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VEGF Trap as a Novel Antiangiogenic Treatment Currently in Clinical Trials for Cancer and Eye Diseases, and VelociGene®-based Discovery of the Next Generation of Angiogenesis Targets

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The concept that tumors can be controlled by directly targeting their vascular supply has finally come of age, because clinical trials using a humanized monoclonal antibody that blocks VEGF have demonstrated exciting efficacy in cancer patients, as well as in vascular eye diseases that can lead to blindness. However, data suggest that these current regimens may not provide complete VEGF inhibition and, thus, that the maximum therapeutic potential of VEGF blockade has not yet been achieved. We describe the status of a very potent and high-affinity VEGF blocker, termed the VEGF Trap, that may provide the opportunity to maximize the potential of VEGF blockade in cancer as well as in vascular eye diseases. We also describe use of the VEGF Trap as a research tool, when coupled to high-throughput mouse genetics approaches such as *VelociGene®* that can be exploited in strategies to discover and validate the next generation of angiogenesis targets.

The concept that tumors can be controlled by directly targeting their vascular supply has finally come of age. The first antiangiogenesis approach to be validated in human cancer patients involves blocking vascular endothelial growth factor (VEGF-A). In this regard, the most advanced clinical data have been generated with a humanized monoclonal antibody termed bevacizumab (Avastin) that directly binds and blocks all isoforms of VEGF-A (Ferrara et al. 2004). Despite the promising data achieved to date, dose-response studies suggest that higher doses of bevacizumab may provide even greater benefit (Yang et al. 2003; Yang 2004), implying that current bevacizumab regimens may not provide optimal VEGF inhibition and thus may not have yet demonstrated the maximum potential of VEGF blockade in cancer. In addition to the promise of anti-VEGF approaches in cancer, blocking VEGF-A has also been impressive in maintaining and improving vision in wet age-related macular degeneration (AMD), a disease marked by leaky and proliferating vessels which distort the retina, and these data suggest that VEGF blockade may provide benefit in other eye diseases involving vascular leak and proliferation (Bergsland 2004). Efficacy in wet AMD has most notably been achieved using a modified fragment of the bevacizumab antibody, termed ranibizumab (Lucentis), delivered via monthly intraocular injections (Brown et al. 2006; Heier et al. 2006).

In this paper, we focus on the development and status of a novel VEGF-blocking agent, termed the VEGF Trap, that retains many of the advantages of a blocking antibody but may offer further potential (Holash et al. 2002). The VEGF Trap consists of portions of VEGF receptors that have been fused to the constant region of an antibody, resulting in a fully human biologic with exceedingly high affinity that blocks not only all isoforms of VEGF-A, but also related VEGF family members such as placental growth factor (PlGF). The VEGF Trap also displays extended pharmacological half-life, allowing long-term as well as very high affinity blockade. The VEGF Trap has performed impressively in extensive animal studies of cancer and eye diseases, and initial clinical trials appear promising. The VEGF Trap may provide the opportunity to explore the potential of more complete VEGF blockade in cancer, as well as the opportunity for more complete blockade and even longer-interval dosing regimens in eye diseases. To conclude this paper, we describe how the VEGF Trap can be used as a research tool in efforts to discover and validate the next generation of targets in the field of angiogenesis.

DISCOVERY OF VEGF AND ITS REQUISITE ROLES DURING NORMAL DEVELOPMENT AND IN DISEASE SETTINGS

Initial studies by Dvorak and his colleagues (Senger et al. 1986; Dvorak et al. 1999) identified a protein in tumor ascites fluid that was capable of inducing vascular leak and permeability, which they termed vascular permeability factor (VPF). Independent efforts by Ferrara and his colleagues to identify secreted factors that could promote tumor angiogenesis led to the discovery of a protein in bovine pituitary follicular cell conditioned medium with mitogenic properties for endothelial cells which they termed vascular endothelial cell growth factor (VEGF) (Ferrara and Henzel 1989; Leung et al. 1989). Upon sequencing and further studies, this VEGF protein was unexpectedly found to correspond to the VPF previously identified by the Dvorak lab. These findings set the stage for a concerted effort to define the role of VEGF/VPF (hereon VEGF) in cancer angiogenesis as well as other settings of vascular disease, which have led to the realization that both of its initially realized actions—i.e., promoting vascular

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permeability and vascular growth—appear critical to understanding its roles during normal biology and in disease.

