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The RON Receptor Tyrosine Kinase in Pancreatic Cancer Pathogenesis and Its Potential Implications for Future Targeted Therapies

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Abstract

Pancreatic cancer remains a devastating disease with a mortality rate that has not changed substantially in decades. Novel therapies are therefore desperately needed. The RON receptor tyrosine kinase has been identified as an important mediator of KRAS oncogene addiction and is over-expressed in the majority of pancreatic cancers. Preclinical studies that inhibition of RON function decrease pancreatic cancer cell migration, invasion and survival and can sensitize pancreatic cancer cells to chemotherapy. This article reviews the current state of knowledge regarding RON biology and pancreatic cancer and discusses its potential as a therapeutic target.

Introduction

Pancreatic cancer is one of the most lethal human malignancies. Despite recent advances in our understanding of pancreatic cancer biology, five year survival for this disease continues to be approximately 6%¹. Most cases of pancreatic cancer are diagnosed at advanced stage, and less than 20% are amenable to surgical extirpation². Even in cases of potentially curative resection, the incidence of systemic and local recurrence is high (80%), with the majority of patients developing recurrent disease within 1 year of surgery³. Five year survival for operated patients therefore remains a disappointing 15–20%³.

Until recently, gemcitabine has been the first-line therapy for advanced pancreatic cancer. Previous clinical trials have investigated the use of gemcitabine in combination therapy with additional cytotoxic agents and biologic agents, such as 5-fluorouracil, capecitabine, cisplatin, irinotecan, oxaliplatin, cetuximab and bevacizumab, all of which failed to demonstrate any survival benefit^{4–11}. Two recent Phase III trials separately compared gemcitabine to a combination of 5-FU/leucovorin, oxaliplatin, irinotecan (FOLFIRINOX)

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and gemcitabine/nab-paclitaxel. These studies each demonstrated improvements in overall survival to 11 versus 7 and 8.5 versus 6.8 months, respectively^{12,13}. Despite these recent encouraging results, there remains an urgent need for the development of more effective therapeutic strategies in this disease. Ideally, uncovering the molecular mechanisms that underlie pancreatic carcinogenesis and metastatic progression will reveal potential therapeutic targets that may result in better tolerated and more effective cancer therapies.

Of the molecules important to epithelial tumorigenesis, none have been as successfully targeted as the receptor tyrosine kinases (RTKs), including the epidermal growth factor receptors (EGFRs), PDGFR, VEGFR, IGFR, C-KIT and others. These signaling molecules are frequently and aberrantly expressed in human cancers, and activate intracellular pathways that regulate cell growth, survival, migration and invasion^{14,15}. Both small molecule kinase inhibitors, as well as antibodies directed against these receptors and/or their ligands have been developed. These agents have demonstrated therapeutic efficacy in a variety of human malignancies. As a result, targeting RTKs remains an attractive strategy for the further development of new cancer therapies.

RON, *recepteur d'origine nantis*, is a RTK, belonging to the MET proto-oncogene family¹⁶. Altered RON expression and activation has been associated with cancer progression and decreased survival in many human cancers, including breast, colon, gastric, hepatocellular, non-small cell lung, bladder, renal cell, and ovary^{17–26}. Studies from multiple laboratories have begun to investigate the role of RON in pancreatic carcinogenesis and therapeutic resistance. In this review, we will summarize the important emerging evidence that suggests a critical role for RON in the pathogenesis of pancreatic cancer, and the future clinical applications of RON-targeted therapy will be discussed.

