Published in final edited form as:
Curr Signal Transduct Ther. 2011 ; 6(2): 146–151. doi:10.2174/157436211795659955.

The Hepatocyte Growth Factor Receptor: Structure, Function and Pharmacological Targeting in Cancer

Fabiola Cecchi[1], **Daniel C. Rabe**, and **Donald P. Bottaro**
Urologic Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892

Abstract

Under normal conditions, hepatocyte growth factor (HGF)-induced activation of its cell surface receptor, the Met tyrosine kinase (TK), is tightly regulated by paracrine ligand delivery, ligand activation at the target cell surface, and ligand activated receptor internalization and degradation. Despite these controls, HGF/Met signaling contributes to oncogenesis and tumor progression in several cancers and promotes aggressive cellular invasiveness that is strongly linked to tumor metastasis. The prevalence of HGF/Met pathway activation in human malignancies has driven rapid growth in cancer drug development programs. Pathway inhibitors can be divided broadly into biologicals and low molecular weight synthetic TK inhibitors; of these, the latter now outnumber all other inhibitor types. We review here Met structure and function, the basic properties of HGF/Met pathway antagonists now in preclinical and clinical development, as well as the latest clinical trial results. The main challenges facing the effective use of HGF/Met-targeted antagonists for cancer treatment include optimal patient selection, diagnostic and pharmacodynamic biomarker development, and the identification and testing of optimal therapy combinations. The wealth of basic information, analytical reagents and model systems available concerning HGF/Met oncogenic signaling will continue to be invaluable in meeting these challenges and moving expeditiously toward more effective disease control.

Keywords

Hepatocyte growth factor; Met

1. Introduction

The *MET* oncogene was first isolated from a human osteosarcoma-derived cell line on the basis of its transforming activity *in vitro*, caused by a DNA rearrangement where sequences from the *TPR* (translocated promoter region) locus on chromosome 1 were fused to *MET* sequence on chromosome 7 (*TPR-MET*) [1]. A similar gene rearrangement was later found in patients with gastric carcinoma [2,3]. Isolation of the full-length *MET* proto-oncogene sequence revealed that it encoded a receptor tyrosine kinase (TK) [2]. The Met tyrosine kinase is activated by a single ligand known as hepatocyte growth factor (HGF) or scatter

[1]Correspondence: Urologic Oncology Branch, Center for Cancer Research, National Cancer Institute, Bldg 10 CRC Rm 1W-5832, 10 Center Drive MSC 1107, Bethesda, MD 20892-1107 USA, Telephone (301) 402-6499, Fax (301) 402-0922, cecchif@mail.nih.gov.

factor (SF). This molecule is secreted by mesenchymal cells [4] especially fibroblasts and smooth muscle cells [5,6] and activates the Met protein via paracrine mechanisms [7,8]. The identification of hepatocyte growth factor (HGF) as the natural ligand for the Met receptor protein [9], and the identity of scatter factor (SF) and HGF united a collection of findings demonstrating that a single receptor transduced multiple biological activities including motility, proliferation, survival and morphogenesis [10–13].

Both HGF and Met proteins are processed proteolytically from single chain precursors into mature disulfide linked heterodimers. Both are widely expressed early in development and deletion of either gene lethally disrupts embryogenesis [10,11,13]. The widespread expression of both *MET* and *HGF* genes persists throughout adulthood and upregulation of *HGF* expression after kidney, liver or heart injury suggests that pathway activation protects against tissue damage and promotes tissue repair and regeneration [14–18].

2. Met: Structure and Function

The *MET* gene is located on chromosome 7 band 7q21–q31 and spans more than 120 kb in length, consisting of 21 exons separated by 20 introns [19]. The primary *MET* transcript produces a 150 kDa polypeptide [20] that is partially glycosylated to produce a 170 kDa precursor protein. This 170 kDa precursor is further glycosylated to a mass of approximately 190 kDa and then cleaved into a 50 kDa beta chain and 140 kDa alpha chain which are linked via disulfide bonds [21].

The Met beta chain has seven conserved subdomains which have functional significance and homology with other cell signaling proteins. The amino-terminal semaphorin (or Sema) domain has a 7-bladed beta-propeller fold [22,23] that serves as a key element for ligand binding, and is also found in the plexin family of semaphorin receptors [8,21]. The presence of the semaphorin domain, as well as the more highly conserved tyrosine kinase domain, places Met in a subfamily of tyrosine kinases that includes Ron and the avian Ron ortholog, Sea [20]. Carboxyl-terminal to the Sema domain is the PSI domain, so named because it is found in plexins, semaphorins and integrins [21]. Further downstream are four immunoglobulin domains, also referred to as IPT repeats, because they are found in immunoglobulins, plexins and transcription factors [21]. The PSI domain is thought to function as a linking module to orient the extracellular fragment of Met for proper ligand binding [24]. Although several reports claim that the sema domain is the sole HGF binding domain in Met [25], a recent report claims that IPT repeats 3 and 4, located closest to the transmembrane domain, also function in HGF binding [26].

Like all tyrosine kinases, the Met transmembrane domain contains a single alpha helix [8]. The most amino terminal cytoplasmic subdomain, the juxtamembrane (JM) region, contains two protein phosphorylation sites: S985 and Y1003 (numbered according to GenBank accession no. J02958). Phosphorylation of S985 negatively regulates kinase activity [27] and phosphorylation of Y1003 recruits c-Cbl, which monoubiquinates Met and interacts with endophilin, targeting Met for internalization and degradation [1]. A PEST sequence, which may serve as a site for this ubiquitination, is present in the JM domain [28]. A specific protein tyrosine phosphatase (PTP-S) is also reported to bind to this region [29].

