Molecular Pathways: Can Activin-like Kinase Pathway Inhibition Enhance the Limited Efficacy of VEGF Inhibitors?

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Abstract

The vascular endothelial growth factor (VEGF) pathway is critical for tumor angiogenesis. However, VEGF pathway inhibition has been limited by intrinsic and acquired resistance. Simultaneously targeting multiple steps involved in tumor angiogenesis is a potential means of overcoming this resistance. Activin like kinase 1 (ALK1) and endoglin (ENG) have effects on angiogenesis that are distinct from those of VEGF. Whereas VEGF is important for vessel initiation, ALK1 and endoglin are involved in vessel network formation. Thus, ALK1 and endoglin pathway inhibitors are attractive partners for VEGF-based combination antiangiogenic therapy. Genetic evidence supports a role for this receptor family and its ligands, bone morphogenetic proteins (BMP) 9 and 10, in vascular development. Patients with genetic alterations in ALK1 or endoglin develop hereditary hemorrhagic telangiectasia, a disorder characterized by abnormal vessel development. There are several inhibitors of the ALK1 pathway advancing in clinical development for treatment of various tumor types, including renal cell and ovarian carcinomas. Targeting of alternate angiogenic pathways, particularly in combination with VEGF pathway blockade, holds the promise of optimally inhibiting angiogenically driven tumor progression. Clin Cancer Res; 20(11); 2838–45. ©2014 AACR.

Background

Molecular signaling of the ALK1/ENG pathway
Activin like kinase (ALK)-1 is a type I transforming growth factor (TGF) β serine/threonine kinase receptor that binds to bone morphogenetic proteins (BMP) 9 and 10 (1). These cytokines are members of the TGFβ superfamily of ligands that includes TGFβ, activins, growth and differentiation factors (GDF), and the other BMPs. The functional BMP9/10 signaling complex contains the type I receptor (ALK1) and a type II TGFβ receptor [BMP receptor II, Activin receptor IIA (ActR1IA) or ActRIBB]. Upon ligand binding, the type II TGFβ receptor phosphorylates the type I receptor, which leads to the phosphorylation and activation of SMADs 1, 5, and 8 (2–5). SMAD phosphorylation then leads to expression of downstream genes including the DNA-binding protein inhibitor ID-1 and transmembrane protein 100 (TIMP100; refs. 6, 7). Another member of the TGFβ superfamily, TGFβ1, uses a similar receptor complex, TGFβRII (a type II receptor), and ALK5 (a type I receptor) and activates SMAD2, 3 signaling. ENG is a type I integral membrane protein with a large extracellular domain and a short cytoplasmic tail lacking a kinase signaling motif. Although there are some reports of signaling by endoglin (8, 9), in general it has been regarded as a coreceptor in this family. Endoglin binds BMP9 and an anti-endoglin antibody has been shown to regulate BMP9-induced signaling (8). ENG expression is upregulated by hypoxia and TGFβ (10). A soluble form of ENG can be generated via cleavage at the membrane, releasing sENG (11).

ALK1 and ENG are involved in the development of vascular networks
Extensive genetic evidence in humans and mice supports the essential role of the ALK/ENG pathway in the development of vascular networks. Hereditary hemorrhagic telangiectasia (HHT, Osler–Weber–Rendu syndrome; refs. 12, 13) is an autosomal dominant disorder seen in individuals with mutations in either ACVRL1 (the gene encoding ALK1) or ENG genes. Patients with HHT type 1 (ENG mutation) and HHT type 2 (ALK1 mutation) develop vascular abnormalities, including telangiectasias and arterial venous malformations (AVM). Telangiectasias are clusters of abnormally dilated thin-walled blood vessels, typically found in the skin and mucous membranes. Patients with HHT commonly develop recurrent epistaxis or nosebleeds and gastrointestinal bleeding from telangiectasias in the nasal and gastrointestinal mucosa frequently later in life. AVMs are characterized by abnormal connections between arteries and veins and are commonly found in the internal organs such as liver, lung, and brain of patients with HHT.

