

## Review

## Thirty Years of Research on Met Receptor to Move a Biomarker from Bench to Bedside

Alessandro Furlan<sup>1</sup>, Zoulika Kherrouche<sup>1</sup>, Rémi Montagne<sup>1</sup>, Marie-Christine Copin<sup>1,2</sup>, and David Tulasne<sup>1</sup>

### Abstract

Met receptor tyrosine kinase was discovered in 1984 as an oncogene. Thirty years later, Met and its ligand hepatocyte growth factor/scatter factor are promising targets for the novel therapies developed to fight against cancers, with more than 240 clinical trials currently conducted. In this review, we offer to trace and highlight the most recent findings of the exemplary track record of research on Met receptor, which allowed moving this biomarker from bench to bedside. Indeed, three decades of basic research unravelled the structural basis of the ligand/receptor interaction and their complex downstream signaling network. During this period, animal models highlighted their crucial role in the development and homeostasis of epithelial organs. In parallel, involvement of Met in tumorigenesis was confirmed by the direct association of its deregulation to poor prognosis in numerous cancers. On the basis of these data, pharmaceutical companies developed many Met inhibitors, some of which are in phase III clinical trials. These impressive achievements should not detract from many questions that still remain, such as the precise Met signaling involvement in development or homeostasis of specific epithelial structures. In addition, the processes involving Met in resistance to current therapies or the appearance of resistances to Met-targeted therapies are far from being fully understood. *Cancer Res*; 74(23); 6737–44. ©2014 AACR.

Many phases II and III clinical trials are evaluating targeted therapies against Met in various types of carcinomas. It seems obvious nowadays that Met, like other receptor tyrosine kinases (RTK), is a promising target in our fight against cancers. However, a long way of basic and applied research was necessary to place this RTK as a druggable actor of tumorigenesis. These multiple discoveries can be divided into three main steps: (i) Met physiologic role and its downstream signaling pathways, (ii) its involvement in tumorigenesis, and (iii) the design and evaluation of the targeted therapies against it.

### Step 1: Met Physiologic Role and Its Downstream Signaling Pathways

#### Discovery of HGF/SF and Met

The Met receptor and the hepatocyte growth factor (HGF), its high affinity ligand, were both discovered in 1984. Met was characterized from the TPR-Met oncogene in the human osteosarcoma cell line HOS treated by a carcinogen. This fusion protein results from the rearrangement between the *tpr* gene and a novel gene, *met*, named in reference to the carcinogen used, the N-methyl-N'-nitro-N-nitrosoguanidine (1). The

TPR part of fusion proteins induces their constitutive dimerization and thus activation of Met kinase domain, resulting in transforming activity. The HGF was isolated from the plasma of rats as a mitogen for cultured hepatocytes (2). Three years later, Stoker and colleagues identified a factor inducing epithelial cells scattering in fibroblast conditioned media so-called scatter factor (SF; ref. 3). In 1991, HGF and SF were recognized as the same protein encoded by the same gene and inducing similar biologic responses through binding to the Met receptor (4).

