cooperating to express novel transcripts in endothelial cells (38). Combined VEGF and HGF/c-Met signaling has a greater effect on the prevention of endothelial cell apoptosis and the increase of vascular

Table 1. Summary of HGF/c-Met inhibitors in clinical development

Compound Name	Type	Company	Target(s)	Phase of Development
AMG102 (76)	Antibody	Amgen	human HGF	Phase I/II
MetMAb (23, 54, 77)	Monovalent antibody	Genentech	human c-Met	Phase I
ARQ197 (23, 59, 60)	Selective kinase inhibitor, non-ATP competitive	ArQule	c-Met	Phase I/II
JNJ-38877605 (61)	Selective kinase inhibitor, ATP competitive	Johnson and Johnson	c-Met	Phase I
PF-04217903 (62)	Selective kinase inhibitor, ATP competitive	Pfizer	c-Met	Phase I
SGX523 (63)	Selective kinase inhibitor, ATP competitive	SGX Pharmaceuticals	c-Met	Discontinued*
PF-02341066 (23, 66)	Multikinase inhibitor, ATP competitive	Pfizer	c-Met, ALK	Phase I/II
XL184 (71, 72)	Broad-spectrum kinase inhibitor, ATP competitive	Exelixis	c-Met, VEGFR1-3, Ret, Kit, Flt-3, Tie-2	PhaseI/II/III
XL880 (67, 69, 78, 79)	Broad-spectrum kinase inhibitor, ATP competitive	Exelixis	c-Met, Ron, VEGFR1-3, PDGFR, Kit, Flt-3, Tie-2	Phase I/II
MP470 (23, 73)	Broad-spectrum kinase inhibitor, ATP competitive	SuperGen	c-Met, Ret, Rad51, mutant forms of Kit, PDGFR, Flt-3	Phase I
MGCD265 (74)	Broad-spectrum kinase inhibitor, ATP competitive	Methylgene	c-Met, VEGFR1-3, Tie-2, Ron, Kit, Flt-3	Phase I
MK-2461 (75)	Broad-spectrum kinase inhibitor	Merck	c-Met, KDR, FGFR1-3, and Flt 1,3,4.	Phase I/II

NOTE: Inhibitor clinical development information current as of November 2008 from the United States National Institutes of Health registry of federally and privately supported clinical trials conducted in the United States and around the world. [Available from: http://www.clinicaltrials.gov].

Abbreviations: HGF, hepatocyte growth factor; ALK, anaplastic lymphoma kinase; VEGFR, vascular endothelial growth factor receptor; Ret, rearranged during transfection; Flt-3, FMS-like tyrosine kinase 3; Tie-2, angiopoietin receptor 2; Ron, recepteur d'origine nantais; PDGFR, platelet-derived growth factor receptor; Rad51, *E. coli* RecA homolog; KDR, kinase insert domain receptor; FGFR1-3, fibroblast growth factor receptor 1–3.

*Clinical development of SGX523 was discontinued by the company as of May 2008 after initial Phase I trials. [Available from: http://www.biospace.com/news_story.aspx?NewsEntityId=96099].

tubulogenesis *in vitro*, the formation of capillaries *in vivo*, and the increase of the microvessel density (MVD) within tumors (27). Thus, targeting inhibition of HGF/c-Met is both a means of enhanced VEGF/VEGFR axis-mediated inhibition of angiogenesis at the time of initial therapy and a response to the expected hypoxia within tumors induced by antiangiogenic therapy.

- c-Met and c-Src have been implicated in cooperating as mediators of EGFR tyrosine phosphorylation and cell growth in the presence of EGFR inhibitors (39). Thus, c-Met inhibition, either alone or in combination with an EGFR inhibitor, may confer clinical benefit in the setting of EGFR inhibitor resistance.

- The combination of a c-Met inhibitor plus the EGFR inhibitor erlotinib more potently inhibited NSCLC tumor xenograft growth in mice compared with either inhibitor alone, indicating that simultaneous targeting of c-Met and EGFR may have a great impact on NSCLC tumors in which coactivation of these receptor pathways is frequently observed (40).