RON Receptor Structure and Ligand

RON, also known as plasminogen-related growth factor receptor 2 (PRGFR-2), CD136, or macrophage stimulating protein receptor (MST1R), is a member of the MET proto-oncogene family of RTKs. This family also includes c-Met, Stk (a murine homolog of RON), and c-Sea (chicken cell–surface receptor)^{16,27}. RON and c-MET are the only MET family members expressed in humans. The human RON gene comprises 20 exons and 19 introns, and is located on chromosome 3p21. It was initially isolated and identified via the screening of complementary DNA (cDNA) libraries prepared from human foreskin keratinocytes¹⁶. RON is synthesized as a single-chain precursor, pro-RON, which is then cleaved into a 40-kDa alpha chain and a 150-kDa beta chain²⁸. A single disulfide bond links these chains to form a 180-kDa heterodimer. The alpha chain is completely extracellular, whereas the beta chain contains extracellular, transmembrane, and intracellular regions composed of a functional tyrosine kinase segment as well as multiple regulatory elements (Figure 1). The extracellular region of the RON receptor contains the SEMA domain, which regulates ligand binding, receptor dimerization, and phosphorylation^{29,30}. The RON receptor shares approximately 60% structural homology with the c-MET receptor³¹. As a result, RON and c-MET have overlapping functions, signaling, and engage in cross-talk³².

The ligand for RON is macrophage stimulating factor (MSP), which is also known as HGF-like protein (HGFL) or scatter factor (SF-2)³³. MSP was originally discovered as a serum protein that enhanced murine macrophage activity in response to complement factor C5a³⁴. The MSP gene is also located on chromosome 3p21 in close proximity to the RON gene. The c-MET receptor, as well as its ligand, hepatocyte growth factor (HGF), are expressed in various tissues and cell types. In contrast, RON is more restricted and is minimally expressed in pancreatic epithelial cells²⁰. Tissue macrophages, bone marrow megakaryocytes, osteoclasts, and neurons are also known to express RON^{35–38}. Hepatocytes are the major source of MSP, which is secreted in biologically inactive form, pro-MSP. This protein undergoes proteolytic cleavage in tissues, releasing a biologically active protein molecule capable of binding to and activating the RON receptor³⁹. Several enzymes of the blood clotting cascade (including kallikrein, factor Xia, and factor XIIa), as well as tissue and macrophage surface proteases can cleave pro-MSP into the active form of MSP^{40,41}.

Multiple splice variants of the RON receptor have been identified in various cancer tissues. These include RON 165, RON 160, and RON 155, RON 170, RON 110, and RON 52^{42–44}. Additionally, a truncated RON receptor (short-form RON; sf-RON) lacking a majority of the extracellular domain has been described. Short-form RON is constitutively active, leading to increased intrinsic tyrosine kinase activity in both normal and malignant human tissues⁴⁵.

Oncogenic Signal Transduction of RON

Multiple mechanisms of aberrant RON signaling have been described. Classically, ligand binding induces receptor dimerization, forming either homodimers with additional RON receptors on the cell surface or heterodimers with alternative RTKs. Alternatively, RON overexpression on the cell surface can lead to spontaneous homodimerization and autophosphorylation²¹. Also, RON transactivation via dimerization with other activated membrane receptors, mutations in the RON kinase domain, as well as spliced variants of the RON receptor, can lead to constitutive activation^{46–48}. Receptor activation triggers a downstream signaling cascade that ultimately results in activation of multiple molecules and pathways, including β -catenin/TCF-4, Src, Ras/Raf/MEK/ERK/MAPK, JNK/STAT, SMAD/TGF β , and PI3K/AKT^{28,49–51}. These pathways have been well characterized in the literature, and are known to be key regulators of multiple cellular processes critical for tumorigenesis. Aberrant RON signaling has been linked to increased cellular proliferation, branching morphogenesis, cell scattering, migration, epithelial to mesenchymal transition (EMT), adhesion, invasion, inhibition of apoptosis and anoikis, and metastasis (Figure 1).

RON Expression in Human Pancreatic Cancer

The demonstration of RON overexpression and constitutive activation in several epithelial malignancies, including breast (47%), colorectal (59.2%), and ovarian carcinoma (55%), has supported the potential role of RON in tumor progression and metastasis in human cancer^{21,42,52}. Until recently, the role of RON signaling in pancreatic cancer was unknown. RON expression has been investigated in pancreatic cancer cell lines. According to flow cytometric, western blot, and gene logic analyses, BXPC-3, Capan-2, HPAC, HPAFII,