Carboxyl terminal to the JM region is the tyrosine kinase (TK) domain, which shares homology with insulin growth factor I receptors and the Tyro 3 family of immunoregulatory molecules, and lastly, a carboxy-terminal tail region. Upon HGF binding, Met autophosphorylation occurs on tyrosine residues Y1234 and Y1235 (numbered per GenBank accession no. J02958) within the activation loop of the TK domain, inducing kinase activity, while phosphorylation on Y1349 and Y1356 in the carboxyl terminal region forms a docking site for intracellular adapters that transmit signals downstream [11,13]. An intact docking site is required for transformation and metastasis [13]. Critical signaling mediators in this pathway include Grb2, Gab1, phosphatidylinositol 3-kinase (PI3K), phospholipase C-gamma (PLCγ), Shc, Src, Shp2, Ship1 and STAT3 [11,13].

3. Met Mutations Associated with Cancer

Under normal conditions, HGF-induced Met TK activation is tightly regulated by paracrine ligand delivery, ligand activation at the target cell surface, and ligand activated receptor internalization and degradation. Despite these multiple controls, pathway deregulation occurs in a variety of neoplasms. Among the hundreds of genes upregulated by HGF are those encoding proteases required for HGF and Met processing, as well as *MET*, creating the potential for its overexpression through persistent ligand stimulation [11]. Indeed, *MET* overexpression is characteristic of several epithelial and mesenchymal cancers and is an independent prognostic factor associated with adverse outcome [30]. Other mechanisms of oncogenic pathway activation include aberrant paracrine or autocrine ligand production, constitutive kinase activation in the presence or absence of *MET* gene amplification, and *MET* gene mutation [10,31,32]. Missense *MET* mutations occur in several cancers; the earliest reported mutations were found exclusively in the Met TK domain and were associated with hereditary and sporadic forms of papillary renal cell carcinoma (PRC) [33,34]. Mutations throughout the *MET* coding sequence were later found in lung cancer and in head and neck cancers [8,35].

The impact of specific *MET* mutations has been studied act at the molecular, cellular and organismal levels. Structural modeling of the Met TK domain indicated that activating PRC mutations interfere with an intrinsic mode of autoinhibition [36,37]. Early cell-based investigations confirmed that kinase activity was deregulated in various mutant forms and revealed that these could have distinct biological effects. For example, the PRC-associated mutations D1228H/N and M1250T showed enhanced kinase activity, Ras pathway activation and focus formation, while L1195V and Y1230C more effectively activated PI3K, promoting cell survival, soft agar colony formation and matrix invasion [38,39]. Although mutations that were reconstituted in HGF-producing cells (such as NIH3T3) could not rigorously address the role of ligand binding in oncogenesis, later studies showed that mutations expressed in epithelial cells required added ligand for soft agar colony formation and that colony formation by NIH3T3 bearing Met M1250T could be blocked by ligand binding antagonists [40]. PRC-associated *MET* mutations also have been investigated in mice by engineering changes in the murine *MET* locus [41]. Interestingly, mice harboring D1226N, Y1228C, and both M1248T and L1193V mutations developed sarcomas with high frequency and some lymphomas, whereas the M1248T mice developed carcinomas and lymphomas; no mice developed PRC [41]. Furthermore, analogous to the trisomy of

chromosome 7 frequently observed in human PRC tumors, trisomy of chromosome 6 (containing the murine *MET* locus) and preferential duplication of the mutant *MET* allele was observed in most tumors. These results independently confirm the oncogenicity of PRC-associated *MET* mutations *in vivo* and suggest that distinct mutations influence the types of cancers that develop in mice [41].

Other alterations in the *MET* coding sequence have been identified in regions encoding the extracellular semaphorin domain (E168D, L229F, S323G, and N375S) and the intracellular JM domain (R988C, T1010I, S1058P, and exon 14 deletions) of non-small cell lung carcinoma (NSCLC)-derived cell lines, in 12.5 % of small lung cell cancer (SCLC) cases, as well as in 8% of samples of lung adenocarcinoma tissues [35,42–44]. Some of these mutations activate proliferation, motility and invasiveness in cultured cells [35]. As noted earlier, Y1003 is phosphorylated in response to HGF binding and recruits c-Cbl, leading to Met ubiquitination and degradation [1]. In Met JM domain mutants missing exon 14, the loss of Y1003 results in Met accumulation at the cell surface and persistent HGF-stimulated signaling that leads, in turn, to increased transforming activity and tumorigenic potential [1].

The capacity for JM mutations R988C and T1010I to contribute to oncogenesis has been a topic of debate. First identified by Schmidt and colleagues [36], T1010I was thought to represent a rare polymorphism, owing to lack of disease segregation and failure to induce focus formation or constitutive Met phosphorylation in NIH3T3 cells. Although this potential polymorphism did not stimulate NIH3T3 cell growth in soft agar, it was more active than the wild-type Met in the athymic nude mice tumorigenesis assay, suggesting that it may have effects on tumorigenesis [45] and lead to altered cytoskeletal functions [46]. Recently Tyner and colleagues found these variants in a wide variety of malignancies as well as individuals without cancer, suggesting that R988C and T1010I are indeed rare polymorphisms that may predispose an individual toward cancer when combined with an oncogene that drives cellular proliferation [47].

