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Commentary

# Antiangiogenic agents and targets: A perspective

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ABSTRACT

The first generation of clinically useful antiangiogenic agents focused on VEGF and targets in the VEGF pathway. The strengths and limitations of these therapeutics are now clear. Some tumors do not respond to VEGF-directed therapies de novo and others become non-responsive or resistant over time by switching to other angiogenic pathways. The next generation of angiogenesis-directed therapeutics will expand the field beyond the VEGF pathway and become more disease selective. Placental growth factor, a protein closely related to VEGF, is induced as tumors lose responsiveness to VEGF-directed therapies. Angiopoietins 1 and 2 are being targeted with a unique peptibody, a human recombinant Fc constant region fused to peptides, in clinical trials. The HGF/c-Met pathway is upregulated in some tumors as an alternate angiogenic pathway. The CXCL12 (SDF-1)/CXCR4 pathway represents a stromal chemokine axis involved in tumor angiogenesis. CXCR2 is a G-protein coupled receptor with several ligands including interleukin-8 and other angiogenic cytokines and may represent a useful target for antiangiogenic agents. The notch pathway is being investigated as a target in the setting of tumor angiogenesis. Sphingosine-1-phosphate is a bioactive lipid that can be neutralized with a monoclonal antibody. The anti-S-1-P antibody is under investigation as an antiangiogenic agent. Finally, several multi-targeted kinase inhibitors each with a unique pattern of inhibitory potency are in clinical trial with a focus on antiangiogenic activity. The expansion of the scope of potential antiangiogenic agents in or entering clinical trial should allow the development of antiangiogenic combination regimens and single agents that address diseases refractory to VEGF-directed therapeutics.



## 1. Introduction

Over the past 15 years, the vascular endothelial growth factor and its signal transduction pathway has been the focus of antiangiogenic therapeutics in cancer [1]. Now, much of the enthusiasm generated for antiangiogenic therapy in oncology has been replaced by the sobering reality that the benefits resulting from the current approaches are often modest [2]. The discovery and elucidation of the importance of vascular endothelial growth factor (VEGF) in embryo development, adult angiogenesis and cancer stimulated the development of several VEGF neutralizing agents especially bevacizumab and kinase inhibitors directed toward blocking intracellular signal transduction by VEGF cell surface receptors (Table 1). Bevacizumab, an antibody which specifically neutralizes human VEGFA's, was a major breakthrough and established antiangiogenic therapy as a valid component of cancer therapeutics [1,3]. The clinical development of bevacizumab by Genentech has been an effort unlikely ever to be duplicated. Nearly 1000 clinical trials have been carried out examining bevacizumab single agent activity and use in combination regimens (www.cancer.gov/clinicaltrials). Bevacizumab is now an integral therapeutic component in the treatment of several major malignancies. Still there are important diseases such as breast cancer and pancreatic cancer where the benefit of neutralizing VEGF has been modest or none even when results from human tumor xenograft models have looked promising [4–8]. The benefits of bevacizumab are clear and the potential adverse events are known. Bevacizumab has been combined with numerous cytotoxic chemotherapy regimens usually without untoward increases in toxicity. Other promising biological VEGF-directed agents include aflibercept, a VEGF-Trap or decoy receptor, and ramucirumab, an antibody targeting VEGF receptor 2 [8,9]. Both are in Phase III clinical trials.

In addition, multiple small molecule kinase inhibitors of varied selectivity for the VEGFRs and other kinases entered the field. Three have been FDA approved and eight are in late clinical trials (Table 1). The kinase inhibitors sorafenib, sunitinib and pazopanib have undergone extensive clinical trial and have established sufficient single agent activity for regulatory approval in renal cell carcinoma (sunitinib, pazopanib) and gastrointestinal stromal tumors (sunitinib) and hepatocellular carcinoma (sorafenib) [10–14]. The adverse events that occur with these drugs are

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understandable and frequent [9,15,16]. Although some preclinical studies have been promising [17,18], it has been more difficult to incorporate the small molecule kinase inhibitors into combination chemotherapy regimens than it has been to incorporate bevacizumab into these regimens and recently three combination regimen Phase III clinical with sunitinib, 2 in breast cancer and 1 in colorectal cancer, have been discontinued [19]. Sorafenib and pazopanib are at earlier stages of combination regimen clinical trials. Sorafenib in Phase II trials has had mixed results as had pazopanib in Phase I clinical trial [20–23].