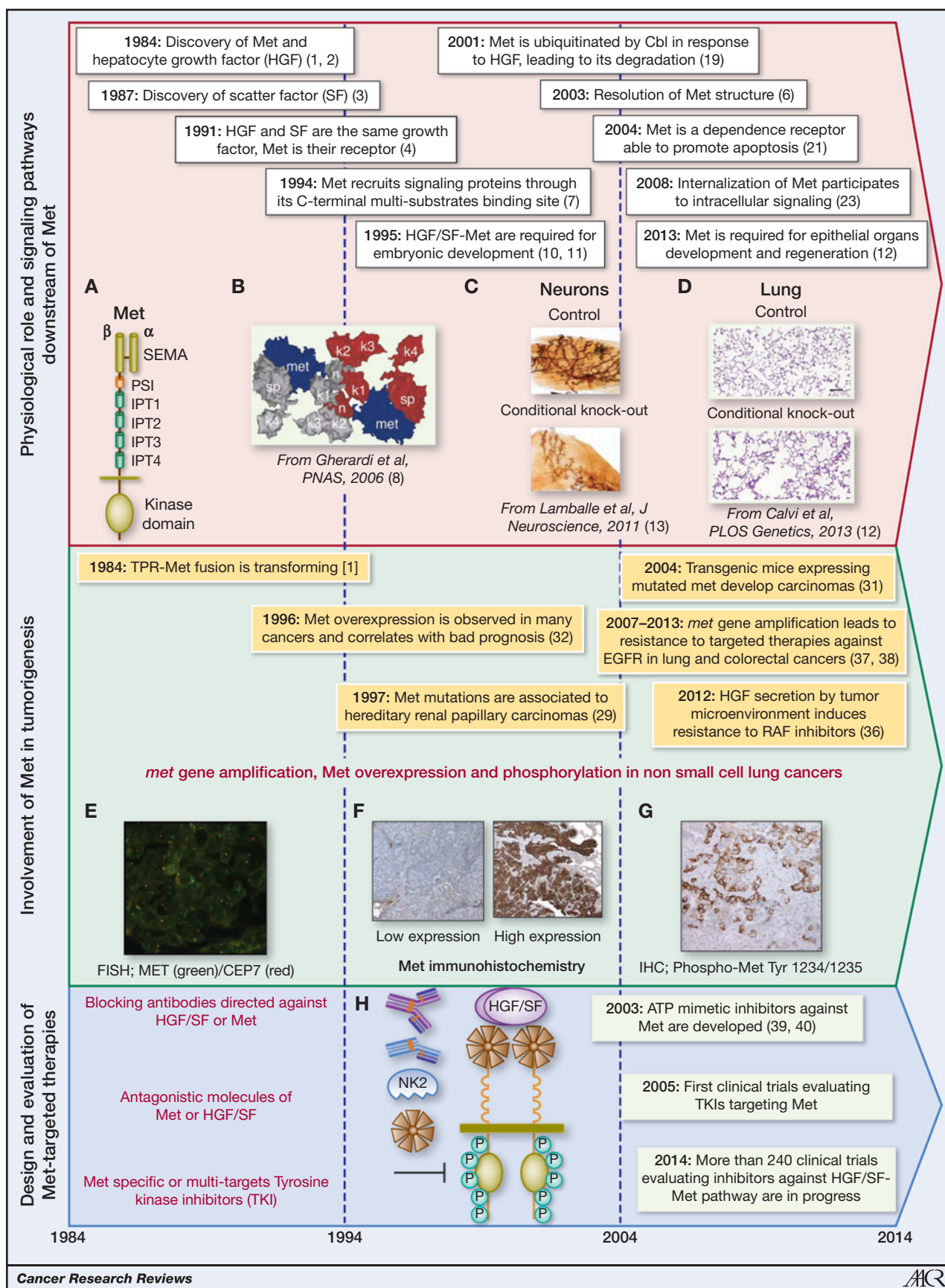
HGF/SF is synthesized as an inactive pro-HGF matured by a proteolytic cleavage, leading to generation of an active 90-kDa heterodimer consisting of an  $\alpha$  and a  $\beta$  subunit bound by disulfide bridges. The  $\alpha$  subunit includes an N-terminal (N) and four *kringle* (K1-K4) domains when the  $\beta$  subunit consists of a serine protease homology (SPH) domain. Although SPH domain lacks enzymatic activity, a zymogen activator peptide selectively able to bind the activation pocket within the serine protease-like  $\beta$ -chain induces activation of pro-HGF-dependent Met signaling, suggesting that the protease-like structure of HGF/SF plays a crucial role in its activation (5). Met is synthesized as a 170-kDa precursor matured into a heterodimeric receptor composed of an extracellular  $\alpha$  subunit linked to a single-pass transmembrane  $\beta$  subunit by a disulfide bond. The extracellular part of Met contains a N-terminal SEMA domain (also found in semaphorins, axon guidance proteins) encompassing the  $\alpha$  subunit and the first amino acids of the  $\beta$  subunit, followed by a PSI domain (named from its presence in plexins, semaphorins, and integrins) and four immunoglobulin-like domains called IPTs (Fig. 1A). The crystal structure of Met extracellular region, resolved in 2003, showed the SEMA domain organized in a seven bladed  $\beta$ -propeller