Of interest, another novel germ-line missense mutation P1009S (numbered per GenBank accession no. J02958) (exon 14) that affects the JM domain of Met has been detected in a patient with gastric carcinoma. P1009S caused colony formation in soft agar, was tumorigenic in athymic nude mice, but appears to be oncogenic by a different mechanism: while Met mutations in the tyrosine kinase domain are constitutively activated, the P1009S Met mutant, after HGF/SF treatment, stays phosphorylated for a significantly longer time (24–48 h) than wild-type Met, but it is not constitutively activated. This suggests that the downregulation of Met, which occurs after receptor activation and tyrosine phosphorylation, may be impaired by this mutation [45].

Overall, *MET* mutation occurs at a lower frequency than most other mechanisms of pathway activation in tumors; nonetheless, mutations provide strong direct evidence of the pathway's oncogenic potential and may identify patients most likely to benefit from Met-targeted therapeutics.

Consistent with the role of this pathway in organogenesis, oncogenic Met signaling resembles developmental transitions between epithelial and mesenchymal cell types

normally regulated by HGF: increased protease production coupled with cell dissociation and motility promotes cellular invasion through extracellular matrices, enabling tumor invasiveness and metastasis. Conversely, silencing the endogenous, overexpressed *MET* gene in tumor cells suppresses tumor growth and metastasis, and induces the regression of established metastases in mouse models [48]. In addition, HGF/Met signaling in vascular endothelial cells stimulates tumor angiogenesis, facilitating tumor growth for cancers that are growth-limited by hypoxia, and independently promoting tumor metastasis. Hypoxia alone upregulates *MET* expression and enhances HGF signaling in cultured cells and mouse tumor models [49].

4. Pharmacological Inhibitors of the HGF/Met Pathway

The prevalence of HGF/Met pathway activation in human malignancies has driven rapid growth in drug development programs. Agents currently under development as HGF/Met pathway inhibitors can be broadly subdivided into biologicals and low molecular weight synthetic compounds. Biologicals, or protein-based agents, act through a variety of mechanisms and possess target selectivity and pharmacokinetic properties that are predictable and often desirable. Nonetheless, their size typically restricts their action to extracellular events and their complexity impacts drug manufacture, routes of administration and shelf-life. Thus it is not surprising that synthetic, low molecular weight TK inhibitors (TKIs) presently outnumber every other class of HGF/Met therapeutic.

4.1. Biological HGF/Met Pathway Antagonists

Biologicals are primarily directed against ligand-receptor binding or related cell-surface events such as receptor clustering, and include: [1] truncated proteins product of a naturally occurring alternative *HGF* mRNA transcript such as NK2 or NK4. Although, the potential anti-oncogenic efficacy of NK2 was shown to be compromised by its intrinsic motogenic activity, which enhanced HGF-driven metastasis in mouse models [50–54], NK4 has proven to be a complete competitive antagonist of HGF/Met oncogenic signaling in a variety of preclinical models and is now entering human clinical trials. [2] antagonistic HGF forms that resist proteolytic activation or its conformational consequences exploit the requirement for proteolytic cleavage that converts pro-HGF to a biologically active heterodimer [55–58]. [3] truncated soluble forms of the Met ectodomain such as soluble Met Sema domain constructs that sequester HGF and interfere with Met homodimerization suppressed HGF-induced tumor cell migration [59], as well as tumor growth and metastasis in mice [60]. [4] among HGF/Met-targeted biologicals, the most advanced drug candidates are mAbs directed against either HGF or Met. The majority of these block HGF/Met binding, although at least one anti-Met mAb decreases Met activation by inducing ectodomain shedding and degradation [61]. Neutralizing mAbs against human HGF, such as L2G7, AMG102 and SCH900105 (formerly AV299) each potently suppressed the growth of tumor xenografts in mice [62–66]. AMG102, currently in phase I and II clinical trials [67], binds to the HGF light chain (K_d of 0.22 nM) and blocks HGF-Met binding (IC_{50} of 2.1 nM). AMG 102 was well tolerated in humans and adverse events (AEs), were predominantly low grade (fatigue, constipation, anorexia, nausea and vomiting) [68]. AMG102 was maintained in the body with a mean half-life of 15.4 hours [68]. SCH900105 is currently in phase I trials: this

antibody was also very well tolerated in patients with a half-life of 15 h. In its first completed trial, SCH900105 treatment was associated with stable disease (SD) in half of the patients, the longest for 34 weeks [64–66]. A humanized, bivalent anti-Met monoclonal antibody, h224G11, inhibits Met phosphorylation and dimerization and blocks proliferation, migration, invasion, morphogenesis and angiogenesis in cell-based studies [66,69]. Another anti-Met mAb that blocks ligand binding, MetMab (formerly OA5D5), is an engineered monovalent antibody that has been shown to inhibit tumor growth in animal models by more than 95 percent [70]. MetMab (IC_{50} of 2.6 to 8.7 nM in intact cells), downregulates constitutively active Met in tumor cell lines [71], and is currently in phase I/II human clinical trials in comparison with erlotinib in patients with NSCLC [67].

4.2. Small Synthetic Met Kinase Inhibitors

Most Met TKIs competitively antagonize occupancy of the intracellular ATP binding site, preventing phosphorylation, TK activation and downstream signaling. These agents are in various stages of development; they are discussed here starting with preclinical candidates and ending with those now entering phase III clinical trials.

