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Emergence of dual VEGF and PDGF antagonists in the treatment of exudative age-related macular degeneration

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Abstract

Neovascular ('wet') age-related macular degeneration (AMD) is the leading cause of blindness among Caucasians over the age of 55 in the USA and is an important cause of ocular morbidity worldwide. Progress in oncology, and more recently ophthalmology, led to the development of VEGF antagonists, three of which are now approved for the treatment of wet AMD. Recent discoveries in ophthalmology and vascular biology, however, suggest that combined inhibition of VEGF and platelet-derived growth factor (PDGF) may be more beneficial than inhibition of VEGF alone. Accordingly, numerous studies are underway to evaluate the role of anti-VEGF/PDGF combination therapies for the treatment of wet AMD. This review discusses the biology of VEGF and PDGF and current preclinical and clinical data exploring the use of combined VEGF/PDGF inhibitors in the treatment of neovascular age-related macular degeneration.

Keywords

angiogenesis; clinical trials; combination therapy; neovascular age-related macular degeneration; ophthalmology; preclinical studies; PDGF; VEGF; wet AMD

Age-related macular degeneration (AMD) is the leading cause of blindness among Caucasians in the USA and is a major cause of blindness among other ethnic groups. According to the 2000 US census data, AMD accounts for 54% of blindness among Caucasians, 28.6% among Hispanics and 4.4% among blacks [1]. Furthermore, the prevalence of AMD is expected to increase substantially by 2050 [2]. Models indicate that cases of early AMD will increase from 9.1 million in 2010 to 17.8 million in 2050. Wet AMD, which accounts for 10–20% of AMD, is responsible for 80–90% of blindness associated with AMD [3,4].

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Pathologically, AMD is characterized by degeneration of retinal pigment epithelium (RPE) and/or fluid accumulation in the subretinal space [5]. The RPE supports photoreceptors and is separated from the choroid by Bruch's membrane. Changes in Bruch's membrane result in decreased diffusion of oxygen to the pigment epithelium, which leads to RPE degeneration and/or neovascularization of choroidal vessels. In conjunction, weaknesses in Bruch's membrane facilitate extravasation of choroidal vessels into the subretinal space, leakage of fluids and central vision loss. Central vision loss can also be caused by RPE degeneration in isolation.

AMD is classified into early, intermediate and advanced stages based on the Age-Related Eye Disease Study (AREDS) [6,7]. This classification schema has been described extensively [6,7]. Of note, advanced AMD is characterized by geographic atrophy (advanced dry form) or choroidal neovascularization (CNV, wet form). CNV involves leakage of fluid, lipid and blood from choroidal vessels into the retina or subretinal space, which leads to scarring and reduced vision [8].

Current US FDA-approved treatments for wet AMD include laser photocoagulation, photodynamic therapy (PDT) and injectable VEGF antagonists, though the latter is considered the first line of treatment.

Major technologic and biologic discoveries have advanced the treatment of wet AMD. The development of the argon laser in 1964 led to the creation and validation of laser photocoagulation in the 1980s [9–12]. This technology, which causes non-selective thermal tissue destruction [13,14], was improved upon in the 1990s with the development of PDT [14–18]. PDT is more specific for vessels than laser photo-coagulation because PDT uses light to excite a vessel-selective dye, resulting in destruction of blood vessels and immediately surrounding tissue [19,20].

While laser photocoagulation and PDT were being developed, VEGF emerged as a key player in ocular disease [21]. The isolation of human cDNA clones encoding VEGF, the physiologic characterization of VEGF and the identification of the VEGF receptor in the 80s and 90s [22–24] facilitated the development of VEGF antagonists for the treatment of ocular and other neovascular disorders [25–31]. Although VEGF was initially discovered for its angiogenic properties, additional studies have suggested that VEGF also contributes to inflammation/immune dysregulation in CNV lesions. Hence, VEGF antagonists likely target multiple and distinct processes in wet AMD [32]. A number of VEGF antagonists for wet AMD have been FDA approved, such as pegaptanib [33,34], ranibizumab [35–40] and aflibercept [41], or are in late stage development, such as MP0122 [42–44]. Currently, ranibizumab or closely related bevacizumab, but not pegaptanib, is used as first-line therapy in wet AMD.

