Targeting the Met signaling pathway in renal cancer

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Renal cell carcinoma (RCC), the most common form of kidney cancer, accounts for 3% of all adult malignancies and its incidence has significantly increased over the last 20 years. RCC claims 13,000 lives annually in the USA and more than 100,000 worldwide. A better understanding of the molecular basis of RCC has facilitated the development of novel and more selective therapeutic approaches. An important role in RCC oncogenesis is played by the receptor for HGF, Met, which has attracted considerable attention, more recently as a molecular target for cancer therapy, and several drugs selectively targeting this pathway are now in clinical trials. This review will focus on efforts to understand the role of the Met signaling pathway in renal cancer and how this has contributed to the development of potent and selective drug candidates.

**KEYWORDS**: HGF • HPRC • Met • RCC • renal cell carcinoma • targeted therapy • TFE3

Renal cell carcinoma (RCC) represents 85% of all primary renal neoplasms and its incidence has increased significantly over the last 20 years. Approximately 39,000 people will be newly diagnosed in 2008; 13,000 will die in the USA alone and more than 100,000 worldwide annually [1]. Patients who are found to have localized disease can have long-term disease-free survival; however, when the diagnosis is made after the disease has become metastatic, the prognosis is poor, with only a 18% survival rate at 2 years [2]. Immunologic therapy with IL-2 is associated with a dramatic response in 10–20% of patients with advanced disease [3]; however, more effective forms of therapy are needed that will benefit a higher percentage of patients. Moreover, IL-2 therapy is also associated with severe toxicity.

These circumstances clearly highlight the necessity for developing novel therapeutic approaches to improve the outcome of RCC. A better understanding of the molecular pathogenesis of RCC, obtained through the study of families affected with inherited forms of kidney cancer, have allowed better classification of kidney cancer as a number of different types of cancer [4]. Relating these pathogenic features to the more common sporadic renal cancers has, in turn, greatly improved our global understanding of RCC. We discuss four types of familial renal cancer syndromes, based on genetic, histologic and clinical criteria.

Clear-cell renal carcinoma is the most common type, accounting for 75% of RCC. Patients affected with von Hippel-Lindau (VHL) disease present with multiple, bilateral kidney cancers of the clear-cell type, accompanied by a number of other different features [5]. The VHL tumor-suppressor gene product forms a multimeric complex that includes elongins C and B [6,7], Cul2 [8] and Rbx1 [9], targeting the hypoxia-inducible factors HIF1α and HIF2α for ubiquitination and subsequent degradation [10,11]. Nearly 100% of VHL families have germline mutations of the VHL gene [12], and VHL inactivation by mutations or promoter hypermethylation has been described in more than 60% of patients with sporadic clear-cell RCC.

Papillary renal carcinoma (PRC) is the second most common type of kidney cancer and has been further divided into two subtypes based upon histological criteria and distinctive gene expression profile: type I (hereditary papillary renal carcinoma [HPRC]) and type II. In HPRC, mutations in the gene encoding the receptor for HGF, MET, are associated with the onset of multiple bilateral type I papillary carcinomas [13–15]; these tumors tend to be low grade and have a better prognosis. Type II lesions are generally high grade and have a poorer prognosis.

Hereditary leiomyomatosis and renal cell cancer (HLRCC) is a hereditary syndrome characterized by the occurrence of cutaneous and uterine leiomyomas, and by the development of an aggressive form of kidney cancer [16] that tends to spread early and are histologically classified mostly as type II papillary renal cancer. Defects in the gene encoding the Krebs cycle
Table 1. Characteristics of renal cell carcinoma subtypes.

| Type/histology       | Frequency (%) | Gene | Tumor multiplicity | Age of onset |
|----------------------|--------------|------|--------------------|--------------|
| Clear cell           | 75           | VHL  | Multiple, bilateral| Adolescence  |
| Papillary type 1     | 5            | MET  | Multiple, bilateral| 40–49 years  |
| HLRCC/papillary type 2 | 10          | FH   | Single or multiple | 10–20 years  |
| Chromophobe/ondocytoma | 5–10      | BHD/Folliculin | Multiple, bilateral| 30–39 years  |

*Indicates the genetic defect associated with the hereditary form of renal cell carcinoma, and by implication and direct evidence, in the corresponding sporadic form.

†Indicates portion of total annual renal cell carcinoma cases.

HLRCC: Hereditary leiomyomatosis and renal cell cancer.

enzyme fumarate hydratase were identified as causative, and high levels of HIF1α and HIF2α can be found in HLRCC tumor samples [17–19].

Birt–Hogg–Dubé (BHD) syndrome is caused by germline mutations in the BHD gene on chromosome 17p11.2 [20,21], acting as a tumor-suppressor gene and encoding the protein folliculin. This syndrome is characterized by the development of pulmonary cysts, cutaneous fibrofolliculomata and multifocal renal tumors [22,23].

The HGF/Met pathway has attracted increasing attention in recent years as a promising molecular target for cancer therapy. An increasing understanding of the involvement of this pathway in kidney development and in renal pathological conditions has suggested the targeting of this pathway as a promising strategy for the treatment of kidney cancer, particularly papillary type 1 RCC. In addition to direct involvement through germline activating mutations in HPRTCC type 1, HGF/Met signaling is implicated in the pathogenesis of sporadic RCC in a broader manner, as described later.

**HGF/Met signaling in renal cancers**

**Hereditary renal cell carcinoma type 1 & sporadic papillary RCC**

Through clinical, histopathological and cytogenetic analysis of families with multiple members affected by PRC, Zbar et al. described an inherited form of PRC characterized by bilateral, multifocal papillary kidney lesions that tend to grow slowly and develop late in life [13,24]; rare cases of early onset have been described more recently [25]. Linkage analysis by Schmidt et al. localized the HPRC gene to chromosome 7q31–34, where the MET gene resides [26].