Early studies of Met-targeted TKIs, such as SU11274 (IC_{50} of 20 nM) [42,72,73] and PHA665752 (IC_{50} of 9 nM) [31,74], established that Met TKIs could potently suppress oncogenesis and provided a platform for improving potency, selectivity and other drug properties. RP1040 (IC_{50} of 1.3 nM) [75] and CEP-A (IC_{50} of 13 nM) [76] are recent preclinical candidates; RP1040 shows good oral availability and displays a half-life of up to 9 h in intact cells [75]. CEP-A shows sustainable pharmacodynamic (PD) effects in mouse studies, resulting in significant tumor growth inhibition, stable disease (SD) and partial regression [76].

Met TKIs now entering phase I clinical trials to establish safety and tolerability include JNJ-38877605 and PF-04217903. The former shows >1000-fold selectivity for the Met kinase relative to >200 related receptor TKs [77], while the latter targets Met as well as anaplastic lymphoma kinase (ALK) [78]. AMG 208 selectively inhibits both ligand-dependent and ligand-independent Met activation [79], while E7050 targets both Met and VEGFR2 [80]. A phase I study of MK8033 (IC_{50} of 1.3 nM), which targets Met and the Met family member Ron, is also underway [67]. MP470, inhibiting PDGFR, Kit and Met sensitized glioblastoma cells to radiotherapy in mice and combined with erlotinib inhibited prostate cancer cell proliferation and tumor xenograft growth [81]. Phase 1 clinical trials were discontinued for SGX523 after renal toxicity was observed in patients receiving relatively low doses [82].

Several Met TKIs are in phase I/II clinical trials that further test safety and efficacy. BMS777607 (IC_{50} of 3.9 nM) has completed a phase I/II study in metastatic cancer patients (results are not yet available) [83]. MGCD265, targeting Met, VEGFR1-3, Ron, and Tie2 is currently in phase I/II studies in combination with erlotinib or standard of care (SOC) treatments; safety trials have shown a half-life of 20–30 hours with no grade 2 or higher AEs [84,85]. MK2461 has completed phase I/II trials and showed a half-life of approximately 6 hours, few AEs above grade 1 (anorexia, fatigue and nausea), and a best response of SD for six treatment cycles [86,87].

Foretinib (GSK1363089; formerly XL880) and ARQ197 have shown promising results in multiple phase II trials. Foretinib targets Met and VEGFR2; trials have shown a half-life of 60 hours, the most common AEs were grade 1 or 2 (fatigue, hypertension, nausea, anorexia and vomiting). Several studies have shown SD for at least 10 months and some patients have experienced >20 percent reduction in tumor size [88–91]. ARQ197 may represent a new class of low molecular weight TKI; ARQ197 binds to a region of Met outside of the ATP binding site and impairs kinase activation allosterically; it is reported to be highly selective for Met (IC_{50} of 50 nM *in vitro*) although its mechanism of action is not yet completely defined. Current phase II clinical trials compare ARQ197 with TKIs against other targets, (results are not yet available) [92].

Met TKIs furthest in development include XL184 and PF02341066, both now entering phase III clinical trials. XL184 targets Met, VEGFR2, and Ret and has a half-life of 80–90 hours [93]. On average, patients show SD greater than 3 months with several up to 6 months while on treatment [94]. A current phase III trial investigates XL184 as a first line treatment, compared to placebo, in patients with medullary thyroid cancer [67]. PF-02341066, which has greater Met selectivity relative to PF-04217903 [95], is currently recruiting for phase I, II and III clinical trials [67]; preclinical studies indicate it is highly effective against the product of the *EML4-ALK* translocation found in a subset of NSCLC patients [96,97].

Conclusions

In closing, the wealth of basic knowledge about HGF/Met biology has enabled an accurate assessment of the pathway's oncogenic potential and provided the insight needed to develop potent and selective inhibitors and use them with relative safety in humans. Patient selection, of primary importance, will advance as more robust methods are developed to analyze the many known potential diagnostic biomarkers of pathway activity. Methods that rely on DNA or RNA (*e.g.* detecting *MET* gene amplification or mutation) are now faster and more sensitive than those available for quantitating Met protein content and phosphorylation state, but efforts to improve both are underway. Similarly, the need for PD markers that track drug effect and patient response is recognized and clinical PD marker studies currently underway reveal solid candidates. Finally, the emergence of primary and acquired resistance to TKIs from pre-existing or de novo mutations, respectively, must be addressed in the design of future clinical studies. For many cancer types, combining Met inhibitors with standard of care therapies may reduce the risk of acquired resistance to either single treatment alone, while at the same time providing a safe and expedient route to approval. Less is known about how combinations of new targeted therapies should be selected or administered safely. Such combinations are also likely to reduce the risk of acquired drug resistance, and may potentially offer the most effective treatment when information for patient selection is abundant; but most will require more preclinical research before effective and practical clinical trials can be designed.

Acknowledgments

Web site addresses are provided as an informational resource, not as an endorsement of any product or manufacturer. This work was supported by the Intramural Research Program of the NIH, National Cancer Institute, Center for Cancer Research.