## 2. Resistance

As with other anticancer therapeutics, tumors frequently become refractory or no longer responsive to antiangiogenic agents after several courses of treatment [24–26]. Two paths to antiangiogenic agent resistance are frequently cited depending upon whether the therapeutic is a protein or a small molecule. With small molecule therapeutics, mutation in the kinase domain of the target receptor tyrosine kinases is known to occur [26]. Resistance to small molecule kinase inhibitors has been shown to sometimes arise from selection of clones in the tumor that express a mutant form of the proteins that are not effectively inhibited by the compounds. This observation has given rise to a second generation of kinase inhibitors selected to be potent inhibitors of frequently seen mutant forms of the receptor; thus kinase inhibitors useful as second and third line therapeutics. With protein therapeutics such as bevacizumab, the upregulation of an alternative or more than one alternative angiogenic pathway has been found. It is well known that VEGF is not the only proangiogenic factor involved in tumor growth; however, other proangiogenic factors seem to have much more limited spectrums of activity and, thus, are likely require an understanding of specific disease situations in which they have an important role for inhibitors to have a clinical impact [27,28].

## 3. Placental growth factor

Among the alternate angiogenic factors, placental growth factor (PlGF) has been shown to be the most highly inducible after treatment with bevacizumab or sunitinib in renal cell carcinoma, and colorectal carcinoma [27,28]. Although some controversy has arisen regarding the efficacy of PlGF blockade in primary mouse tumors [29,30], in several clinical malignancies including colorectal carcinoma, non-small cell lung cancer, malignant mesothelioma, breast cancer and uterine cervix cancer, RT-PCR studies of PlGF mRNA and immunohistochemical staining for PlGF protein of patient tumor samples correlation was found to PlGF expression and disease progression, and tumor microvessel density [31–34]. Interestingly, serum levels of PlGF tend to be much lower than serum levels of VEGF even under conditions when PlGF has been upregulated. Similarly, serum levels of soluble VEGFR2 are much higher than serum levels of soluble VEGFR1, the receptor for PlGF. It is possible that lower serum levels of PlGF may provide an angiogenic thrust similar to that of higher levels of VEGF which tends to be bound to soluble VEGFR2 [8]. PlGF was first described,

**Table 1**
Approved and investigational small molecule and protein antiangiogenic agents listed by progress in clinical trials.

| Agent | Target cell surface | Status | Company | Refs. |
|---|---|---|---|---|
| Sunitinib | VEGFR, PDGFR | Approved | Pfizer | [10,13–16] |
| Sorafenib | VEGFR, PDGFR | Approved | Bayer Schering | [9,11,15] |
| Pazopanib | VEGFR, PDGFR | Approved | GlaxoSmithKline | [12] |
| Axitinib | VEGFR, PDGFR | Phase III | Pfizer | [13,25] |
| Cediranib | VEGFR | Phase III | AstraZeneca | [13,25] |
| Motesanib | VEGFR | Phase III | Amgen | [85,86] |
| Vandetanib | VEGFR, EGFR | Phase III | AstraZeneca | [25] |
| Intedanib (BIBF1120) | VEGFR, PDGFR, FGFR | Phase III | Boehinger Ingelheim | [84,94] |
| Dovitinib (TKI-258) | VEGFR, FGFR, PDGFR | Phase II | Novartis | [82,83,92] |
| Brivanib | VEGFR, FGFR | Phase III | BristolMyersSquib | [2,26] |
| XL-184 | RTKs | Phase III | Exelixis | [2,26] |
| Linifanib | Flt3, PDGFR, VEGFRs | Phase III | Abbott | [2,26,89] |
| CHIR-258 | VEGFR, FGFR, PDGFR, c-Kit | Phase II | Novartis | [2,26,89] |
| Vatalanib | VEGFR | Phase II | Novartis | [2,26] |
| RG-4733 | Notch | Phase II | Roche | [58–62] |
| Foretinib | VEGFR, c-Met, Flt3, c-Kit | Phase II | Exelixis | [74–78] |
| Plerixafor | CXCR4 | Phase I | Genzyme | [46–48] |
| PF-4217903 | c-Met | Phase I | Pfizer | [73–78] |
| JNJ-38877605 | c-Met | Phase I | JnJ/Ortho Biotech | [73–78] |