<sup>1</sup>CNRS UMR 8161, Institut de Biologie de Lille, Institut Pasteur de Lille, Université de Lille 1, Université de Lille 2, Lille, France. <sup>2</sup>Institut de Pathologie, CHR-U de Lille, Université de Lille 2, Lille, France.

**Corresponding Author:** David Tulasne, CNRS UMR 8161, Institut de Biologie de Lille, Institut Pasteur de Lille, Université de Lille 1, Université de Lille 2, SIRIC ONCOLille, FRE3642, 1 rue Pr Calmette, Lille 59021, France.

doi: 10.1158/0008-5472.CAN-14-1932

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followed by stalk shaped PSI and IPT domains (6). The intracellular region contains the tyrosine kinase domain and a C-terminal tail necessary to recruit signaling proteins following Met activation by HGF/SF binding (7).

Met has two binding sites for HGF/SF: the IPT3 and IPT4 domains bind the N domain of HGF/SF and the SEMA domain binds SPH domain of HGF/SF. HGF/SF dimerizes via top and tail interactions of N and K1 domains, resulting in Met dimerization (Fig. 1B; ref. 8). HGF/SF can also bind to sulphate glycoproteins, like heparins, which improve its oligomerization and thus Met dimerization.

### HGF/SF-Met involvement in development and tissue homeostasis

Upon HGF/SF binding, Met can induce various biologic responses, including proliferation and motility, at the origin of their discovery, but also, survival, morphogenesis, angiogenesis, or neurite growth. All these effects are consistent with their role *in vivo*. Indeed, description of HGF/SF and Met expression patterns suggested from early 1990s their importance in formation and homeostasis of numerous tissues. At the early stages of development, HGF/SF and Met display a concomitant expression in endoderm and mesoderm and likely act in an autocrine fashion. From organogenesis, Met is detected in epithelial cells of many organs (liver, kidney, lung, skin), whereas HGF/SF is expressed by adjacent mesenchymal cells. This complementary expression suggests that HGF/SF contributes in a paracrine fashion to the development of epithelial organs (9). Besides, Met is expressed in some myoblasts and neuronal precursors, suggesting a role in setting of muscular and nervous structures as well.

During the same decade, knockout mice confirmed HGF/SF and Met crucial role in embryogenesis, as *met* and *hgf/sf*-null mice die *in utero* at E15 and express similar phenotypes, confirming their functional link. Organization defect of the placental labyrinth, responsible for impaired exchanges between maternal and fetal blood, explains such lethality (10, 11). Embryos also display reduced liver size, a consequence of decreased cell survival and proliferation and a lack of muscles in limbs, diaphragm, and tongue resulting from the

impaired migration of myogenic precursors. In the last few years, conditional Met knockout provided additional information about its role in the formation of individual structures. Thus, Met invalidation in lung severely impairs formation of airspaces (12), and its extinction in central nervous system induces loss of motor neurons innervating pectoral muscles (Fig. 1C and D; ref. 13). In adult, Met is crucial for epithelial tissue homeostasis as conditional Met invalidation impairs regeneration of liver, kidney, or skin (14). On the contrary, injury of kidney, spinal cord, or liver is followed by a rise in HGF/SF and its ectopic addition favors their regeneration.

### Met and downstream signaling pathways' activation

Met receptor signaling began to be described from the early 1990s, shortly after its identification as the receptor for HGF/SF. Met interaction with its ligand favors its dimerization and its autophosphorylation on two tyrosine residues in its catalytic domain (Y1234 et 1235). Other tyrosine residues located outside the kinase domain are then phosphorylated, notably tyrosine 1003 in the juxtamembrane domain and tyrosines 1349 et 1356 at the C-terminal tail. Those latter residues are able to bind many effectors, such as Gab1, Grb2, Shc, PI3K, Src, STAT3 or PLC $\gamma$ . This multisubstrate docking site plays a key role in Met-induced biologic responses, as its mutation in mice triggers phenotypes similar to those of Met-deficient mice (15).