- Preclinical and clinical c-Met diagnostics: The large number of patients who might benefit from Met-targeted therapies raises the issue of how best c-Met might be identified in the tumor. Few antibodies have been shown to work well for detecting c-Met in formalin-fixed, paraffin-embedded (FFPE) tissues (41). Recently, however, a monoclonal antibody, MET4, that is directed against the extracellular domain of human MET has been described. MET4 has been shown to accurately and reproducibly detect c-MET in FFPE tissues, and the MET4 reagent displays high sensitivity with low background (42).

Clinical-Translational Advances

The c-Met receptor, once activated, signals various pathways leading to tumorigenesis. Hence, it has been proposed that targeting the c-Met receptor by novel biological agents will inhibit cancer progression at the molecular level. Several different strategies are being explored to reach this goal, including the development of (a) competitors of MET/HGF, (b) monoclonal antibodies directed against HGF and c-Met, and (c) small-molecule tyrosine kinase inhibitors directed against c-Met. Besides the use of selective inhibitors, strategies to inhibit multiple targets involved in the c-Met signaling pathway are currently under study. This is especially relevant for the role of HGF/c-Met inhibition in angiogenesis with VEGF inhibition. Inhibition of multiple targets is achieved in two ways. Highly selective agents can be combined to create a broader spectrum of inhibition and maximize the benefit while minimizing unwanted toxicity with the greatest possible precision. Another approach is to utilize a single agent that targets multiple specific members of the c-Met signaling pathway or other signaling pathways involved in crosstalk with c-Met, thereby inhibiting crosstalk as a mechanism of resistance. The use of a broad-spectrum agent would lessen the possibility of drug-drug interactions, but it may affect other unintended kinases, given kinome family structural relationships. Several selective and broad-spectrum c-Met and HGF inhibitors have entered clinical trials (Table 1). A brief summary of the latest advances in therapies involving HGF/c-Met inhibition is provided here.

Competitors of MET/HGF

Binding of HGF ligand to the c-Met receptor can be inhibited by subregions of HGF or c-Met that can act as decoys or antagonists. These decoys and antagonists stoichiometrically compete with the ligand or receptor without leading to c-Met activation, thereby preventing activation of downstream pathways and biological outcomes. Several HGF and c-Met variants have been validated experimentally as antagonists both *in vitro* and *in vivo* and work by blocking ligand binding or preventing c-Met dimerization (13, 21). In addition, molecular analogs to HGF that have been shown to compete with HGF in Met binding have been developed. Preclinical work with NK4, a variant comprised solely of the N-terminal region and four kringle domains of HGF, has demonstrated c-Met inhibitory activity *in vitro* and *in vivo* (4). A soluble, recombinant, enzymatically inactive decoy c-Met molecule corresponding to the entire c-Met intracellular domain has been engineered and was shown to interact with both HGF and full-length c-Met to block ligand binding and prevent receptor dimerization (43). Preclinical experiments have shown that both decoy c-Met and NK4 synergize with radiotherapy in inducing tumor regression (43).

Monoclonal Antibodies Directed against HGF and c-Met

The use of HGF- or c-Met-specific antibodies prevents ligand/receptor binding, resulting in growth inhibition and tumor regression by inhibiting proliferation and enhancing apoptosis. A combination of three monoclonal antibodies (A-mix) displayed high neutralizing activity to HGF *in vitro* and *in vivo* and showed significant tumor growth inhibition against autocrine HGF-Met-expressing glioma xenograft tumors (44). The strategy of using monoclonal antibodies allows for exclusive specificity against HGF/c-Met, a relatively long half-life compared to small-molecule kinase inhibitors, and the potential to elicit a host immune response against tumor cells (23). Unfortunately, the use of antibodies also carries a high manufacturing cost and may result in suboptimal tumor penetration compared to other strategies.