| Agent | Target ligand(s) | Status | Company | Refs. |
|---|---|---|---|---|
| Bevacizumab | VEGF-A | Approved | Roche/Genentech | [3,4,27] |
| Aflibercept | VEGF-A, PlGF | Phase III | SanofiAventis/Regeneron | [6,7] |
| Ramucirumab | VEGFR2 | Phase III | Lilly/Imclone | [8] |
| AMG-386 | Angiopoietin- 1&2 | Phase III | Amgen | [41–43] |
| Rilotumamab | HGF | Phase II | Amgen | [73–78] |
| AV-299 | HGF | Phase II | Merck/Aveo | [73–78] |
| REGN-421 | Delta-like 4 | Phase I | Sanofi-Aventis/Regeneron | [58–62] |
| Sonepcizumab | S-1-P | Phase I | Merck Serono/Lpath | [70–72] |
| TB-403 | PlGF | Phase I | Roche/Thrombogenics | [29–38] |
| Bavituximab | Phosphatidylserine | Phase II | Peregrine | [2] |
| Rilotumamab | HGF | Phase II | Amgen | [73–78] |
| Anti-NRP1 | Neuropilin | Phase I | Roche/Genentech | [1,2] |
| Anti-EGFL7 | EGFdomain-like7 | Phase I | Roche/Genentech | [1,2] |
| AV-299 | HGF | Phase II | Merck/Aveo | [73–78] |
| MEDI-575 | PDGFR | Phase I | AstraZeneca/MedImmune | [89] |
| IMC-18F1 | VEGFR1 | Phase I | Lilly/Imclone | [24,32–34,40] |
| TAK-701 | HGF | Phase I | Takeda/Galaxy | [73,79] |
| SCH900105 | HGF | Phase I | Schering-Plough | [73,80] |
| MetMab | c-Met | Phase I | Genentech | [73,81] |

crystallized and identified as a ligand for VEGFR1 in the early 1990s [35]. The functional biology of PlGF is still being explored. VEGFR1 is expressed on the surface of bone marrow-derived myeloid cells infiltrating tumors to support tumor growth and angiogenesis. PlGF acts as a vascular remodeling factor leading to more normalized tumor vasculature toward large well-organized vessels with complete pericyte coverage [36,37]. PlGF secreted by proangiogenic macrophage infiltrating tumors is critically involved new blood vessel stalk and tip cell activities and [38]. PlGF appears to have direct effects on some malignant cells and to increase cell proliferation and migration [39]. The therapeutic potential of an antibody to PlGF has been explored preclinically and has moved into Phase 1 clinical trial (Table 1) [39,40].

