Angiogenesis is a fundamental mechanism in biology that describes the multistep process of new blood vessel formation from existing vasculature. The role of angiogenesis in both normal biology and pathology is now firmly established. Angiogenesis occurs during normal tissue turnover and organogenesis, including vertebrate embryonic development, menstruation, and wound repair (1). Conversely, aberrant angiogenesis may contribute to the pathogenesis of a variety of both nonneoplastic (e.g., diabetic retinopathy) and neoplastic disorders (1, 2). In cancer, early angiogenesis facilitates tumor cell growth through the delivery of nutrients and the removal of metabolic waste products from the tumor environment. Initially, in the course of tumor growth and expansion, tumor cells surround the microvasculature, and the resulting capillary "cuff" facilitates their growth. Subsequently, an "angiogenic switch" characterized by the expression of multiple proangiogenic factors is thought to push cells out of a state of relative dormancy and into one characterized by the invasive phenotype—a hallmark of cancer pathogenesis (3, 4). Among the many contributors to this process is the vascular endothelial growth factor (VEGF) family of ligands and receptors. Here, we review briefly the biology of this family and focus on ongoing efforts to develop highly specific monoclonal antibodies to VEGF receptor-2 (VEGFR-2; or kinase insert domain-containing receptor) as therapeutic agents in cancer.

VEGFs and VEGFRs

VEGF is the prototype of a large family of angiogenic and lymphangiogenic growth factors, which includes six structurally homologous, secreted glycoproteins called VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placenta growth factor (5). VEGF-A (commonly referred to as VEGF) was the first such agent to be identified by virtue of its ability to induce vascular permeability (6). The subsequent cloning of the VEGF gene revealed isoforms of various sizes (121, 145, 165, 183, 189, and 206 amino acids) that result from alternative splicing (5, 7). The most abundant being VEGF121 and VEGF165.

Differences in expression levels of VEGF isoforms may relate to distinct roles in normal and abnormal angiogenesis (5, 8). Beyond structural and quantitative variations, however, VEGF isoforms also exhibit differences in bioavailability, binding affinity to residues in the extracellular matrix (e.g., heparin and heparan sulfate), and mitogenic potency (see ref. 7 for review). For example, VEGF121 is readily secreted and present in the systemic circulation, whereas VEGF189 and VEGF206 are sequestered in the extracellular microenvironment after secretion and released only after proteolytic cleavage (9, 10). Moreover, the oligomerization of VEGF isoforms further adds to the biological complexity of the control of angiogenesis. VEGF ligands can form either homodimers or heterodimers, which can bind differentially to and activate the cognate receptors (7). The rich variety of these agents leads to a certain degree of redundancy in some cases, synergy in others, or specialization of function ranging from normal physiologic processes, such as the establishment of new vascular or lymphatic channels and

Abstract

Angiogenesis is a fundamental mechanism of cancer growth and invasion. Current translational approaches are using both small-molecule inhibitors and antibodies that modulate various steps of these processes, and several such compounds have already received regulatory approval for the therapy of specific indications in cancer. Among the many molecular targets involved in the control of angiogenesis, the vascular endothelial growth factor receptor-2 (VEGFR-2; or kinase insert domain-containing receptor) is attractive as shown in part by the efficacy of small-molecule inhibitors directed to this receptor. Two small-molecule inhibitors that target VEGFR-2 have recently been granted approval for the treatment of renal cell cancer and gastrointestinal stromal tumors. The development of antibodies that can selectively block VEGFR-2 could potentially result in improved potency or tolerability. Here, we discuss the role of VEGFR-2 in cancer and ongoing efforts to develop highly specific monoclonal antibodies for cancer therapy.

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maintenance of vascular tone, to a broad array of pathologic ones (5, 8–11).

Biology and Target Validation of VEGFR-2

The VEGF ligands trigger biological effects on their interaction with specific cell surface receptors. The diversity of these receptors also adds to the biological complexity of angiogenesis and lymphangiogenesis. Two receptors were originally identified on vascular endothelial cells: VEGFR-1 (a 180-kDa transmembrane protein also called fms-like tyrosine kinase-1; ref. 12) and VEGFR-2 (a 200-kDa transmembrane protein also called kinase insert domain-containing receptor; ref. 13). A third structurally related tyrosine kinase receptor is the 180-kDa VEGFR-3, which is expressed broadly on endothelial cells during early embryogenesis but becomes restricted to endothelial cells of adult lymphatic tissues and is necessary for adult lymphangiogenesis (14). Two additional receptors with short intracellular domains are neuropilin-1 and neuropilin-2, which are not capable of signal transduction but may instead function as coreceptors for VEGFR-1 and VEGFR-2 to enhance their interactions with their respective ligands (5, 7).