Although targeting VEGF for the treatment of wet AMD has marked an important advancement in the field of ophthalmology, retina specialists acknowledge the need for other targets in the treatment of wet AMD [45]. In fact, growing clinical and laboratory evidence suggest that dual inhibition of VEGF and PDGF may be more effective than targeting VEGF alone. Angiogenesis requires coordinated activity of VEGF and PDGF, but PDGF may also

contribute to distinct aspects of wet AMD pathology, such as fibrosis. Studies examining post-natal remodeling of the retina provided initial clues as to the importance of VEGF and PDGF in wet AMD [46], while work in cancer models provided the final push to pursue anti-VEGF/PDGF combination therapy for the treatment of wet AMD [47,48].

Clinical trials for dual therapy look promising although, to date, no dual VEGF/PDGF antagonist has received FDA approval for ocular disease. This review describes preclinical and clinical evidence for dual VEGF/PDGF inhibition in the treatment of wet AMD.

VEGF & PDGF signaling

VEGF, PDGF and their cognate receptors are critical for normal and pathologic angiogenesis. Additionally, VEGF and PDGF are important in immunity and scar formation. This section describes VEGF and PDGF signaling, while the next two sections discuss VEGF and PDGF in angiogenesis, immunity and fibrosis. Additional details are available in a number of excellent reviews [49–55]. Figures 1 & 2 describe VEGF and PDGF signaling in angiogenesis. Briefly, VEGF family members include VEGF-A, -B, -C, -D, -E, -F and PlGF [49,51]. VEGF-A induces angio-genesis, while -C and -D induce lymphangiogenesis [56,57]. VEGF-A has four isoforms, VEGF121, VEGF165, VEGF189, VEGF206 [58,59], which interact with receptor tyrosine kinases, including VEGFRs 1, 2 and 3 and coreceptors NRP1 and 2 [49]. VEGF is produced by mesenchymal, epithelial and tumor cells in order to interact with nearby VEGF receptors located on endothelial cells [60]. Knockout studies indicate that VEGFR2 is required for angiogenesis [61]. Receptor activation results in increased migration, vascular permeability/survival and proliferation via CDC42/p38MAPK, PI3K/Akt and PLC- γ /Raf/MEK/ERK, respectively [51]. Hypoxia induces VEGF through induction of transcription factor HIF-1 [62].

PDGF is a hetero- or homodimer of A and B polypeptide chains or a homodimer of C or D chains [54,63–65]. Although PDGF can be released by a variety of cell types, platelets are a major source of PDGF [53]. PDGF binds PDGF receptors, which are located on diverse cell types, including fibroblasts, pericytes and vascular smooth muscle [53,66]. Ligand binding induces hetero- and homodimerization of α and β receptors [55,67,68]. All PDGF molecules but DD bind $\alpha\alpha$ receptors, only BB and DD bind $\beta\beta$ receptors, and but AA bind $\alpha\beta$ receptors [69]. PDGF dimers activate various signaling pathways, including PI3K for cell migration and survival [70,71], Ras for cell growth [72–74] and PLC- γ [75]. Further, examination of $\alpha\alpha$ and $\beta\beta$ receptors indicates that distinct receptors exhibit overlapping yet distinct functions [53,68]. Functionally, VEGF and PDGF exhibit coordinated expression to regulate vessel development, as described below.

The role of VEGF & PDGF in physiologic ocular neovascularization

VEGF and PDGF play related yet separate roles in neovascularization. VEGF facilitates new vessel growth while PDGF stabilizes maturing vessels by supporting pericyte–endothelial interactions [47,48]. In tumor models, VEGF inhibition induces regression of newly formed vessels that are not associated with pericytes, while treatment with PDGF inhibitors disrupts pericyte–endothelial interactions and sensitizes VEGF-resistant vessels to VEGF antagonists

[47,48]. Further, combined inhibition of VEGF and PDGF has been found to be more effective in preventing tumor growth and facilitating tumor regression than inhibition with either molecule alone [47,48].

Evidence that VEGF and PDGF are also important in ocular neovascularization came from a study examining the role of VEGF and PDGF in the developing retina of rats [46]. The rodent retina is a good model to study neovascularization because it exhibits postnatal vascular development and is easily manipulated. Benjamin *et al.* first investigated the developmental timeline of the endothelial plexus and pericyte–endothelial interactions [46]. In accordance with findings in tumor models [47], they observed that the endothelial plexus forms before pericytes spread out to cover secondary and tertiary branches of the vascular tree.

