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Review

Molecular cancer therapy: Can our expectation be MET?

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ABSTRACT

Altered regulation of tyrosine kinase receptors (RTKs) is frequent in solid tumours and it is often associated with the acquisition of an aggressive phenotype. Thus, therapies targeting these receptors have been proposed as molecular approaches to treat human cancers.
The MET proto-oncogene, encoding the tyrosine kinase receptor for hepatocyte growth factor (HGF), controls genetic programmes leading to cell growth, invasion and protection from apoptosis. Germ-line mutations of MET in patients affected by hereditary papillary renal carcinomas (HPRC) have provided strong genetic evidences for its role in human malignancies; moreover, constitutive activation of this receptor, as a consequence of different mechanisms such as over-expression, autocrine stimulation or point mutations, is frequent in sporadic cancers.
Several strategies to block the activation of MET are under development, such as the use of tyrosine kinase inhibitors or monoclonal antibodies and some of these compounds have already been used in clinical trials.
In this review, we will discuss the molecular mechanisms underlying MET involvement in tumourigenesis and present pre-clinical and clinical data obtained with compounds aimed at targeting MET in the frame of cancer therapy.

1. Introduction

During these years the concept of cancer progression has been widely accepted as a multi-step programme in which the acquisition of genetic lesions – activating oncogenes and inactivating tumour suppressor genes in an instable genetic background – is the driving force for the tumourigenic process. Many efforts have been made to identify and untangle the pathways responsible for this phenomenon, to understand which are the crucial protagonists in neoplastic lesion appearance, growth, maintenance and, even more interestingly, in the last and worst step, metastasis.

It is now clear that amongst all the players, a key role is covered by receptor tyrosine kinases (RTKs). In physiological conditions, RTKs are involved in different processes such as cell growth, differentiation, organ morphogenesis, neo-vascularisation and tissue repair. Conversely, their deregulation due to mutation, gene rearrangement, amplification or over-expression, is often implicated in the progression of several human cancers and provides the rationale for the development of molecular therapies targeting these molecules (e.g. *Imatinib* in gastrointestinal associated stromal tumours – GIST – with mutated c-kit or *Trastuzumab* in HER-2 over-expressing breast cancers).

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MET, also known as hepatocyte growth factor receptor (HGFR), is a member of the RTK family and is involved in the control of motility, proliferation, survival and morphogenesis of normal and cancer cells. Moreover, the HGF–MET pathway also contributes to tumour progression by promoting angiogenesis through the recruitment of new vessels and the induction of sprouting of the pre-existing ones.

In this review, we will give an overview of MET role in tumour progression and will discuss why it can be considered a suitable target in cancer therapy; moreover, we will describe which are the available tools nowadays to inhibit this receptor, some already being in clinical trials.

2. What does MET do?

Met, discovered as an oncogene two decades ago,[1] encodes for the tyrosine kinase receptor for hepatocyte growth factor (HGF).[2,3] This receptor is normally expressed in epithelial tissues, while its ligand is produced by mesenchymal cells. *MET* mRNA is first translated as a single amino-acidic chain that is then cleaved to generate a disulphide-linked heterodimer formed by an extracellular α chain and a transmembrane β chain. HGF binding to the extracellular portion induces receptor dimerisation and activation of the catalytic activity. The tyrosine kinase catalytic domain contains the major phosphorylation site, represented by the tyrosine residues 1234 and 1235, which is essential for full activation of the enzyme.[4,5] Upon phosphorylation of these residues, the enzymatic activity of the MET kinase is strongly up-regulated in an autocatalytic fashion.[6] The C-terminal tail domain of the MET receptor is crucial for its biological activity: it comprises a short sequence containing two tyrosines that become phosphorylated upon HGF binding and is alone responsible for mediating high-affinity interactions with multiple SH2-containing cytoplasmic effectors such as GRB-2, p85-PI3K, PLCγ, STAT3, SHC and GAB1[7–10] (Fig. 1).

Met activation evokes pleiotropic biological responses, both *in vitro* and *in vivo*, often referred to as 'invasive growth'. This is a complex genetic programme, specifically induced by the receptors of MET family. It consists of a series of obligate rate-limiting steps that occur physiologically during embryogenesis and tissue repairing, and pathologically during oncogenesis. In the first step of this process, the cells acquire the ability to dissociate from their neighbours, by breaking intercellular adherent junctions ('scattering').[12] This event requires Matrix Metalloproteasis-mediated cleavage of cadherins from the cell surface, tyrosine phosphorylation of catenins and further transcriptional down-regulation of molecules involved in intercellular adhesion. In the second step, cells leave their original environment by degrading the basement membrane and reach the circulation ('directional migration' and 'invasion'). Cell survival in the blood stream is facilitated by *MET*-induced protection from apoptosis. Finally, cells extravasate, face the new environment, proliferate and eventually undergo terminal differentiation.[11]

During embryogenesis, invasive growth is an essential step that ensures the correct structural tissue organisation: in fact, its proper activation is crucial for the formation of the placenta and the liver and thus *MET*- or HGF-KO mice die very early intra-uterus.[13,14] In adulthood, when the architectural tissue organisation is already well established, *MET* activity becomes dispensable but it is still required when tissues are damaged and cells have to reacquire the ability to dissociate, migrate and repair the regenerating tissues. These findings have been consolidated by data obtained in inducible *MET*-KO mice: if the MET pathway is active during embryogenesis but it is turned off after birth, mice have almost no defects, except for the loss of the ability to regenerate tissues (especially liver) after an injury.[15] However, it is important to underline that the activation of the *invasive growth* programme in embryogenesis is as crucial as its inhibition in adulthood: in fact, aberrant activation of HGF–MET signalling is involved in cancer progression and metastasis. Indeed, during tumourigenesis cancer cells detach one from the other, invade the basement membrane, reach the blood stream and finally metastasise to different districts, somehow recapitulating the *invasive growth* programme.

Furthermore, MET signalling is involved in the regulation of tumour angiogenesis, either directly, through the pro-angiogenic activity of HGF that induces the formation of new vessels and the sprouting of the pre-existing ones, or indirectly, through the regulated secretion of angiogenic factors, such as VEGFA,[18] interleukin-8 (IL-8) and thrombospondin-1.[16,17] Moreover, not only endothelial cells, but also macrophages[19] and other leucocytes[20,21] express MET and it has been shown that its activation in these cells can contribute to tumour growth and metastasis. Moreover, experimental evidences have demonstrated that therapeutic MET targeting also impairs the function of inflammatory cells, interfering with the pro-tumourigenic role of the tumour microenvironment.[17]

The main proof of the direct involvement of MET in tumourigenesis was given by the identification of germ-line activating mutations in patients with hereditary renal papillary carcinoma (HRPC).[23] Activating mutations have also been described in sporadic tumours such as childhood hepatocellular carcinomas,[24] sporadic papillary renal carcinomas,[23] gastric carcinomas[25] and head and neck squamous cell carcinomas.[26] Lot of effort has been made to better characterise MET deregulation in human cancers, to understand when and how the alteration of MET signalling is mandatory for tumour progression. Nowadays, it is clear that gene amplification and transcriptional over-expression (induced by activation of oncogenes – such as ras,[27] or ets[28] – or by hypoxic stimuli) are the most frequent alterations in several human cancers (carcinomas, multiple myelomas and gliomas). Receptor over-expression leads to spontaneous dimerisation and activation of the receptor, also in a ligand-independent manner. In few cases, MET can be activated by its ligand, HGF, in an autocrine manner; autocrine activation occurs when tumour cells aberrantly express both HGF and its receptor, as shown in osteosarcomas,[29] rhabdomyosarcomas,[30] gliomas[31] and some carcinomas of thyroid,[32] breast,[33] and lung.[34]