VEGFR-2 Expression and Function

VEGFR-2 is expressed in most if not all adult vascular endothelial cells as well as on circulating endothelial progenitor cells, pancreatic duct cells, retinal progenitor cells, and megakaryocytes (see ref. 15 for review). Accordingly, the safety profile of VEGFR-2–targeting agents may be influenced, in part, by patterns of VEGFR-2 expression. Interestingly, both epithelial and mesenchymal tumor cells more typically express VEGFR-1 than VEGFR-2 (7, 16). Nevertheless, increased expression of VEGFR-2 has been noted on a few tumor cell types, including hematopoietic malignancies (17) and melanoma (18, 19). The significance of tumor-specific expression may not always be evident due partly to technical concerns about assay sensitivity or specificity and partly to biological factors. However, in selected instances, tumor cell–specific VEGFR-2 expression may be a critical driver in the pathogenesis of tumors; this contention is based on observations from in vitro models, such as the induction of proliferative responses in cell culture models (i.e., in the absence of the tumor microenvironment) following exposure of tumor cells to VEGF (19). Thus, it is possible that VEGFR-2 expression on tumor cells in vivo may be an independent mediator of tumor pathogenesis or perhaps potentiate the indirect antitumor effect conferred via the control of the microvasculature.

Recent studies also have provided structural evidence that a single VEGF homodimer binds two molecules of either VEGFR-2 or VEGFR-1. Studies with deletion mutants of VEGFR-2 have revealed that the extracellular immunoglobulin-like domains 2 and 3 are sufficient for high-affinity binding of VEGF, whereas domains 5 and 6 are important for ligand dissociation. VEGF binding induces conformational changes within VEGFR-2 followed by receptor dimerization and autophosphorylation of tyrosine residues in the intracellular kinase domain. Four tyrosine residues, Tyr951, Tyr996, Tyr1054, and Tyr1059, represent critical autophosphorylation sites and serve as high-affinity docking sites for a variety of signaling proteins, including phospholipase Cγ, Ras-GAP, focal adhesion kinase, Src family of tyrosine kinases, phosphoinositide 3-kinase, Akt, protein kinase C, Raf-1, and mitogen-activated protein kinase/extracellular signal-regulated kinase kinase. The interaction of one or more of these molecules with VEGFR-2 may then lead to alterations in cell proliferation, migration, differentiation, tube formation, increase in vascular permeability, and vascular integrity (7, 15).

VEGFR-2 as a Therapeutic Target

Among the many reasons to pursue therapeutic development in this arena are that such agents will likely manifest a safer profile than conventional nonspecific cytotoxic agents. In addition, in contradistinction to cancer cells, their principal targets, the endothelial cells, are genetically stable and thus less likely to develop resistance to their effects as a result of newly acquired somatic mutations in this pathway (20).

Several levels of evidence are typically sought to establish the validity of a particular molecule or pathway for suitability as a therapeutic target. One such level may relate to the expression of the molecular target. VEGF and its receptors are highly expressed in many human cancers. These include carcinomas of gastrointestinal tract, pancreas, breast, bladder, kidney, endometrium, and Kaposi’s sarcoma. In addition, increased expression is also noted in von Hippel-Lindau syndrome and in the majority of renal cell cancer (RCC) associated with von Hippel-Lindau mutations (21), the sine qua non of the VEGF-driven tumor.

Beyond expression levels, the modulation of tumor growth with anti-VEGFR-2 antibodies and small-molecule VEGFR-2 inhibitors has also added to the larger body of evidence that validates VEGFR-2 as a therapeutic target. A comprehensive review of these data is beyond the scope of this review. However, the preclinical experience with DC101, a rat anti-mouse Flk1 (the murine version of VEGFR-2) antibody, serves to illustrate this point. DC101 has been studied extensively in mouse models of angiogenesis, mouse tumors, and human tumor xenografts (7, 15, 22–25). Treatment with DC101 has consistently shown a robust inhibition of dissemination and growth of metastases in several models. In one particularly instructive experiment, DC101 was used in a model of liver metastasis in the mouse in which the tumor cells per se did not express VEGFR-2. Thus, the tumor cells in this case were at best indirect targets of anti-VEGFR-2 therapy. The systemic administration of DC101 resulted in apoptosis of vascular endothelial cells, which was followed by apoptosis of tumor cells. These observations show the potent, albeit indirect, effect of this antibody-mediated strategy targeting VEGFR-2 in tumor control (23). The downstream effects of DC101 may well have more pleiotropic effects downstream of VEGFR-2, such as the modulation of tumor hypoxia that may occur before any noticeable effects on microvessel density (23), and it is possible that one or more such effect is species specific. Nevertheless, it is important to note that no overt toxicity was observed in long-term DC101-treated tumor-bearing or non–tumor-bearing mice. These data suggest that anti-VEGFR-2 antibodies suitable for human use may have similar potency and safety characteristics with large therapeutic windows.
Therapeutic Advances