Previous reports using a knockout mouse indicated that endothelial secreted PDGF-B was required to recruit PDGF- β receptor-positive pericytes to the vascular endothelium [76]. Based on these findings, Benjamin *et al.* next asked whether PDGF was important in pericyte recruitment in the eye. To this end, they administered exogenous PDGF-B and observed disruptions in endothelial–pericyte interactions as well as plexus remodeling.

Lastly, Benjamin *et al.* examined VEGF and pericytes in an animal model that recapitulates the pathogenesis of retinopathy of prematurity (ROP). ROP arises from therapeutic administration of oxygen to the newborn. Hyperoxia induces vessel regression, leading to hypoxia and blindness once oxygen delivery is stopped. Interestingly, hyperoxia does not induce ROP when administered after a specific period of susceptibility. Benjamin *et al.* examined the hypothesis that vessel maturation via pericyte coating protects vessels from hyperoxia-induced injury. In their rat model of ROP, they found that only uncoated vessels were susceptible to hyperoxia-induced injury. Further, they observed that administration of VEGF accelerates pericyte coating and protects rats from hyperoxia-induced regression, indicating a role for VEGF in pericyte migration. Consistent with these results, other groups have observed that VEGF and PDGF localize to blood vessels in the human retina [77–79]. These studies highlight the mutual interaction of VEGF, PDGF, pericytes and endothelial cells in physiologic ocular neovascularization.

VEGF & PDGF in immunity & fibrosis

Wet AMD is a complex disease with multiple pathogenic mechanisms, including vascular hyperproliferation, dysregulated immunity and fibrosis. In addition to their role in vasoproliferation, VEGF and PDGF contribute to dysregulated immunity and fibrosis. VEGF has been shown to induce ocular pro-inflammatory factors, such as matrix metalloproteinases [80,81], which interact with other molecules in CNV lesions, such as monocyte chemotactic factor [82], angiopoietins and Tie receptors [83,84], to form a pathologic inflammatory network in CNV lesions. PDGF has been shown to recruit and stimulate profibrotic cells such as macrophages and fibroblasts and likely contributes to fibrosis in the eye as in other tissues [55]. Hence, dual inhibition of VEGF and PDGF target dysregulated immunity and fibrosis in addition to pathologic neovascularization.

VEGF antagonists for treatment of wet AMD

The success of VEGF antagonists in wet AMD (Table 1) has confirmed the value of targeting angiogenesis in CNV lesions and has led to the development of novel anti-angiogenics, such as dual VEGF/PDGF inhibitors. Furthermore, existing marketed anti-VEGF agents are being studied in combination with novel PDGF inhibitors for dual therapy. Thus, it is important to consider the history of VEGF antagonists for the treatment of wet AMD in order to better understand the rationale for dual VEGF/PDGF inhibition strategies.

In December 2004, pegaptanib became the first anti-VEGF agent approved by the US FDA for the treatment of wet AMD [33,34]. It is a 28 nucleotide PEGylated RNA aptamer that binds and blocks the VEGF 165 isoform, which is involved in pathologic ocular neovascularization [85]. Pegaptanib was discovered by Gilead Sciences and licensed to Eyetech and Pfizer in 2000 for late stage development.

Ranibizumab (Genentech) is an affinity matured Fab against VEGF-A. It was FDA approved in June 2006 based on the MARINA and ANCHOR trials, in which ranibizumab outperformed PDT [21,35–37]. Bevacizumab, an anti-VEGF mAb with a similar mechanism of action, had been prescribed off-label prior to ranibizumab approval; however, Genentech postulated that ranibizumab would exhibit improved tissue penetration and potency and avoid immunopathology against the Fc fragment [38–40]. In 2011, however, the CATT trial did not observe a difference in visual outcomes when comparing ranibizumab with bevacizumab despite an approximately 30-fold difference in cost per dose [40].