Finally, it must be underlined that MET is not alone on the cell surface: in fact, it has been widely proven that this receptor interacts with several membrane proteins that can modulate its activation.[35] The physiological meaning of these interactions and the whole panel of their consequences is

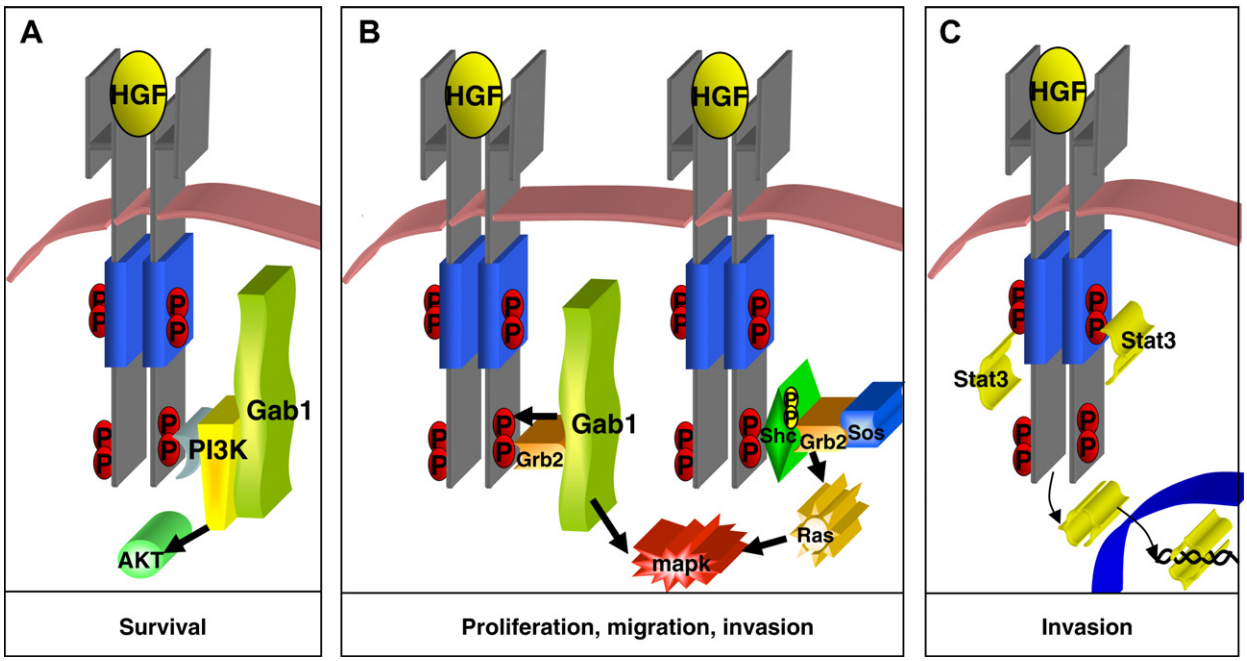

Fig. 1 – Main signalling pathways activated by MET. Upon HGF binding, MET triggers the activation of different signalling pathways. Their role in the biological responses elicited by HGF stimulation has been deeply studied. (A) A major role for the anti-apoptotic response is played by PI3K and Gab1 that mediate the activation of AKT; (B) proliferation and motility require the activation of MAPK, mediated by (i) the Gab1–Grb2 system, (ii) Gab1 alone or (iii) Shc phosphorylation that leads to Grb2/Sos recruitment: all these events result in the activation of the Ras pathway; (C) a critical role for HGF-stimulated invasive ability is played by the activation of STAT3 proteins which translocate to the nucleus where they act as transcription factors for genes involved in cellular invasiveness.

not completely understood. However, the available data suggest that these cross-talks are not essential for cell survival but that they allow a better integration of signals present in the extracellular environment and it has been convincingly proven that these interactors can cooperate in promoting tumourigenesis and/or metastasis. Recent studies, in fact, indicate that MET and integrin signalling can interact at least at three levels: (i) physical association and subsequent reciprocal regulation of cascade activation at the plasma membrane; (ii) cooperation in the activation of common intracellular transducers (such as FAK and Src); and (iii) reciprocal regulation of expression.[36] Amongst the very wide integrin family, the α6β4 member seems to play the major role: in fact, it has been shown that this integrin physically interacts with MET leading to its ligand-independent activation in carcinoma cells where MET is over-expressed, thus enhancing the invasive growth programme.[37] Together with integrins, other adhesive receptors cooperate in increasing MET activation: that is the case of the CD44 family of transmembrane receptors for hyaluronic acid, a major component of the extracellular matrix. In particular, it has been shown that the CD44v6 isoform can bind both HGF and MET and promote HGF–MET interaction and activation of some transducers, thus acting as a signal amplifying platform.[38] Furthermore, also plexins (receptors for a family of ligands named Semaphorins)[39] associate with MET[40] and it has been demonstrated that the interaction of activated plexins with MET induces the invasive growth programme. Finally, it is becoming clear that MET interaction with other RTKs can be important in several pathological settings. It has been shown that aberrant EGFR activation induces MET expression and phosphorylation in thyroid carcinoma cells[41] and that both EGFR and GPCR can transactivate MET in pancreatic and hepatocellular carcinoma cell lines.[42] Moreover, a notable example of cross-talk between members of the EGFR family and MET has been recently highlighted in lung tumours with acquired resistance to EGFR small-molecule inhibitors.[43,44] In such tumours, resistance to EGFR inhibitors is due to amplification of the MET gene, which leads to MET hyperactivation and MET-dependent phosphorylation of HER-3, thus leading to the sustained activation of PI3K and AKT pathways. All together these data show that these receptors can either synergise or replace each other to generate signals that are required for tumour maintenance.

3. Which tumours might be candidates for MET targeted therapy?

One of the major problems of clinical trials utilising drugs that target specific molecules is to identify the correct pathological context in which to use these drugs.

From the clinical experience, it appears clear that a gene is an easier target if it is altered, mutated or over-expressed. The reason is simple: in all these cases, tumour cells present some features that render them different from the other cells of the body. They can in fact express a new and different protein (in case of fusion proteins), a hyperactive kinase with an altered conformation (for the presence of activating mutations) or a

huge and unusual amount of a wild-type protein (due to gene amplification or to transcriptional up-regulation).

Starting from these considerations, in which tumours have genetic alterations or transcriptional deregulations of MET been observed?