L3.6pl, Hs766.T, ASPC-1, and CFPAC-1 express the RON receptor. However, RON expression in MIA-PACA-2 is minimal⁵³. Recent studies have demonstrated that RON is overexpressed and activated in human pancreatic tumor specimens when compared with non-malignant pancreatic tissue²⁰. Immunohistochemical analysis shows that 33–96% of human pancreatic cancer specimens expressed RON^{19,53,54}. The incidence of RON expression appears to increase during pancreatic carcinogenesis. RON is rarely expressed in normal pancreatic ducts or early pancreatic intraepithelial neoplasia (PanIN1). However, nearly all high grade PanINs (PanIN 2–3), as well as primary and metastatic pancreatic cancers abundantly express phosphorylated RON protein, suggesting a potential role for RON in pancreatic carcinogenesis and metastatic progression^{20,54}. Greater than 90% of human pancreatic cancers harbor KRAS mutations, which is thought to be the most potent driver of this disease⁵⁵. Unfortunately, effective therapeutic strategies targeting mutant Kras have been elusive. Recently, RON has been identified as an important mediator of KRAS oncogene addiction, and its cell surface expression as a cancer specific RTK makes it an attractive therapeutic target⁵⁶.

RON Signaling and Pancreatic Carcinogenesis

The increasing frequency of RON expression in high grade PanIN lesions, as well as primary and metastatic pancreatic tumor specimens suggests that aberrant RON signaling may play a role in tumor formation and metastasis²⁰. We have developed a transgenic mouse model that incorporates RON overexpression in the setting of oncogenic Kras. This model was developed using a pancreatic specific promoter, Pdx-1, to target RON overexpression specifically to the pancreas (Pdx-1-RON), and results in pancreatic tumor development at long latency (18 months). RON overexpression in the presence of mutant Kras [(Kras LSL-G12D × Pdx-1-RON) × Pdx-1-cre, RCK] accelerates PanIN progression to primary and metastatic pancreatic cancer. In this model, PanINs were detectable at 6 weeks, with invasive carcinoma and metastasis appearing as early as 6 months compared to Kras LSLG12D × Pdx-1-cre (CK) controls (one year average latency to tumor development)⁵⁷. This model supports a causal role for RON signaling in pancreatic carcinogenesis, and further validates the RON receptor as a potential therapeutic target⁵⁷.

Other work has demonstrated that the RON receptor is highly expressed in pancreatic cancer stem cells (CSCs) characterized by CD44, CD24, and epithelial-specific antigen (ESA) expression⁵⁸. Pancreatic CSCs are thought to contribute to tumorigenesis via hypothesized mechanisms of tumor initiation, drug resistance, and metastasis. Early metastasis and acquired chemoresistance are two of the major clinical challenges in pancreatic cancer, and CSCs may contribute to the aggressive features of this disease^{59,60}. Therefore, elevated RON expression in CSCs (CD24⁺/CD44⁺/ESA⁺) suggests that RON may be a beneficial molecular target. Taken together, these results prove a solid preclinical background for validating the therapeutic efficacy of anti-RON therapeutic strategies.

RON Signaling in Epithelial to Mesenchymal Transition (EMT) and Migration

Cells undergoing EMT are known to be highly mobile and invasive, and EMT is associated with cancer cell invasion and malignant metastasis⁶¹. EMT is characterized by the

development of a spindle-like cell morphology, loss of epithelial cell surface markers (i.e. E-cadherin), and increased expression of mesenchymal proteins (i.e. vimentin and α -smooth muscle actin)⁶². In one study, MSP stimulation and subsequent RON activation in L3.6pl pancreatic cancer cells resulted in altered cell morphology similar to EMT. These cells became spindle-shaped, with a loss of polarity, increased intercellular separation, and increased pseudopodia formation⁵⁴. Ribosomal protein S6 kinase-2 (RSK2), a downstream signaling protein of the Ras-Erk1/2 pathway, was shown to be the principal molecule linking MSP induced RON signaling to EMT. Additionally, specific siRNA-mediated silencing of RSK2 in L3.6pl pancreatic cancer cells significantly inhibited the MSP-induced EMT phenotype and cell migration⁶³.