Additional ocular VEGF antagonists, such as aflibercept and MP0122, have been developed. The primary goal of these novel antagonists is to reduce the dosing schedule. Regenron's aflibercept is a decoy receptor consisting of portions of VEGFR1 and VEGFR2 fused to the Fc portion of IgG1 [41]. It was approved for the treatment of wet AMD in 2011. Compared with bevacizumab and ranibizumab, which are more effective than pegaptanib, evidence suggests that aflibercept dosing may be extended to an 8-week interval regimen versus every 4 weeks as approved for ranibizumab [41].

MP0122 (Molecular Partners, Allergan) is a DARPin-based biologic that antagonizes VEGF-A [42]. It has gone through Phase I/IIa clinical trials for wet AMD and diabetic macular edema [43,44]. Evidence suggests that at high doses it has the potential to be effective for 12–16 weeks. If these effects are validated, it would represent a substantial extension in the dosing interval compared with currently approved anti-VEGF injectables [43,44]. Nonetheless, further clinical studies are required to substantiate the safety and efficacy of MP0122 for treatment of wet AMD.

Preclinical data supporting the use of dual VEGF/PDGF antagonism in the treatment of wet AMD

Dual inhibition of VEGF and PDGF has been an important treatment strategy for numerous diseases. As of 2007, there were over 15 therapies in use or in development that involved combined inhibition of VEGF and PDGF [86]. Some of these agents, such as sorafenib, have

been validated in major clinical trials [87]. Broadly, VEGF and PDGF inhibitors fall into two categories: small molecule inhibitors of the active kinase domains of VEGF and PDGF receptors (VEGFR, PDGFR) [88–90] and biologic agents (e.g., antibodies, aptamers and decoy receptors) that bind directly to VEGF or PDGF and prevent ligation with their cognate receptors [91]. Due to similarities in the kinase domains of VEGFR and PDGFR, many small molecule inhibitors have some degree of cross-inhibition between these receptors [86]. By contrast, biologic agents tend to have high affinity and specificity for the individual VEGF and PDGF peptides; thus cross-reactivity between targets does not occur and two separate biologic agents are required to simultaneously target both VEGF and PDGF pathways.

The benefit of dual VEGF/PDGF therapy has been demonstrated in animal models of ocular disease using small molecules and antibody-derivatives targeting VEGF and PDGF (Table 1). Jo *et al.* conducted one of the first preclinical studies examining VEGF and PDGF inhibition in a laser-induced CNV model in mice [92]. In this study, it was shown that combined administration of anti-VEGF and anti-PDGF aptamers was superior to anti-VEGF therapy alone for both prevention and treatment of laser-induced CNV.

Preclinical studies have also examined the use of multi-kinase small molecule inhibitors, such as sunitinib and pazopanib, in models of pathologic ocular neovascularization [88,90]. Sunitinib is a small molecule receptor tyrosine kinase inhibitor that prevents phosphorylation of VEGFR2 and PDGFR- β *in vivo* [93] and is approved for use in the treatment of renal and gastrointestinal cancers [94,95]. In 2010, Perez-Santonja *et al.* reported that administration of sunitinib is more effective than bevacizumab at reducing corneal neovascularization in a suture-induced corneal neovascularization model in rabbits. Sunitinib reduced corneal neovascularization 83.3% in comparison with a reduction of 28.5% with bevacizumab [88].

Pazopanib is a small molecule inhibitor of VEGFR, PDGFR and c-Kit that is approved for the treatment of renal cell carcinoma and certain types of soft tissue sarcoma [96,97]. In 2009, Takahashi *et al.* reported that pazopanib reduces neovascularization in mice with laser-induced CNV [90]. In this study, mice were administered drug or vehicle by gavage or injection for 7 days. Twice-daily administration of 100 mg/kg pazopanib by gavage resulted in a 71% reduction in CNV while once-daily administration of 100 μ g pazopanib by injection resulted in a 40% reduction in CNV [90].

Together, these preclinical data indicate that both antibody and small kinase-based VEGF/PDGF antagonists are effective in animal models of pathologic ocular neovascularization and that combined VEGF/PDGF inhibition is more effective than VEGF inhibition alone.