As mentioned before, no gene rearrangement involving MET has been described in human cancers, the only exception being a rare chromosome translocation leading to the fusion of the MET gene with Tpr sequences; this rearrangement was first identified in cells treated *in vitro* with a chemical carcinogen[1] and subsequently found at low levels in some cell lines derived from human gastric tumours.[45] On the other hand, several kinase activating mutations have been identified both in hereditary[46] and in sporadic papillary renal cell carcinomas.[47] Nevertheless, it seems that the presence of the mutation in heterozygosity – at least in hereditary cancers – is not sufficient to promote tumour formation but that the duplication of the mutated gene is further required, usually as part of a whole chromosome 7 trisomy.[23]

The most common genetic alteration of MET in human tumours is gene amplification, leading to receptor over-expression. Gene amplification in primary tumours seems to be restricted to gastric carcinomas[48,49] and colorectal cancers.[50] While gene amplification is quite rare in primary tumours, it is more frequent in metastases; this observation further strengthens the hypothesis that MET activation contributes critically to tumour cell invasiveness.

It has recently been observed that MET amplification can be found in tumour cells that become resistant to therapies targeting other RTKs. This happens, for example, in lung tumours with acquired resistance to the EGFR inhibitors gefitinib and erlotinib.[43,44] The authors of these two works, in fact, have independently shown that the MET gene is amplified in around 20% of lung tumours displaying acquired resistance to EGFR inhibitors and that constitutive MET activation leads to HER3-dependent activation of the PI3 kinase-Akt pathway. They also show that while single inhibition of either MET or EGFR is ineffective in these contexts, concomitant inhibition of both the receptors results in severe impairment of cell growth and viability. These works thus suggest that MET amplification and constitutive activation may be responsible for acquisition of resistance to inhibitors targeting different tyrosine kinase receptors.

Receptor over-expression is by far the most frequent alteration of MET in human tumours. It can be induced by cell-autonomous mechanisms (such as activation of other oncogenes) or by non-cell autonomous mechanisms (such as hypoxia in the microenvironment). At the moment it is not clear if MET over-expression, after its onset, becomes independent from the inducing stimuli, for example, as a consequence of epigenetic modifications. MET over-expression has been identified in around 70% of papillary and poorly differentiated thyroid carcinomas and in 25% of follicular thyroid carcinomas, while it is not detectable either in benign thyroid diseases or in the normal gland.[51] It is still subject of debate if this over-expression correlates with a poor clinical outcome: while Belfiore et al. showed an inverse correlation between MET expression and clinical prognosis,[52] other authors reported opposite evidences.[32] Additionally, MET over-expression has been described in a variety of other human cancers such as renal cell (68% of tumours; correlation with poor prognosis),[53] prostate,[54] ovarian and colorectal carcinomas.[55]

4. How can we target MET expression/activity?

The image stemming from the available literature depicts MET as receptor widely expressed, almost dispensable in adulthood, often over-expressed in primary tumours and amplified in metastases. Moreover, the main role of MET seems to be accomplished during the metastatic process, a step of tumour progression for which very few therapies are available.

On these premises, is it possible to start a clinical trial targeting MET expression/activation? To answer this question, it is important to review which are the tools to target MET, already tested in pre-clinical studies, with a particular interest for those closest to therapeutic application; eventually, we will describe the preliminary results of the first clinical trials targeting MET, already performed or still ongoing.

5. Pre-clinical trials

As in most of the cases, MET activation requires the interaction with its ligand, HGF, it is possible to interfere with the activation of this system by acting on either MET or HGF or both.

Many strategies have been developed to efficiently block MET activity: (i) MET/HGF competitors; (ii) anti-HGF or anti-MET monoclonal antibodies; and (iii) MET kinase inhibitors (Fig. 2). From a clinical point of view, these last two approaches are the most promising ones: in fact, analogue compounds, targeting other RTKs, are already available and are providing promising results in the clinical setting.

5.1. *MET/HGF competitors*

The first attempts to interfere with cancer progression by targeting the HGF/*MET* system came in the late 1990s and aimed at interfering with HGF binding to MET, through the use of antagonistic compounds ('competitors').

One of the most promising competitors is NK4, a variant of HGF comprising only the four-kringles of the α chain; NK4 binds to MET without inducing receptor activation and thus behaves as a full antagonist.[56] Moreover, as a consequence of its structural similarity to angiostatins, but independently from its effect on MET signalling, NK4 is able to inhibit angiogenesis induced by vascular endothelial cell growth factor (VEGF) and basic fibroblast growth factor (bFGF).[57] This bifunctional action of NK4 on tumour cells and on the surrounding vasculature results in inhibition of tumour growth, invasion and metastatic dissemination in mouse models.[58] Its major limit relies in its inability to interfere with the development of tumours in which MET is activated in a HGF-independent manner.

A chimeric factor containing selected domains of HGF and MSP and able to signal through MET/Ron heterodimers was proven to be able to dissociate the trophic properties of HGF, such as proliferation and protection against apoptosis, from its pro-invasive ability. This opened the possibility of exploit-

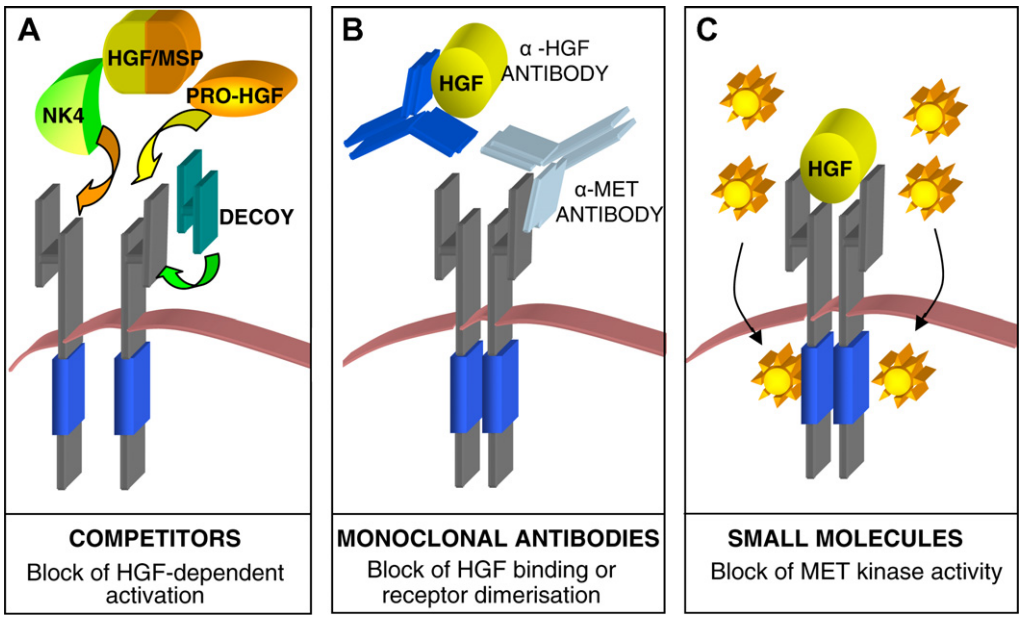

Fig. 2 – Strategies to interfere with MET activation. MET activation can be blocked by: (A) Competitors such as: (i) a portion of HGF (NK4) that, upon binding to the receptor, acts as a full antagonist; (ii) the fusion protein HGF/MSP that is endowed with trophic properties; (iii) an uncleavable form of the ligand, the pro-HGF, that prevents HGF binding to the receptor and competes for the proteolytic activation of the endogenous HGF; and (iv) the extracellular portion of the receptor, the decoy-MET, that sequesters circulating HGF and blocks receptor dimerisation; (B) monoclonal antibodies directed against HGF (able to prevent the interaction with the receptor) or the receptor (able to prevent receptor dimerisation or to induce shedding of Met extracellular portion); (C) small molecules that block MET kinase activity, mainly interacting with the ATP binding domain of the receptor, displaying different grades of specificity for MET.