Following the recruitment of these various adaptors by Met, several signaling cascades will be triggered via other downstream proteins, which can be associated to biologic responses. For instance, small G proteins such as Ras, Rac, p21-activated kinase (PAK), and RAP1 control the cytoskeletal rearrangement and motility in response to HGF/SF (16). With regard to PI3K, its activation is involved in motility and also plays a key role in cell survival via Akt activation (17). Met is also able to orientate p53 activity toward survival via a cascade implying Abl and p38-MAPK (18).

### Met internalization and cleavages: beyond degradation

Since 2000, various mechanisms negatively regulating Met have been evidenced. Met autophosphorylation on Y1003 leads to Cbl E3 Ubiquitin ligase recruitment and to Met

**Figure 1.** Timeline of the main discoveries on Met receptor from 1984 to nowadays. We describe here several milestones that allow the research on Met receptor to move from bench to bedside from 1984 to nowadays. We divided them into three parts: the physiologic role and signaling pathway downstream of Met (pink background color); Met involvement in tumorigenesis (green background color); and the design and evaluation of Met-targeted therapies (blue background color). A, the Met receptor is constituted by  $\alpha$  and  $\beta$  chains linked by a disulfide bridge. The extracellular part is composed of the SEMA domain shared between the two chains, a PSI domain (plexins, semaphorins, and integrins) and four IPT domains (immunoglobulin-like fold shared by plexins and transcription factors). B, the crystal structure of the Met SEMA domain with its ligand revealed that two HGF/SF molecules interact via their N and K1 domains associated head to tail. Each molecule of HGF/SF interacts with one SEMA domain via a type 2:2 interaction (two receptors for two ligands; ref. 8). C, the importance of HGF/SF and Met during embryonic development and in adult has been shown through inactivation of their genes in mice. Conditional extinction of Met in nervous system prevents survival of a motoneurons subgroup innervating the pectoralis minor muscle, leading to motor defects (13). D, Met invalidation in lung severely impairs airspaces formation (12). E, FISH MET/CEP7 (Zytovision Dual Color; Zytolight SPEC MET/CEN7). Invasive adenocarcinoma of acinar type showing a high copy number of *met* gene. The Met hybridization results in green signals while the CEP7 hybridization results in red signals. F, example of immunostaining with an antibody directed against Met (anti-Total c-MET SP44 CONFIRM; Ventana, Roche) on lung adenocarcinoma. Left, an invasive adenocarcinoma of acinar type without expression of Met. Entrapped normal epithelium shows moderate level of Met expression (2+). Right, an invasive adenocarcinoma of acinar type with high level of Met expression (3+; magnification,  $\times 25$ ). G, example of immunostaining with an antibody directed against phospho-Met (clone D26; Cell Signaling Technology; Tyr 1234/1235) showing high level of expression of phospho-Met in an adenocarcinoma score Met 3+. H, inhibition strategies against Met aim at interfering with HGF/SF-Met interaction or with Met tyrosine kinase activity. Inhibitors of the ligand-receptor interaction are blocking antibodies directed against HGF/SF or Met extracellular region, or antagonists able to bind Met without activating it, such as HGF/SF subdomain derived from natural variant NK2 or subdomains of Met used as decoy against HGF/SF. The TKIs are mainly ATP mimetics able to occupy Met ATP pocket to inhibit its activity.



ubiquitinylation. Met receptor is then internalized and degraded (19). Y1003 mutation promotes Met activation and transforming capacities, highlighting the importance of this attenuation process.