The past decade has witnessed major advances in the development of therapeutic agents that modulate tumor angiogenesis. Indeed, both VEGF ligands and receptors are now widely acknowledged as bona fide therapeutic targets. Bevacizumab (Avastin), a monoclonal antibody directed against VEGF ligands, has become a mainstay in the treatment of advanced colon cancer, and it has also received regulatory approval for the treatment of lung cancer (7, 26). From a scientific perspective, the success of bevacizumab has amply validated angiogenesis as a therapeutic target in cancer.

Several additional strategies to modulate angiogenesis are being pursued. Both small-molecule inhibitors of VEGF receptors and monoclonal antibodies have entered clinical development, and a partial list of such agents is shown (Tables 1 and 2). Notable among these are the small-molecule inhibitors sunitinib malate (Sutent) and sorafenib tosylate (Nexavar), which have received regulatory approvals (27, 28). Sutent is currently approved for gastrointestinal stromal tumor and RCC (27), and Nexavar is approved for RCC (28). For gastrointestinal stromal tumor, the relevant molecular target is most likely KIT, although an ancillary effect through VEGFR-2 cannot be excluded. For RCC, the most common specific histology (clear cell histology) evaluated in the pivotal studies is one that is associated with a high incidence of von Hippel-Lindau mutations (21), suggesting that VEGFR-2 is likely to be among the most relevant molecular targets for these therapeutics, although not the only one.

Very recently, the manufacturers of sorafenib announced the early closure of a randomized trial comparing this agent to placebo in hepatocellular cancer based on a significant increase in survival noted on the sorafenib-containing arm. Although further details of this trial are not currently available, these data are consistent with the highly vascular nature of this tumor and an antineoplastic effect mediated, at least in part, through the inhibition of VEGFR-2 activity (28, 29).

Rationale for Therapeutic Anti-VEGFR-2 Antibodies

Despite these successes for small molecules in the clinic, several challenges remain to be addressed. Sutent (27) and Nexavar (28) are oral multikinase inhibitors that include VEGFR-2 among their targets. Other kinases inhibited by these compounds include VEGFR1, VEGFR3, the platelet-derived growth factor receptors β, KIT, and fms-like tyrosine kinase-3 (27–30). Placebo-controlled pivotal studies of Sutent in gastrointestinal stromal tumor revealed a remarkable improvement in progression-free survival (24.1 months with Sutent versus 6.4 months with placebo) associated with an improvement in the tumor response rate (31). Similarly, in metastatic RCC, Sutent showed a response rate of 25.5% in one study and 36.5% in a second study (27, 32). A subsequent study in previously untreated RCC also showed a substantial improvement in progression-free survival, as well as improved survival, for patients treated with Sutent compared with IFN-α (33). Similarly, clinical studies of Nexavar (28, 34) showed an improved progression-free survival of 167 days compared with 84 days in a phase III randomized placebo-controlled study of 769 patients with advanced RCC. Overall survival also seemed to be longer in the group treated with Nexavar. These impressive achievements in clinically meaningful end points need to be considered in a greater context that takes into account both the benefit and risks of such therapies. Adverse events with increased frequency noted in patients treated with Nexavar included hand-foot skin rash, hypertension, diarrhea, neuropathy, cardiac ischemia and/or infarction, and fatigue.