In a recent study, we found that RON also binds to and activates Insulin-like Growth Factor-1 Receptor (IGF1-R). IGF1-R signaling induces pancreatic cancer cell migration that is dependent upon RON signaling⁶⁴. Additionally, MSP stimulation induced the RON receptor to complex with plectin and Integrin beta 4 (ITGB4). This complex formation initiates a signaling cascade that leads to breakdown of hemidesmosomes and enhancement of pancreatic cancer cell migration. As plectin was recently identified as a putative biomarker in pancreatic cancer, the relationship between RON and plectin is intriguing, yet remains incompletely understood⁶⁵.

Angiogenesis and VEGF

Multiple preclinical studies have suggested vascular endothelial growth factor (VEGF) as a potential target in treating pancreatic cancer, although clinical trials to date have failed to demonstrate efficacy of VEGF targeted agents (i.e. bevacizumab) in this disease^{66,67,4}. Investigators have speculated that the decreased performance status of the study population, as well as other potential molecular mechanisms including drug resistance, tumor microenvironment effects, and inadequacy of cytotoxic therapies may have contributed to the failure of this and other clinical trials of angiogenesis inhibitors. These results may stem from a limited understanding of the role of angiogenesis in disease progression and the regulatory mechanisms that govern angiogenesis in the pancreatic tumor microenvironment.

The role of RON in mediating angiogenesis has not been thoroughly investigated, but limited studies suggest that RON may play a role in tumor angiogenesis. In one study, functional deactivation of the RON receptor dramatically reduced microvessel formation in a murine model of breast cancer compared with wild-type RON controls⁶⁸. Additionally, we have recently demonstrated that MSP-induced RON activation results in up-regulation of VEGF expression and secretion by pancreatic cancer cells. The conditioned media from pancreatic cancer cells directly augments MAPK signaling-dependent microtubule formation in human microvascular endothelial cells, suggesting a potential role for RON in the process of angiogenesis and tumor progression in pancreatic cancer⁶⁹.

Apoptotic Resistance

RON signaling has been shown to promote apoptotic resistance in multiple preclinical cancer models, including thyroid, gastric, and colon cancer^{18,19,70}. In the context of pancreatic cancer, subcutaneous L3.6pl-induced tumors treated with a RON monoclonal

antibody resulted in a 1.3-fold increase in apoptosis compared with the control group, assessed by TUNEL staining ($p < 0.03$)⁵¹. We have previously shown that inhibiting RON signaling in combination with gemcitabine treatment *in vitro* in BxPc3 cells increased caspase-3 activation by 32% compared to treatment with gemcitabine alone ($p < 0.05$)²⁰. Additionally, we found that shRNA-induced silencing of RON expression in pancreatic cancer cell lines (XPA-1 and FG) enhanced susceptibility to gemcitabine-induced apoptosis in a subcutaneous xenograft model⁷¹. RON-silenced gemcitabine treated tumors took nearly twice as long as RON-expressing tumors (also treated with gemcitabine) to reach 1000 mm³. This was three times longer than untreated tumors, regardless of RON expression ($p < 0.05$)⁷¹. These results suggest that inhibition of RON signaling may sensitize pancreatic cancer cells to chemotherapy. One recent study examined RON as a prognostic factor in pancreatic cancer and found no clear relationship⁷². However, the incidence of RON expression was extremely high, thus limiting the power of the analyses to discover any potential link between RON and therapeutic resistance.

RON and HSP90

Recently, heat-shock protein 90 (HSP90) has been identified as an important component of oncogenic signaling. HSP90 is a chaperone protein whose expression has been associated with the function of epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER-2), c-MET, mutated p53, AKT, ERK, and hypoxia-inducible factor (HIF)-1 α ⁷³. These data suggest that inhibition of HSP90 function may lead to the significant disruption of numerous signal pathways important in tumorigenesis⁷⁴. Interestingly, recent evidence shows that HSP90 antagonists, such as geldanamycins, may be suitable pharmacological agents in cancers that demonstrate aberrant RON signaling⁷⁵. Moser, et al. demonstrated that RON signaling could be disrupted by HSP90 inhibition in pancreatic cancer⁷⁶. In this study, the synthetic HSP90 inhibitor, EC154, resulted in an effective inhibition of cancer cell growth, down-regulated the RON receptor, and disrupted oncogenic MSP induced signaling *in vitro*. Additionally, treatment with EC154 significantly reduced tumor growth and down-regulated RON expression *in vivo*. In previous studies, we found that RON inhibition alone resulted in a transient decrease in therapeutic resistance. Resistant tumors emerged with recovery of RON expression and signaling associated with an increase in c-MET and EGFR expression⁷¹. Considering the potential role for c-MET and EGFR as mediators of resistance to RON directed therapy, HSP90 inhibitors may prove to be active agents given that they can potentially target the function of all three proteins.