ing some 'favourable' effects of HGF to reduce, for example, chemotherapy-related cytotoxicity.[59]

Very recently, it has been shown that a mutated and uncleavable form of pro-HGF (HGF is first produced as a single, inactive precursor that is then cleaved in the two-chains mature form) obtained through a single amino acid substitution that prevents the cleavage of the single chain precursor in the mature form, can both displace HGF from MET and competitively inhibit the proteolytic activation of the endogenous pro-HGF. Local and systemic expression of this molecule through lentiviral technology was able to interfere with tumour growth, angiogenesis and metastasis formation in mice, without altering vital physiological parameters.[60]

Another molecule with a great therapeutic potential is a soluble form of the MET (the so-called decoy-MET), a recombinant protein corresponding to the entire extracellular domain of MET. This molecule acts both on MET and HGF, as it blocks receptor dimerisation and sequesters the circulating HGF. *In vitro* and pre-clinical data suggest that decoy-Met has several biochemical and biological advantages over NK4, such as a higher affinity for the receptor and the ability to block also ligand-independent MET activation. Moreover, it has been shown that NK4 and decoy-MET synergise with radiotherapy in inducing tumour regression.[22]

5.2. *Monoclonal antibodies*

Monoclonal antibodies are currently used to target other RTKs in cancer and are providing good therapeutic results. The best known examples, already approved by FDA, are Cetuximab (against EGFR) in head and neck and colorectal cancer, Trastuzumab (against HER-2) in locally advanced and metastatic breast cancer and Bevacizumab (against VEGF) in metastatic colon cancer and non-small-lung cancer.[61,62]It is important to underline that monoclonal antibodies can interfere with RTKs' activity either targeting the receptor (Cetuximab or Trastuzumab) or the ligand (Bevacizumab).

Concerning the MET–HGF system, promising results have been obtained both with anti-HGF antibodies (one of them has just entered the first phase I clinical trial), and with anti-MET antibodies.

Recently, a panel of fully human monoclonal antibodies that bind to and neutralise human HGF have been developed.[63] *In vitro*, they inhibit HGF-mediated MET phosphorylation, cell proliferation, survival, and invasion and, *in vivo*, they lead to inhibition and even regression of tumours in mice models. Kim and colleagues recently identified another monoclonal antibody, L2G7, active not only *in vitro*, but also able to interfere with tumour growth and to induce tumour regression in mouse models; moreover, this antibody also showed activity within the central nervous system, a site previously believed to be resistant to systemic antibody-based therapies.[64]

The potential use of mAbs targeting MET in human cancer therapy induced the production of a growing number of these molecules. As bivalent antibodies exhibited both agonistic and antagonistic activity towards the receptor, allowing a partial activation of MET downstream pathways,[65] one

monovalent antibody (Fab), named 5D5, was engineered to inhibit HGF-dependent MET activation.[66] Local treatment of glioblastomas harbouring an autocrine activation of Met with the 5D5 monovalent antibody almost completely inhibited intracerebral glioblastoma growth as a consequence of anti-proliferative, anti-angiogenic and pro-apoptotic effects.

Finally, our group identified a mAb, named DN30, that efficiently down-regulates MET receptor through a molecular mechanism involving the proteolytic cleavage of the extracellular portion; this results in 'shedding' of the receptor ectodomain, leading to generation of a molecule similar to the already mentioned competitor *decoy-MET*.[67,68] Chronic treatment of carcinoma cell lines with this mAb resulted, *in vitro*, in impairment of HGF-induced signal transduction, anchorage-independent growth and invasiveness, while *in vivo*, administration of DN30 inhibited tumour growth and metastatic spread to the lung of neoplastic cells.[69]

5.3. *Small molecules*

From a pharmacological point of view, the most promising tools for cancer therapy are believed to be the competitors for the ATP binding site of the receptor, the so-called 'small kinase inhibitors' or 'small molecules'. The reason for the increasing interest in the development of these compounds is due to their good efficacy in clinics (for example Gleevec, targeting c-kit and BCR-ABL, Iressa and Tarceva, targeting EGFR and Sorafenib, a drug targeting several RTKs) and to their ability to inhibit receptor activation due not only to ligand binding but also to over-expression or interaction with co-receptors. This last issue is of particular interest dealing with MET as activation due to receptor over-expression is quite frequent in human tumours.[70] Moreover, as already discussed, several data strongly suggest that MET cross-talk with other membrane receptors may lead to its activation in the absence of the ligand and promote the invasive growth programme.

For all these reasons, it is important to develop compounds able to efficiently switch off MET signal. Despite the potentiality of small molecules in cancer therapy, it must be taken into consideration that if, on one hand, these molecules are very effective and promising, on the other hand, they may create problems for side-effects because no ATP analogue will ever be absolutely specific for a given tyrosine kinase, and thus, toxicity is a big concern.

Initial attempts to identify MET-ATP binding site competitors brought to the identification and characterisation of K252a, a Staurosporine analogue behaving as a broad spectrum kinase inhibitor. At sub-micromolar concentrations, this compound inhibited MET activity *in vivo* but it was not very convincing due to lack of specificity.[71]

Searching for more selective compounds, two new small-molecule inhibitors have been developed: SU11274 and PHA665752. At nanomolar concentrations, they both are at least 50-fold more selective for MET compared to other RTKs and strongly inhibit HGF-induced activation of MET in cultured cells and tumourigenicity in mouse models. Moreover, SU11274 displays differential activity on the diverse MET mutants identified in hereditary papillary renal carcinoma,[72] while PHA665752 demonstrates high effectiveness in cancer cells with MET gene amplification[73]: these findings underline once more how the knowledge of the genetic lesions present in the tumour can modulate the therapeutic design, suggesting the most effective approach.

Recently, Zou and colleagues identified a new small-molecule inhibitor, named PF-2341066: it is an orally available ATP-competitive compound selective for MET. Pre-clinical data demonstrated that this molecule inhibits MET phosphorylation and MET-dependent proliferation, migration and invasion of tumour cells *in vitro*. *In vivo*, this compound showed a good tolerability and a dose-dependent anti-tumour activity.[74]

A novel MET/RON inhibitor (Compound I, from Amgen) has been recently identified and characterised. This molecule specifically inhibits both the receptors belonging to the same RTK family and prevents the activation of the invasive growth programme in response to the interaction with the cognate ligands. Compound I showed specific anti-tumour activity in animal models known to be dependent on either MET or Ron activation.[75]

Finally, an indirect approach to interfere with MET activity has been achieved using geldanamycin (GA), an anti-tumour drug that binds to and inhibits HSP90 chaperone activity by preventing proper folding and functioning of certain oncoproteins and, amongst them, MET.[76] It has been shown that GA and its derivatives inhibit HGF/SF-mediated cell scattering and invasion *in vitro* and tumour cell invasion, *in vivo*.[76]

6. Clinical trials

Recently, some molecules targeting MET reached the access to clinical trials: they all share low levels of toxicity but further investigations are required to optimise the clinical settings (Table 1).