Other negative regulation sites lie in the juxtamembrane domain, such as Serine 983, whose phosphorylation by protein kinase C downregulates Met activity (20). This domain also contains several cleavage sites by proteases. In absence of its ligand and under stress conditions, Met is thus cleaved by caspases into an active fragment able to amplify cell death by favoring mitochondrial permeabilization (21). Via this proapoptotic potential opposed to its antiapoptotic activities in response to its ligand, Met belongs to the dependence receptor family. Met is also submitted to a constitutive cleavage in its extracellular domain by ADAM family metalloproteinases, followed by a second cleavage by  $\gamma$ -secretase in its juxtamembrane domain (22). The so-created intracellular fragments then undergo proteasomal and lysosomal degradations, which participate in the regulation of the receptor half-life.

Met internalization is not only synonymous of degradation but also actively participates in its signaling. Indeed, along its trafficking from early to perinuclear endosomes, Met colocalizes with STAT3 transcription factor and allows its proper nuclear translocation and transcriptional activities, involved in Met-induced morphogenesis and cellular transformation (23).

### Met social network

During the last decade, Met unveiled to us its multiple partners at the plasma membrane, required for an efficient activation of signaling pathways. Met interaction with  $\alpha 6 \beta 4$  integrin is thus important for cellular invasion in response to HGF/SF (24). Met can also associate with  $\alpha 3 \beta 1$  integrin, which contributes to Gab1 and PI3K recruitment and results in the control of the Wnt pathway (25). CD44v6 isoform interaction with Met not only promotes HGF-induced Met phosphorylation but also a more efficient activation of the Ras–MAPK pathway via the association between CD44v6 intracellular part and ERM proteins (Ezrin, Radixin, and Moesin; ref. 26). On the other side, the interaction of Met with plexin-type receptors favors invasion or angiogenesis induced by semaphorin 4D or 5A, respectively (27). Recently, it has been shown that activated Met/tensin-4 interaction favors receptor stability and downstream signaling. Their correlated expression in colon and ovarian carcinoma suggests that TNS4 plays a critical role in Met stability in these cancers (28). Met can also hold a dialogue with other RTKs, such as EGFR, which is especially relevant in tumor cells; this notion will be developed later in this review. Altogether, these data highlight how Met action is highly dependent on its relationships with other membrane partners, and such interactions should probably be taken into account when elaborating Met-targeting therapies.

### Step 2: Met Involvement in Tumorigenesis

HGF/SF–Met abilities to induce proliferation, protection from apoptosis, angiogenesis, and motility are nothing better than many properties potentially contributing to tumorigenesis. Met oncogenic role was initially evidenced in experimen-

tal systems, starting from Met discovery in a screening for cellular transformation. The formal link between Met aberrant activation and cancer development in humans was established a bit more than a decade later, with the identification of Met mutations associated with hereditary renal papillary carcinomas (29). Since then, more than 150 somatic point mutations in *met* sequence have been evidenced in various cancers (source: Catalogue of Somatic Mutations in Cancer). Some of these mutations activate the kinase domain, favor its ligand-induced activation or induce Met recycling at the membrane (30). Consistently, transgenic mice harboring Met mutations in the kinase domain develop several types of cancers (lymphomas, carcinomas, and sarcomas; ref. 31).

Met overexpression is also detected in various cancers and can affect up to 80% of patients suffering from gastric or renal cancers and usually correlates with a poor prognosis (32). Many mechanisms can be involved in Met overexpression. Beyond gene amplification, several oncogenes such as Ras, Ets-1, or Pax-5 increase Met transcription (Fig. 1E and F; refs. 33, 34). Met expression is also repressed by miRNAs such as miR34b, which is controlled by p53 and could link p53 inactivation frequently found in cancers with Met overexpression.

Met aberrant activation can also result from an overexpression of its ligand HGF/SF, which was notably observed in breast, gastric, colon, or lung cancers and associated with a poor prognosis (35). Moreover, recent studies have highlighted a key role for HGF/SF secreted from the tumor microenvironment in the development of drug resistance, especially to RAF inhibitors (36).