An oncogenic derivative of the MET gene was isolated from a chemically mutagenized human osteogenic sarcoma cell line. The oncogenic activity was due to rearrangement of a sequence on chromosome 1 (containing the translocated promoter region, TPPR, locus) and the MET locus on chromosome 7, generating the chimeric gene TPR–MET [27]. This rearrangement was later found in patients with gastric carcinoma [28]. The full-length MET proto-oncogene was found to encode the structural features of a membrane-spanning receptor endowed with intracellular tyrosine kinase (TK) activity [29]. Subsequently, HGF, a pleiotropic heparin-binding protein, was found to be the natural ligand of the Met receptor and capable of stimulating its multiple biological activities, including motility, proliferation, survival and morphogenesis [30,31].

Met is widely expressed in the early phase of development and its expression persists throughout adulthood [32]. Both HGF and Met are upregulated after renal injury, as a general mechanism of tissue repair and regeneration after tissue damage [33]. Upon ligand binding, autophosphorylation at tyrosines Y1234 and Y1235 (all Met residues are numbered per SwissProt Database accession number P08581) within the activation loop of the receptor TK domain significantly increase kinase activity. Phosphorylation on two critical tyrosine residues at the C terminus (Y1349 and Y1356) create a multifunctional docking site [34] that recruits intracellular effectors, such as Grb2, Gab1, PI3K, Shc and Src, among others [32]. In particular, Grb2 directly binds to Y1356, regulating cell cycle progression through the Ras/ MAPK pathway, as well as other intracellular pathways involved in cell migration and invasion [35]. Through paracrine signaling, overexpression, autocrine loop formation, receptor mutations and gene rearrangement, HGF and Met are implicated in a wide variety of human malignancies [36].

Several activating missense mutations of the MET gene have been described in individuals with PRC and HPRC, and in other human cancers. Schmidt et al. described several mutations in the Met tyrosine kinase domain, both in the germline of HPRC families (M1131T, V1188L, D1228N and Y1230C) and in a subset of tumors from patients with sporadic PRGs (L1195V, D1228H, Y1230H and M1250T) [26]. Notably, some of these mutations were located in a codon homologous to a naturally occurring mutation in KIT and in the RET proto-oncogene. Subsequent experiments introducing these mutations in NIH3T3 cells confirmed their oncogenic role through increased levels of tyrosine autophosphorylation, increased focus forming activity, increased cell motility in vitro and tumorigenicity in nude mice [37,38].

Extensive studies of two large North American HPRC families facilitated the identification of a novel oncogenic germline mutation (H1094R) [39]. Using a panel of 79 sporadic PRC specimens, additional mutations were detected, some of which were found also as germline mutations through comparison with matched normal samples [40]. It is noteworthy that most PRC tumors display trisomy 7 even in the absence of MET mutations, and HPRC patients with MET mutations show selective duplication of the mutant MET allele, suggesting that MET mutations confer a proliferative advantage through errors in chromosomal replication during cell division [41].

To further define the mechanisms by which MET mutations act at the molecular and cellular level, Bardelli et al. showed that the M1250T mutation resulted in changes in substrate preferences...
in vitro; in NIH3T3 cells this mutation, as well as the Y1230H and D1228H/N mutations, displayed constitutive association with the key intracellular effector Gab1 [42]. These results showed that oncogenicity is mediated by many known receptor proximal effectors and that interruption of such interactions may be a viable strategy to block mutant Met signaling. Furthermore, different mutations may contribute to disease pathogenesis through distinct downstream molecular pathways [43]. Several lines of evidence suggest that ligand binding may contribute significantly to oncogenesis associated with PRC MET mutations [44]. The observation that the kidney is an abundant source of HGF and its activators, may explain, at least in part, why patients with germline MET mutations exhibit only kidney cancer. These studies also demonstrated that mutated Met might be more easily activated than wild-type Met and more likely to remain activated for longer periods after stimulation [45].

**TFE3 renal carcinoma**

A subgroup of RCC with papillary architecture is associated with Xp11.2 translocation (transcription factor 3 [TFE3] gene fusions) [46]. This entity, referred to as TFE3 renal carcinoma, has been predominantly reported in children, accounting for 5–20% of RCC in young patients. In young adults, the tumors are more aggressive and prognosis is poor due to the advanced stage at presentation, prompting intense investigation into its pathogenesis [47–49]. The TFE3 gene is located at Xp11.2 and is a member of the microphthalmia transcription factor (MiTF) family [50]. A number of translocations involving Xp11.2 can occur; fusion of TFE3 to four distinct genes has been identified (PRCC, ASPL, PSF and NonO) [51–53], which can result in enhanced levels of transcription of oncogenes. Several lines of evidence suggest an important role of these fusion proteins in the initiation and maintenance of the oncogenic phenotype in papillary RCC [54], and are consequently potential targets for the treatment of these tumors.

A recent search for transcriptional targets downstream of TFE3 fusion oncogenes showed that Met activation has an important role in the oncogenesis of several tumors containing the TFE3 fusion, including RCC [55]. Indeed, in contrast to clear-cell RCC, Met protein expression is increased, with phosphorylation at the critical residue Y1234 and Y1235 in the activation loop of the TK domain, as well as phosphorylation at residue Y1349 in the C terminus [56]. Such hyperphosphorylation is associated with the malignant behavior of TFE3 renal carcinoma and its poor survival rates, consistent with other oncogenic phenotypes associated with HGF/Met aberrant signaling. Treatment with the Met selective inhibitor PHA665752 strongly inhibited HGF-dependent Met phosphorylation at Y1234 and Y1235 [58]. Also, the prominent phosphorylation of Met in the multifunctional docking site induced the recruitment and activation of several downstream effectors, including Akt and P44/42 MAPK, further validating Met as a potential and tractable therapeutic target for tumors with the TFE3 fusion.