Murine genetic studies also support the role of ALK1 and ENG in vascular network formation. Two germline ALK1

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(ACVRL1) mutations have been studied in mice. One mutation disrupts transcriptional and translational initiation (14), and the other disrupts exon 8 that encodes the kinase subdomain V of ALK1 (15). Mice lacking ACVRL1 expression die at midgestation around embryonic day 11.5 with abnormal development of vascular networks. One of the earliest steps in the development of the vascular system is the specification of arteries and veins, leading to distinction of vascular beds. Mice lacking ACVRL1 develop large shunts between arteries and veins, resulting in AVM formation. In addition, the vascular smooth muscle cells that develop around vessels fail to develop after AVM formation, and expression of an early molecular marker of arteries, ephrinB2, is reduced in the ACVRL1<sup>−/−</sup> embryos. Conditional deletion of ACVRL1 in restricted vascular endothelia also results in severe vascular malformations (16). ACVRL1 heterozygous mice develop cutaneous lesions in the ear, tongue, and AVMs in liver, lung, spleen, and brain (17). In addition, disruption of ALK1 in zebrafish leads to an abnormal circulation pattern, which is characterized by dilated vessels that fail to perfuse the trunk (violet beauregarde; ref. 18).

Mice lacking ENG expression also die at midgestation with defective vascular development. ENG<sup>−/−</sup> mice die around embryonic day 11.5 with immature disorganized vascular plexi that fail to undergo remodeling and lack vascular branching and sprouting. Lack of vascular smooth muscle development is also seen in these mice (19). Mice harboring a nonsense mutation in ENG also die early in embryogenesis and in addition to abnormalities in vascular development exhibit abnormal yolk sac development and evidence of cardiac defects (20). The abnormal yolk sacs have reduced TGFβ signaling, demonstrating cross-talk between the ENG/ALK1 and TGFβ pathways (21). In contrast with ACVRL1<sup>−/−</sup> mice, ENG<sup>−/−</sup> mice do not develop profound vessel dilation or decrease in ephrinb2 expression (22).

Although ALK1 is expressed at sites of angiogenesis during development, its expression is suppressed in the adult. It can be induced during events requiring neoangiogenesis including tumor angiogenesis (23–25). A study of ALK1 expression in mice in which ALK1 is replaced with the β-galactosidase gene showed that ALK1 is predominantly expressed in developing arterial endothelium. Expression decreases in adult arteries, but is induced in preexisting feeding arteries and newly forming arterial vessels during wound healing and tumor angiogenesis (26). Similarly, ENG is expressed only at low levels in adult human tissues. However, during inflammatory disease and in wound healing models, ENG expression is strongly upregulated and is consistently associated with an infiltrate of inflammatory cells (27). ALK1 is also expressed in several human tumors, including renal cell, ovarian, and head-and-neck carcinoma (28, 29).

**ALK1 and ENG share ligands**

ALK1 and ENG bind to members of the BMP family. BMP9/10 are secreted in an active form and have context-dependent roles in angiogenesis (30, 31). Although there is clear evidence that BMP9 and BMP10 are angiogenic factors (32), their effect on angiogenesis seems to be dependent on timing of expression and whether they are being studied in developmental angiogenesis or tumor angiogenesis. In vitro, BMP9 has been shown to inhibit proliferation and migration of several cultured endothelial cell lines (32–34) and has negative effects on angiogenesis in the mouse sponge assay and the chick chorioallantoic membrane (CAM) assay (35, 36). Recent genetic evidence in BMP9 and BMP10 knockout mice revealed that they are functionally redundant ALK1 ligands required for early postnatal vascular development (37). In the adult, the role of BMP10 is primarily in cardiac development. BMP9 mutations were recently identified in 3 patients with clinical manifestations of HHT but with no mutations in ENG or ALK1 (38), supporting the role of BMP9 in angiogenesis.