Last but not least, with regard to anticancerous therapies, Met overexpression has been observed in response to EGFR-targeting drugs, such as gefitinib in lung cancers (37) or cetuximab in colorectal cancers (38). The activation by Met of downstream signaling pathways actually allows to compensate for EGFR inhibition, especially since signaling networks controlled by EGFR and Met display many similarities. Thus, HGF/SF–Met deregulation has demonstrated to play a key role not only in the development of many cancers, but also in drug resistance mechanisms implemented by tumor cells.

### Step 3: Design and Evaluation of Targeted Therapies against Met

Inhibition of the HGF/Met signaling pathway appeared as an obvious therapeutic strategy since the beginning of 2000. Preclinical experiments assessed the therapeutic potential of two approaches that aimed at disturbing the physical interaction between the Met receptor and its HGF/SF ligand using blocking antibodies or inhibiting the kinase activity of the receptor using small-molecule tyrosine kinase inhibitors (TKI; Fig. 1H). The level of confidence placed by the pharmaceutical groups in these strategies is highlighted by the number of clinical trials launched in these last years with 95 trials registered in [www.clinical.gov](http://www.clinical.gov) in 2011 to more than 240 in 2014. These trials, mainly phase I/II, evaluate the safety and therapeutic potential of 23 different compounds and, interestingly, five compounds already made it to a phase III trial.

Met inhibitors are essentially ATP mimetics that compete with the ATP for access to the kinase-active site then blocking the receptor activity. The first developed Met inhibitor, K252a, a staurosporine analogue, displays a weak selectivity as it inhibits multiple kinases (39). It was rapidly replaced by more specific ATP competitors such as PHA-665752 (40), still widely used in basic research. Tivantinib is the sole Met-specific TKI currently in phase III efficacy evaluation. Although the first phase III trial was prematurely terminated in 2012 due to a lack of clinical benefit in patients with non-small cell lung cancer (NSCLC) compared with a tivantinib and erlotinib association (EGFR-targeting TKI), an improvement of progression-free survival of patients with Met-positive tumors was reached. Therefore, additional phase III trials are ongoing taking into account the Met expression status of the targeted tumors.

Other Met inhibitors with a broader spectrum of action are in their later stage of drug development or even approved by the drug regulatory authorities. For instance, crizotinib, an inhibitor of Met, ALK, and ROS1 kinases was approved for patients with NSCLC harboring ALK translocations. Its efficacy to inhibit multiple kinases is probably a major asset to prevent the development of drug resistance particularly due to *met* gene amplification (41). Moreover, encouraging preliminary results were obtained in patients with Met-positive gastroesophageal adenocarcinoma, thus predicting a more extensive clinical use of the TKI (42).

Development of monoclonal blocking antibodies, which started in 1998, is another promising strategy to inhibit the HGF/Met pathway. Directed against the ligand or the extracellular domain of the receptor, they prevent the HGF/Met interaction. As an example, AMG102/ritumumab, an anti-HGF antibody, is under evaluation in a phase III trial for patients with Met overexpression advanced gastric or esophageal junction carcinomas.

Against Met, the monoclonal humanized antibody MetMab/onartuzumab was originally designed with only one arm to prevent the receptor dimerization responsible for its autoactivation. Crystal structure revealed that onartuzumab binds the Met SEMA domain, blocking the interaction with HGF/SF  $\alpha$  chain (43). Despite encouraging results obtained in preclinical xenograft models and in a phase II trial in NSCLC with an onartuzumab plus erlotinib cotreatment (44), the clinical future of the antibody is uncertain. Indeed, the phase III trial for this cotreatment in patients with advanced NSCLC Met-positive was stopped prematurely for futility.

Interestingly, other monoclonal antibodies directed against the extracellular domain of Met exert their inhibitory action without interfering with the ligand-receptor interaction. DN30 monoclonal antibody, for example, favors Met degradation in mouse models by activating Met cleavages by metalloproteases and  $\gamma$ -secretase complex, thus reducing the tumor growth (45, 46).