## 4. Angiopoietins 1 and 2

Other alternate angiogenic factors include angiopoietins 1 and 2 (ang 1 and ang 2), stromal cell-derived factor-1 (SDF-1, CXCL12), interleukin-8 (IL-8), hepatocyte growth factor (HGF), Delta-like 4 (Dll4) and sphingosine-1-phosphate (S1P). The angiopoietins by signaling through the Tie-2 receptor are important in the angiogenic process. AMG-386 is a peptibody consisting of a fully human recombinant Fc constant region fused to peptides that prevent the interaction of angiopoietin-1 and angiopoietin-2 with the Tie-2 receptor. Preclinical studies demonstrated antiangiogenic activity and antitumor activity for AMG-386 and other constructs that was similar to that observed with inhibitors of the VEGF pathway [41]. AMG-386 proved to be safe and to have acceptable pharmacokinetics in Phase 1 clinical trial in adults with advanced solid tumors [42]. Early trials also evaluated the safety and pharmacokinetics of AMG-386 in combination with FOLFOX, carboplatin and paclitaxel or docetaxel and concluded that AMG-386 could be safely added to each chemotherapeutic regimen [43]. AMG-386 moved forward into multiple Phase II clinical trials including combination with FOLFIRI in colorectal carcinoma, with sunitinib in renal cell carcinoma, with sorafenib in hepatocellular carcinoma and with cisplatin and capecitabine in gastric, gastroesophageal and distal esophageal adenocarcinoma.

## 5. CXCL12/CXCR4

The binding of CXCL12 to CXCR4 induces intracellular signaling through several divergent pathways initiating signals related to chemotaxis, cell survival, and proliferation. CXCR4 is expressed on multiple cell types including lymphocytes, hematopoietic stem cells, endothelial and epithelial cells, and cancer cells. The CXCL12/CXCR4 axis is involved in tumor progression, angiogenesis, metastasis and survival [44]. Kioi et al. recently demonstrated that irradiation induces recruitment of bone marrow derived cells into an intracranial glioblastoma xenograft model, restoring the radiation-damaged vasculature by vasculogenesis, thereby allowing the growth of surviving tumor cells. Bone marrow derived cells are recruited to tumors in part through the interaction between the HIF-1-dependent CXCL12 and CXCR4. Pharmacologic inhibition of the CXCL12/CXCR4 interaction using CXCR4 neutralizing antibodies or plerixafor prevented the influx of bone marrow derived cells, and development of tumor vasculature resulting in abrogation of tumor regrowth [45]. Plerixafor is used to aid the mobilization of hematopoietic stem cells for use in autologous stem cell transplantation of patients with non-Hodgkin's lymphoma and other malignancies [46,47]. Because the CXCL12/CXCR4 pathway is responsible for retention of acute lymphoid leukemia and acute myeloid leukemia cells in the bone marrow; plerixafor is undergoing clinical trial as a chemosensitizer in the treatment of patients with relapsed or refractory acute myeloid leukemia [48].

## 6. CXCR2

There are 7 known proangiogenic chemokines which are ligands for the chemokine receptor CXCR2 [49]. Among these, interleukin-8 (CXCL8) is a mitogen for endothelial cells and stimulates angiogenesis in vivo. CXCL8 is secreted by macrophages leading to macrophage-associated angiogenesis in malignant disease. Human intestinal microvessel endothelial cells express CXCR2 and malignant colonic epithelial cells overexpress CXCL8 supporting the notion that CXCR2 blockade may be a valid target for anti-angiogenic therapy in colorectal cancer. In addition, a positive correlation has been found between the levels of tumor-associated macrophage (TAM) (macrophage index) in many human cancers and tumor angiogenesis in breast, prostate, cervical, endometrial, liver, bladder, kidney, brain, oral cancers and melanoma [50]. Hypoxic conditions as frequently occur in tumors cause up-regulation of CXCL8 secretion by macrophage [51]. In cancer, neutrophils can also mediate CXCL8-induced angiogenesis [51]. Over-expression of CXCL8 correlates with tumor stage as well as disease progression and recurrence. In bladder cancer, CXCL8 expression was increased in invasive tumors both preclinically and clinically. Serum levels of CXCL8 have been considered a potential tractable clinical biomarker in melanoma [52]. CXCL8 was evaluated as a therapeutic target using a fully human anti-CXCL8 (ABX-IL8) neutralizing antibody. Although the antibody had little effect in cell culture, it produced a significant decrease on the growth of human tumor xenografts indicating a potential effect on the tumor microenvironment. Unfortunately, the antibody was discontinued due limited activity in clinical trial. More recently, in preclinical studies, CXCR2 was targeted with an antagonistic antibody [53]. Treatment of mice bearing orthotopically implanted with a clonal GFP-transfected subline of BxPC3 human pancreatic cancer with a goat polyclonal anti-mouse CXCR2 resulted in a decreased tumor volume, lower Ki-67 proliferation index and factor VIII-positive microvessel density compared with controls. The tumor growth delay produced by intraperitoneal injection of 20 mg/kg 3-time per week was 12.5 days [53]. This same polyclonal anti-mouse CXCR2 slowed the growth of a Snail overexpressing subline of human H441 adenocarcinoma [54]. Small molecule inhibitors such as repertaxin, an inhibitor of CXCR1 and SB-225002 or SB-332235 small molecule inhibitors of CXCR2 have been tested in inflammatory diseases; dual CXCR1/CXCR2 inhibitors such as SCH-479833 and SCH-527123 have been evaluated preclinically in cancer [50,55]. Using a tumor growth inhibition experimental design, when mice subcutaneously bearing a metastatic variant of A375 human melanoma xenografts were treated by gavage with 100 mg/kg SCH-479833 or SCH-527123 once per day for 21 days, there resulted 20 days and 23 days of tumor growth delay, respectively. SCH-527123 has undergone clinical trials in chronic obstructive pulmonary disease (COPD), allergen-induced asthma, neutrophilia-induced asthma and psoriasis and is currently in a Phase 2b clinical trial in chronic obstructive pulmonary disease.