**ALK1/Eng and VEGF affect distinct stages in angiogenesis**

The development of arteriovenous networks is a multiprocess in which vascular endothelial growth factor (VEGF) plays a critical role (Fig. 1; refs. 39, 40). VEGF is an initiator of angiogenesis, along with fibroblast growth factor (FGF), stimulating proliferation and migration of endothelial cells. VEGF and Notch pathway proteins then signal to initiate and support sprouting of endothelial tubes (41). Subsequent basement membrane remodeling by extracellular matrix proteases continues to support sprouting and branching of vessels. Maturation and stabilization of early branched vessels with subsequent development of functional vascular beds is a complex process supported by several factors, including angiopoietins, platelet-derived growth factor, sphingosine phosphate receptors, and the ALK1/ENG pathway (31). Much of the information known about vessel maturation comes from genetic studies and some in vivo angiogenesis models. The exact function of these molecules in tumors is not fully understood due to a lack of adequate models of tumor angiogenesis. In vitro studies using cultured endothelial cell lines and in vivo studies such as Matrigel and chick CAM assays often fail to recapitulate tumor–host interactions. Thus, optimal sustained inhibition of tumor angiogenesis may require coordinated inhibition of multiple components of the angiogenic program.

**Clinical–Translational Advances**

**Inhibitors of ALK1/ENG signaling**

The growing understanding of the important contributions of the ALK1/ENG pathway to angiogenesis has led to efforts to develop functional inhibitors of the pathway. The role of ALK1 and ENG in cancer has been studied largely in the context of these inhibitors. Currently, there are two classes of inhibitors under development: inhibitors of ALK1 and of ENG (Fig. 1). Several of these agents have already entered into clinical development. Two ALK1 inhibitors have entered clinical trials, ACE-041 (dalantercept;...
Acceleron Pharma) and PF-03446962 (Pfizer). ACE-041 is a fusion protein of the extracellular domain of ALK1 fused to the IgG1 human Fc. It binds to both BMP9 and 10 and acts as a ligand trap of BMP9/10 (32). ALK1-Fc blocked BMP9 signaling in cultured endothelial cells as shown by a reporter assay of SMAD binding elements and downregulation of ID-1. This inhibitor also reduced endothelial cord formation (32, 36) and neovascularization in the CAM angiogenesis model. In an orthotopic breast cancer model (MCF-7) ALK1-Fc-treated mice displayed an approximately 70% reduction in tumor burden versus vehicle-treated mice ($P < 0.01$; ref. 32). Our group has also shown that ALK1-Fc decreased tumor growth in two renal cell carcinoma (RCC) models and that large dilated vascular structures were present in tumors of treated mice (42).

In a RIPTag2 model of endocrine pancreatic tumorigenesis, BMP9 and TGFβ were upregulated during tumor progression. Neutralization of BMP9 with ALK1-Fc inhibited angiogenic sprouting and led to dose-dependent growth inhibition of both small early tumors (73% reduction in mean tumor burden; $P < 0.001$) and larger established tumors. Treatment also resulted in decreased vascular density and decreased perfusion as assessed by detection of an injected labeled lectin. ALK1-Fc also decreased sprouting and migration of endothelial cells in cultured explanted angiogenic pancreatic islets (36).

PF-03446962 is a human monoclonal antibody against ALK1 (Anti-ALK1) that interferes with BMP9 and 10 signaling (29, 43). Anti-ALK1 interferes with BMP9/10 signaling in human umbilical vein endothelial cells (HUVEC) and with endothelial sprouting and tube formation. The ALK1 antibody also blocks ENG recruitment to the receptor complex and competes with BMP9 for binding to ALK1. Anti-ALK1 antibody treatment produced 59% tumor growth inhibition in the MDA-MB-231 human breast xenograft tumor model ($P < 0.05$; ref. 29). In treated tumors, microvessel
ALK1 and VEGF Inhibition: A Promising New Combination

density was decreased and lymphatic vessel density was moderately decreased. Reduction in microvessel density was also seen in anti-ALK1–treated human melanoma murine xenografts. Anti-ALK1 administration also inhibited the development of functional vessels as measured by contrast-enhanced ultrasound (CE-US; ref. 29).