At a preclinical level, additional strategies to inhibit the HGF/Met signaling are inspired from the natural HGF/SF variant NK2, an antagonistic molecule capable of binding Met without activating it (Fig. 1H). For instance, NK4 constructed with the N and first four K domains of HGF/SF, inhibits tumorigenesis and angiogenesis in mouse models (47). Simi-

larly, antagonistic molecules corresponding to Met extracellular region or to subdomains (i.e., SEMA), are developed to generate an HGF/SF decoy (48).

Preclinical models already anticipate potential mechanisms of resistance against Met-targeted therapies. An increased *met* gene copy number has thus been highlighted in cancer cells resistant to monovalent DN30 antibody (49), as well as *met* and *KRAS* amplification mediating acquired resistance to Met TKIs (50). Another study has evidenced that activation of HER family members allowed the resistance to PHA665752 (51), mirroring the role of Met in the resistance to EGFR-targeted therapies, probably due to the high similarity between signaling networks downstream these receptors. Finally, in mice models and cell cultures, acquired resistance to crizotinib involved a mutation in the Met kinase activation loop, which could alter interaction with the TKI (52). Two other key aspects to consider in the emergence of cancer resistance to targeted therapies are the preexistence and selection by the treatments of clones harboring gene amplifications (53) and the role of environmental growth factors in innate and acquired resistance to kinase inhibitors (54).

With this in mind, one can try to think about the last failures of phase III clinical trials with Met-targeting agents, onartuzumab and tivantinib. Both treatments did not meet their primary endpoint of increasing the overall survival of patients with NSCLC in combination with erlotinib, although they had shown strong efficiency in preclinical studies of mice xenografts with autocrine or paracrine HGF-Met stimulation loops. One may first reflect about the patients recruited in the trials, which were in their second- or third-line of treatment, thus meaning that previous treatments may have promoted the emergence of resistant clones. New phase III trials are ongoing, with tivantinib proposed in monotherapy as a second-line treatment in hepatocellular carcinomas, and with onartuzumab  $\pm$  erlotinib as a first-line treatment in NSCLCs, which may improve their therapeutic efficacy. Moreover, it has to be noted that NSCLCs represent tumors in which Met is overexpressed in nearly half of the patients as evaluated by immunohistochemistry (IHC). However, this overexpression does not necessarily mean that Met is activated in these tumors, thus leading to an overestimation of likely responders. Met phosphorylation, notably in its kinase domain, better reflects Met activation. Several specific antibodies recognizing Met tyrosine phosphorylation can be used by IHC (Fig. 1G), and it has been shown that only about 5% of the NSCLCs display Met tyrosine phosphorylation while receptor overexpression is much higher (55). Nevertheless, the stability of these phosphorylation sites *ex vivo* may require particular care for a routine use in clinic. HGF/SF status in human lung cancer patients represents another key biologic feature that is so far not exploited but should prove to be useful, especially for strategies aimed at interfering with the ligand-receptor interaction. It has also recently been evidenced that Met mutations in the exon 14 are more frequent than originally thought in NSCLCs (56). The impact of Met-targeted therapies on cells bearing this kind of alteration has to be determined.

Results of ongoing clinical trials revealed this year at the ASCO meeting suggest that *met* gene amplification could be as

well a good predictive biomarker. Patients with NSCLC displaying *met* gene amplification with a ratio of 5 or more *met* gene copies per cell were thus prospectively selected for a phase I clinical trial evaluating crizotinib (Met and ALK inhibitor). Crizotinib induced an objective response rate in about two thirds of this restricted subgroup (57). Similar promising responses on *met*-amplified patients were reported also for Met inhibitor AMG337 in gastric cancer (58). These studies should be now strengthened from larger initial cohorts to have more patients displaying *met* gene amplification.