Clinical data supporting the use of dual VEGF/PDGF antagonism in the treatment of wet AMD

The identification of the cDNA for human VEGF in the late 1980s and characterization of its physiologic role in the early 1990s facilitated the development and approval of multiple VEGF antagonists, such as ranibizumab, pegaptanib and aflibercept, for the treatment of wet

AMD [21,41,98]. However, combination therapy with VEGF and PDGF antagonists offers the theoretical benefit of targeting both endothelial cells and pericytes as well as preventing subretinal fibrosis, which is also mediated by PDGF [99,100]. In this way, dual blockade of VEGF and PDGF has the potential to be a more potent inhibitor of pathologic angiogenesis and prevent the insidious subretinal scarring that occurs following CNV regression. It is the latter that ultimately limits the visual potential in AMD after the CNV has been stabilized. Clinical studies evaluating dual VEGF/PDGF inhibitors in wet AMD are described in Table 1.

Sorafenib is a small molecule that inhibits VEGFR, PDGFR and Raf kinases and is approved for the treatment of advanced renal cell carcinoma and hepatocellular carcinoma [87,101]. In 2008, Diago *et al.* reported two cases in which addition of oral sorafenib to ranibizumab resulted in marked improvement in patients with wet AMD [102]. Oral sorafenib was administered three-times per week for 1 month following ranibizumab injection. Visual acuity improved from 20/70 to 20/50 in the first patient and stabilized between 20/20 and 20/40 in the second patient. Intraretinal fluid also decreased for both patients by the end of treatment [102].

Pazopanib (GlaxoSmithKline), a multi-kinase inhibitor, is currently being tested in clinical trials as a topical eye drop and tablet ([Clinicaltrials.gov](https://clinicaltrials.gov) identifiers: NCT01134055, NCT01154062). In a Phase I/II trial, oral pazopanib was delivered to patients with wet AMD for 28 days. Pazopanib was well tolerated and resulted in improvements in vision and retinal edema [103].

E10030 (Ophthotech), an anti-PDGF pegylated aptamer, is being evaluated in clinical trials as an adjunct to ranibizumab ([Clinicaltrials.gov](https://clinicaltrials.gov) identifier: NCT01089517). Ophthotech has also reported successful completion of Phase I and II trials for E10030. In June 2012, the company announced that co-administration of E10030 with ranibizumab to patients with wet AMD resulted in a 62% increase in visual outcome compared with ranibizumab alone [104]. Patients were administered 0.5 mg of ranibizumab alone or with 0.3 or 0.5 mg of E10030 once every 4 weeks over 24 weeks in a prospective, randomized, fully masked trial. This 2012 announcement is in light of a 2009 ARVO report that E10030 was well tolerated in patients with wet AMD [91]. In his report, E10030 was administered to patients with wet AMD as a single injection or in three monthly injections in conjunction with ranibizumab for 3 months. No drug-related adverse events were observed; the only adverse events were caused by intravitreal injection. Together, results from these trials suggest that E10030 is well tolerated and performs better than ranibizumab alone.

Xcovery Vision recently announced initiation of a Phase I/II trial of an oral VEGFR/PDGFR kinase inhibitor, X-82, in patients with AMD ([Clinicaltrials.gov](https://clinicaltrials.gov) identifiers: NCT01674569) [105]. This study will explore safety and preliminary biologic activity at escalating doses of X-82. Prior studies of X-82 in oncology patients suggest a relatively good tolerability profile compared with earlier generation kinase inhibitors [106]. Oral therapy for wet AMD offers significant advantages over existing injectable formulations with regard to patient comfort and ocular safety and has the potential to prevent disease in the fellow eye if conversion to wet AMD has not yet occurred.

Although these isolated cases of sorafenib therapy and early clinical trials with pazopanib and E10030 do not offer conclusive evidence of the benefits of dual VEGF and PDGF inhibition for wet AMD, they do suggest the potential for further development in this area. Basic scientific studies and animal models of diseases clearly suggest these mechanisms are complimentary for inhibition of angiogenesis [47,88,90,92], and such strategies have proven useful in other therapeutic areas such as oncology [87,101,107,108]. As these programs advance into late-stage clinical trials, we hope to learn more about the prospects of dual VEGF/PDGF inhibition for treatment of wet AMD.