Approximately two decades of intensive investigation by numerous laboratories has revealed a great deal about VEGF and its actions. It is now clear that VEGF is perhaps the most critical vascular regulator during normal development as well as in many disease states, and moreover, that its dosage must be exquisitely regulated in a spatial and temporal manner to avoid vascular disaster. Disruption of both VEGF alleles in developing mice, which ablates all VEGF production, results in complete failure to develop even a primordial vasculature, demonstrating that VEGF is absolutely essential for the earliest stages of blood vessel development. Still more remarkably, disruption of even a single VEGF allele in developing mice, which decreases VEGF levels by half, also results in embryonic lethality due to severe vascular abnormalities (Carmeliet et al. 1996; Ferrara et al. 1996), demonstrating the need for exquisite regulation of VEGF levels to form normal vessels. Reciprocally, modest increases in VEGF levels during development also lead to vascular disaster and lethality (Miquerol et al. 2000). VEGF continues to be critical during early postnatal growth and development, as evidenced by the lethality and major growth disturbances caused by conditional disruption of the VEGF gene or by administration of VEGF blockers (Ravindranath et al. 1992; Carmeliet et al. 1996; Ferrara et al. 1996, 1998; Gerber et al. 1999a; Ryan et al. 1999; Fraser et al. 2000; Zimmermann et al. 2001; Hazzard et al. 2002; Eremina et al. 2003). However, VEGF blockade in older animals is much less traumatic, affecting only those structures that continue to depend on ongoing vascular remodeling, such as occurs in bone growth plates or during remodeling of the female reproductive organs (Ferrara et al. 1998; Gerber et al. 1999a,b). As discussed in greater detail below, vascular remodeling is absolutely required in a variety of pathological settings, such as during tumor growth, providing major therapeutic opportunities for VEGF blockade in the adult setting in which such blockade can be tolerated.

VEGF ISOFORMS, VEGF FAMILY MEMBERS, AND VEGF RECEPTORS

Further study of the gene encoding human VEGF revealed eight exons separated by seven introns, which results in the generation of four isoforms of increasing size—$VEGF_{121}$, $VEGF_{165}$, $VEGF_{189}$, and $VEGF_{206}$ (subscripts refer to number of amino acids comprising the isoform, with the VEGF isoforms varying in length at their carboxyl termini). The main purpose of these isoforms appears to relate to their bioavailability such that the 121 isoform is diffusible, whereas the higher-molecular-weight isoforms remain bound to the extracellular matrix, requiring cleavage to be released (Houck et al. 1992; Park et al. 1993; Keyt et al. 1996).

Because of the discovery of additional members of the VEGF family, VEGF is now often referred to as VEGF-A. Other members of the VEGF family were identified based on their homology with VEGF, as well as their ability to interact with a related set of cell-surface receptors (Eriksson and Alitalo 1999; see below). The first VEGF relative to be identified is PlGF, and until recently, little was known about its normal function (Maglione et al. 1991). Whereas mice lacking PlGF appear to undergo normal vascular development, recent findings indicate that adult mice lacking PlGF exhibit deficiencies in certain models of adult vascular remodeling, including in tumors and eye disease models, raising the interesting possibility that the activity of PlGF may be limited to these settings and that blockade of PlGF may provide enhanced efficacy when combined with VEGF blockade (Persico et al. 1999; Carmeliet 2000). Little is known about VEGF-B, and mice lacking VEGF-B are overtly healthy and fertile. VEGF-C and D seem to play more critical roles in the lymphatic vasculature than in the blood vasculature, showing specificity for a VEGF receptor (see below) expressed on this vasculature; administration of both of these factors leads to lymphatic vessel hyperplasia (Joukov et al. 1996; Orlandini et al. 1996; Olofsson et al. 1999).