Altogether, these data suggest that selecting the right patients is critical to get successful Met-targeted therapies. A multiplexed molecular diagnostic of Met/HGF status may be required to identify those tumors in which Met represents an Achilles heel. From that point of view, the stratified analysis of last phase III trials is expected with much impatience, to understand whether Met status and accompanying genetic alterations can retrospectively identify subpopulations responsive or refractory to such treatments. At the same time, we can envision that different Met-targeted therapies may profit to distinct patient populations.

## Perspectives

The question is frequently asked about the time necessary to move a biomarker from bench to bedside. This time highly depends on the nature of the target. Abl inhibition with drugs such as Gleevec took four decades from the observation of Philadelphia chromosome, the identification of bcr-abl fusion product in the early 1980s, to the development of clinical drugs (for review, see ref. 59). The huge progresses made since then in the field of molecular biology should help fastening the transition from bench to bedside. Anyhow, some promising targets are still waiting for therapeutic drugs. For example, Myc ubiquitous expression in most proliferating cells raise toxicity issues, and strategies to disrupt Myc–Max interaction are hindered by the large and relatively featureless surface of interaction (for review, see ref. 60). In parallel, RAS mutations in cancers were discovered nearly at the same time, as was Met, but their therapeutic targeting was so far limited by the high affinity of GTP to RAS at picomolar levels. In contrast, ALK rearrangements in NSCLCs benefited from the previous clinical development of crizotinib as a Met inhibitor (but it also inhibits ALK) to become biomarkers and targets of efficient crizotinib treatments only 3 years after their discovery.

For Met, 30 years separate its discovery in 1984 to the actual promising clinical trials. In three decades, the signaling network required for embryonic development and epithelial organs regeneration was finely decorticated. In parallel, Met

deregulation in tumorigenesis was fully demonstrated and associated with a poor prognosis in numerous cancers ([www.vai.org/Met/](http://www.vai.org/Met/)). Then, pharmacologic inhibitors were rapidly designed and the first administration to human began in 2005. Nowadays, two multiple TKIs are already prescribed and a few Met-specific inhibitors are currently under clinical testing. These impressive achievements should not, however, detract from the work that still remains. Indeed, fundamental research is still fuelling our knowledge of Met. For instance, the importance of Met relationships with other membrane proteins has been again evidenced recently with the involvement of tensin-4 in Met stabilization and transformation, or by the "liaisons dangereuses" between Met and EGFR in lung cancers. Moreover, even if Met role in development has been well documented for almost 20 years, its involvement in lung alveolar formation or in specific muscle innervation was demonstrated only recently. The use of conditional animal models will more than likely lead to the identification of Met participation to the development and cell homeostasis of other organs.

With regard to signaling mechanisms, despite huge progresses made in the last decade, Met signaling networks are still far from being fully elucidated in the various settings in which Met is involved. Moreover, a new paradigm is emerging with the identification of distinct phenotypes elicited whether Met is activated via its overexpression or by the binding of its ligand (61). All these novel insights in Met action will probably lead to a better understanding of Met complex activity in cancers. This should help to refine therapeutic strategies and to overcome the development of resistance to Met targeting agents, already illustrated in cellular models.

The combined efforts which have allowed moving Met from the bench to the bedside in 30 years will now meet the challenges of identifying the most efficient therapeutic window and limiting the development of resistance to Met-targeted therapies.

## Disclosure of Potential Conflicts of Interest

D. Tulasne receives speakers' bureau honoraria from Roche. No potential conflicts of interest were disclosed by the other authors.

## Grant Support

This work was supported by the CNRS, the Institut Pasteur de Lille, and INSERM, and by grants from the Ligue Contre le Cancer, Comité Nord, the Association pour la Recherche sur le Cancer, the Institut National du Cancer, the Cancéropôle Nord-Ouest and the Site de Recherche intégrée sur le cancer de Lille, SIRIC ONCOLille.

Received June 30, 2014; revised September 5, 2014; accepted September 7, 2014; published OnlineFirst November 19, 2014.

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## Thirty Years of Research on Met Receptor to Move a Biomarker from Bench to Bedside

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*Cancer Res* 2014;74:6737-6744. Published OnlineFirst November 19, 2014.

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