TRC105 (TRACON Pharmaceuticals) is a chimeric human IgG1 anti-ENG antibody. It is derived from a monoclonal mouse anti-human ENG antibody (SN6j; ref. 44). This antibody has been shown to inhibit proliferation of HUVECs in vitro and vessel formation in Matrigel (44, 45). In the 4T1 mouse breast cancer model, TRC105 slowed tumor growth (tumor size at day 24 post treatment with control IgG, 888.8 ± 427.5 mm³ vs. anti-ENG, 662.6 ± 285.8 mm³; P < 0.05; ref. 44). Furthermore, it was more effective in immunocompetent mice in a T-cell dependent manner as depletion of CD4 or CD8 cells abrogated the effect of ENG inhibition (46). This suggests that a component of its activity may be due to antibody-dependent cell-mediated cytotoxicity (ADCC). Anti-ENG also prevented metastatic tumor spread in the 4T1 breast cancer and the colon26 models in which a reduction in liver metastatic colonies was observed (control, 10.1 ± 7.2 vs. anti-ENG, 3.2 ± 1.4; P < 0.05; P < 0.03; ref. 44). However, in the genetic model, ENG loss in tumor vessels led to increased tumor metastases (47). The effects of ALK1/ENG pathway inhibitors on tumor vasculature remain to be fully understood. Simply measuring vessel density of treated tumor xenografts may not reflect the complex roles of these pathways in angiogenesis. More studies and models are needed to understand the differences among these inhibitors.

Phase I studies

In a phase I study of dalantercept, toxicities included fatigue, peripheral edema, anemia, and nausea. The dose-limiting toxicity was fluid overload/edema. Interestingly, patients treated at the higher dose levels developed skin telangiectasias. Some patients showed evidence of tumor response including decrease in tumor FDG uptake on positron emission tomography (PET) imaging (48). In a phase I study of PF-03446962 in patients with advanced solid tumors, the most common toxicities included thrombocytopenia and fatigue with no dose-limiting toxicities observed. Grade 1 telangiectasias were seen in 8.3% of patients. There was also some evidence of clinical activity (49). Anti-ENG (TRC105) was tested in patients with advanced solid tumors in a phase I clinical trial. Gastrointestinal hemorrhage was an observed toxicity. Telangiectasias were seen in some patients. Promising clinical activity has led to further testing of TRC105 (50).

Although these three inhibitors do not seem to show overlapping toxicities, a common finding in all three phase I trials was the treatment emergence of telangiectasias in a small subset of patients treated at higher doses. As HHT is characterized by telangiectasias, likely due to defects in ALK1/ENG signaling, the emergence of these skin manifestations in the clinical trials may indicate that each agent is capable of blocking its respective target. In contrast, none of the agents was associated with the common toxicities seen with VEGF pathway inhibitors, including hypertension and proteinuria. Future studies of the relationship of telangiectasia development to dose, blood level of each agent, treatment exposure, and clinical outcome will likely provide insights into the optimal dosing and relevance of this pathway in patients with specific tumor types. Another important finding from all three trials was the evidence of clinical activity (partial responses and stable disease) even in patients whose disease had developed resistance to VEGF pathway inhibitors. Importantly, evaluating the effects of these inhibitors on tumor blood flow and other parameters of tumor vasculature will help assess target engagement and function. Thus, it will be important to incorporate vascular imaging into future trials.

Importance of combination therapy

VEGF is one of the critical mediators of angiogenesis; however, the clinical activity of VEGF pathway inhibitors is limited by short duration of benefit even in the more sensitive tumor types (e.g., clear cell RCC). Determining how to augment and extend the activity of VEGF pathway inhibitors is an area of intensive investigation.

ALK1 or ENG pathway inhibition has shown the ability to enhance the antitumor activity of VEGF pathway inhibitors in preclinical models (9, 29, 32). Anti-ALK1 was shown to improve the activity of bevacizumab in a murine melanoma model in which the combination showed a 58% tumor growth inhibition with the addition of bevacizumab (P < 0.05; ref. 29). Combination therapy led to disruption of pericyte–endothelial contacts in this model. Similarly, ENG+/− RIP-TAG mice demonstrated a more marked sensitivity to the VEGFR tyrosine kinase inhibitor (TKI), AG-028262, and to the VEGFR2 antibody, DC101, than ENG+/+ mice, suggesting benefit from dual pathway inhibition (47).