The only trial targeting MET with monoclonal antibodies is the one performed by Amgen, utilising a fully human IgG_2 monoclonal antibody against HGF (AMG 102), that is able to prevent the interaction between HGF and MET. In pre-clinical studies, this antibody showed good pharmacokinetic and safety profiles in cynomolgus monkeys[77] and synergism with temozolomide and docetaxel in a U-87 MG xenograft model *in vivo*[78] allowing it to enter in a phase I trial. It is a first in a human, open-label, sequential dose-escalation study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of AMG 102 in patients with advanced solid tumours (http://meeting.ascopubs.org/cgi/content/abstract/

Table 1 – Clinical trials ongoing/performed with the different MET/HGF inhibitors

Name	Type	Phase	Ref.
AMG 102	mAb	Phase I	Kakkar et al.[77]
SGX523	Kinase inhibitor	Phase I	SGX Pharmaceuticals
MGCD265	Kinase inhibitor	Phase I	MethylGene
XL-184	Kinase inhibitor	Phase I	Exelixis
ARQ197	Kinase inhibitor	Phase II (2 trials)	ArQule Inc.
XL880	Kinase inhibitor	Phase II (2 trials)	Exelixis

25/18_suppl/3551). Sequential dose cohorts of 4–6 patients received AMG102 at different doses (0.5, 1, 3, 5, 10 or 20 mg/kg). Patients received a single dose, followed by a 4-week treatment-free period, during which safety was assessed. When no dose-limiting toxicity was observed, treatment was resumed every 2 weeks at the same dose, until patients exhibited drug intolerance or disease progression. Interim results suggest that AMG102 (at doses up to 20 mg/kg) appears to be well tolerated, with preliminary pharmacokinetics data supporting every 2-week administration. On these bases, two global, multi-centre, open-label, single agent, two-stages phase II studies are enrolling patients with advanced renal cell carcinoma and advanced malignant glioma. The purpose of these studies is to evaluate the effectiveness and safety of AMG 102 (http://clinicaltrials.gov/ct2/show/NCT00422019?term=amg102&rank=1).

All the other trials planned or opened until now involve small molecules that block MET kinase activity, with different grades of selectivity.

SGX523 (from SGX Pharmaceuticals), a new ATP-competitive inhibitor, has been first characterised *in vitro*, where it was able to inhibit MET at low nM concentrations (IC = 17 nM for inhibition of MET autophosphorylation; IC = 93 nM for inhibition of proliferation of GTL-16 carcinoma cells, expressing a constitutively active MET). SGX523 was also screened against a panel of 213 human kinases; only METwas significantly inhibited at concentrations lower than 1 μM. This compound is orally available and showed good pharmacokinetic properties in mice, rats and dogs. Moreover, SGX523 demonstrated potent anti-tumour activity when administered orally in human tumour xenograft models, with no overt toxicity. Pharmacodynamic studies showed a good correspondence between *in vivo* anti-tumour activity and inhibition of MET phosphorylation. On the bases of these results, SGX523 has been proposed for a phase I trial in humans (http://www.sgxpharma.com/pipeline/documents/SGX523METAACR07.pdf).[79–81]

Similar potentialities have been demonstrated by MGCD265 (from MethylGene), which is a multi-kinase inhibitor targeting c-MET, VEGFR1, VEGFR2, VEGFR3, Tie-2 and Ron receptor tyrosine kinases. This agent is currently in late preclinical studies and filing of an Investigational New Drug application was expected by the end of 2007 (http://www.methylgene.com/content.asp?node=227).

Already in phase I trial, XL-184 (from Exelixis) is an orally available small-molecule inhibitor which primary targets Met and VEGFR2/KDR; additional targets include KIT, FLT3 and Tie-2. XL184 was well tolerated (no drug-related dose-limiting toxicity has been observed but two patients experienced grade three toxicity) and demonstrated a mild anti-tumour activity (6 out of 21 patients displayed partial response or disease stabilisation) (http://meeting.ascopubs.org/cgi/content/abstract/25/18_suppl/14031).[82]

The selective MET inhibitor ARQ 197 (from ArQule Inc.) is a non-ATP-competitive molecule that binds to MET in a region close to the ATP binding site. This compound, after having provided encouraging results in xenograft mouse models, successfully completed the phase I dose-escalation trial, demonstrating a good tolerability (no therapy interruption due to drug adverse effects was observed and no dose-limiting toxicity was reached) and a mild anti-tumour response (three partial responses and 18 stable diseases in 35 patients affected by different solid metastatic tumours resistant to prior therapy), (http://meeting.ascopubs.org/cgi/content/abstract/25/18_suppl/3525).[83,84] Two phase II studies have now been approved: (i) in patients with MiT (microphthalmia transcription factor) tumours (clear cell sarcoma, alveolar soft part sarcoma and translocation-associated renal cell carcinoma (RCC)), which are biologically linked through a common chromosomal abnormality that is believed to drive the over-expression of MET and thereby the development of cancer. Tumours with this abnormality tend to spread throughout the body and to resist all known therapies and (ii) in patients affected by pancreatic cancers (http://www.pharmalive.com//News/index.cfm?articleid=488744&categoryid=21).

One of the most promising compounds, for which two phase II studies are now ongoing, is the orally bioavailable small molecule XL880 (from Exelixis): this drug inhibits preferentially MET activity but also other tyrosine kinases with growth promoting and angiogenic properties like VEGFR, PDGFR, c-KIT, FLT3 and Tie-2. In the phase I trial, this compound has been generally well tolerated (no high grade toxicity even at the highest dose tested), with evidences of biological and clinical activity (10 of 22 patients showed stable disease for >3 months after treatment initiation) (http://meeting.ascopubs.org/cgi/content/abstract/25/18_suppl/3526).[85,86] After these encouraging results, XL880 is now in two phase II studies: (i) in the first trial, patients enrolled had preferentially a histologically confirmed, poorly differentiated metastatic gastric carcinoma (since it is known that MET amplification plays a critical role in the pathogenesis of this kind of tumour) but also renal cell carcinomas and, generally, metastatic solid tumours. The primary aim of the study is to determine the response rate (particularly for the gastric cancers), the safety and the tolerability of the drug, and, secondarily, the progression-free survival, the duration of the response and pharmacokinetic and pharmacodynamic parameters (http://clinicaltrials.gov/ct2/show/record/NCT00415480). (ii) The second trial enrolled patients with histological diagnosis of metastatic or unresectable papillary renal carcinoma. In this setting, XL880 demonstrated a good anti-tumour activity as disease control was obtained in all the 19 patients; 15 of them also showed a decrease of tumour size (http://meeting.ascopubs.org/cgi/content/abstract/25/18_suppl/15601).