**Clear-cell RCC**

As mentioned earlier, loss of the VHL tumor-suppressor gene function is responsible for familial and most sporadic clear-cell carcinoma, leading to abnormal expression of genes involved in cell proliferation, invasion and angiogenesis. The protein encoded by VHL (pVHL) forms a stable complex with other proteins possessing E3 ubiquitin ligase activity. This complex is best known for targeting hypoxia-inducible factors (HIFs) for polyubiquitination and subsequent proteasomal degradation [57]. Under normoxic conditions, pVHL suppresses HIF protein levels and consequently their activity. Under hypoxic conditions or when the VHL gene is mutated or lost, HIFs accumulate and several HIF target genes are upregulated, including VEGF, PDGF, TGF-α, erythropoietin and Met [57,4]. HGF signaling is also increased by hypoxia through other mechanisms, leading to invasive growth in cultured cells and in mouse tumor models [58]. Cultured VHL-negative RCC cells accumulate HIF proteins aberrantly and respond to HGF treatment with matrix metalloproteinase production, increased motility, matrix invasion and tubulogenesis [59]. These HGF-driven activities are abolished when wild-type VHL expression is reconstituted in RCC cells, directly linking loss of VHL function to an invasive phenotype [59].

Investigating the mechanism by which VHL loss of function resulted in increased HGF-driven invasiveness, Peruzzi et al. examined downstream mediators of Met signaling with proven oncogenic potential that might be negatively regulated by ubiquitin-directed proteasomal degradation [60]. Among these candidates is β-catenin [61,62], which links cadherins to the actin cytoskeleton and also functions in the transcriptional activation of genes involved in normal growth and development. β-catenin and E-cadherin are important in mesenchymal-to-epithelial transition processes during renal development, particularly during tubule formation [63,64], and dysregulation of β-catenin signaling can be potently oncogenic [65]. Peruzzi et al. showed that HGF stimulated the redistribution of β-catenin from peripheral to cytoplasmic, perinuclear and nuclear pools, leading to β-catenin target gene activation in VHL-negative RCC cells, and that restoration of normal VHL expression repressed these activities [60]. Ectopic expression of an ubiquitination-resistant β-catenin mutant in RCC cells transfected with wild-type VHL reversed this repression by interaction with pVHL [60].

**Table 2. Summary of MET tyrosine kinase domain mutations.**

| Swissprot | Genbank | Germline/somatic | Ref. |
|----------|---------|------------------|------|
| H1094R   | H1112R  | Germline/somatic | [39] |
| M1131T   | M1149T  | Germline         | [123]|
| V1188L   | V1206L  | Germline         | [26] |
| L1195V   | L1213V  | Somatic          | [26] |
| D1228N   | D1246N  | Germline         | [26] |
| D1228H   | D1246H  | Somatic          | [26] |
| Y1230C   | Y1248C  | Germline         | [26] |
| Y1230H   | Y1248H  | Somatic          | [26] |
| Y1235D   | Y1265D  | Somatic          | [124,125]|
| M1250T   | M1268T  | Somatic          | [26] |

Mutations are listed by codon position in Swissprot (accession P08581) or Genbank (accession J02958) sequence contexts.
pVHL, and expression of a dominant-negative form of T-cell factor blocked the invasive response of VHL-negative cells [60]. Thus, Met/β-catenin signaling contributes to the invasive phenotype of VHL-negative clear-cell RCC, revealing another potential target for biomarker and drug development.

Low levels of pro-HGF are present in the systemic circulation and HGF-induced Met activation at target cell surfaces requires proteolytic processing of HGF to its mature, two-chain form [66–70]. Several serine proteases are capable of activating HGF, including HGF activator [71–73], hepsin [74,75] and plasminogen activators [76]. This process is further controlled by the Kunitz-type inhibitors and HGF activator inhibitor (HAI)-1 and -2 [77–79]. Several groups have demonstrated that an increased ratio of HGF activators to HAI-1 or -2 correlates with malignant progression and poor prognosis in a variety of carcinomas [80–81], emphasizing the important balance between HGF activators and their cognate inhibitors for normal HGF pathway activation in tissue homeostasis. Betsunoh et al. showed that hepsin was frequently upregulated in advanced RCC, a feature that correlated with distant metastasis and proved to be a reliable independent prognostic indicator of reduced overall survival [80]. HAI-2 is also implicated in the pathogenesis of clear-cell and non-clear-cell RCC [84], consistent with prior reports of downregulation of HAI-1 and -2 expression in RCC, coupled with Met and HGF activator upregulation [85].

Inhibition of Met TK activity
Tyrosine kinase inhibitors have shown success in treating many malignancies. Not surprisingly, the number of pharmaceutical and biotechnology companies that have announced drug development programs targeting the Met TK has grown considerably in the last 10 years. Several programs to develop highly selective synthetic inhibitors of the Met ATP-binding site have yielded compounds effective in nanomolar concentrations in cultured cells and in various animal models [95]. Of these, the indolinoone compounds SU11274 and PHA665752 display a minimum of 50-fold selectivity for Met relative to several other TKs, and potently blocked HGF-stimulated activities in cultured cells and tumorigenicity in Met-driven xenograft models [96,97]. Analysis of SU11274 using cells that express HPRC-associated MET mutants revealed interesting differences in sensitivity [96]: this compound was able to inhibit the Met mutant M1250T, but other mutations, such as L1195V and Y1230H, were insensitive. Another novel, orally available Met small-molecule inhibitor, PF2341066, evaluated against a panel of NIH3T3 cells expressing various Met mutations, demonstrated a markedly diminished activity against mutants Y1230C and Y1235D in the TK domain activation loop, compared with wild-type or other TK domain mutations [98]. More recently, similar drugs with conserved or enhanced activity against mutants have been described [99,100]. The drug XL880/GSK1363089, a multit kinase inhibitor with potent anti-Met activity that is currently in Phase II clinical trials in patients with PRC, was found to be effective in a gefitinib/erlotinib-resistant lung tumor cell line with acquired MET amplification [101]. Increased sensitivity to the inhibitor PHA665752 was observed in gastric cancer cells with MET gene amplification [102], strongly reinforcing the concept that knowledge of genetic alterations should help predict the efficacy of Met TK inhibitors for specific patient groups.