Other growth factors implicated in wet AMD: PlGF, IGF-1, angiopoietin & PEDF

In addition to VEGF and PDGF, other growth factors may contribute to CNV. PlGF is a member of the VEGF family. It has been found in human and experimental CNV membranes and blocking PlGF in mice prevents laser-induced CNV [109]. IGF-1 is a downstream effector of GH. It has been found in human CNV membranes and can induce VEGF release from cultured RPE cells [110]. Angiopoietin is a factor secreted by angiogenic endothelial cells. It binds Tie-2 tyrosine kinase receptor. Isoforms 1 and 2 have been observed in surgically excised subfoveal membranes in patients with advanced AMD [83]. Pigment epithelium-derived factor (PEDF) is an inhibitor of angiogenesis that is produced by RPE [111]. In addition to reducing neovascularization in animal models [112], results from Phase I trials using an adenoviral delivery vector for PEDF suggest that PEDF may have antiangiogenic effects in patients with wet AMD [113]. Aside from PEDF, which has undergone Phase I trials, non-VEGF/PDGF growth factors have received less attention as targets of ocular neovascularization. Additional research should be conducted to determine if any of these factors are viable targets for wet AMD.

Expert commentary

Neovascular AMD is a major cause of visual disability worldwide, yet current treatment strategies have substantial limitations [1–4]. Advancements in vascular biology, in part fueled by cancer research, led to the development and the US FDA approval of the first pharmacotherapies for wet AMD: pegaptanib, ranibizumab and recently aflibercept [33,35–39,41,85,114]. Although the development of VEGF inhibitors for wet AMD has been a major therapeutic advancement, work in oncology and vascular biology indicates that combined inhibition of VEGF and PDGF in wet AMD may be more effective than VEGF inhibition alone. VEGF stimulates early vessel growth while PDGF stabilizes maturing vessels by recruiting pericytes to the vascular endothelium [47,48]. Hence, dual inhibition offers the opportunity to target both immature and maturing vessels. Additionally, PDGF inhibition has the added theoretical benefit of reducing subretinal scarring that follows CNV regression [99,100]. Such scarring limits the visual potential in AMD after stabilization of the CNV. Recent case studies with sorafenib and early-stage clinical trials with pazopanib (GSK) and E10030 (Ophthotech) suggest that combined VEGF/PDGF inhibition is more effective than anti-VEGF monotherapy [102–104]. Although these early studies are

promising, we hope to learn more about the potential for dual VEGF/PDGF inhibition for wet AMD as programs for pazopanib and E10030 advance into late-stage clinical trials.

Five-year view

Neovascular AMD is a major cause of visual impairment worldwide despite available therapies. Preclinical and clinical evidence suggest that dual VEGF/PDGF inhibition may result in greater visual improvement than VEGF inhibition alone. PDGF inhibition also has the added theoretical benefit of reducing subretinal scarring following CNV regression, although clinically this has not been evaluated. Due to patient discomfort and the potential risk and side effects of intravitreal injection, a goal of many novel ocular injectables, including VEGF antagonists for wet AMD, is to reduce the dosing regimen. It is currently not known whether dual VEGF/PDGF antagonists will be successful in an 8-week or better schedule, as has been observed with some of the newer VEGF antagonists. Nonetheless, we are excited for the potential impact dual VEGF/PDGF inhibition could have on wet AMD and hope to learn more as clinical programs advance into late-stage trials.

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Key issues

- Age-related macular degeneration (AMD) is a major cause of visual impairment worldwide, it accounts for 54% of blindness among Caucasians in the USA and early cases are expected to increase from 9.1 million in 2010 to 17.8 million in 2050.
- Although wet AMD accounts for 10–20% of AMD, it is responsible for 80–90% of blindness associated with AMD.
- In wet AMD, changes in Bruch's membrane lead to choroidal neovascularization (CNV) and leakage of fluid, lipid and blood into the retina or subretinal space.
- VEGF antagonists are currently the preferred form of treatment for wet AMD; approved agents include pegaptanib, ranibizumab and aflibercept.
- VEGF stimulates development of the endothelial plexus, while PDGF induces pericyte recruitment to vascular endothelium, facilitating vessel maturation.
- Dual VEGF/PDGF therapies have been approved for the treatment of other neovascular diseases such as cancer.
- In wet AMD, dual VEGF/PDGF inhibition offers the potential to induce vascular regression, which is not seen with current VEGF antagonists. PDGF inhibition could also reduce subretinal scarring that follows vascular regression.
- Anti-VEGF and PDGF aptamers, sunitinib and pazopanib have been successful in animal models of ocular neovascularization.
- Additional research should be conducted on non-VEGF/PDGF growth factors, such as PlGF, IGF-1, angiopoietin and pigment epitheliumderived factor (PEDF), to determine if these could be viable targets in the treatment of wet AMD.
- Isolated case studies with sorafenib and early clinical trials with pazopanib and E10030, an anti-PDGF adjunct to ranibizumab, suggest that dual VEGF/PDGF inhibition has the potential for significant clinical improvement over VEGF antagonism alone in the treatment of wet AMD