Table 1. Anti-VEGFR-2 small molecules in clinical development

<table>
<thead>
<tr>
<th>Drug</th>
<th>Category</th>
<th>Company</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nexavar (sorafenib)</td>
<td>TKI</td>
<td>Bayer and Onyx</td>
<td>Approved for RCC</td>
</tr>
<tr>
<td>Sutent (sunitinib)</td>
<td>TKI</td>
<td>Pfizer</td>
<td>Approved for GIST and RCC</td>
</tr>
<tr>
<td>Vatalanib (PTK787)</td>
<td>TKI</td>
<td>Novartis and Schering AG</td>
<td>Phase III; being developed in colon cancer</td>
</tr>
<tr>
<td>AEZ788</td>
<td>TKI (also inhibits EGFR and ErbB2)</td>
<td>Novartis</td>
<td>Phase I</td>
</tr>
<tr>
<td>Vandetanib (Zactima, ZD6474)</td>
<td>TKI (also inhibits EGFR)</td>
<td>AstraZeneca plc</td>
<td>Phase III; being developed in non–small cell lung cancer, medullary thyroid cancer, and hormone-resistant prostate cancer</td>
</tr>
<tr>
<td>Cediranib (Recentin, AZD2171)</td>
<td>TKI</td>
<td>AstraZeneca plc</td>
<td>Phase II/III; being developed in non–small cell lung cancer and colon cancer</td>
</tr>
<tr>
<td>Pazopanib (786034)</td>
<td>TKI</td>
<td>GlaxoSmithKline</td>
<td>Phase II (solid tumors)</td>
</tr>
<tr>
<td>XL999</td>
<td>TKI</td>
<td>Exelixis</td>
<td>Phase II (solid tumors and hematologic malignancies)</td>
</tr>
<tr>
<td>XL880</td>
<td>TKI (also inhibits Met)</td>
<td>Exelixis</td>
<td>Phase II (papillary RCC, head and neck cancer, gastric cancer)</td>
</tr>
<tr>
<td>XL647</td>
<td>TKI</td>
<td>Exelixis</td>
<td>Phase II (non–small cell lung cancer)</td>
</tr>
<tr>
<td>XL184</td>
<td>TKI</td>
<td>Exelixis</td>
<td>Phase I</td>
</tr>
<tr>
<td>XL820</td>
<td>TKI</td>
<td>Exelixis</td>
<td>Phase I</td>
</tr>
<tr>
<td>Neovastat (AE941)</td>
<td>Natural product; prevents VEGF binding to VEGFR</td>
<td>Aeterna Zentaris</td>
<td>Phase III; development interrupted</td>
</tr>
<tr>
<td>BIBF1120</td>
<td>TKI</td>
<td>Boehringer Ingelheim</td>
<td>Phase I/II</td>
</tr>
<tr>
<td>BMS-582664</td>
<td>TKI</td>
<td>Bristol-Myers Squibb</td>
<td>Phase I</td>
</tr>
</tbody>
</table>

Abbreviations: GIST, gastrointestinal stromal tumor; TKI, tyrosine kinase inhibitor; EGFR, epidermal growth factor receptor.
The latter can be particularly distressing and lead to premature discontinuation from therapy. Both drugs are also subject to binding by plasma proteins and metabolism by cytochrome P450 enzymes; thus, systemic exposure may be subject to interpatient or racial variability due to genetic or biochemical differences. In addition, bioavailability may be altered by the coadministration of food (28).

Although small molecules have clearly shown the value of VEGFR-directed approaches, the promiscuous nature of these drugs with regard to their interaction with several receptors that have similar homologous cytoplasmic domains precludes the conclusion that their antineoplastic effects are mediated by inhibiting a particular receptor. Monoclonal antibodies that specifically block the interaction of angiogenic ligands to particular receptors, specifically VEGFR-2, can establish unequivocally the molecular target responsible for the antineoplastic effect. This, in turn, may result in the development of safer therapeutic products as the toxicities encountered with small molecules can be circumvented if these are due to off-target effects. Finally, concerns about bioavailability and interindividual variability are substantially less with therapeutic monoclonal antibodies. Thus, the field of cancer therapeutics is poised for the development of anti-VEGFR-2 monoclonal antibodies, thereby improving incrementally on the clinical advances already made with small-molecule inhibitors.

### Clinical Progress of Anti-VEGFR-2 Antibodies

To our knowledge, three antibodies directed against VEGFR-2 have entered clinical development. The first of these antibodies was IMC-1C11, a mouse/human chimeric IgG1 (35). In preclinical studies, IMC-1C11 inhibited retinal neovascularization in newborn dogs induced by high concentration of oxygen, modulated menstruation in a monkey model, and significantly prolonged the survival in a leukemia model of immunodeficient mice (35). A subsequent dose escalation phase I clinical trial evaluated the feasibility of administering IMC-1C11 by i.v. infusion at doses ranging from 0.2 to 8.0 mg/kg weekly for 4 weeks and every-other-week schedule in the last cohort. No serious toxicities were observed. Five of 14 enrolled patients had stable disease as their best response by week 4 and continued on therapy, with 1 patient experiencing stable disease for 6 months (36).