AMG102 (Amgen, Inc.), is a fully human IgG$_2$ monoclonal antibody that selectively binds and neutralizes HGF, thereby preventing its binding to c-Met and subsequent activation (45, 46). AMG102 in preclinical paracrine HGF models shows potent inhibition of Met-dependent tumor growth (47). Phase I trials of AMG102 have been completed with an acceptable safety profile. Recently reported interim results from a Phase II trial of AMG102 in patients with glioblastoma multiforme showed 1 partial and 1 minor response and 2 reports of stable disease in the first 20 patients treated (48). Grade 3 or 4 adverse events were observed in five patients: peripheral edema (n = 2), hypophosphatemia (n = 3), and deep venous thrombosis (n = 1). AMG102 has been shown to enhance the effects of various standard chemotherapeutic agents such as temozolomide and docetaxel *in vitro* and in xenografts when combined (49). A Phase I study of AMG102 administered in combination with the antiangiogenesis agents bevacizumab or motesanib

showed a decrease in the sum of tumor diameters and a best response of stable disease in 8 of 10 evaluable patients without dose-limiting toxicity (DLT) (ref. 50).

One-armed 5D5 (OA5D5, MetMAb; Genentech) is a humanized, monovalent, antagonistic anti-c-Met antibody derived from the agonistic monoclonal antibody 5D5 (51–53). MetMAb binds to c-Met with high affinity and remains on the cell surface with c-Met, preventing HGF binding and subsequent c-Met phosphorylation as well as downstream signaling activity and cellular responses. Recent preclinical studies show that MetMAb is a potent anti-c-Met inhibitor that has promise as a therapeutic antibody in human cancer, especially in combination with EGFR and/or VEGF inhibitors (40, 54, 55). In preclinical ligand-independent and ligand-dependent models, a triple combination of MetMAb with an EGFR and VEGF inhibitor had more robust antitumor effects than any two agents alone (56). Notably, local treatment of MetMAb on glioblastomas containing a c-Met-activating mutation resulted in near complete inhibition of intracerebral glioblastoma growth in a mouse model (55). Phase I clinical studies of MetMAb have begun, and results from an initial Phase I trial indicate that MetMAb is safe and well tolerated as a single agent at doses up to 30 mg/kg (57).

Small-Molecule Tyrosine Kinase Inhibitors

The known roles of intracellular effectors in cellular transformation have led to the testing of therapies that limit their interactions in the hope of disrupting c-Met-driven tumorigenesis. Small-molecule inhibitors of c-Met target the catalytic activity of the receptor, whereas a variety of other inhibitors target downstream effectors in the c-Met signaling pathway. Because crosstalk between c-Met and other membrane receptors may lead to activation of the receptor without ligand binding, a strategy of targeting c-Met along with downstream effectors may yield the best results (22). Such strategies will likely be tumor dependant, predicated on the presence of c-Met mutations versus receptor overexpression.

ARQ197 (ArQule) is a non-ATP-competitive agent highly selective for the c-Met receptor. When ARQ197 was biochemically assessed in a panel of 230 kinases, only c-Met was inhibited to any appreciable extent (58). In preclinical experiments, ARQ197 potently inhibited HGF-stimulated and constitutive c-Met phosphorylation in multiple human cancer cell lines and decreased phosphorylation of several c-Met downstream effectors, including AKT, MAPK, and STAT-3 (58). A Phase 1 dose-escalation study of ARQ197 in metastatic patients who failed standard therapy showed that ARQ197 was well tolerated, and no DLT was observed (59). Of 33 evaluable patients, 2 achieved a partial response and 19 reported stable disease. Another Phase I trial examining the pharmacodynamics of ARQ197 in patients with advanced, safely biopsiable, solid tumors reported 1 DLT (grade 3 fatigue) in 14 patients treated to date (60). Inhibition of c-Met phosphorylation was observed. Several Phase I and Phase II studies of ARQ197, alone or in combination, are currently ongoing.[5]