7. Conclusion

The MET gene was discovered around 20 years ago,[1] but the formal proof of its involvement in human tumours was obtained only in the 1990s.[23] From then on, much progress has been made to try to understand its role in human tumours and to try to engineer drugs or compounds able to inhibit MET tyrosine kinase activity; these compounds have then been tested in pre-clinical and, more recently, in clinical settings. From all these studies, a general message is coming out: at present, many tools to block MET are available and have proved to be able to interfere with tumour/metastasis development in pre-clinical settings.

Clinical trials have started very recently and although data on the anti-tumour activity of the anti-MET compounds are not yet available, these studies have shown that MET inhibition results in low-grade toxicity, in agreement with the pre-clinical analyses performed in animal models. This observation is in line with the idea that MET activation is probably not critical in steady-state conditions, when cells are not exposed to environmental stresses. This means that MET function is probably dispensable for 'healthy' cells and thus its inhibition does not lead to important toxicities. It is likely that multi-targeting inhibitors, acting not only on MET but also on other RTKs, will also display increased toxicities. Thus, moving towards multi-targeting compounds will probably increase the therapeutic activity, at the expense of enhanced toxicities. It is also advisable that new drugs will be orally available, endowed with a half life long enough to allow less frequent intake.

A lot of work has still to be performed to better understand which tumours might obtain the highest benefit from MET inhibition. This is due to the fact that we are just beginning to uncover which cancer type depends on MET activity for the maintenance of the malignant phenotype. Works by us and others[87,88] have shown that constitutive activation of Met can result in 'addiction' of tumour cells to the signalling pathways generated by this receptor and can predict clinical responses to its inhibition. Moreover, recent researches have highlighted the concept of 'context-dependent addiction'; each receptor, in fact, is able to activate several signalling pathways that are part of molecular circuitries shared with other receptors and that are negatively and positively controlled at multiple levels. In this scenario, the ultimate effect of the activation of a single receptor can lead to different outcomes depending on the genes that, in a distinct cancer cell, are activated or lost. This means that the inhibition MET might be useless if downstream effectors (such as RAS or PI3K) are constitutively activated or if parallel pathways (such as those driven by EGFR family members) are turned on. At the moment, there is not yet a clear evidence of which drug associations are more likely to be effective and of how they have to be administered.

It has to be underlined that during the tumourigenic process, MET is believed to play a critical role in the advanced, metastatic phases of the disease. In this context, MET inhibitors would probably be more effective in advanced phases of tumour progression. At the moment, there are not enough experimental proofs supporting the idea that the early use of anti-MET inhibitors could be effective in preventing metastasis, but this is of course a very intriguing field that deserves careful investigation.

Another important and still unsolved issue is the identification of markers useful to evaluate the efficacy of MET inhibition. In the case of EGFR, for example, the status of EGFR-dependent molecules (such as phosphorylated MAPK, p27 or phosphorylated STAT3) in skin biopsies and the appearance of rashes or other cutaneous adverse events, have been considered as possible surrogate markers for the efficacy of EGFR-targeting treatments. Unfortunately, the above-mentioned markers are not useful when evaluating MET inhibition, as this receptor seems to be silent in peripheral tissues and, thus, not sensitive to inhibitors' activity. One alternative option, still to be carefully evaluated, is the quantification of the soluble extra-cellular portion of MET in the plasma of treated patients. Several studies have shown that the extracellular domain of Met is shed and released as a consequence of several biological mechanisms[89] and it has been proposed that its evaluation can be used to monitor both the activity of the inhibitors and the evolution of the pathology.

Recent data show that MET can be involved in the appearance of resistance to therapies targeting other RTKs; this observation has to be kept in mind as the rationale at the basis of targeting drugs is radically changing. While in the past, the main effort was aimed at developing highly specific inhibitors, acting on single RTKs, now there is a general agreement that molecules interfering simultaneously with multiple RTKs might be more effective than single target agents. It is this perspective, drugs targeting MET, amongst other RTKs, which could deprive cells of a possible mechanism of drug resistance.

In conclusion, even if MET is relatively a new player in the complex scenario of anti-cancer therapy, it is an interesting and promising target that has to be included amongst the already available ones.

Conflict of interest statement

None declared.

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REFERENCES

1. Cooper CS, Park M, Blair DG, et al. Molecular cloning of a new transforming gene from a chemically transformed human cell line. *Nature* 1984;**311**:29–33.
2. 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**:802–4.
3. Naldini L, Vigna E, Narsimhan RP, et al. Hepatocyte growth factor (HGF) stimulates the tyrosine kinase activity of the receptor encoded by the proto-oncogene c-MET. *Oncogene* 1991;**6**:501–4.
4. Ferracini R, Longati P, Naldini L, Vigna E, Comoglio PM. Identification of the major autophosphorylation site of the Met/hepatocyte growth factor receptor tyrosine kinase. *J Biol Chem* 1991;**266**:19558–64.
5. Longati P, Bardelli A, Ponzetto C, Naldini L, Comoglio PM. Tyrosines1234–1235 are critical for activation of the tyrosine kinase encoded by the MET proto-oncogene (HGF receptor). *Oncogene* 1994;**9**:49–57.
6. Naldini L, Vigna E, Ferracini R, et al. The tyrosine kinase encoded by the MET proto-oncogene is activated by autophosphorylation. *Mol Cell Biol* 1991;**11**:1793–803.
7. 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* 1994;**77**:261–71.