References

1. Peschard P, Park M. From Tpr-Met to Met, tumorigenesis and tubes. Oncogene. 2007; 26:1276–1285. [PubMed: 17322912]
2. Furge KA, Zhang YW, Vande Woude GF. Met receptor tyrosine kinase: enhanced signaling through adapter proteins. Oncogene. 2000; 19:5582–5589. [PubMed: 11114738]
3. Yu J, Miehlke S, Ebert MP, et al. Frequency of TPR-MET rearrangement in patients with gastric carcinoma and in first-degree relatives. Cancer. 2000; 88:1801–1806. [PubMed: 10760755]
4. Sonnenberg E, Meyer D, Weidner KM, Birchmeier C. Scatter factor/hepatocyte growth factor and its receptor, the c-met tyrosine kinase, can mediate a signal exchange between mesenchyme and epithelia during mouse development. J Cell Biol. 1993; 123:223–235. [PubMed: 8408200]
5. Naldini L, Weidner KM, Vigna E, et al. Scatter factor and hepatocyte growth factor are indistinguishable ligands for the MET receptor. EMBO J. 1991; 10:2867–2878. [PubMed: 1655405]
6. Kim ES, Salgia R. MET pathway as a therapeutic target. J Thorac Oncol. 2009; 4:444–447. [PubMed: 19333071]
7. Stoker M, Gherardi E, Perryman M, Gray J. Scatter factor is a fibroblast-derived modulator of epithelial cell mobility. Nature. 1987; 327:239–242. [PubMed: 2952888]
8. Ma PC, Maulik G, Christensen J, Salgia R. c-Met: structure, functions and potential for therapeutic inhibition. Cancer Metastasis Rev. 2003; 22:309–325. [PubMed: 12884908]
9. Bottaro DP, Rubin JS, Faletto DL, et al. Identification of the hepatocyte growth factor receptor as the c-met proto-oncogene product. Science. 1991; 251:802–804. [PubMed: 1846706]
10. Birchmeier C, Birchmeier W, Gherardi E, Vande Woude GF. Met, metastasis, motility and more. Nat Rev Mol Cell Biol. 2003; 4:915–925. [PubMed: 14685170]
11. Zhang YW, Vande Woude GF. HGF/SF-met signaling in the control of branching morphogenesis and invasion. J Cell Biochem. 2003; 88:408–417. [PubMed: 12520544]
12. Rosario M, Birchmeier W. How to make tubes: signaling by the Met receptor tyrosine kinase. Trends Cell Biol. 2003; 13:328–335. [PubMed: 12791299]
13. Corso S, Comoglio PM, Giordano S. Cancer therapy: can the challenge be MET? Trends Mol Med. 2005; 11:284–292. [PubMed: 15949770]
14. Matsumoto K, Nakamura T. Hepatocyte growth factor: Renotropic role and potential therapeutics for renal diseases. Kidney International. 2001; 59:2023–2038. [PubMed: 11380804]
15. Morishita R, Aoki M, Hashiya N, et al. Therapeutic angiogenesis using hepatocyte growth factor (HGF). Curr Gene Ther. 2004; 4:199–206. [PubMed: 15180586]
16. Huh CG, Factor VM, Sanchez A, Uchida K, Conner EA, Thorgeirsson SS. Hepatocyte growth factor/c-met signaling pathway is required for efficient liver regeneration and repair. Proc Natl Acad Sci U S A. 2004; 101:4477–4482. [PubMed: 15070743]
17. Borowiak M, Garratt AN, Wustefeld T, Strehle M, Trautwein C, Birchmeier C. Met provides essential signals for liver regeneration. Proc Natl Acad Sci U S A. 2004; 101:10608–10613. [PubMed: 15249655]
18. Liu Y. Renal fibrosis: new insights into the pathogenesis and therapeutics. Kidney Int. 2006; 69:213–217. [PubMed: 16408108]
19. Rong S, Segal S, Anver M, Resau JH, Vande Woude GF. Invasiveness and metastasis of NIH 3T3 cells induced by Met-hepatocyte growth factor/scatter factor autocrine stimulation. Proc Natl Acad Sci U S A. 1994; 91:4731–4735. [PubMed: 8197126]
20. Maulik G, Shrikhande A, Kijima T, Ma PC, Morrison PT, Salgia R. Role of the hepatocyte growth factor receptor, c-Met, in oncogenesis and potential for therapeutic inhibition. Cytokine Growth Factor Rev. 2002; 13:41–59. [PubMed: 11750879]
21. Sattler M, Ma PC, Salgia R. Therapeutic targeting of the receptor tyrosine kinase Met. Cancer Treat Res. 2004; 119:121–138. [PubMed: 15164876]
22. Antipenko A, Himanen JP, van LK, et al. Structure of the semaphorin-3A receptor binding module. Neuron. 2003; 39:589–598. [PubMed: 12925274]