The combination of VEGFR tyrosine kinase inhibition and ALK1 inhibition has also been investigated in RCC xenograft models. The defect seen in the von Hippel–Lindau (VHL) tumor suppressor in the majority of clear cell RCC leads to a unique dependence of RCC on VEGF-driven angiogenesis. VHL loss in RCC leads to upregulation of hypoxia-inducible factor (HIF) and its downstream factors (including VEGF) even in the absence of hypoxia, contributing to the sensitivity of RCC to VEGFR TKIs such as sunitinib, sorafenib, pazopanib, and axitinib. Each of these agents has produced tumor responses in a large proportion of patients with RCC and prolonged median progression-free survival, leading to their approval by the FDA for this indication. However, responses are virtually always partial and treatment resistance invariably develops at a median of 6 to 12 months. Resistance to these agents has been shown to be related to ability of tumors to use alternative proangiogenic mechanisms to restore angiogenesis. In a VHL-deficient RCC murine xenograft model of VEGFR TKI resistance, VEGFR TKI therapy in combination with ALK1 inhibition (using ALK1-Fc) led to prolonged disease stabilization (42), suggesting that ALK1-Fc may inhibit a mechanism...
of angiogenic escape. Another rationale for combined VEGFR and ALK1 inhibition is that the two pathways affect sequential steps in angiogenesis. Our group has shown that the combination of VEGFR and ALK1 inhibition is more effective at slowing tumor growth with a 52% decrease in tumor burden in combination ALK1-Fc + sunitinib–treated mice versus single-agent sunitinib treatment (P < 0.005). In addition, combination VEGFR and ALK1 inhibition led to greater reduction in tumor blood flow than either agent alone (42). On the basis of these data, it seems that combined inhibition of both early and later angiogenic processes can provide more effective antiangiogenic activity than either alone.

This relationship of VEGF and ALK1/ENG has been studied in vascular formation models. Walker and colleagues have developed a model of brain AVM formation using brain-specific conditional deletions of ALK1 (51), and Choi and colleagues have performed similar studies with ENG (52). When mice harboring deletion of ALK1 or ENG in the brain are injected with an adenovirus expressing VEGF, enlarged vessels are seen. These vessels are AVMs as evidenced by altered arteriovenous molecular markers and evidence of blood shunting. Thus, the combination of VEGF stimulation and ALK1/ENG deficiency leads to large dysplastic vessels, but in the absence of VEGF signaling the number of abnormal vessels is reduced.

This relationship of ALK1/ENG and VEGF is also seen in patients with HHT, who can benefit from VEGF pathway inhibition (53–55). Patients with HHT exhibit enlarged abnormal blood vessels that are prone to bleeding. The clinical picture is consistent with unopposed endothelial cell proliferation in a setting in which there are defects in the regulation of vessel proliferation and in vessel maturation. Thus, it was hypothesized that blocking VEGF-driven angiogenesis could limit the abnormal vessel development and reduce the resultant clinical complications (53, 56). Early clinical reports suggest that patients with HHT treated with bevacizumab could experience amelioration of HHT-related bleeding (57, 58). Currently, bevacizumab is being studied in clinical trials in patients with HHT with recurrent epistaxis (59, 60).

We hypothesize that tumors treated with ALK1 inhibitors have vessels that resemble the pathology seen in HHT and that dual VEGFR/ALK1 inhibition mimics anti-VEGF–treated HHT in producing multistep inhibition of tumor angiogenesis. This pathophysiology helps shed further light on the potential value of combination VEGF and ALK1 pathway inhibition.

Two phase II trials of ALK1/ENG pathway inhibitors are planned in patients with metastatic RCC who have failed prior VEGFR TKI therapy. In each case, patients will be treated with a combination of dalantercept or TRC105 and axitinib or axitinib alone. This design is based on the assumption that tumors developing resistance to anti-VEGF therapy can respond to ALK1/ENG inhibition and that continued VEGFR inhibition is important for optimal antiangiogenesis. This is likely due to the fact that blood vessels that are able to form in the absence of VEGF would still require BMP9/10 for vessel development. Table 1 summarizes all the ongoing phase II trials of ALK1/ENG pathway–inhibiting agents.