## 7. Notch

Preclinical and clinical evidence support a pro-oncogenic and pro-angiogenic function for Notch signaling in several solid tumors, particularly in breast cancer [56]. The Notch pathway may be important in the generation and maintenance of tumor stem cells, a finding which has stimulated the search for Notch-directed therapeutics. The Notch pathway, specifically the ligands, Delta-like 4 (Dll4) and Jagged1 and the receptor Notch1, is recognized as important in tumor angiogenesis [57,58]. The VEGF and Notch pathways interact and intersect such that the VEGF pathway stimulates angiogenesis while the Notch pathway helps

to guide cell fate decisions that appropriately shape the activation. Delta-like 4 and Jagged1 are expressed by tumor cells and tumor endothelium. Dll4/Notch signaling decreases angiogenesis by suppressing endothelial tip cell formation while blocking Dll4/Notch signaling increases non-productive angiogenesis and decrease the growth of VEGF-sensitive and -resistant tumors. VEGF induces Dll4/Notch signaling while Dll4/Notch signaling modulates the VEGF pathway. Blocking both pathways markedly inhibits tumor growth in preclinical models [59]. Notch1 knockout and Dll4 and Jagged1 knockout are embryonic lethal in mice. A Notch1 decoy, a soluble form of Notch1, which blocks both Dll4 and Jagged1, was able to cause restriction of tumor vessel growth in the mouse mammary Mm5MT model [57].

Gamma-secretase inhibitors block Notch signaling. A clinical trial of the oral gamma-secretase inhibitor, MK-0752 was conducted using transcriptional profiling of human plucked hair follicles as readout [60]. MK-0752 administration produced decreases in Notch and PI3K pathway gene expression and at later time points, upregulation of Wnt and epithelial to mesenchymal transition pathway gene expression. Using a Notch1 decoy and bevacizumab in combination resulted in additive tumor endothelial cell killing [61]. Some time ago, Genentech generated a specific Dll4-neutralizing phage antibody, YW152F [62]. Treatment of mice bearing human tumor xenografts with YW152F increased tumor vascular density but decreased tumor growth due to the poor quality of the vessels resulting in markedly decreased perfusion of the tumor. However, normal tissue toxicity precluded moving anti-Dll4 forward. More recently, the discrete functions of Notch1 and Notch2 have been elucidated. Inhibition of Notch2 signaling results in severe intestinal toxicity. However, selective blocking of Notch1 inhibits tumor growth in preclinical models through inhibition of cancer cell growth and deregulation of angiogenesis [62]. An antibody specific for Notch1, anti-NRR1, was a very effective therapeutic in multiple human tumor xenograft models. Another Notch1 specific antibody that binds to the Notch1 ligand binding domain prevented ligand binding and repressed Notch1-dependent signaling in mouse models [63].