Inhibition of Met/effector interactions
Disrupting the interaction between Met and intracellular signaling effectors is another attractive strategy to target this pathway. Several signal transducers, such as Gab1, PI3K, Grb2 and STAT3, are important in Met-driven cell transformation and constitute potential targets [34,42,43]. In particular, the SH2 domain of the adaptor protein Grb2 has been successfully targeted, taking advantage of its unique structure among SH2 domains [103], providing the basis for the development of small selective binding antagonists [35]. Further refinement of these early structures has yielded compounds that block HGF-stimulated cell motility, matrix invasion and morphogenesis in normal and tumor-derived cultured cells, as well as vascular endothelial cells, at low nanomolar concentrations [104,105]. The same compounds have been shown to inhibit tumor metastasis in two animal models [106]. Other downstream signaling proteins activated by Met or other receptors have been successfully targeted; one notable example is the serine/threonine kinase mTOR. mTOR inhibition has been explored in a variety of cancers, including RCC, and the inhibitor temsirolimus was approved by the US FDA in 2007 for advanced RCC [107].
The PI3K/Akt signaling cascade, important for survival and mitogenic signaling, is another potential therapeutic target for RCC. Higher PI3K expression has been reported in late-stage and high-grade RCC and correlates with poor survival [108]. At present, no PI3K or Akt inhibitors are approved for clinical use in RCC, but studies are underway that explore this possibility [109].

**Treatment combinations**

Finally, as a strategy to overcome drug resistance and toxicity, combinations of treatments targeting the Met pathway with other agents or therapeutic approaches are under investigation. Compounds that block HSP90/client interactions, such as geldanamycin [110], also potently block Met oncogenic signaling [111,112]. For several cancers where the Met pathway is active, clinical trials of geldanamycin-related compounds are ongoing [113]. Combining agents, such as geldanamycin, which attenuate the supply of new receptors to the cell surface, with inhibitors of other specific receptor functions such as kinase activity, could lower the effective dose of each, reducing the likelihood of drug toxicity and the selection pressure for drug-resistant mutations.

Several other signaling pathways can enhance HGF-driven Met activation, and MET gene amplification can result in ligand-independent Met kinase activation. In light of this, combination strategies have been explored with other TK inhibitors [114,115]. Recent findings that gefitinib-resistant nonsmall-cell lung cancers develop MET amplification [116], further reinforce the rationale of these combinations, and clinical trials combining Met and EGFR TK inhibitors are currently under consideration. Tumor angiogenesis is another important feature of RCC. Currently, the use of bevacizumab (a monoclonal antibody directed against VEGF) and interferon is the only combination approved by the FDA, but other similar combination strategies are also currently under investigation [115].

Combining Met-targeted therapy with traditional chemotherapy is another option. AMG102 combined with temozolomide or docetaxel [117], and cisplatin and SU11274 [118], have been shown to be effective in models of glioblastoma. Further preclinical evaluation of these combinations is needed to identify which will be more effective at the bedside. Finally, changes in Met signaling as an effect of ionizing radiation [119] and evidence that Met activation can interfere with cell death induced by ionizing radiation treatment [120,121], suggest that combining HGF/Met-selective targeted therapies with radiotherapy may increase tumor cell survival. Interestingly, it has been demonstrated that a Met-activating mutation (Y1235D) in oropharyngeal cancer can interfere with the normal response to radiotherapy [122]. It will be interesting to extend these studies to other mutations found in RCC tumors.

**Expert commentary**

Building on the knowledge derived from more than two decades of intense investigation, refined approaches to targeting Met and its signaling pathway have been developed [95]. The study of families with inherited forms of kidney cancer has provided critical genetic insights into oncogenesis, and now offers an opportunity to target this pathway in genetically defined disease populations. The use of rationally targeted therapies for cancer necessitates the accurate assessment of patients prior to treatment in order to identify those most likely to benefit from a given selective therapy. Ultimately, panels of biomarkers may be needed to predict the best choice of therapeutics.

Several novel drugs targeting HGF and Met are entering the clinical arena and their efficacy will provide some indication as to the importance of this pathway in different tumors. Of particular interest will be investigations of these agents in RCC tumors bearing Met mutations or other genetic evidence of pathway activation. Together with structural studies of novel Met drugs bound to various Met mutant forms, the information obtained from these studies will contribute to the development of more refined Met inhibitors, the development of improved pharmacodynamic indicators of drug activity, insights into effective drug combinations and strategies to overcome drug resistance.

**Five-year view**

Several novel HGF- and Met-targeted drugs are under preclinical and clinical investigation. In the near future we expect these efforts to result in the approval of several new therapeutics with greater efficacy and reduced toxicity. It will become progressively important to identify the specific mechanisms of Met activation present in each patient to reduce the risk of ineffective treatments.

**Key issues**

- Met signaling has been shown to be important in renal cell carcinoma (RCC).
- The rational design and development of MET inhibitors for the treatment of RCC and other cancers has yielded a considerable increase in the number of potent and selective agents.
- Hereditary papillary renal cell carcinoma, where MET mutations drive the pathology, is an ideal RCC tumor for the study of MET-targeted therapies.
- MET mutants respond differentially to various MET inhibitors.
- MET is a direct transcription target in transcription factor 3-renal carcinomas and represents another rational target for therapy of this form of RCC.
- The receptor encoded by MET, as an HIF target gene, is also a potential target in clear-cell RCC.
- Prescreening patients with RCC for genetic and molecular defects will become progressively more important in selecting among targeted therapies.
- Combinations of targeted therapies or combining these therapies with more traditional cytotoxic therapies, based on the specific molecular patterns expressed in patient tumors, may provide more effective treatment regimes.
and increase disease stasis and/or reversal. Additional molecular
prognostic and pharmacodynamic markers that are practical to
use in patient-care settings, and that provide precise measure-
ments over a substantial dynamic range and over time are urgently
needed. Finally, continued basic research into the molecular basis
of kidney cancer should reveal concomitantly activated signaling
pathways and novel molecular targets for developing the most
effective drug combinations.

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References
Papers of special note have been highlighted as:
• of interest
•• of considerable interest

1 Jemal A, Siegel R, Ward E et al. Cancer statistics, 2008. CA Cancer J. Clin. 58(2), 71–96 (2008).
2 Linehan WM. Kidney cancer: opportunity for disease-specific targeted therapy. Urol. Oncol. 26(5), 542 (2008).
3 Coppin C, Porzsolt F, Awa A, Kumpf J, Coldman A, Wilt T. Immunotherapy for advanced renal cell cancer. Cochrane Datab. Syst. Rev. 1, CD001425 (2005).
4 Linehan WM, Pinto PA, Srinivasan R et al. Identification of the genes for kidney cancer: opportunity for disease-specific targeted therapeutics. Clin. Cancer Res. 13(2 II), (2007).
5 Lonser RR, Glenn GM, Walther M et al. Von Hippel-Lindau disease. Lancet 361(9374), 2059–2067 (2003).
• Excellent review on von Hippel-Lindau disease.