Potential Application of RON Directed Therapy to Pancreatic Cancer

Various strategies have been described that effectively block RON signaling pathways, including 1) blocking the ligand-receptor interaction, 2) blocking anti-RON monoclonal antibody therapy to prevent receptor activation, 3) siRNA-mediated silencing of RON mRNA expression, and 4) small-molecule inhibitors (SMIs) that block the receptor tyrosine kinase domain by either ATP competitive or non-competitive inhibition⁷⁷.

Few monoclonal antibodies specifically targeting RON have been reported. MH Wang, et al. initially developed two agonistic murine monoclonal antibodies that are able to activate both

human WT RON as well as the splice variant RON 160⁷⁸. These antibodies were able to stimulate RON phosphorylation, as well as activate downstream signaling molecules including ERK1/2 and Akt. Additionally, these antibodies induced morphological changes and proliferation consistent with RON activation *in vitro*, and enhanced tumor growth *in vivo*. This same group has recently reported on the development of three additional antibodies, Zt/g4, Zt/f2, and Zt/c9, with inhibitory activity specific to the RON receptor. In particular, Zt/g4 was able to down-regulate RON expression through mechanisms of increased internalization and degradation via lysosomal and proteasomal pathways. Zt/g4 also demonstrated decreased phosphorylation of downstream ERK1/2 and Akt, as well as increased cell sensitivity to gemcitabine-induced cytotoxicity⁷⁹.

IMC-41A10 is a human monoclonal antibody identified by ImClone Systems Inc. that is capable of binding the RON receptor and blocking ligand binding without having agonistic activity on the receptor itself⁵³. This antibody successfully decreased MSP-induced RON phosphorylation under serum-starved conditions *in vitro*. Additionally, IMC41A10 was able to decrease phosphorylation of downstream effector molecules including ERK1/2 and Akt in multiple cell lines. IMC41A10 inhibited MSP-mediated cell migration, and showed significant inhibition of tumor growth in murine xenografts. A newer antibody with more favorable RON binding characteristics (RON-8, also developed by ImClone Systems Inc.) is now in Phase I trials. RON-8 binds the receptor with 10-fold greater affinity than the native ligand, MSP and has no agonist activity. Finally, other companies including XOMA Inc. and AVEO Pharmaceuticals Inc. have developed RON antibodies that are in preclinical testing at present, but none have yet advanced to the clinic.

The ideal method to effectively target RON signaling awaits further preclinical studies to ascertain the relevance of RON isoform expression to RON function *in vivo*. Further, it remains unclear whether agents with a broader spectrum of kinase inhibition, such as dual inhibitors of c-Met and RON, would be favored over more specific approaches to RON inhibition (i.e. monoclonal antibody therapy). Some specific combined c-MET and RON-directed therapeutics, such as monoclonal antibodies and SMIs, are currently in phase I and II clinical trials⁷⁷.

Compound I was the first small molecule TKI to be described with combined activity against both RON and c-Met. This molecule inhibited both HGF and MSP dependent cell signaling and cell growth *in vitro* in pancreatic and colorectal cell lines. Additionally, it demonstrated evidence of tumor growth inhibition in human colorectal and glioblastoma xenograft models that were either dependent on c-Met or demonstrated constitutive RON activation⁸⁰. To date, only one study has reported on the development of RON specific small molecule TKIs. Raepal, et al. (MethylGene) recently reported on the development of a series of potent tyrosine kinase inhibitors, in particular, compounds 4 and 13 from their study demonstrated unique specificity for the RON receptor with minimal activity against other human RTKs, including c-Met and VEGFR⁸¹. Compound 4 demonstrated potent inhibition of RON phosphorylation and cellular proliferation *in vitro*. Other agents that target c-Met have been developed that also display anti-RON activity. These are generally Class II tyrosine kinase inhibitors, including BMS 77607, AM7, XL880, XL184, and MGCD265, that have a more extended structure that binds the c-Met active site and spans

the distance between the kinase linker to the C-helix pocket⁸². These molecules tend to demonstrate activity against multiple kinase targets, including RON, with variable potency to that observed for c-Met.