IMC-1121B is a second-generation, fully human anti-VEGFR-2 IgG1 antibody that currently is in clinical development (7, 15). This antibody specifically binds VEGFR-2 with an affinity of 50 pmol/L, and at 1 nmol/L, it results in 50% inhibition of the interactions between VEGF and VEGFR-2. In addition, it strongly inhibits VEGF-induced migration of human leukemia cells in vitro and, when administered in vivo, significantly prolongs the survival of immunodeficient mice inoculated with VEGFR-2–expressing human leukemia cells (7, 15). Phase I clinical trials of IMC-1121B are currently in progress in patients with advanced malignancies. Two different schedules of administration are being evaluated (37, 38). Cohorts of three to six patients with advanced cancer but no significant cardiovascular, thrombotic, or bleeding disorders received escalating doses of IMC-1121B. In a weekly administration schedule, a single initial dose with extended pharmacokinetic sampling was followed by weekly infusions starting at 2 mg/kg and to a maximum of 16 mg/kg. To date, 23 patients have entered the study at the first five dose levels. Toxicities have been tolerable and readily manageable. Of note is that hypertension has been noted only sporadically, which suggests that antibodies to VEGFR-2 may differ from small molecules and bevacizumab in this respect. None of the safety findings has been prohibitive with regard to dose escalation. However, all of these observations need to be taken with caution as these studies have not yet been completed.

In these ongoing studies, there have been two confirmed instances of tumor shrinkage designated as partial responses, one in melanoma refractory to multiple previous regimens of anticancer therapy and another in gastric cancer (38). It is interesting to note that some melanoma cells are known to express VEGFR-2 (18, 19). Thus, the antitumor effect in this case may have been due to both direct and indirect effects on tumor cells and vasculature, respectively. Importantly, both objective responses were associated with long durations of stable disease, and one of the two responses occurred after a prolonged phase of stable disease. Seven other patients with a variety of tumors have also had stable disease as their best response. No human anti-human antibodies have been detected. Noncompartmental pharmacokinetic analysis revealed dose-dependent elimination and nonlinear exposure, consistent with saturable clearance mechanisms. Target trough levels required for antitumor activity established from preclinical xenograft studies have also been achieved. Although these studies need to reach maturity, these findings are encouraging and bode well to receptor-directed approaches with blocking antibodies. Moreover, the responses that have occurred in refractory tumors are distinct from those seen with small molecules or with bevacizumab, indicating that treatment with IMC-1121B as a single agent could exhibit a unique potency mechanism that is distinct from these molecules.

Another anti-VEGFR-2 antibody is CDP791, an engineered antibody fragment that has two components: a humanized antibody with two antigen-binding fragments (di-Fab), comprising two molecules of Fab’ cross-linked covalently at their hinge region, and polyethylene glycol attached to the cross-
Conclusions

Angiogenesis has proven to be fertile ground for some of the most remarkable advances in translational research. In cancer, this effort has culminated in the regulatory approval of several novel drugs for use in a variety of settings. Although three agents that modulate key molecular targets in angiogenesis have received such approval, both as monotherapy and in combinations with cytotoxic agents, the development of second-generation agents is being pursued vigorously for several reasons. The major motivation driving this effort is to bring forward novel drugs that are ideally more potent and less encumbered by the side effects of their predecessors. The development of monoclonal antibodies to VEGFR-2 may represent a reasonable strategy toward the fulfillment of this promise. The three anti-VEGFR-2 monoclonal antibodies that have been subjected to testing in patients have shown adverse event profiles that seem to be reversible and readily manageable by clinicians. In addition, the utility of selected pharmacokinetic and pharmacodynamic variables is likely to lead to more rational and predictable dosing and scheduling with antibodies. Finally, the provocative new observation that at least one of these agents is able to produce tumor regressions can potentially stimulate new developmental paradigms in cancer research. In one sense, it recapitulates the observation from certain preclinical models and suggests that antiangiogenic therapy per se can have tumor-killing potential. Therefore, such agents should not simply be regarded as chaperones that improve the delivery of cytotoxic agents to tumor sites without doing much else. It also suggests that tumors beyond RCC that may not necessarily harbor von Hippel-Lindau mutations could still be addicted to signaling by specific molecules involved in angiogenesis and that interdiction in such tumors with antiVEGFR-2 or other antiangiogenic agent could have favorable effects. Ultimately, however, the greatest therapeutic benefit may be derived with combination therapy using other targeted agents, cytotoxics, or both. Thus, angiogenesis continues to harbor biological mysteries and hold significant new promise for the future of cancer therapy.
Review: Monoclonal Antibodies to the Vascular Endothelial Growth Factor Receptor-2 in Cancer Therapy

Hagop Youssoufian, Daniel J. Hicklin and Eric K. Rowinsky


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