## 8. Sphingosine-1-phosphate

Sphingosine-1-phosphate is a bioactive lipid that regulates many cellular and physiological processes including cell proliferation, survival, motility, angiogenesis, vascular maturation, immunity and lymphocyte trafficking. The extracellular actions of sphingosine-1-phosphate are mediated through 5 G-protein coupled receptors $S1P_{1\text{-}5}$. Sphingosine-1-phosphate is produced intracellularly by the isozymes sphingosine kinase1 and sphingosine kinase2. In the cell, nuclear histone deacetylases are targets of sphingosine-1-phosphate, thus linking sphingosine-1-phosphate to epigenetic regulation of gene expression [64]. Sphingosine-1-phosphate has emerged as a potent modulator of the integrity of biological barriers such as the blood–brain barrier through modulation of its receptors. Sphingosine-1-phosphate receptors, previously called endothelial differentiation gene receptors, were discovered in the early 1990s, in parallel with the immunosuppressive myriocin analog FTY720, a prodrug that requires phosphorylation to induce immunosuppression, by acting as an agonist on receptors of the structurally similar endogenous ligand, sphingosine-1-phosphate [65]. The sphingosine kinase1/sphingosine-1-phosphate pathway modulates HIF-1α activity under hypoxic conditions [66]. Sphingosine-1-phosphate induces chemotaxis and regulates migration of osteoclast precursors in culture and in vivo contributes to the dynamic control of bone mineral homeostasis [67]. Treatment of ovarietomized mice with a $S1P_1$ agonistic small molecule stimulated motility of osteoclast precursor-containing monocytoid populations and relieved ovariectomy-induced osteoporosis in the mice by reducing the number of mature osteoclasts attached to the bone surface. In gastric cancer patients, higher expression of sphingosine kinase1 was associated with shorter survival times [68]. Inhibition of sphingosine kinase1 increased the sensitivity of tumor cells to chemotherapy and decreased the growth of human tumor xenografts [69].

A specific high affinity anti-sphingosine-1-phosphate was effective in blocking sphingosine-1-phosphate-mediated secretion of the pro-angiogenic and prometastatic cytokine CXCL8 by human ovarian carcinoma cells. In vivo anti-sphingosine-1-phosphate demonstrated anti-angiogenic activity in the murine choroidal neovascularization model. Intravenous administration of anti-sphingosine-1-phosphate had a marked effect on lymphocyte trafficking. Anti-sphingosine-1-phosphate appeared to act a "molecular sponge" to selectively deplete sphingosine-1-phosphate [70]. The crystal structure of an anti-sphingosine-1-phosphate:antigen complex has been determined. A Phase 1 clinical trial of the anti-sphingosine-1-phosphate, sonepcizumab, has been completed [71]. The antibody was well-tolerated up to doses of 24 mg/kg with some patients experiencing long-term stable disease. Decreased lymphocyte counts suggested biologic activity of the antibody in humans. Anti-sphingosine-1-phosphate is also under investigation in angiogenesis related eye conditions such as age-related macular degeneration [72].