23. Love CA, Harlos K, Mavaddat N, et al. The ligand-binding face of the semaphorins revealed by the high-resolution crystal structure of SEMA4D. Nat Struct Biol. 2003; 10:843–848. [PubMed: 12958590]
24. Kozlov G, Perreault A, Schrag JD, et al. Insights into function of PSI domains from structure of the Met receptor PSI domain. Biochem Biophys Res Commun. 2004; 321:234–240. [PubMed: 15358240]
25. Gherardi E, Youles ME, Miguel RN, et al. Functional map and domain structure of MET, the product of the c-met protooncogene and receptor for hepatocyte growth factor/scatter factor. Proc Natl Acad Sci U S A. 2003; 100:12039–12044. [PubMed: 14528000]
26. Basilico C, Arnesano A, Galluzzo M, Comoglio PM, Michieli P. A high affinity hepatocyte growth factor-binding site in the immunoglobulin-like region of Met. J Biol Chem. 2008; 283:21267–21277. [PubMed: 18495663]
27. Gandino L, Longati P, Medico E, Prat M, Comoglio PM. Phosphorylation of serine 985 negatively regulates the hepatocyte growth factor receptor kinase. J Biol Chem. 1994; 269:1815–1820. [PubMed: 8294430]
28. Crepaldi T, Pollack AL, Prat M, Zborek A, Mostov K, Comoglio PM. Targeting of the SF/HGF receptor to the basolateral domain of polarized epithelial cells. J Cell Biol. 1994; 125:313–320. [PubMed: 8163548]
29. Villa-Moruzzi E, Puntoni F, Bardelli A, Vigna E, De RS, Comoglio PM. Protein tyrosine phosphatase PTP-S binds to the juxtamembrane region of the hepatocyte growth factor receptor Met. Biochem J. 1998; 336(Pt 1):235–239. [PubMed: 9806906]
30. 2009. http://www.vai.org/vari/metandcancer
31. Smolen GA, Sordella R, Muir B, et al. Amplification of MET may identify a subset of cancers with extreme sensitivity to the selective tyrosine kinase inhibitor PHA-665752. PNAS. 2006; 103:2316–2321. [PubMed: 16461907]
32. Lengyel E, Prechtel D, Resau JH, et al. C-Met overexpression in node-positive breast cancer identifies patients with poor clinical outcome independent of Her2/neu. Int J Cancer. 2005; 113:678–682. [PubMed: 15455388]
33. Schmidt C, Bladt F, Goedecke S, et al. Scatter factor/hepatocyte growth factor is essential for liver development. Nature. 1995; 373:699–702. [PubMed: 7854452]
34. Dharmawardana PG, Giubellino A, Bottaro DP. Hereditary papillary renal carcinoma type I. Curr Mol Med. 2004; 4:855–868. [PubMed: 15579033]
35. Lengyel E, Sawada K, Salgia R. Tyrosine kinase mutations in human cancer. Curr Mol Med. 2007; 7:77–84. [PubMed: 17311534]
36. Schmidt L, Junker K, Nakaigawa N, et al. Novel mutations of the MET proto-oncogene in papillary renal carcinomas. Oncogene. 1999; 18:2343–2350. [PubMed: 10327054]
37. Miller M, Ginalski K, Lesyng B, Nakaigawa N, Schmidt L, Zbar B. Structural basis of oncogenic activation caused by point mutations in the kinase domain of the MET proto-oncogene: modeling studies. Proteins. 2001; 44:32–43. [PubMed: 11354004]
38. Bardelli A, Longati P, Gramaglia D, et al. Uncoupling signal transducers from oncogenic MET mutants abrogates cell transformation and inhibits invasive growth. Proc Natl Acad Sci U S A. 1998; 95:14379–14383. [PubMed: 9826708]
39. Giordano S, Maffe A, Williams TA, et al. Different point mutations in the met oncogene elicit distinct biological properties. FASEB J. 2000; 14:399–406. [PubMed: 10657996]
40. Michieli P, Basilico C, Pennacchietti S, et al. Mutant Met-mediated transformation is liganddependent and can be inhibited by HGF antagonists. Oncogene. 1999; 18:5221–5231. [PubMed: 10498872]
41. Graveel CR, London CA, Vande Woude GF. A mouse model of activating Met mutations. Cell Cycle. 2005; 4:518–520. [PubMed: 15738649]
42. Ma PC, Jagadeeswaran R, Jagadeesh S, et al. Functional Expression and Mutations of c-Met and Its Therapeutic Inhibition with SU11274 and Small Interfering RNA in Non-Small Cell Lung Cancer. Cancer Research. 2005; 65:1479–1488. [PubMed: 15735036]