6 Duan DR, Pause A, Burgess WH et al. Inhibition of transcription elongation by the VHL tumor suppressor protein. Science 269(5229), 1402–1406 (1995).
7 Kibel A, Iliopoulos O, DeCaprio JA, Kaelin J. Binding of the von Hippel-Lindau tumor suppressor protein to elongin B and C. Science 269(5229), 1444–1446 (1995).
8 Pause A, Lee S, Worrell RA et al. The von Hippel-Lindau tumor-suppressor gene product forms a stable complex with human CUL-2, a member of the Cdc53 family of proteins. Proc. Natl Acad. Sci. USA 94(6), 2156–2161 (1997).
9 Kamura T, Koepp DM, Conrad MN et al. Rhx1, a component of the VHL tumor suppressor complex and SCF ubiquitin ligase. Science 284(5414), 657–661 (1999).
10 Iliopoulos O, Levy AP, Jiang C, Kaelin J, Goldberg MA. Negative regulation of hypoxia-inducible genes by the von Hippel-Lindau protein. Proc. Natl Acad. Sci. USA 93(20), 10585–10599 (1996).
11 Kaelin J. The von Hippel-Lindau gene, kidney cancer, and oxygen sensing. J. Am. Soc. Nephrol. 14(11), 2703–2711 (2003).
12 Stolle C, Glenn G, Zbar B et al. Improved detection of germline mutations in the von Hippel-Lindau disease tumor suppressor gene. Hum. Mutat. 12(6), 417–423 (1998).
13 Zbar B, Tory K, Merino M et al. Hereditary papillary renal cell carcinoma. J. Urol. 151(3), 561–566 (1994).
• Original description of hereditary papillary renal cell carcinoma.

14 Lubensky IA, Schmidt L, Zhuang Z et al. Hereditary and sporadic papillary renal carcinomas with c-met mutations share a distinct morphological phenotype. Am. J. Pathol. 155(2), 517–526 (1999).
15 Dharmawardana PG, Giubellino A, Bottaro DP. Hereditary papillary renal carcinoma type I. Curr. Mol. Med. 4(8), 855–868 (2004).
16 Launonen V, Vieirama O, Kiuru M et al. Inherited susceptibility to uterine leiomyomas and renal cell cancer. Proc. Natl Acad. Sci. USA 98(6), 3387–3392 (2001).
17 Tomlinson IPM, Alam NA, Rowan AJ et al. Germline mutations in FH predispose to dominantly inherited urogenital fibromatoses. Nat. Genet. 30(4), 406–410 (2002).
18 Toro JR, Nickerson ML, Wei MH et al. Mutations in the fumarate hydratase gene cause hereditary leiomyomatosis and renal cell cancer in the multiple leiomyoma consortium. Nat. Genet. 30(4), 406–410 (2002).
19 Schmidt LS, Nickerson ML, Angeloni D et al. Early onset hereditary papillary renal carcinoma: germline missense mutations in the tyrosine kinase domain of the MET proto-oncogene. J. Urol. 172(4 I), 1256–1261 (2004).
20 Schmidt L, Duh FM, Chen F et al. Germline and somatic mutations in the tyrosine kinase domain of the MET proto-oncogene in papillary renal carcinomas. Nat. Genet. 16(1), 68–73 (1997).
• Original description linking MET mutations to hereditary papillary renal carcinoma.

21 Nickerson ML, Warren MB, Toro JR et al. Mutations in a novel gene lead to kidney tumors, lung wall defects, and benign tumors of the hair follicle in patients with the Birt-Hogg-Dubé syndrome. Cancer Cell 2(2), 157–164 (2002).
22 Birt AR, Hogg GR, Dube WJ. Hereditary multiple fibrofolliculomas with trichodiscomas and acrochordons. Arch. Dermatol. 113(12), 1674–1677 (1977).
23 Zbar B, Alvoid WG, Glenn G et al. Risk of renal and colon neoplasms and spontaneous pneumothorax pneumothorax in the Birt–Hogg–Dubé syndrome. Cancer Epidemiol. Biomark. Prev. 11(4), 393–400 (2002).
24 Zbar B, Glenn G, Lubensky L et al. Hereditary papillary renal cell carcinoma: clinical studies in 10 families. J. Urol. 153(3 II), 907–912 (1995).
25 Schmidt LS, Nickerson ML, Angeloni D et al. Early onset hereditary papillary renal carcinoma: germline missense mutations in the tyrosine kinase domain of the MET proto-oncogene. J. Urol. 172(4 I), 1256–1261 (2004).
26 Schmidt L, Duh FM, Chen F et al. Germline and somatic mutations in the tyrosine kinase domain of the MET proto-oncogene in papillary renal carcinomas. Nat. Genet. 16(1), 68–73 (1997).

27 Cooper CS, Park M, Blair DG. Molecular cloning of a new transforming gene from a chemically transformed human cell line. Nature 311(5981), 29–33 (1984).
28 Jun Y, Miehlke S, Ebert MPA et al. Inhibition of transcription elongation by the VHL tumor suppressor protein. Science 269(5229), 1402–1406 (1995).
29 Kamura T, Koepp DM, Conrad MN et al. Rhx1, a component of the VHL tumor suppressor complex and SCF ubiquitin ligase. Science 284(5414), 657–661 (1999).
30 Iliopoulos O, Levy AP, Jiang C, Kaelin J, Goldberg MA. Negative regulation of hypoxia-inducible genes by the von Hippel-Lindau protein. Proc. Natl Acad. Sci. USA 93(20), 10595–10599 (1996).

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factor receptor as the c-Met proto-oncogene product. Science 251(4995), 802–804 (1991).