Following rapidly on the heels of the discovery of VEGF came the identification of two closely related high-affinity receptors for VEGF—FLT1 (FMS-like tyrosine kinase) now termed VEGFR1 (de Vries et al. 1992), and KDR or Flk1, now termed VEGFR2 (Shibuya et al. 1990; Terman et al. 1992; Millauer et al. 1993). These high-affinity receptors share features of many other growth factor receptors, in that they contain an extracellular domain which binds and is dimerized by ligand, and a cytoplasmic tyrosine kinase domain that can be regulated upon binding of ligand to the extracellular domain. VEGFR2 seems to be the receptor which mediates the major growth and permeability actions of VEGF, whereas VEGFR1 may have a negative role, either by acting as a decoy receptor or by suppressing signaling through VEGFR2. Thus, mice engineered to lack VEGFR2 fail to develop a vasculature and have very few endothelial cells (Shalaby et al. 1995), phenocopying mice lacking VEGF, whereas mice lacking VEGFR1 seem to have excess formation of endothelial cells that abnormally coalesce into disorganized tubules (Fong et al. 1995). Mice engineered to express only a truncated form of VEGFR1, lacking its kinase domain, appear rather normal, consistent with the notion that the primary role of VEGFR1 may be that of a decoy receptor (Hiratsuka et al. 1998), and supporting only a minor role for the cytoplasmic kinase domain. The third member of this receptor family, initially called Flt-4 and now termed VEGFR3, does not bind to VEGF-A nor PlGF, and instead binds to VEGF-C and VEGF-D and seems to mediate the actions of these latter two factors on the lymphatic vasculature (Taipale et al. 1999).

In addition to these primary receptors, a number of potential accessory receptors for the VEGFs have been identified, although the requisite roles of these receptors in mediating VEGF responses have not been clearly elucidated. These potential accessory receptors include the neuropilins (Soker et al. 1998).

ROLE OF VEGF IN TUMOR ANGIOGENESIS SUPPORTS CONCEPT OF BLOCKING VEGF AS AN ANTITUMOR STRATEGY

One area of intense study after the discovery of VEGF was the analysis of VEGF expression levels in different tumor types using in situ hybridization. VEGF was found to be expressed in a number of different tumors such as renal, gastrointestinal, breast, ovarian, pancreatic, and lung, but the variability in expression across the tumor and between different tumor types made the simple correlation between VEGF and severity of the cancer impossible (Yoshiji et al. 1996; Sowter et al. 1997; Volm et al. 1997; Ellis et al. 1998; Tomisawa et al. 1999). However, out of these studies came the interesting finding that one tumor type, renal cell carcinoma, had particularly high VEGF expression which correlated with inactivation of the von Hippel Lindau locus, resulting in loss of control of the tumor's oxygen sensor, hypoxia-inducible factor (HIF) (Iliopoulos et al. 1996; Lonser et al. 2003). The upregulation of VEGF in an attempt to reoxygenate the tumor through revascularization led to the belief that this tumor may either be highly sensitive to anti-VEGF therapy or highly refractory. Fortunately, the former seems to be the case (Yang et al. 2003).

Concomitant with the analysis of human tumors for VEGF expression came the development of animal models of cancer where the hypothesis that VEGF was required for tumor vasculature, and thus tumor growth, could be tested. In 1993, 4 years after their discovery of VEGF, Ferrara and colleagues demonstrated that a mouse monoclonal antibody to human VEGF (A.4.6.1) could inhibit the growth of several human tumor types in nude mice with inhibition ranging from 70% to more than 90% (Kim et al. 1993). Subsequent to this observation, a number of laboratories using different strategies to inhibit VEGF signaling have shown to a greater or lesser extent that inhibition of VEGF can have a major impact on tumor growth in mice. In addition to numerous studies using the VEGF-blocking antibody, other strategies to block VEGF in tumor models included blocking antibodies targeting VEGFR2 (Prewett et al. 1999), soluble VEGF receptors acting as circulating decoys to capture VEGF and preventing it from binding cell-surface receptors (Ferrara et al. 1998; Gerber et al. 1999a,b; Liang et al. 2006), dominant-negative VEGF receptors expressed at high levels on tumor surfaces, small-molecule inhibitors of VEGF receptor kinases and other kinases (Smith et al. 2004), antisense oligonucleotides targeting VEGF, and VEGF siRNA (Grunweller and Hartmann 2005; Lu et al. 2005).