<table>
<thead>
<tr>
<th>Table 1. Ongoing trials of ALK1/ENG pathway inhibitors</th>
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<tr>
<td><strong>Tumor type</strong></td>
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<tr>
<td>Dalantercept</td>
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<tr>
<td>Squamous cell cancer</td>
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<td>Endometrial cancer</td>
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<tr>
<td>RCC</td>
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<tr>
<td>Epithelial ovarian, fallopian tube, primary peritoneal cancer</td>
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<tr>
<td>Advanced solid tumors, multiple myeloma</td>
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<tr>
<td>Hepatocellular cancer</td>
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<tr>
<td>Advanced solid tumors</td>
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<tr>
<td>Transitional cell cancer of the bladder</td>
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<tr>
<td>PF-03446962</td>
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<tr>
<td>Metastatic breast cancer</td>
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<tr>
<td>Advanced solid tumor</td>
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<tr>
<td>RCC</td>
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<tr>
<td>Glioblastoma multiforme</td>
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<tr>
<td>Advanced urothelial carcinoma</td>
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<tr>
<td>Glioblastoma multiforme</td>
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<tr>
<td>Recurrent ovarian cancer, fallopian tube carcinoma, primary peritoneal carcinoma</td>
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<td>Hepatocellular carcinoma</td>
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<td>Metastatic castrate-resistant prostate cancer</td>
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<td>Hepatocellular carcinoma</td>
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<td>Advanced solid cancer</td>
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<td>Glioblastoma multiforme</td>
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<td>Advanced RCC</td>
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Future trials

The next 3 to 5 years will be critical for validation of the importance of targeting this pathway and identification of the optimal patient population and setting for these therapies. With the wide range of therapeutic choices, it will be important to identify biomarkers that inform in which patients and at what point during their course of treatment, certain agents will be useful. For example, circulating BMP9/10 may be an indicator of activation of the ALK1/ENG pathway, but these cytokines are often bound to extracellular matrix and, thus, plasma levels are not likely to represent local tumor BMP signaling. Imaging techniques that assess tumor blood flow may be useful in the future but cannot identify which angiogenic molecules are driving angiogenesis at a given time point. Tumor tissue from resected primary tumors is often used as a surrogate for the metastatic disease being treated but may not necessarily reflect all the changes a tumor undergoes over the course of multiple therapies. Tumor biopsies of metastatic lesions will likely need to be incorporated into future studies and, despite current technical limitations of biopsy procurement and tumor heterogeneity, may be the most useful means of assessing pathway activation to select treatments for specific patients.

In addition, the molecular study of the exact mechanisms of action of ALK1/ENG inhibitors has been challenging and complicated by the heterogeneity of angiogenic model systems. Given the complexity of vessel development in vivo, cultured endothelial cell studies yield context-dependent results that are difficult to interpret. Other models, such as chick CAM and Matrigel assays, are also challenging to interpret, especially because these have been performed in the setting of abundant VEGF. Better models of tumor angiogenesis are needed for mechanistic studies. In addition, mechanistic studies may lead to identification of better markers of sensitivity to this pathway and of target engagement.

In conclusion, the ALK1/ENG pathway seems to play a pivotal role in angiogenesis. Years of molecular pathway analysis and genetic studies have paved the way for development of several pathway inhibitors. Although it seems that all three currently studied inhibitors are similar and will yield similar clinical results, the differences among the molecular pathways inhibited may be interesting to consider in the future. The ALK1 and endoglin pathway inhibitors represent a novel class of antiangiogenic agents that have the potential to enhance the treatment of a number of tumor types and improve outcomes of VEGFR TKI therapy.

Disclosure of Potential Conflicts of Interest

R.S. Bhatt reports receiving a commercial research grant from Acceleron Pharma and is a consultant/advisory board member for Acceleron Pharma and Eli Lilly. M.B. Atkins is a consultant/advisory board member for Acceleron Pharma and Eli Lilly.

Authors' Contributions

Conception and design: R.S. Bhatt, M.B. Atkins
Development of methodology: R.S. Bhatt
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): R.S. Bhatt
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): R.S. Bhatt
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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): R.S. Bhatt
Study supervision: R.S. Bhatt

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