31 Weidner KM, Sachs M, Birchmeier W. The Met receptor tyrosine kinase transduces motility, proliferation, and morphogenic signals of scatter factor/hepatocyte growth factor in epithelial cells. J. Cell Biol. 121(1), 145–154 (1993).

32 Birchmeier C, Birchmeier W, Gherardi E, Vande Woude GF. Met, metastasis, motility and more. Nat. Rev. Mol. Cell Biol. 4(12), 915–925 (2003).

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33 Matsumoto K, Nakamura T. Hepatocyte growth factor: renotropin role and potential therapeuticies for renal diseases. Kidney Int. 59(6), 2023–2038 (2001).

34 Ponzetto C, Bardelli A, Zhen Z et al. A multifunctional docking site mediates signaling and transformation by the hepatocyte growth factor/scatter factor receptor family. Cell 77(2), 261–271 (1994).

35 Giubellino A, Burke J, Bottaro DP. Grb2 signaling in cell motility and cancer. Expert Opin. Ther. Targets. 12(8), 1021–1033 (2008).

36 Gentile A, Trusolino L, Comoglio PM. The Met tyrosine kinase receptor in development and cancer. Cancer Metast. Rev. 27(1), 85–94 (2008).

37 Jeffers M, Schmidt L, Nakaigawa N et al. Activating mutations for the Met tyrosine kinase receptor in human cancer. Proc. Natl Acad. Sci. USA 94(21), 11445–11450 (1997).

38 Jeffers M, Fiscella M, Webb CP, Anver M, Koochekpour S, Vande Woude GF. The mutationally activated Met receptor mediates motility and metastasis. Proc. Natl Acad. Sci. USA 95(24), 14417–14422 (1998).

39 Schmidt L, Junker K, Weirich G et al. Two North American families with hereditary papillary renal carcinoma and identical novel mutations in the MET proto-oncogene. Cancer Res. 58(8), 1719–1722 (1998).

40 Schmidt L, Junker K, Nakaigawa N et al. Novel mutations of the MET proto-oncogene in papillary renal carcinomas. Oncogene 18(14), 2343–2350 (1999).

41 Zhuang Z, Park WS, Pack S et al. Trisomy 7-harbou ring non-random duplication of the mutant MET allele in hereditary papillary renal carcinomas. Nat. Genet. 20(1), 66–69 (1998).

42 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. USA 95(24), 14379–14383 (1998).

43 Giordano S, Maffe A, Williams TA et al. Different point mutations in the met oncogene elicit distinct biological properties. FASEB J. 14(2), 399–406 (2000).

44 Michieli P, Basilico C, Pennacchietti S et al. Mutant Met-mediated transformation is ligand-dependent and can be inhibited by HGF antagonists. Oncogene 18(37), 5221–5231 (1999).

45 Miller M, Ginalska K, Lesnyb 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. Prot. Struct. Funct. Genet. 44(1), 32–43 (2001).

46 Argani P, Ladanyi M. The evolving story of renal translocation carcinomas. Am. J. Clin. Pathol. 126(3), 332–334 (2006).

47 Argani P, Lal P, Hutchinson B, Lui MY, Reuter VE, Ladanyi M. A aberrant nuclear immunoreactivity for TFE3 in neoplasms with TFE3 gene fusions: a sensitive and specific immunohistochemical assay. Am. J. Surg. Pathol. 27(6), 750–761 (2003).

48 Argani P, Olgac S, Tickoo SK et al. Xp11 translocation renal cell carcinoma in adults: expanded clinical, pathologic, and genetic spectrum. Am. J. Surg. Pathol. 31(8), 1149–1160 (2007).

49 Bruder E, Passera O, Harms D et al. Morphologic and molecular characterization of renal cell carcinoma in children and young adults. Am. J. Surg. Pathol. 28(9), 1117–1132 (2004).

50 Hemesath TJ, Steigermirsson E, McGill G et al. Microphthalmia: a critical factor in melanocyte development, defines a discrete transcription factor family. Genes Dev. 8(22), 2770–2780 (1994).

51 Clark J, Lu YJ, Sidhar SK et al. Fusion of splicing factor genes PSF and NonO (p54(nrb)) to the TFE3 gene in papillary renal cell carcinoma. Oncogene 15(18), 2233–2239 (1997).

52 Sidhar SK, Clark J, Gill S et al. The t(X;1)(p11.2;q21.2) translocation in papillary renal cell carcinoma fuses a novel gene PRCC to the TFE3 transcription factor gene. Hum. Mol. Gen. 5(9), 1333–1338 (1996).

53 Weterman MAJ, Wilbrink M, Van Kessel AG. Fusion of the transcription factor TFE3 gene to a novel gene, PRCC, in t(X;1)(p11;q21)-positive papillary renal cell carcinomas. Proc. Natl Acad. Sci. USA 93(26), 15294–15298 (1996).

54 Argani P, Ladanyi M. Translocation carcinomas of the kidney. Clin. Lab. Med. 25(2), 363–378 (2005).

55 Tsuda M, Davis IJ, Argani P et al. TFE3 fusions activate MET signaling by transcriptional up-regulation, defining another class of tumors as candidates for therapeutic MET inhibition. Cancer Res. 67(3), 919–929 (2007).

56 Sagara Y, Miyata Y, Nomata K et al. TFE3-renal carcinoma in an adult patient: a case with strong expression of phosphorylated hepatocyte growth factor (HGF)/MET. Pathol. Res. Pract. 205(1), 57–61 (2009).

57 Kaelin J. Molecular basis of the VHL hereditary cancer syndrome. Nat. Rev. Cancer 2(9), 673–682 (2002).

58 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 3(4), 347–361 (2003).

59 Koochekpour S, Jeffers M, Wang PH et al. The von Hippel-Lindau tumor suppressor gene inhibits hepatocyte growth factor/scatter factor-induced invasion and branching morphogenesis in renal carcinoma cells. Mol. Cell. Biol. 19(9), 5902–5912 (1999).

60 Peruzzi B, Athauda G, Bottaro DP. The von Hippel-Lindau tumor suppressor gene product represses oncogenic β-catenin signaling in renal carcinoma cells. Proc. Natl Acad. Sci. USA 103(39), 14531–14536 (2006).