43. Ma PC, Kijima T, Maulik G, et al. c-MET mutational analysis in small cell lung cancer: novel juxtamembrane domain mutations regulating cytoskeletal functions. Cancer Res. 2003; 63:6272–6281. [PubMed: 14559814]
44. Kong-Beltran M, Seshagiri S, Zha J, et al. Somatic mutations lead to an oncogenic deletion of met in lung cancer. Cancer Res. 2006; 66:283–289. [PubMed: 16397241]
45. Lee JH, Han SU, Cho H, et al. A novel germ line juxtamembrane Met mutation in human gastric cancer. Oncogene. 2000; 19:4947–4953. [PubMed: 11042681]
46. Ma PC, Kijima T, Maulik G, et al. c-MET mutational analysis in small cell lung cancer: novel juxtamembrane domain mutations regulating cytoskeletal functions. Cancer Res. 2003; 63:6272–6281. [PubMed: 14559814]
47. Tyner JW, Fletcher LB, Wang EQ, et al. MET receptor sequence variants R970C and T992I lack transforming capacity. Cancer Res. 2010; 70:6233–6237. [PubMed: 20670955]
48. Corso S, Migliore C, Ghiso E, De RG, Comoglio PM, Giordano S. Silencing the MET oncogene leads to regression of experimental tumors and metastases. Oncogene. 2008; 27:684–693. [PubMed: 17684486]
49. Pennacchietti S, Michieli P, Galluzzo M, Mazzone M, Giordano S, Comoglio PM. Hypoxia promotes invasive growth by transcriptional activation of the met protooncogene. Cancer Cell. 2003; 3:347–361. [PubMed: 12726861]
50. Stahl SJ, Wingfield PT, Kaufman JD, et al. Functional and biophysical characterization of recombinant human hepatocyte growth factor isoforms produced in Escherichia coli. Biochemical Journal. 1997; 326:763–772. [PubMed: 9307026]
51. Montesano R, Soriano JV, Malinda KM, et al. Differential effects of hepatocyte growth factor isoforms on epithelial and endothelial tubulogenesis. Cell Growth and Differentiation. 1998; 9:355–365. [PubMed: 9607557]
52. Otsuka T, Horiguchi N, Kanda D, et al. Overexpression of NK2 inhibits liver regeneration after partial hepatectomy in mice. World J Gastroenterol. 2005; 11:7444–7449. [PubMed: 16437714]
53. Toyoda M, Takayama H, Horiguchi N, et al. Overexpression of hepatocyte growth factor/scatter factor promotes vascularization and granulation tissue formation in vivo. FEBS Lett. 2001; 509:95–100. [PubMed: 11734213]
54. Yu Y, Merlino G. Constitutive c-Met signaling through a nonautocrine mechanism promotes metastasis in a transgenic transplantation model. Cancer Res. 2002; 62:2951–2956. [PubMed: 12019177]
55. Gak E, Taylor WG, Chan AM, Rubin JS. Processing of hepatocyte growth factor to the heterodimeric form is required for biological activity. FEBS Lett. 1992; 311:17–21. [PubMed: 1383032]
56. Hartmann G, Naldini L, Weidner KM, et al. A functional domain in the heavy chain of scatter factor/hepatocyte growth factor binds the c-Met receptor and induces cell dissociation but not mitogenesis. Proc Natl Acad Sci U S A. 1992; 89:11574–11578. [PubMed: 1280830]
57. Lokker NA, Mark MR, Luis EA, et al. Structure-function analysis of hepatocyte growth factor: identification of variants that lack mitogenic activity yet retain high affinity receptor binding. EMBO J. 1992; 11:2503–2510. [PubMed: 1321034]
58. Naka D, Ishii T, Yoshiyama Y, et al. Activation of hepatocyte growth factor by proteolytic conversion of a single chain form to a heterodimer. J Biol Chem. 1992; 267:20114–20119. [PubMed: 1328193]
59. Kong-Beltran M, Stamos J, Wickramasinghe D. The Sema domain of Met is necessary for receptor dimerization and activation. Cancer Cell. 2004; 6:75–84. [PubMed: 15261143]
60. Michieli P, Mazzone M, Basilico C, et al. Targeting the tumor and its microenvironment by a dualfunction decoy Met receptor. Cancer Cell. 2004; 6:61–73. [PubMed: 15261142]
61. Petrelli A, Circosta P, Granziero L, et al. Ab-induced ectodomain shedding mediates hepatocyte growth factor receptor down-regulation and hampers biological activity. Proc Natl Acad Sci U S A. 2006; 103:5090–5095. [PubMed: 16547140]
62. Kim KJ, Wang L, Su YC, et al. Systemic anti-hepatocyte growth factor monoclonal antibody therapy induces the regression of intracranial glioma xenografts. Clin Cancer Res. 2006; 12:1292–1298. [PubMed: 16489086]

63. Burgess T, Coxon A, Meyer S, et al. Fully human monoclonal antibodies to hepatocyte growth factor with therapeutic potential against hepatocyte growth factor/c-Met-dependent human tumors. Cancer Res. 2006; 66:1721–1729. [PubMed: 16452232]
64. Meetze, AK.; Boudrow, A.; Connoly, K.; Huang, R.; Rideout, W.; Gyuris, J.; Han, M. Anti-tumor activity of SCH 900105 (AV299), an anti-HGF antibody in non-small cell lung cancer models. AACR; Nov 2009; Boston. 2009. Abstract C173
65. Meetze, AK.; COnnoly, K.; Boudrow, A.; Venkataraman, S.; Medicherla, S.; Gyuris, J.; Han, M. Preclinical efficacy and pharmacodynamics of SCH 900105 (AV-299) and anti-HGF antibody in an intracranial glioblastoma. AACR; Nov 2009; Boston. 2009. Abstract C181
66. Ramanathan, RK.; Paymo, CF.; Papadopoulos, PK., et al. A Phase 1 first-in-human study of SCH 900105, an antihepatocyte growth factor (HGF) monoclonal antibody, in subjects with advanced solid cancer. AACR; Nov 2009; Boston. 2009. Abstract A100
67. 2009. www.clinicaltrials.gov
68. Gordon MS, Mendelson DS, Sweeney C, et al. Interim results from a first-in-human study with AMG102, a fully human monoclonal antibody that neutralizes hepatocyte growth factor (HGF), the ligand to c-Met receptor, in patients (pts) with advanced solid tumors. J Clin Oncol (Meeting Abstracts). 2007; 25:3551.
69. Corvaïa N, Gonzalez A, Boute N, Beau-Larvor C, Fabre-Lafay S, Géronimi F, Broussas Lepecquet AM, et al. First bivalent fully antagonist anti-c-Met antibody targeting the c-Met receptor: I) *in vitro* mechanism of action. 2009
70. Martens T, Schmidt N-O, Eckerich C, et al. Inhibition of intracerebral glioblastoma growth by treatment with a novel one-armed anti-Met antibody. 2005
71. Cheng JQ, Lindsley CW, Cheng GZ, Yang H, Nicosia SV. The Akt/PKB pathway: molecular target for cancer drug discovery. Oncogene. 2005; 24:7482–7492. [PubMed: 16288295]
72. Sattler M, Pride YB, Ma P, et al. A novel small molecule met inhibitor induces apoptosis in cells transformed by the oncogenic TPR-MET tyrosine kinase. Cancer Res. 2003; 63:5462–5469. [PubMed: 14500382]
73. Berthou S, Aebersold DM, Schmidt LS, et al. The Met kinase inhibitor SU11274 exhibits a selective inhibition pattern toward different receptor mutated variants. Oncogene. 2004; 23:5387–5393. [PubMed: 15064724]
74. Christensen JG, Schreck R, Burrows J, et al. A Selective Small Molecule Inhibitor of c-Met Kinase Inhibits c-Met-Dependent Phenotypes in Vitro and Exhibits Cytoreductive Antitumor Activity in Vivo. Cancer Research. 2003; 63:7345–7355. [PubMed: 14612533]
75. Viswanadha, S.; Muthuppalaniappan, M.; Varanasi, KVS., et al. Pharacological and pharmacokinetic characterization of RP1040, a novle and potent c-Met tyrosine kinase inhibitor. AACR; Nov 2009; Boston. 2009. Abstract C212
76. Miknyoczki, SJ.; Underiner, T.; Aimone, T., et al. Identification of orally active small molecule c-Met inhibitors. AACR; Nov 2009; Boston. 2009. Abstract A1747
77. Eder JP, Vande Woude GF, Boerner SA, LoRusso PM. Novel therapeutic inhibitors of the c-Met signaling pathway in cancer. Clin Cancer Res. 2009; 15:2207–2214. [PubMed: 19318488]
78. Sattler M, Salgia R. The MET axis as a therapeutic target. Update Cancer Ther. 2009; 3:109–118. [PubMed: 20368753]
79. 2009. http://www.amgen.com/science/pipe_amg_208.html.
80. Nakagawa T, Tohyama O, Yamaguchi A, et al. E7050: A dual c-Met and VEGFR-2 tyrosine kinase inhibitor promotes tumor regression and prolongs survival in mouse xenograft models. Cancer Sci. 2009
81. Qi W, Cooke LS, Stejskal A, et al. MP470, a novel receptor tyrosine kinase inhibitor, in combination with Erlotinib inhibits the HER family/PI3K/Akt pathway and tumor growth in prostate cancer. BMC Cancer. 2009; 9:142. [PubMed: 19432987]
82. 2009. www.sgxpharma.com.
83. Schroeder GM, An Y, Cai ZW, et al. Discovery of N-(4-(2-Amino-3-chloropyridin-4-yloxy)-3-fluorophenyl)-4-ethoxy-1-(4-fluor ophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (BMS-777607), a Selective and Orally Efficacious Inhibitor of the Met Kinase Superfamily. J Med Chem. 2009; 52:1251–1254. [PubMed: 19260711]