Figure 1. VEGF signaling in angiogenesis.

VEGF-A and VEGFR2 are the major VEGF and VEGFR family members involved in angiogenesis. Epithelial, mesenchymal and tumor cells release VEGF-A, activating VEGFR2 on endothelial cells. Subsequent activation of CDC42, PI3K and PLC- γ results in EC migration, increased vascular permeability and survival and increased proliferation, respectively. Collectively, induction of these three signaling cascades results in growth of immature blood vessels.

Figure 2. PDGF signaling in angiogenesis.

PDGF is formed from homodimers of A, B, C and D chains and heterodimers of A and B chains. Platelets release PDGF, which binds PDGF receptors on pericytes and other cells. Receptor binding results in homo- and heterodimerization of α and β receptors. Subsequent activation of PI3K, Ras and PLC- γ results in pericyte migration, survival and proliferation. Collectively, induction of these three signaling cascades results in pericyte recruitment to vascular endothelia and vessel maturation.

Table 1.
Overview of clinical and preclinical evidence for dual VEGF/PDGF inhibition in the treatment of neovascular AMD.

Study (year) [†]	Conclusions	Significance	Ref.
<i>Clinical</i>			
Gragoudas <i>et al.</i> (2004)	Pegaptanib is effective in wet AMD	Randomized trial resulted in the US FDA approval of the first VEGF inhibitor for wet AMD	[34]
MARINA Trial (2006)	Ranibizumab is effective in wet AMD (minimal adverse effects)	Randomized trial resulted in FDA approval of ranibizumab, the current first-line treatment for wet AMD	[102]
Diago <i>et al.</i> (2008)	PDGF inhibition augments VEGF inhibition in wet AMD (2 cases)	One of the first reports that PDGF inhibition can augment VEGF inhibition in patients with wet AMD	
ANCHOR Trial (2009)	Ranibizumab > verteporfin PDT for wet AMD	Randomized trial resulted in shift of the first-line therapy for wet AMD from verteporfin PDT to ranibizumab	
CATT Trial (2011)	Efficacy ranibizumab = efficacy bevacizumab in wet AMD	Randomized trial demonstrated that bevacizumab (off-label) is as efficacious as ranibizumab in the treatment of wet AMD	
VIEW-1 & VIEW-2 (2012)	Efficacy bimonthly aflibercept = efficacy of monthly ranibizumab	Randomized trial demonstrated successful development of injectable VEGF antagonist with superior dosing and equal efficacy to ranibizumab	
Pazopanib (NCT01134055, NCT01154062) E10030 (NCT01089517) X-82 (NCT01674569)	Investigational VEGF/PDGF inhibitors exhibit preliminary safety (all) and efficacy (pazopanib, E10030; X-82 ongoing) in early clinical trials (conference proceedings)	Further clinical studies are necessary to evaluate safety and efficacy of dual VEGF/PDGF inhibitors in the treatment of wet AMD	[43]
<i>Preclinical</i>			
Bergers <i>et al.</i> (2003)	Anti-VEGF/PDGF combo > VEGF or PDGF alone in mouse model of pancreatic islet cancer	One of the first <i>in vivo</i> demonstrations that dual inhibition of VEGF and PDGF is more effective than inhibition of VEGF or PDGF alone in a disease model	
Jo <i>et al.</i> (2006)	PDGF inhibition augments VEGF inhibition in models of ocular neovascularization	One of the first demonstrations that PDGF inhibition augments VEGF inhibition in animal models of ocular neovascularization	[92]

[†]Selective clinical trials, case reports and preclinical studies for VEGF and combined VEGF/PDGF antagonists in wet AMD.

AMD: Age-related macular degeneration.