61 Shibamoto S, Hayakawa M, Takeuchi K et al. Tyrosine phosphorylation of β-catenin and plakoglobin enhanced by hepatocyte growth factor and epidermal growth factor in human carcinoma cells. Cell Adhes. Comm. 1(4), 295–305 (1994).

62 Herynk MH, Tsan R, Radinsky R, Gallick GE. Activation of c-Met in colorectal carcinoma cells leads to constitutive association of tyrosine-phosphorylated β-catenin. Clin. Exp. Metast. 20(4), 291–300 (2003).

63 Perantoni AO. Renal development: perspectives on a Wnt-dependent process. Semin. Cell Dev. Biol. 14(4), 201–208 (2003).

64 Van Adelsberg J, Sehgal S, Kukes A et al. Activation of hepatocyte growth factor (HGF) by endogenous HGF activator is
required for metanephric kidney morphogenesis in vitro. J. Biol. Chem. 276(18), 15099–15106 (2001).

Paul S, Dey A. Wnt signaling and cancer development: therapeutic implication. Neoplasma 55(3), 165–176 (2008).

Gak E, Taylor WG, Chan AML, Rubin JS. Processing of hepatocyte growth factor to the heterodimeric form is required for biological activity. FEBS Lett. 311(1), 17–21 (1992).

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. USA 89(23), 11574–11578 (1992).

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. 11(7), 2503–2510 (1992).

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. 267(28), 2014–2019 (1992).

Naldini L, Tamagnone L, Vigna E et al. Extracellular proteolytic cleavage by urokinase is required for activation of hepatocyte growth factor/scatter factor. EMBO J. 11(13), 4825–4833 (1992).

Shimomura T, Ochiai M, Kondo J, Morimoto Y. A novel protease obtained from FBS-containing culture supernatant, that processes single chain form hepatocyte growth factor to two chain form in serum-free culture. Cytotechnology 8(3), 219–229 (1992).

Miyazawa K, Shimomura T, Kitamura A, Kondo J, Morimoto Y, Kitamura N. Molecular cloning and sequence analysis of the cDNA for a human serine protease responsible for activation of hepatocyte growth factor. Structural similarity of the protease precursor to blood coagulation factor XII. J. Biol. Chem. 268(14), 10024–10028 (1993).

Shimomura T, Miyazawa K, Komiyama Y et al. Activation of hepatocyte growth factor by two homologous proteases, blood-coagulation factor XIIa and hepatocyte growth factor activator. Eur. J. Biochem. 229(1), 257–261 (1995).

Herter S, Piper DE, Aaron W et al. Hepatocyte growth factor is a preferred in vitro substrate for human hepsin, a membrane-anchored serine protease implicated in prostate and ovarian cancers. Biochem. J. 390(1), 125–136 (2005).

Kircherhofer D, Peek M, Lipari MT, Billeci K, Fan B, Moran P. Hepsin activates pro-hepatocyte growth factor and is inhibited by hepatocyte growth factor activator inhibitor-1B (HAI-1B) and HAI-2. FEBS Lett. 579(9), 1945–1950 (2005).

Mars WM, Zarrasegar R, Michalopoulos GK. Activation of hepatocyte growth factor by the plasminogen activators uPA and tPA. Am. J. Pathol. 143(3), 949–958 (1993).

Denda K, Shimomura T, Kawaguchi T, Miyazawa K, Kitamura N. Functional characterization of Kuniz domains in hepatocyte growth factor activator inhibitor type I. J. Biol. Chem. 277(16), 14053–14059 (2002).

Kircherhofer D, Peek M, Li W et al. Tissue expression, protease specificity, and Kuniz domain functions of hepatocyte growth factor activator inhibitor-1B (HAI-1B), a new splice variant of HAI-1. J. Biol. Chem. 278(38), 36341–36349 (2003).

Shia S, Stamos J, Kircherhofer D et al. Conformational lability in serine protease active sites: structures of hepatocyte growth factor activator (HGFA) alone and with the inhibitory domain from HGFA inhibitor-1B. J. Mol. Biol. 346(5), 1335–1349 (2005).

Betsunoh H, Mukai S, Akiyama Y et al. Activation of hepatocyte growth factor activator inhibitor type II expression, protease specificity, and Kuniz domain functions of hepatocyte growth factor activator inhibitor-1B (HAI-1B), a new splice variant of HAI-1. J. Biol. Chem. 278(38), 36341–36349 (2003).

Jin H, Yang R, Zheng Z et al. The Sema domain of Met is necessary for receptor dimerization and activation. Cancer Cell 6(1), 61–73 (2004).

Kong-Beltran M, Stamos J, Wickramasinghe D. The Sema domain of Met is necessary for receptor dimerization and activation. Cancer Cell 6(1), 75–84 (2004).

Jin H, Yang R, Zheng Z et al. MetMAb, the one-armed anti-c-Met antibody inhibits orthotopic pancreatic tumor growth and improves survival. Cancer Res. 68(11), 4360–4368 (2008).

Cao B, Su Y, Oskarsson M et al. Neutralizing monoclonal antibodies to hepatocyte growth factor/scatter factor (HGF/SF) display antitumor activity in animal models. Proc. Natl Acad. Sci. USA 98(13), 7443–7448 (2001).

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. 12(4), 1292–1298 (2006).

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. 66(3), 1721–1729 (2006).

Comoglio PM, Giordano S, Trusolino L. Drug development of MET inhibitors: targeting oncogene addiction and expediency. Nat. Rev. Drug Discov. 7(6), 504–516 (2008).
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96 Berthou S, Aebersold DM, Schmidt LS et al. The Met kinase inhibitor SU11274 exhibits a selective inhibition pattern toward different receptor mutated variants. Oncogene 23(31), 5387–5393 (2004).

97 Christensen JG, Burrows J, Salgia R. c-Met as a target for human cancer and characterization of inhibitors for therapeutic intervention. Cancer Lett. 225(1), 1–26 (2005).