## 9. HGF/c-Met

The c-Met activating ligand, hepatocyte growth factor (HGF), is normally secreted by fibroblasts and smooth muscle cells, but can also be produced by tumor cells. The HGF/c-Met tyrosine kinase signaling pathway is upregulated in many cancers resulting in invasive growth consisting of physiological processes including proliferation, invasion and angiogenesis [73]. The pathway normally promotes mitosis, cell motility and cell survival of epithelial cells and the endothelium; but in cancer it can also promote cell proliferation, invasion, metastasis, and angiogenesis. HGF/c-Met signaling induces tumor angiogenesis by stimulating proliferation and migration of endothelial cells; by inducing VEGF expression; as well as by downregulating thrombospondin 1 (TSP-1), a negative regulator of angiogenesis. The c-Met receptor and VEGF receptor cooperate to promote tumor survival. The HGF/c-Met pathway is an independent angiogenic factor in tumor angiogenesis, that may interact with angiogenic proliferation and survival signals promoted through VEGF and other angiogenic proteins. HGF/c-Met signaling increases VEGF levels in tumors and VEGFR2 on endothelial cells [74]. Increased HGF/c-Met signaling cooperates with VEGF signaling to increase expression of VEGF-regulated genes, and to express novel transcripts in endothelial cells. Combined VEGF and HGF/c-Met signaling has a greater effect on the prevention of endothelial cell apoptosis and increased tube formation in vitro, capillaries growth in vivo, and increased microvessel density within tumors. Thus, targeting inhibition of HGF/c-Met produces enhanced VEGF/VEGFR axis-mediated inhibition of angiogenesis at the time of initial therapy and increased response to tumor hypoxia induced by antiangiogenic therapy.

Small molecule kinase inhibitors, antibodies to HGF and c-Met, peptides and decoy receptors have been used to target the pathway therapeutically [75]. Head and neck cancer may be a particularly promising target disease for HGF/c-Met blockade [76]. NK4, an HGF antagonist, prevents lung metastasis in preclinical models [77]. A novel inhibitor of HGF and VEGF receptor tyrosine kinases EXEL-2880 inhibited tumor growth, invasion and metastasis [78]. TAK-701, a humanized anti-HGF, binds to HGF and inhibits HGF/c-Met-mediated human tumor proliferation in preclinical studies and is in early clinical trial [79]. SCH900105 is a humanized anti-HGF with potent antitumor effects in vitro and xenograft models has

completed Phase 1 clinical trial [80]. MetMAb, a monovalent antagonist antibody to the receptor Met, has completed Phase 1b clinical trial in combination with bevacizumab [81].

## 10. Multi-targeted kinase inhibitors

Several small molecules and antibodies targeting additional proangiogenic cell surface molecules are under investigation as antiangiogenic agents. Dovitinib (TKI-258), a potent VEGF, FGF and PDGF receptor kinase inhibitor, is being tested for the treatment of hematological malignancies and solid tumors including renal cell carcinoma [82,83]. Intedanib (BIBF-1120), a small molecule inhibitor of VEGF, FGF and PDGF receptors, is being explored as an antiangiogenic therapy in non-small cell lung, ovarian prostate and colorectal cancers as well as renal cell carcinoma and hepatocellular carcinoma [84]. Motesanib (AMG-706), a selective small molecule inhibitor of VEGFR, PDGFR and Kit kinases, is in Phase III clinical trial in non-squamous non-small cell lung cancer and in Phase I/II clinical trial in breast cancer [85,86]. Anti-FGFR3, an anti-fibroblast growth factor receptor (IMC-D11), has shown activity in bladder cancer models in combination with cisplatin. The pro-angiogenic functions of ephrin-B2 in the VEGF signaling pathway have been detailed for VEGFR3, the receptor for VEGF-C and for VEGFR2, the receptor for VEGF-A. In the absence of ephrin-B2, the internalization of VEGFR3 in cultured cells and mutant mice was defective compromising downstream signal transduction [87]. VEGFR3 signaling is coupled to receptor internalization and ephrin-B2 is a key regulator of this process. Ephrin-B2 reverse signaling involving PDZ interactions regulates endothelial tip cell guidance to control angiogenic sprouting and branching [88]. Ephrin-B2 PDZ-signaling-deficient mice exhibit a reduced number of tip cells with fewer filopodial extensions at the vascular front in the retina. Ephrin-B2 controls VEGFR2 internalization which is necessary for activation and downstream signaling of the receptor and is required for VEGF-induced tip cell filopodial extension. Thus, ephrin-B2 at the tip cell filopodia regulates the proper spatial activation of VEGFR2 endocytosis and signaling to direct filopodial extension. Blocking ephrin-B2 reverse signaling may be a useful antiangiogenic therapy strategy to disrupt VEGFR2 and VEGFR3 function in tumor angiogenesis.