Three other selective c-Met inhibitors have recently entered initial clinical evaluations. JNJ-38877605 (Johnson and Johnson) is a small-molecule, ATP-competitive inhibitor of the catalytic activity of c-Met. JNJ-38877605 showed ~600-fold selectivity for c-Met compared with a panel of ~250 diverse tyrosine and serine-threonine kinases and was found to potently inhibit HGF-stimulated and constitutively activated c-Met phosphorylation *in vitro* (61). PF-04217903 (Pfizer) is an orally available, ATP-competitive small-molecule inhibitor of c-Met that demonstrated selectivity of > 1000-fold for c-Met compared with a screening panel of > 150 protein kinases (62). Clinical evaluations of JNJ-38877605 and PF-04217903 have just begun, and no data are yet available.[5] SGX523 (SGX Pharmaceuticals) is another highly selective, ATP-competitive inhibitor of c-Met. SGX523 showed > 1,000-fold selectivity for c-Met over all other kinases in a screening panel of 213 protein kinases and demonstrated potent antitumor activity when dosed orally in human xenograft models with no overt toxicity (63, 64). However, unexpected toxicity was observed in early Phase I studies, including compromised kidney function, as evidenced by increased serum creatinine.[6] Analysis of patient samples from these clinical studies revealed a metabolism profile that differed markedly from that observed in preclinical experiments. As a result of the observed toxicity, further clinical development of SGX523 has been discontinued.[6]

PF-02341066 (Pfizer) is a multitargeted tyrosine kinase inhibitor with activity against both c-Met and anaplastic lymphoma kinase (ALK) (refs. 65, 66). PF-2341066 potently inhibited c-Met phosphorylation and c-Met-dependent proliferation, migration, or invasion of human tumor cells *in vitro* as well as inhibited HGF-stimulated endothelial cell survival or invasion and serum-stimulated tubulogenesis *in vitro*, suggesting that this agent also exhibits antiangiogenic properties. PF-02341066 more potently inhibited a variety of diverse mutant variants of c-Met in cellular assays compared to wild-type c-Met, suggesting that different mutant variants of c-Met may be preferentially targeted by different c-Met inhibitors (66). Phase I trials are ongoing.

GSK 1363089/XL880 (Exelixis) targets c-Met at an IC_{50} of 0.4 nM. Binding affinity is high to both c-Met and VEGFR2, causing a conformational change in the kinase to move XL880 deeper into the ATP-binding pocket. The time on target is > 24 hours for both receptors (67). In preclinical experiments, XL880 caused central necrosis and peripheral hemorrhage in tumors and produced regressions at all tumor sizes *in vivo*. XL880 has good oral bioavailability, and it is a CYP450 substrate, but not an inhibitor or inducer (68). Two Phase I clinical trials examined different administration schedules of XL880, either on a 5 day on/9 day off schedule (Study 1) or as a fixed daily dose (Study 2). The DLT was schedule dependant (Study 1 only); reversible increases in hepatic transaminases and pancreatic lipase were seen (67, 69). Hypertension was seen in > 27% of patients, but was grade 3 in only 5% and was manageable with medication. Of 41 patients reported in Study 1, 4 had confirmed partial responses (> 30% shrinkage of tumor by RECIST criteria), 4 had minor responses (RECIST response > 20% and < 30%), and 7 patients had stable disease.

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[5] United States National Institutes of Health. Registry of federally and privately supported clinical trials conducted in the United States and around the world. [Available from: http://www.clinicaltrials.gov].

[6] Biospace.com. SGX Pharmaceuticals, Inc. (SGXP) Discontinued Development of SGX523; Announces First Quarter Financial Results 5/13/2008. [Available from: http://www.biospace.com/news_story.aspx?NewsEntityId=96099].

The longest response is over 54 months. Thus, the spectrum of selectivity for XL880 differs from the extended spectrum agents that target angiogenesis, like sorafenib and sunitinib, which act within a single therapeutic area at one point in time (with significant clinical benefits in certain tumor types). It also differs from the angiogenesis inhibitors vandetanib and XL647, which act on two separate pathways that may or may not have overlapping effects in tumor cells. XL880 acts on two cooperating pathways for proliferation and survival at different points in time, already providing a therapeutic solution for tumor response to the initial assault on tumor angiogenesis. Phase II trials have started in multiple tumor types, including papillary renal cancer, gastric cancer, and head and neck cancers.