98 Zou HY, Li Q, Lee JH et al. An orally available small-molecule inhibitor of c-Met, PF-2341066, exhibits cytoreductive antitumor efficacy through antiproliferative and antiangiogenic mechanisms. Cancer Res. 67(9), 4408–4417 (2007).

99 Bellon SF, Kaplan-Lefko P, Yang Y et al. c-Met inhibitors with novel binding mode show activity against several hereditary papillary renal cell carcinoma-related mutations. J. Biol. Chem. 283(5), 2675–2683 (2008).

100 Dussault I, Bellon SF. c-Met inhibitors with different binding modes: two is better than one. Cell Cycle 7(9), 1157–1160 (2008).

101 Bean J, Brennan C, Shih JY et al. MET amplification occurs with or without T790M mutations in EGFR mutant lung tumors with acquired resistance to gefitinib or erlotinib. Proc. Natl Acad. Sci. USA 104(52), 20932–20937 (2007).

102 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. Proc. Natl Acad. Sci. USA 103(7), 2316–2321 (2006).

103 Rahuel J, Gay B, Erdmann D et al. Structural basis for specificity of GRB2–SH2 revealed by a novel ligand binding mode. Nat. Struct. Biol. 3(7), 586–590 (1996).

104 Aratbe N, Gao Y, Yao ZJ et al. Potent blockade of hepatocyte growth factor-stimulated cell motility, matrix invasion and branching morphogenesis by antagonists of Grb2Src homology 2 domain interactions. J. Biol. Chem. 276(17), 14308–14314 (2001).

105 Soriano JV, Liu N, Gao Y et al. Inhibition of angiogenesis by growth factor receptor bound protein 2 Src homology 2 domain binding antagonists. Mol. Cancer Ther. 3(10), 1289–1299 (2004).

106 Giubellino A, Gao Y, Lee S et al. Inhibition of tumor metastasis by a growth factor receptor bound protein 2 Src homology 2 domain-binding antagonist. Cancer Res. 67(13), 6012–6016 (2007).

107 Malizia LJ, Hsu A. Temsirolimus, an mTOR inhibitor for treatment of patients with advanced renal cell carcinoma. Clin. J. Oncol. Nurs. 12(4), 639–646 (2008).

108 Merseburger AS, Hennenlotter J, Kuehs U et al. Activation of PI3K is associated with reduced survival in renal cell carcinoma. Urol. Int. 80(4), 372–377 (2008).

109 Park JY, Lin PY, Weiss RH. Targeting the PI3K–Akt pathway in kidney cancer. Expert Rev. Anticancer Ther. 7(6), 863–870 (2007).

110 Neckers L, Neckers K. Heat-shock protein 90 inhibitors as novel cancer chemotherapeutic agents. Expert Opin. Emerg. Drugs 7(2), 277–288 (2002).

111 Webb CP, Hose CD, Koochekpour S et al. The geldanamycins are potent inhibitors of the hepatocyte growth factor/scatter factor–Met–urokinase plasminogen activator–plasmin proteolytic network. Cancer Res. 60(2), 342–349 (2000).

112 Xi Q, Gao CF, Shinomiya N et al. Geldanamycins exquisitely inhibit HGF/SF-mediated tumor cell invasion. Oncogene 24(23), 3697–3707 (2005).

113 Pearl LH, Prodromou C, Workman P. The Hsp90 molecular chaperone: an open and shut case for treatment. Biochem. J. 410(3), 439–453 (2008).

114 Sattler M, Salgia R. c-Met and hepatocyte growth factor: potential as novel targets in cancer therapy. Curr. Oncol. Rep. 9(2), 102–108 (2007).

115 Heng DYC, Bukowski RM. Anti-angiogenic targets in the treatment of advanced renal cell carcinoma. Curr. Cancer Drug Targets 8(8), 676–682 (2008).

116 Engelmann JA, Zejnilullah K, Mitsudomi T et al. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. Science 316(5827), 1039–1043 (2007).

117 Jun HT, Sun J, Rex K et al. AMG 102, a fully human anti-hepatocyte growth factor/scatter factor neutralizing antibody, enhances the efficacy of temozolomide or docetaxel in U-87 MG cells and xenografts. Clin. Cancer Res. 13(22), 6735–6742 (2007).

118 Huang PH, Mukasa A, Bonavia R et al. Quantitative analysis of EGFR/IIIH cellular signaling networks reveals a combinatorial therapeutic strategy for glioblastoma. Proc. Natl Acad. Sci. USA 104(31), 12867–12872 (2007).

119 Fan S, Wang JA, Yuan RQ et al. Scatter factor protects epithelial and carcinoma cells against apoptosis induced by DNA-damaging agents. Oncogene 17(2), 131–141 (1998).

120 Fan S, Ma YX, Wang JA et al. The cytokine hepatocyte growth factor/scatter factor inhibits apoptosis and enhances DNA repair by a common mechanism involving signaling through phosphatidylinositol 3’ kinase. Oncogene 19(18), 2212–2223 (2000).

121 Aebersold DM, Kollar A, Beer KT, Laisseau J, Greiner RH, Djonov V. Involvement of the hepatocyte growth factor/scatter factor receptor c-Met and of Bcl-xL in the resistance of oropharyngeal cancer to ionizing radiation. Int. J. Cancer 96(1), 41–54 (2001).

122 Aebersold DM, Landt O, Berthou S et al. Prevalence and clinical impact of Met Y1253D-activating point mutation in radiotherapy-treated squamous cell cancer of the oropharynx. Oncogene 22(52), 8519–8523 (2003).

123 Schmidt L, Duh FM, Chen F et al. Germline and somatic mutations in the tyrosine kinase domain of the MET proto-oncogene in papillary renal carcinomas. Nat. Genet. 16(1), 68–73 (1997).

124 Di Renzo MF, Olivero M, Martone T et al. Somatic mutations of the MET oncogene are selected during metastatic spread of human HNSC carcinomas. Oncogene 19(12), 1547–1555 (2000).

125 Lorenzato A, Olivero M, Patane S et al. Novel somatic mutations of the MET oncogene in human carcinoma metastases activating cell motility and invasion. Cancer Res. 62(23), 7025–7030 (2002).

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