As the number of studies increased comparing the different modes of inhibiting VEGF, it became apparent that blocking tumor-derived VEGF without blocking stromal VEGF was not as efficacious, implicating stromal VEGF as a crucial player in tumor growth and angiogenesis. Thus, antibodies such as A.4.6.1 which only block human VEGF did not fare as well in blocking human tumor growth in immunocompromised mice as reagents blocking both tumor and host stroma-derived VEGF (Gerber et al. 2000; Liang et al. 2006).

DEVELOPMENT OF VEGF TRAP

The clinical promise of initial anti-VEGF approaches highlighted the need to optimize blockade of this pathway. Early studies indicated that one of the most effective ways to block the VEGF signaling pathway is to prevent VEGF from binding to its endogenous receptors by administering soluble decoy receptors (Ferrara et al. 1998; Gerber et al. 1999b). In particular, a soluble decoy receptor created by fusing the first three immunoglobulin-like (Ig) domains of VEGFR1 to the constant region (Fc portion) of human IgG1 resulted in a forced homodimer that acted as a very high affinity blocking reagent with 5–20 picomolar binding affinity for VEGF, and in tumor experiments this VEGFR1-Fc reagent was efficacious at approximately 500-fold lower concentration than a similar VEGFR2-Fc construct (Kuo et al. 2001). Despite its high affinity, the VEGFR1-Fc was not a feasible clinical candidate because of its poor pharmacokinetic profile; in rodent studies, this protein had to be administered frequently and at very high doses to achieve efficacious levels. In addition, this agent appeared to have nonspecific toxicity effects that did not seem to be accounted for by its blocking of VEGF (Kuo et al. 2001). We decided to exploit our Trap technology platform (Economides et al. 2003), which involves defining and fusing minimal binding units from different receptor components to generate chimeric fusion proteins that act as high-affinity soluble blockers, in an attempt to create a potent and well-behaved Trap for VEGF. The result was a chimeric fusion protein containing a modified domain 2 of VEGFR1 and the third Ig domain of VEGFR2 fused to the Fc region of human IgG1, resulting in a fully human protein that we term VEGF Trap (Holash et al. 2002). This reagent has the advantage of being fully human and thus potentially non-immunogenic, as well as being substantially smaller than previous fusion proteins and antibodies, raising the possibility that it might allow improved tissue and tumor penetration. In addition, this VEGF Trap had greatly improved pharmacological bioavailability as compared to the initial VEGFR1-Fc reagent, exhibiting about a 300-fold increase in the maximum concentration achieved in the circulation (i.e., C_{max}), as well as about a 1000-fold increase in total circulation exposure (i.e., AUC) (Holash et al. 2002). Importantly, the affinity of VEGF Trap binding to both mouse and human VEGF isoforms (0.58 pM, 0.46 pM) was superior to that of the parental VEGFR1-Fc (~ 5–20 pM) (Holash et al. 2002). In addition, the VEGF Trap also bound PlGF with high affinity (1.8 pM).

To determine whether the improved pharmacological bioavailabity and high-affinity binding of VEGF Trap translated into superior performance in vivo, we first used a short-term and quantitative in vivo model of VEGF activity in which a single dose of VEGF induces a stereotypic reduction in blood pressure. In this acute assay model, we found that equivalent doses of VEGF Trap were indeed far superior to that of the parental VEGFR1-Fc (Holash et al. 2002).

VEGF TRAP EXHIBITS IMPRESSIVE EFFICACY IN PRECLINICAL TUMOR MODELS

On the basis of the above evidence suggesting that the VEGF Trap was a potent VEGF blocker that was efficacious in vivo, we moved to evaluate the VEGF Trap in tumor models. Initial studies confirmed the remarkable efficacy of the VEGF Trap. Not only did the VEGF Trap blunt tumor growth in the early models, but it could completely block tumor angiogenesis in many cases, resulting in completely avascular tumors (Holash et al. 2002). These initial studies inspired exploration of the VEGF Trap in multiple tumor models, in the laboratories of many different investigators, with impressive results in almost every case. In addition to its activity in multiple subcutaneous models of melanoma, glioma, and rhabdomyosarcoma tumors (Holash et al. 2002), the VEGF Trap has been shown to work in multiple pancreatic cancer models (Fukasawa and Korc 2004), Wilms' tumor (Huang et al. 2003), Ewing's sarcoma (Dalal et al. 2005), glioblastoma (Wachsberger et al. 2005), and models of ovarian cancer as well as associated malignant ascites (Hu et al. 2005).