Platelet derived growth factor receptor-$\alpha$ is involved in tumor angiogenesis and maintenance of the tumor microenvironment and has been implicated in metastasis. Platelet derived growth factor receptors contribute prominently to neovascularization and modulate mesenchymal stem cell recruitment and differentiation toward vascular cells [89]. Platelet derived growth factor receptor-based therapeutic strategies exploit mesenchymal stem cells during vascular repair and regeneration, and control pathological neovascularization. Fibroblast growth factors are involved in several mitogenic, cytoprotective and angiogenic activities [90]. Antibodies to fibroblast growth factors and to fibroblast growth factor receptors and small-molecule FGF receptor kinase inhibitors are being explored in the treatment of cancer (Table 1). Dovitinib has demonstrated inhibition of VEGFR and the FGFRs in clinical trials [92]. BGJ398, an orally bioavailable, selective inhibitor of the FGFRs, is in Phase 1 clinical trial [93]. Intedanib (BIBF 1120) has been described as a triple angiokinase inhibitor of VEGFR, PDGFR and FGFR kinase activity and is in late clinical trial [94]. Finally, TSU-68 which as completed Phase I/II clinical trial, also inhibits the kinase activity of VEGFR, PDGFR and FGFR [95].

Tumor-associated CD11b + Gr1 + myeloid cells contribute to refractoriness to antiangiogenic therapy with an anti-VEGF-A antibody [91]. However, the mechanisms of peripheral mobilization and tumor-homing of CD11b + Gr1 + cells are unclear. Compared with other cytokines granulocyte-macrophage colony stimulating factor (GM-CSF), stromal derived factor 1$\alpha$, and placenta growth factor, G-CSF and the G-CSF-induced Bv8 protein have preferential expression in refractory tumors. Treatment of refractory tumors with the combination of anti-VEGF and anti-G-CSF (or anti-Bv8) reduced tumor growth compared with anti-VEGF-A monotherapy. Anti-G-CSF treatment dramatically suppressed circulating or tumor-associated CD11b + Gr1 + cells, reduced Bv8 levels, and affected the tumor vasculature. Conversely, G-CSF delivery to animals bearing anti-VEGF sensitive tumors resulted in reduced responsiveness to anti-VEGF-A treatment through induction of Bv8-dependent angiogenesis. Thus, G-CSF expression by tumor or stromal cells can be a determinant of refractoriness to anti-VEGF-A treatment.

## 11. Conclusion

It is likely that, as the field evolves, combination antiangiogenic regimens directed to specific malignancies will be developed. Tumor types that have little or no response to VEGF pathway blockade are likely dependent on other angiogenic factors from the outset and tumors which eventually stop responding to VEGF pathway inhibitors have developed alternate angiogenic strategies. Ideally, analysis of a panel of circulating proangiogenic factors will become a routine part of a personalized medicine approach and the antiangiogenic agents most likely to benefit the patient will be selected. The current shortage of validated biomarkers and limited patient screening limits the possibilities of choosing drugs for specific patients; however, learning more about the angiogenic programs of various tissues and organs will enable selection of more appropriate antiangiogenic treatment regimens in the shorter term. The limited initial view of angiogenesis and antiangiogenic therapeutics to a single focus on the endothelial cell has expanded to targeting a variety of cell types involved in tumor vessel structure and promotion. Pericytes which stabilize tumor vasculature and provide endothelial cells with survival benefits are being selectively targeted through the angiopoietin pathways and through the platelet-derived growth factor pathways to decrease the number of pericytes and to disrupt pericyte-endothelial cell association in tumors. The hope is that tailoring antiangiogenic therapies to tumor type and then further to specific patients will increase improvements in survival achieved so far.

The VEGF pathway inhibitors gave the field a great 'lift-off', the refinements coming along will make antiangiogenic agents an even more effective component of anticancer therapy.

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