Multiple lines of research implicate RON as a potential therapeutic target in pancreatic cancer. It is important to consider, however, that multiple previous clinical trials of targeted therapies have failed to improve survival outcomes in pancreatic cancer. For example, the VEGF neutralizing antibody, bevacizumab, failed to improve survival in advanced pancreatic cancer patients⁴. Similarly, cetuximab, an antibody directed against EGFR, also failed to improve outcome^{5,83}. Ultimately, the hypothesis that blockade of EGFR would interrupt EGFR-mediated signal transduction and lead to tumor suppression in pancreatic cancer has translated into only modest improvement in survival outcomes in clinical studies^{5,83}. A Phase III trial demonstrated a statistically significant improvement between combination therapy with erlotinib and gemcitabine compared to gemcitabine alone. However, the survival advantage was not meaningful enough (OS, 6.24 months in the erlotinib group vs. 5.91 months in the control group, $p=0.038$, PFS, 3.75 month vs. 3.55 month, $p=0.004$) to justify the routine application of anti-EGFR treatment in clinical practice, as erlotinib therapy was associated with more frequent and severe rash, diarrhea, infection and stomatitis⁸⁴.

There are numerous challenges associated with using strategically targeted therapies in the treatment of human cancers. First and foremost, most cancers, including pancreatic cancer, are heterogeneous, and have acquired multiple genetic mutations, aberrant protein expression profiles, and dysregulated signal transduction pathways by the time of clinical diagnosis due to their inherent genetic instability. In cases of clear oncogene addiction, where tumor cell survival can be demonstrated to be directly dependent on the mutation of a specific oncogene, the strategy of targeting that oncogene and the protein products of its aberrant transcription has a high likelihood of success. However, in most cases it remains unclear exactly which aberrant proteins, signal pathways, and genetic mutations are critical to tumor development, progression, and metastasis. Despite this complexity, the development of single agent, target-based therapies, such as trastuzumab and imatinib, against various receptor tyrosine kinases have demonstrated that these agents can be of significant clinical benefit in the treatment of solid human tumors. As we have gained experience using these molecules for treatment, it has become increasingly apparent that cross-talk between members of the various RTK families becomes an important mechanism of resistance to single agent therapy. As more drugs are developed and the specificity of those molecules for their targets is refined, it will be possible to begin engineering combined therapeutic strategies to more effectively inhibit the downstream signaling mechanisms essential for tumorigenesis. It is likely that in the future, patients will require an individually tailored combination of targeted treatments in order to obtain the maximal benefit of treatment.

Second, RTKs such as RON have multiple binding partners and initiate multiple signal transduction cascades that are difficult to define. Even when a potential drug is developed with high specificity for its target, it is often difficult to quantitate the downstream inhibition of signaling pathways in vitro, let alone confirm these effects in clinical treatment.

Third, particularly in the case of RON, the presence of various isoforms of the receptor makes the task of developing therapeutic molecules with high specificity for their target more challenging. The presence of a variety of splice variants and truncated forms of RON that exist as intracellular proteins also raises concern about the efficacy of drug delivery to the cytoplasm of these neoplastic cells. Most monoclonal antibodies are able to exert their anti-tumorigenic properties via a ligand-dependent mechanism. It remains unclear whether these antibodies would have similar effects in tumors that demonstrate constitutive RON activation or that express spliced variants that lack an extracellular ligand-binding domain.

Fourth, the significance of the tumor microenvironment, the tumor's ability to recruit and maintain an adequate vascular supply, and the variability in patient immune responses to the development of tumors is poorly understood. These likely represent critical components that will be of increasing importance as we migrate away from traditional cytotoxic therapies and toward more strategic molecular targets. It will be important to determine how the microenvironment effects drug delivery to the tumor tissue, as well as how changes in the surrounding tissues may act in a paracrine fashion to enhance and/or inhibit tumor progression. The ability of a tumor to stimulate angiogenesis is also a vital component of tumor survival. Additionally, the interaction between tumor cells and the surrounding lymphatic and vascular endothelial cells is of particular importance in tumors that demonstrate early and aggressive metastatic potential.