8. Pelicci G, Giordano S, Zhen Z, et al. The motogenic and mitogenic responses to HGF are amplified by the Shc adaptor protein. *Oncogene* 1995;**10**:1631–8.
9. Weidner KM, Di CS, Sachs M, et al. Interaction between Gab1 and the c-Met receptor tyrosine kinase is responsible for epithelial morphogenesis. *Nature* 1996;**384**:173–6.
10. Boccaccio C, Ando M, Tamagnone L, et al. Induction of epithelial tubules by growth factor HGF depends on the STAT pathway. *Nature* 1998;**391**:285–8.
11. Giordano S, Zhen Z, Medico E, et al. Transfer of motogenic and invasive response to scatter factor/hepatocyte growth factor by transfection of human MET protooncogene. *Proc Natl Acad Sci USA* 1993;**90**:649–53.
12. Birchmeier W, Weidner KM, Behrens J. Molecular mechanisms leading to loss of differentiation and gain of invasiveness in epithelial cells. *J Cell Sci Suppl* 1993;**17**:159–64.
13. Uehara Y, Minowa O, Mori C, et al. Placental defect and embryonic lethality in mice lacking hepatocyte growth factor/scatter factor. *Nature* 1995;**373**:702–5.
14. Schmidt C, Bladt F, Goedecke S, et al. Scatter factor/hepatocyte growth factor is essential for liver development. *Nature* 1995;**373**:699–702.
15. Huh CG, Factor VM, Sanchez A, et al. Hepatocyte growth factor/c-met signaling pathway is required for efficient liver regeneration and repair. *Proc Natl Acad Sci USA* 2004;**101**:4477–82.
16. Rosen EM, Grant DS, Kleinman HK, et al. Scatter factor (hepatocyte growth factor) is a potent angiogenesis factor in vivo. *Symp Soc Exp Biol* 1993;**47**:227–34.
17. Zhang YW, Su Y, Volpert OV, Vande Woude GF. Hepatocyte growth factor/scatter factor mediates angiogenesis through positive VEGF and negative thrombospondin 1 regulation. *Proc Natl Acad Sci USA* 2003;**100**:12718–23.
18. Gille J, Khalik M, Konig V, Kaufmann R. Hepatocyte growth factor/scatter factor (HGF/SF) induces vascular permeability factor (VPF/VEGF) expression by cultured keratinocytes. *J Invest Dermatol* 1998;**111**:1160–5.
19. Galimi F, Cottone E, Vigna E, et al. Hepatocyte growth factor is a regulator of monocyte–macrophage function. *J Immunol* 2001;**166**:1241–7.
20. Skibinski G. The role of hepatocyte growth factor/c-met interactions in the immune system. *Arch Immunol Ther Exp (Warsz)* 2003;**51**:277–82.
21. Skibinski G, Skibinska A, James K. The role of hepatocyte growth factor and its receptor c-met in interactions between lymphocytes and stromal cells in secondary human lymphoid organs. *Immunology* 2001;**102**:506–14.
22. Michieli P, Mazzone M, Basilico C, et al. Targeting the tumor and its microenvironment by a dual-function decoy Met receptor. *Cancer Cell* 2004;**6**:61–73.
23. 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* 1997;**16**:68–73.
24. Park WS, Dong SM, Kim SY, et al. Somatic mutations in the kinase domain of the Met/hepatocyte growth factor receptor gene in childhood hepatocellular carcinomas. *Cancer Res* 1999;**59**:307–10.
25. Lee JH, Han SU, Cho H, et al. A novel germ line juxtamembrane Met mutation in human gastric cancer. *Oncogene* 2000;**19**:4947–53.
26. 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* 2000;**19**:1547–55.
27. Long IS, Han K, Li M, et al. Met receptor overexpression and oncogenic Ki-ras mutation cooperate to enhance tumorigenicity of colon cancer cells in vivo. *Mol Cancer Res* 2003;**1**:393–401.
28. Gambarotta G, Boccaccio C, Giordano S, et al. Ets up-regulates MET transcription. *Oncogene* 1996;**13**:1911–7.
29. Ferracini R, Di Renzo MF, Scotlandi K, et al. The Met/HGF receptor is over-expressed in human osteosarcomas and is activated by either a paracrine or an autocrine circuit. *Oncogene* 1995;**10**:739–49.
30. Ferracini R, Olivero M, Di Renzo MF, et al. Retrogenic expression of the MET proto-oncogene correlates with the invasive phenotype of human rhabdomyosarcomas. *Oncogene* 1996;**12**:1697–705.
31. Koochekpour S, Jeffers M, Rulong S, et al. Met and hepatocyte growth factor/scatter factor expression in human gliomas. *Cancer Res* 1997;**57**:5391–8.
32. Ramirez R, Hsu D, Patel A, et al. Over-expression of hepatocyte growth factor/scatter factor (HGF/SF) and the HGF/SF receptor (cMET) are associated with a high risk of metastasis and recurrence for children and young adults with papillary thyroid carcinoma. *Clin Endocrinol (Oxf)* 2000;**53**:635–44.
33. Tuck AB, Park M, Sterns EE, Boag A, Elliott BE. Coexpression of hepatocyte growth factor and receptor (Met) in human breast carcinoma. *Am J Pathol* 1996;**148**:225–32.
34. Tokunou M, Niki T, Eguchi K, et al. c-MET expression in myofibroblasts: role in autocrine activation and prognostic significance in lung adenocarcinoma. *Am J Pathol* 2001;**158**:1451–63.
35. Corso S, Comoglio PM, Giordano S. Cancer therapy: can the challenge be MET? *Trends Mol Med* 2005;**11**:284–92.
36. Chan PC, Chen SY, Chen CH, Chen HC. Crosstalk between hepatocyte growth factor and integrin signaling pathways. *J Biomed Sci* 2006;**13**:215–23.
37. Trusolino L, Bertotti A, Comoglio PM. A signaling adapter function for alpha6beta4 integrin in the control of HGF-dependent invasive growth. *Cell* 2001;**107**:643–54.
38. van der Voort R, Taher TE, Wielenga VJ, et al. Heparan sulfate-modified CD44 promotes hepatocyte growth factor/scatter factor-induced signal transduction through the receptor tyrosine kinase c-Met. *J Biol Chem* 1999;**274**:6499–506.
39. Kruger RP, Aurandt J, Guan KL. Semaphorins command cells to move. *Nat Rev Mol Cell Biol* 2005;**6**:789–800.
40. Giordano S, Corso S, Conrotto P, et al. The semaphorin 4D receptor controls invasive growth by coupling with Met. *Nat Cell Biol* 2002;**4**:720–4.
41. Bergstrom JD, Westermark B, Heldin NE. Epidermal growth factor receptor signaling activates met in human anaplastic thyroid carcinoma cells. *Exp Cell Res* 2000;**259**:293–9.
42. Fischer OM, Giordano S, Comoglio PM, Ullrich A. Reactive oxygen species mediate Met receptor transactivation by G protein-coupled receptors and the epidermal growth factor receptor in human carcinoma cells. *J Biol Chem* 2004;**279**:28970–8.
43. Engelman JA, Zejnullahu K, Mitsudomi T, et al. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. *Science* 2007;**316**:1039–43.
44. 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* 2007;**104**:20932–7.
45. Soman NR, Correa P, Ruiz BA, Wogan GN. The TPR–MET oncogenic rearrangement is present and expressed in human gastric carcinoma and precursor lesions. *Proc Natl Acad Sci USA* 1991;**88**:4892–6.
46. Lindor NM, Dechet CB, Greene MH, et al. Papillary renal cell carcinoma: analysis of germline mutations in the MET proto-oncogene in a clinic-based population. *Genet Test* 2001;**5**:101–6.