In addition to the above published studies, recent unpublished temporal studies indicate that vascular regression can be seen in most tumors within hours of VEGF Trap treatment, resulting in marked and widespread hypoxia within the tumors. In addition, transcription profiling studies during these temporal studies have revealed a set of endothelial-specific genes that are rapidly and profoundly regulated in response to VEGF Trap treatment. Further studies on some of these genes have led to their identification as potential targets for new antiangiogenesis therapies (see below).

In summary, animal tumor studies have indicated that treatment with VEGF Trap effectively inhibited tumor growth of a wide variety of murine, rat, and human tumor cell lines implanted either subcutaneously or orthotopically in mice. VEGF Trap treatment inhibited the growth of tumors representing a variety of tumor types, including melanoma, glioma, rhabdomyosarcoma, ovarian, pancreatic, renal, and mammary tumor tissue, with a broad therapeutic index. Growth of small established tumors was also inhibited. Histological analysis indicated that treatment with VEGF Trap resulted in the formation of largely avascular and necrotic tumors, demonstrating that tumor-induced angiogenesis was blocked. VEGF Trap was also active in blocking tumor growth in similar animal tumor models in combination with paclitaxel, docetaxel, or radiation, and was synergistic with 5-fluorouracil. VEGF Trap as a single agent and in combination with paclitaxel also prevented the formation of ascites in mouse tumor models (Byrne et al. 2003; Hu et al. 2005).

VEGF TRAP IN CLINICAL TRIALS FOR CANCER

The above results in animal tumor models supported the exploration of the VEGF Trap in human studies. Initial clinical studies are promising (Dupont et al. 2005; Mulay et al. 2006; Rixe et al. 2006) in that the VEGF Trap as a single agent has resulted in objective radiographic responses in several advanced cancer patients suffering from multiply treated chemotherapy-refractory disease, as well as long-term stable disease in patients. Similar data are being generated in patients treated with VEGF Trap in combination with various chemotherapeutic agents. The VEGF Trap is now entering an assortment of additional exploratory as well as potentially pivotal efficacy studies, both as a single agent and in combination with chemotherapy.

VEGF TRAP EXHIBITS IMPRESSIVE EFFICACY IN PRECLINICAL MODELS OF VASCULAR EYE DISEASES

In addition to the role for VEGF in tumor angiogenesis, a variety of studies have indicated that VEGF may play a key pathological role in vascular eye diseases, in particular in diabetic edema and retinopathy settings, and in age-related macular degeneration (AMD), which are leading causes of vision loss and blindness. In these diseases, excess VEGF is thought to result in vascular leak that contributes to abnormal swelling of the retina and resulting vision impairment, as well as in the abnormal growth of choroidal and retinal vessels that can destroy normal retinal architecture. Consistent with these possibilities, the VEGF Trap has demonstrated impressive efficacy in an assortment of animal models of these eye diseases.

Preclinical studies in rodents have shown that VEGF Trap can inhibit choroidal (Saishin et al. 2003) and corneal (Wiegand et al. 2003) neovascularization, as well as suppress vascular leak into the retina (Qaum et al. 2001), and that the VEGF Trap can also promote the survival of corneal transplants by inhibiting associated neovascularization (Cursiefen et al. 2004). In addition, in a primate model of AMD, in which choroidal neovascular lesions and vascular leak are induced by using a laser to create small lesions in the retinas of adult cynomolgus macaques, both systemically and intravitreally delivered VEGF Trap not only prevented development of vascular leak and neovascular membranes when administered prior to laser lesion, but also induced regression when administered after lesions had developed (Wiegand et al. 2005). These preclinical results support a role for VEGF blockade, and in particular for local delivery of the VEGF Trap, in multiple vascular eye diseases ranging from AMD and diabetic eye diseases to corneal injury and transplantation.

VEGF TRAP IN CLINICAL TRIALS FOR VASCULAR EYE DISEASES

The above results in animal models have supported the exploration of the VEGF Trap in human studies of vascular eye diseases. Initial clinical studies in human patients suffering from both AMD and diabetic edema and retinopathy appear quite promising, with evidence in early trials that the VEGF Trap can rapidly and impressively decrease retinal swelling, and that these changes

can be associated with improvement in visual acuity (Nguygen et al. 2006; Shah et al. 2006). The VEGF Trap is now entering more advanced clinical trials in vascular eye diseases.