XL184 (Exelixis) is a novel, orally administered, small-molecule anticancer compound that, in preclinical models, has demonstrated potent inhibition of both MET and VEGFR2. XL184 has also exhibited potent inhibition of other important RTKs that have been implicated in various forms of cancer, including Ret, Kit, Flt-3, and Tie-2. In preclinical efficacy studies, XL184 has inhibited tumor growth and induced the regression of large tumors in a broad range of human tumor xenograft models, including breast cancer, lung cancer, and glioma. XL184 has also been recently suggested to resensitize cells resistant to the EGFR inhibitors gefitinib and erlotinib; the combination of XL184 with EGFR inhibitors was found to have impressive synergistic activity compared to either drug alone in preclinical cellular and xenograft models (70). Early clinical experience has indicated promising signs of antitumor activity at doses not associated with toxicity (71, 72). Most notably, results of 17 patients with medullary thyroid cancer (MTC) treated with XL184 indicated a > 50% response rate and a 100% disease control rate. Of the patients with MTC, nine were previously treated with tyrosine kinase inhibitors.

MP470 (SuperGen) is a novel, orally bioavailable small molecule with inhibitory activity against c-Met as well as several other protein tyrosine kinase targets, including mutant forms of c-Kit, mutant PDGFRα, and mutant Flt-3 (73). In addition, MP470 sensitizes cancer cells to platinum-based DNA-damaging agents and to radiation therapy, presumably through the suppression of Rad51, a key component of the cellular repair machinery in response to DNA double-strand breaks. Early clinical data indicated that MP470 was well tolerated and that Rad51 expression was modulated in a dose-dependent manner, supporting the rationale for combining MP470 with DNA-damaging agents due to the ability of MP470 to suppress the Rad51 DNA repair mechanism (73). Additional clinical studies, including combination studies with standard chemotherapies, are ongoing.

The clinical evaluation of other novel broad-spectrum c-Met inhibitors has recently begun. MGCD265 (Methylgene) potently inhibits c-Met, Ron, VEGFRs, and Tie-2 enzymatic activities *in vitro* and has been reported to abrogate HGF-dependent cellular endpoints, such as cell scatter and wound healing, as well as VEGF-dependent responses such as *in vitro* angiogenesis and *in vivo* vascular permeability (74). MK-2461 (Merck) is a potent inhibitor of c-Met, KDR, FGFR1/2/3, and Flt 1/3/4 that is especially active in preclinical models with *Met* gene amplification, in which c-Met is constitutively phosphorylated. MK-2461 has been well tolerated in early Phase I evaluation (75).

Conclusions

In the last several years, the introduction of molecularly targeted agents in cancer has achieved impressive results. Inhibition of RTKs that initiate (i.e., Bcr-abl in chronic myelogenous leukemia) or sustain (i.e., EGFR^{mut} in NSCLC; c-Kit in gastrointestinal stromal tumors) tumor survival by small, targeted molecules as single agents has demonstrated significant clinical benefit in cancer patients in several select circumstances. Highly selective monoclonal antibodies have also shown efficacy in a broader number of human cancers when combined with other agents, especially cytotoxic chemotherapy. The inhibition achieved by tyrosine kinase inhibitors of multiple factors and pathways involved in tumor angiogenesis (i.e., VEGFR2, PDGFR) has demonstrated clinical benefit in renal cell cancer as well. The HGF/c-Met axis offers a potentially high-value target for cancer drug development. Although HGF/c-Met is the driving mutation in hereditary and papillary renal cancer, as well as some glioblastomas, gastric, hepatocellular, and soft tissue cancers, overexpression of HGF and c-Met in a very high percentage of patients with solid tumors are associated with a poor outcome and could benefit from Met-targeted therapies. The known biological consequences of c-Met activation are invasion, cellular morphogenesis, motility, metastasis, immortalization, and angiogenesis, and they read like a list of the most undesirable properties associated with cancer. In addition to its own unique effects, c-Met signaling enhances tumor angiogenesis mediated by the VEGF axis. The response to hypoxia that increases HGF release and c-Met signaling enhances metastasis in untreated tumors and may be important in the resistance to VEGF-targeted agents in cancer therapy. EGFR Met inhibitors in combination can have synergistic activity, and simultaneous targeting of c-Met and VEGF, if achieved in a balanced manner by either a combination of agents or a single dually targeted agent, may offer benefits that exceed the inhibition of either target alone.

Disclosure of Potential Conflicts of Interest

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