47. Schmidt L, Junker K, Nakaigawa N, et al. Novel mutations of the MET proto-oncogene in papillary renal carcinomas. *Oncogene* 1999;**18**:2343–50.
48. Seruca R, Suijkerbuijk RF, Gartner F, et al. Increasing levels of MYC and MET co-amplification during tumor progression of a case of gastric cancer. *Cancer Genet Cytogenet* 1995;**82**:140–5.
49. Rajcevic U, Juvan R, Gazvoda B, Repse S, Komel R. Assessment of differential expression of oncogenes in gastric adenocarcinoma by fluorescent multiplex RT-PCR assay. *Pflugers Arch* 2001;**442**:R190–2.
50. Umeki K, Shiota G, Kawasaki H. Clinical significance of c-met oncogene alterations in human colorectal cancer. *Oncology* 1999;**56**:314–21.
51. Farid NR, Shi Y, Zou M. Molecular basis of thyroid cancer. *Endocr Rev* 1994;**15**:202–32.
52. Belfiore A, Gangemi P, Costantino A, et al. Negative/low expression of the Met/hepatocyte growth factor receptor identifies papillary thyroid carcinomas with high risk of distant metastases. *J Clin Endocrinol Metab* 1997;**82**: 2322–8.
53. Pisters LL, el-Naggar AK, Luo W, Malpica A, Lin SH. C-met proto-oncogene expression in benign and malignant human renal tissues. *J Urol* 1997;**158**:724–8.
54. Pisters LL, Troncoso P, Zhau HE, et al. c-met proto-oncogene expression in benign and malignant human prostate tissues. *J Urol* 1995;**154**:293–8.
55. Di Renzo MF, Narsimhan RP, Olivero M, et al. Expression of the Met/HGF receptor in normal and neoplastic human tissues. *Oncogene* 1991;**6**:1997–2003.
56. Date K, Matsumoto K, Shimura H, Tanaka M, Nakamura T. HGF/NK4 is a specific antagonist for pleiotrophic actions of hepatocyte growth factor. *FEBS Lett* 1997;**420**:1–6.
57. Kuba K, Matsumoto K, Date K, et al. HGF/NK4, a four-kringle antagonist of hepatocyte growth factor, is an angiogenesis inhibitor that suppresses tumor growth and metastasis in mice. *Cancer Res* 2000;**60**:6737–43.
58. Wen J, Matsumoto K, Taniura N, Tomioka D, Nakamura T. Inhibition of colon cancer growth and metastasis by NK4 gene repetitive delivery in mice. *Biochem Biophys Res Commun* 2007;**358**:117–23.
59. Michieli P, Cavassa S, Basilico C, et al. An HGF-MSP chimera disassociates the trophic properties of scatter factors from their pro-invasive activity. *Nat Biotechnol* 2002;**20**: 488–95.
60. Mazzone M, Basilico C, Cavassa S, et al. An uncleavable form of pro-scatter factor suppresses tumor growth and dissemination in mice. *J Clin Invest* 2004;**114**:1418–32.
61. Barni S, Petrelli F, Cabiddu M, Cazzaniga ME, Cremonesi M. From the trastuzumab era to new target therapies: beyond revolution. *Ann Oncol* 2007;**18**(Suppl. 6):vi1–4.
62. Rocha-Lima CM, Soares HP, Raez LE, Singal R. EGFR targeting of solid tumors. *Cancer Control* 2007;**14**:295–304.
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**:1721–9.
64. 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**:1292–8.
65. Christensen JG, Burrows J, Salgia R. c-Met as a target for human cancer and characterization of inhibitors for therapeutic intervention. *Cancer Lett* 2005;**225**:1–26.
66. Martens T, Schmidt NO, Eckerich C, et al. A novel one-armed anti-c-Met antibody inhibits glioblastoma growth in vivo. *Clin Cancer Res* 2006;**12**:6144–52.
67. Athauda G, Giubellino A, Coleman JA, et al. c-Met ectodomain shedding rate correlates with malignant potential. *Clin Cancer Res* 2006;**12**:4154–62.
68. Nath D, Williamson NJ, Jarvis R, Murphy G. Shedding of c-Met is regulated by crosstalk between a G-protein coupled receptor and the EGF receptor and is mediated by a TIMP-3 sensitive metalloproteinase. *J Cell Sci* 2001;**114**:1213–20.
69. 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 USA* 2006;**103**:5090–5.
70. Desiderio MA. Hepatocyte growth factor in invasive growth of carcinomas. *Cell Mol Life Sci* 2007;**64**:1341–54.
71. Morotti A, Mila S, Accornero P, Tagliabue E, Ponzetto C. K252a inhibits the oncogenic properties of Met, the HGF receptor. *Oncogene* 2002;**21**:4885–93.
72. 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**:5387–93.
73. Ma PC, Schaefer E, Christensen JG, Salgia R. A selective small molecule c-MET Inhibitor, PHA665752, cooperates with rapamycin. *Clin Cancer Res* 2005;**11**:2312–9.
74. 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* 2007;**67**:4408–17.
75. Zhang Y, Kaplan-Lefko PJ, Rex K. Identification and characterization of a novel RON/c-Met small molecule inhibitor. In: AACR–NCI–EORTC – international conference – molecular targets and cancer therapeutics, A223; 2007.
76. Xie Q, Gao CF, Shinomiya N, et al. Geldanamycins exquisitely inhibit HGF/SF-mediated tumor cell invasion. *Oncogene* 2005;**24**:3697–707.
77. Kakkar T, Ma M, Zhuang Y, et al. Pharmacokinetics and safety of a fully human hepatocyte growth factor antibody, AMG 102, in cynomolgus monkeys. *Pharm Res* 2007.
78. 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* 2007;**13**: 6735–42.
79. Mondino A, Giordano S, Comoglio PM. Defective posttranslational processing activates the tyrosine kinase encoded by the MET proto-oncogene (hepatocyte growth factor receptor). *Mol Cell Biol* 1991;**11**:6084–92.
80. Jessen KA, Froning KJ, Felce JD, et al. In vitro and in vivo antitumor activities of SGX523, a novel MET inhibitor. In: AACR–NCI–EORTC – international conference – molecular targets and cancer therapeutics, B233; 2007.
81. Gessert SF, Aubol BE, Do TH, Hendle J. Selective inhibition of MET protein receptor tyrosine kinase by SGX253. In: AACR–NCI–EORTC – international conference – molecular targets and cancer therapeutics, C198; 2007.
82. Salgia R, Hong D, Sherman SI, Chann NG. A phase 1 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. In: AACR–NCI–EORTC – international conference – molecular targets and cancer therapeutics, A152; 2007.
83. Rosen L, Senzer N, Nemunaitis J. A phase 1 dose escalation study and signs of anti-metastatic activity of ARQ197, a selective c-Met inhibitor. In: AACR–NCI–EORTC – international conference – molecular targets and cancer therapeutics, B091; 2007.
84. Anderson KM, Li CJ, Moreau J. ARQ197, a small molecule inhibitor of c-Met, prevents bone metastases in humanized mouse model of breast cancer. In: AACR–NCI–EORTC –

international conference – molecular targets and cancer therapeutics, B184; 2007.
85. Shapiro GI, Heath E, Malburg L. A Phase I dose-escalation study of the safety, pharmacokinetics (PK) and pharmacodynamics of XL880, a VEGFR and MET kinase inhibitor administered daily to patients (pts) with advanced malignacies. In: AACR–NCI–EORTC – International conference – molecular targets and cancer therapeutics, B248; 2007.
86. Ross RW, Srinivasan R, Vaishampayan U. A Phase 2 study of the dual MET/VEGFR2 inhibitor XL880 in patients (pts) with papillary renal carcinoma (PRC). In: AACR–NCI–EORTC – international conference – molecular targets and cancer therapeutics, B249; 2007.
87. Taulli R, Scuoppo C, Bersani F. Validation of met as a therapeutic target in alveolar and embryonal rhabdomyosarcoma. *Cancer Res* 2006;**66**:4742–9.
88. Corso S, Migliore C, Ghiso E, De Rosa G, Comoglio PM, Giordano S. Silencing the MET oncogene leads to regression of experimental tumors and metastases. *Oncogene* 2008;**27**:684–93.
89. Prat M, Crepaldi T, Gandino L, Giordano S, Longati P, Comoglio P. C-terminal truncated forms of Met, the hepatocyte growth factor receptor. *Mol Cell Biol* 1991;**11**:5954–62.