THE NEXT GENERATION OF ANGIOGENESIS TARGETS: ANGIOPOIETINS AND Dll4

Despite the promise of anti-VEGF approaches in general, and that of the VEGF Trap in particular, it is clear both from animal studies and from the emerging human trials that tumors display varying degrees of responsivity to VEGF blockade. Whereas some tumors might show marked regression and/or very long term stabilization, other tumors can continue to grow even in the face of anti-VEGF treatments. The realization that some tumors can be relatively resistant to anti-VEGF approaches raises the need for additional antiangiogenesis approaches that might be useful in such settings. Toward this end, as noted above, we performed transcriptional profiling screens to identify endothelial-specific targets that are markedly regulated either by VEGF blockade or by excess VEGF activity, reasoning that such targets might prove interesting as new antiangiogenesis targets. Confirming the potential of such a screen, one target that was "rediscovered" via such screens was Angiopoietin-2. We had previously independently identified the Angiopoietins as key new angiogenic regulators that seemed to work in tandem with the VEGFs (Davis et al. 1996; Suri et al. 1996; Maisonpierre et al. 1997; Valenzuela et al. 1999; Yancopoulos et al. 2000; Gale et al. 2002), and moreover, obtained substantial data that Angiopoietin-2 in particular was specifically induced in tumor vasculature and that it was important for tumor angiogenesis (Holash et al. 1999); a recent study employing Angiopoietin-2-blocking antibodies confirmed notable antitumor effects (Oliner et al. 2004). On the basis of the confidence in these transcriptional profiling screens engendered by the reidentification of Angiopoietin-2, we explored additional potential targets identified by the screens. Among these targets we have reported the identification of Delta-like ligand 4 (Dll4) (a ligand for the Notch family of receptors) as a gene that is markedly and specifically induced in tumor vasculature (Gale et al. 2004). Moreover, Dll4 is strikingly up-regulated in VEGF-overexpressing tumors and down-regulated in tumors by VEGF blockade. Using VelociGene® technology, which provides a high-throughput approach to create mouse mutants for genes of interest (Valenzuela et al. 2003), we found that mice lacking Dll4 exhibit profound vascular defects early in development (Gale et al. 2004). Remarkably, and as previously seen only for VEGF (see above), deletion of even just one of the two Dll4 alleles in developing embryos resulted in embryonic lethality due to vascular defects (Gale et al. 2004). All this evidence for a critical role for Dll4 in normal as well as tumor angiogenesis provided a rationale to develop blockers for Dll4. Recent testing in tumor models indicates that Dll4 may indeed prove to be an important new antiangiogenesis target, either alone or in combination with the VEGF Trap, or in settings of relative resistance to anti-VEGF therapies. In addition, the success with this screen in terms of yielding Dll4 as an exciting new antiangiogenesis target has led us to rigorously pursue several additional similarly identified targets.

SUMMARY

In summary, using our Trap technology platform (Economides et al. 2003), we have created the VEGF Trap, a very potent VEGF blocking agent with excellent pharmacological properties. This drug has proven to be highly efficacious in a number of diverse preclinical models. It dramatically inhibits the growth of a variety of types of tumors and can even cause frank tumor regression in some settings. In other preclinical cancer models, we have found that combination of VEGF Trap with a cytotoxic agent can result in potency far greater than that of either single agent. Furthermore, the VEGF Trap is also very effective in animal models of vascular eye diseases. The impressive efficacy in preclinical models of cancer and eye diseases provided a rationale for advancement of the VEGF Trap into clinical trials, where it is producing promising initial results in both cancer and eye diseases.

In addition to its potential therapeutic value in cancer and vascular eye diseases, the VEGF Trap is also an invaluable research tool. Transcription profiling screens using VEGF Trap have allowed a number of strategies designed to identify new antiangiogenesis targets. It is hoped that these strategies are helping to identify the next generation of antiangiogenesis targets, which may work either alone or in combination with the VEGF Trap, or in settings of relative resistance to anti-VEGF therapies.

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