84. Hong D, LoRusso P, Kurzrock R, et al. Phase I study of MGCD265 administered intermittently to patients with advanced malignancies (Study 265-102). J Clin Oncol (Meeting Abstracts). 2009; 27:e14516.
85. Kollmannsberger CK, Hurwitz H, Vlahovic G, et al. Phase I study of daily administration of MGCD265 to patients with advanced malignancies (Study 265-101). J Clin Oncol (Meeting Abstracts). 2009; 27:e14525.
86. Jeay, S.; Munshi, N.; Hill, J., et al. ARQ 197, a highly selective small molecule inhibitor of c-Met, with selective antitumor properties in a broad spectrum of human cancer cells. AACR Meeting Abstracts; 2007; 2007. p. 2369
87. Li, Y.; Chen, D.; Zhou, W., et al. Broad spectrum anti-cancer activity of ARQ 197, a highly selective oral c-Met Inhibitor, in multiple xenograft models. AACR Meeting Abstracts; 2007; 2007. p. 2216
88. Ross RW, Stein M, Sarantopoulos J, et al. A phase II study of the c-Met RTK inhibitor XL880 in patients (pts) with papillary renal-cell carcinoma (PRC). J Clin Oncol (Meeting Abstracts). 2007; 25:15601.
89. Srinivasan R, Choueiri TK, Vaishampayan U, et al. A phase II study of the dual MET/VEGFR2 inhibitor XL880 in patients (pts) with papillary renal carcinoma (PRC). J Clin Oncol (Meeting Abstracts). 2008; 26:5103.
90. Jhawer M, Kindler HL, Wainberg Z, et al. Assessment of two dosing schedules of GSK1363089 (GSK089), a dual MET/VEGFR2 inhibitor, in metastatic gastric cancer (GC): Interim results of a multicenter phase II study. J Clin Oncol (Meeting Abstracts). 2009; 27:4502.
91. Eder JP, Heath E, Appleman L, et al. Phase I experience with c-MET inhibitor XL880 administered orally to patients (pts) with solid tumors. J Clin Oncol (Meeting Abstracts). 2007; 25:3526.
92. Gu, X.; Wang, C.; Yu, Y., et al. Inhibition of HGF/c-Met pathway by ARQ 197: Characterization of pharmacodynamic markers in vitro and in vivo. AACR; Nov 2009; Boston. 2009. 2009. Abstract 1748
93. Salgia R, Hong DS, Camacho LH, et al. A phase I dose-escalation study of the safety and pharmacokinetics (PK) of XL184, a VEGFR and MET kinase inhibitor, administered orally to patients (pts) with advanced malignancies. J Clin Oncol (Meeting Abstracts). 2007; 25:14031.
94. Salgia R, Sherman S, Hong DS, et al. A phase I study of XL184, a RET, VEGFR2, and MET kinase inhibitor, in patients (pts) with advanced malignancies, including pts with medullary thyroid cancer (MTC). 2008
95. Timofeevski SL, McTigue MA, Ryan K, et al. Enzymatic characterization of c-Met receptor tyrosine kinase oncogenic mutants and kinetic studies with aminopyridine and triazolopyrazine inhibitors. Biochemistry. 2009; 48:5339–5349. [PubMed: 19459657]
96. 2009. www.pfizer.com
97. Shaw AT, Yeap BY, Mino-Kenudson M, et al. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. J Clin Oncol. 2009; 27:4247–4253. [PubMed: 19667264]