Finally, not all tumors within a given tissue type have the same profile of tyrosine kinase expression. A significant challenge to the use and development of RON-targeted therapies in the future will be the lack of available biomarkers to 1. identify the presence and/or significance of RON overexpression or aberrant activity in individual tumors, and 2. monitor the sensitivity and responsiveness of the tumor to targeted therapy. The identification of such biomarkers will be critical to the further development, testing and ultimately clinical application of RON directed therapies.

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Figure 1. Morphologic structure of the RON receptor tyrosine kinase and its potential downstream signaling pathways

RON is a trans-membrane receptor composed of a disulfide-linked 40 kDa α -chain and a 150 kDa β -chain. RON contains multiple extracellular domains including SEMA, PSI (Plexin, Semaphorin, Integrins), and four IPT (Immunoglobulin-like folds shared by Plexins and Transcriptional factors). The kinase domain with catalytic activity is located in the intracellular portion of the protein.

Table 1

Preclinical studies of c-Met/RON-directed targeted therapy in pancreatic cancer

Author	Year	RON-directed therapeutic design	Findings
O'Toole, et al ⁵³	2006	Anti-RON blocking antibody	<ul style="list-style-type: none"> - IMC-41A10, a human immunoglobulin G1 (IgG1) antibody that binds with high affinity to RON, effectively blocking its interaction with MSP. - IMC-41A10 inhibited tumor growth as a single agent and resulted in significant tumor regression when combined with Cetuximab in a BXP-3 xenograft model.
Camp, et al ⁵⁴	2007	Anti-RON blocking antibody	<ul style="list-style-type: none"> - RON MoAb significantly inhibited growth of L3.6pl subcutaneous tumors by approximately 60% (p<0.03). - RON MoAb decreased the volume of the orthotopic pancreatic tumors by approximately 40%, compared to control tumors treated with PBS (P<0.01).
Thomas, et al ²⁰	2007	Anti-RON blocking antibody	<ul style="list-style-type: none"> - MSP-induced RON activation increased pancreatic cancer cell migration, invasiveness, and apoptotic resistance. - Pre-incubation with inhibitory RON antibody abrogated this MSP-induced effect. - RON receptor inhibition sensitized pancreatic cancer cells to gemcitabine-induced apoptosis
Jin, et al ⁸⁵	2008	Anti-MET blocking antibody	<ul style="list-style-type: none"> - MetMab inhibits HGF-dependent signal transduction and cancer cell proliferation. - MetMab inhibited BxPC-3 tumor xenograft growth in a human HGF osmotic pump model. - MetMab significantly inhibited large orthotopic KP4 tumor growth and improved survival. - MetMab significantly reduced c-Met phosphorylation in orthotopic KP4 tumors with a concomitant decrease in Ki-67 staining.
Logan-Collins, et al ⁷¹	2010	RON silencing by using sh- RON	<ul style="list-style-type: none"> - The growth of pancreatic cancer xenografts was inhibited by shRNA silencing of RON. - Increased cancer cell susceptibility to apoptosis and sensitivity to gemcitabine were found in RON-silenced tumors compared with controls. - Kinase-switching was found in RON-silenced tumors after escape from gemcitabine-induced tumor regression via increased expression of pEGFR, p-met and increased total RON.
Padhye, et al ⁵⁸	2011	Anti-RON antibody-directing doxorubicin-immunoliposomes (Zt/c9-Dox-IL).	<ul style="list-style-type: none"> - Sustained RON expression, activation, and biological activities were found in pancreatic CSCs (CSCs+24/44/ESA). - Zt/c9 is highly specific and sensitive to human RON by recognizing epitopes in the RON extracellular domain. - Zt/c9-Dox-IL was effective in reducing viability in L3.6pl cells and CSCs+24/44/ESA. - Zt/c9-Dox-IL in combination with small molecules further reduced the viability of CSCs+24/44/ESA.