Retinal PHYSICIAN
Article

# VEGF Trap-Eye for Exudative AMD

April 1, 2009

9

## VEGF Trap-Eye for Exudative AMD

**BY JEFFREY S. HEIER, MD**

The vascular endothelial growth factor (VEGF) family is a group of molecules that direct both normal and pathological processes in the body. Certain members of the family and their receptors have been implicated in the angiogenesis underlying pathological disease processes, including the development of eye diseases such as neovascular (wet) age-related macular degeneration (AMD). Despite recent therapeutic advances, wet AMD continues to be debilitating and rapidly progressive,[1] often having a dramatic impact on the lives of patients, as well as their caregivers.[2] It is the leading cause of vision loss in adults aged 50 years and older in many regions, including North America and Europe.[3]

Endothelial growth and angiogenesis, caused by vascular endothelial growth factors, hypoxia, wound healing, and inflammation, are believed to contribute to wet AMD development.[4,5] Blocking VEGF activities has become a mainstay therapy for treating eye diseases that have angiogenesis at their etiological core.[6,7] Although highly effective at delaying disease progression, current therapies do not always prevent loss of visual acuity or consistently improve lost vision. Moreover, treatment often requires frequent office visits and intravitreal injections.[6,8]

### THE VEGF FAMILY AND ITS BIOLOGICAL FUNCTION

Vascular endothelial growth factor has been implicated as a primary player in angiogenesis. The first molecule discovered in this growth factor family was VEGF-A. Other family members found in mammalian species include placental growth factor (PlGF), VEGF-B, VEGF-C, and VEGF-D,[9,10] but VEGF-A and PlGF are believed to be the predominant factors involved in angiogenesis.[11,12] There is evidence that VEGF-A has physiological roles in promoting angiogenesis during development, injury,[13,14] and promoting vascular permeability and thereby wound healing. However, this latter effect can increase leakage in diseases such as wet AMD.[9,10] PlGF has been described as promoting pathological angiogenesis, but its role is less understood than that of VEGF-A.[15,16] Several recent studies using animal models have implicated PlGF purely in disease-related angiogenesis (such as ischemia, inflammation, wound healing, and cancer).[17-21]

There are 2 primary receptors in the VEGF family, VEGFR1 and VEGFR2.[9,10] VEGFR2 is best characterized in terms of its role in angiogenesis: VEGF-A binds to VEGFR2 to stimulate angiogenesis. Although its precise role continues to be investigated, recent research suggests a role for PlGF in promoting pathologic angiogenesis as well. PlGF binds to the VEGFR1, potentially stimulating angiogenesis directly through a signaling pathway through this receptor. Alternatively, the role of PlGF may be to compete with VEGF-A for VEGFR1, allowing VEGF-A to



Exhibit 2362
Page 01 of 07

Samsung v. Regeneron
IPR2023-00442
U.S. Pat. 10,130,681
Exhibit 2362

bind to VEGFR2 and stimulate angiogenesis. PlGF may also serve as a chemoattractant for inflammatory cells stimulating the VEGFR1 on monocytes, increasing their migration and stimulating production of VEGF and other inflammatory mediators. A third receptor, VEGFR3, regulates the development of lymphatic endothelial cells.[9]

---

Jeffrey S. Heier, MD, is a vitreoretinal surgeon at Ophthalmic Consultants of Boston and president of the Center for Eye Research and Education in Boston. He reports moderate financial interest in Regeneron. Writing assistance was provided by Alisa G Woods, PhD and Euro RSCG Life through funding from Regeneron Pharmaceuticals, Inc. and BayerHealthcare.

## VEGF TRAP-EYE DESIGN

Regeneron's VEGF Trap-Eye is a cytokine trap — a soluble fusion protein currently being evaluated to treat retinal diseases. Traps include 2 extracellular cytokine receptor domains and a human Fc region of immunoglobulin G (IgG).[22] Because VEGF Trap-Eye is biologically engineered, specific properties of different naturally occurring component molecules were selected for their therapeutic potential. VEGF Trap-Eye includes specific extracellular components of VEGF receptors 1 and 2 fused to the constant region (Fc) of IgG1.[11,23-25] As seen in **Figures 1 and 2,** this results in 2 identical arms, each constructed from select pieces of both VEGFR1 and VEGFR2. These components were selected based on their high affinity for both VEGF-A and PlGF. VEGF Trap-Eye contains all-human amino acid sequences, giving it a low potential for immunogenicity in humans.[11] VEGF Trap-Eye binds both VEGF-A and PlGF, and it does so with higher affinity than they do to their native receptors. VEGF Trap-Eye uniquely binds both ends of activated dimerized VEGF or PlGF between its arms, preventing it from binding to the native receptors or cross-linking, which is possible due to the binding properties of monoclonal antibodies.[6,11,23,26,27] VEGF Trap-Eye has been developed exclusively for ophthalmic use. The ophthalmic formulation is specifically purified and formulated as an iso-osmotic solution to avoid irritation of the eye.

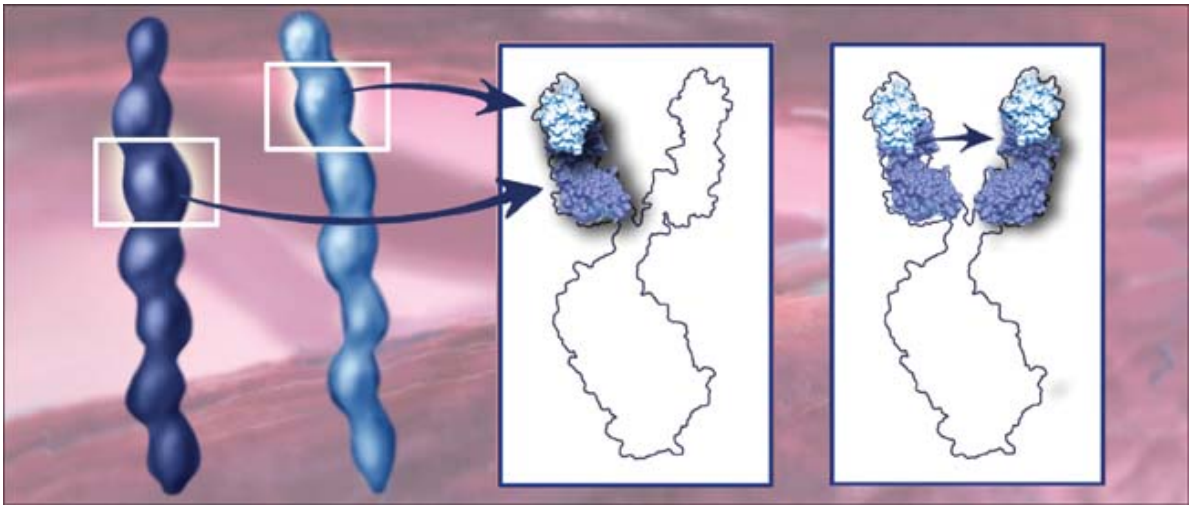

**Figure 1. A key binding domain of VEGFR1 and a key binding domain of VEGFR2 (left) are fused for tight binding affinity for both VEGF-A isomers and PlGF (center). Two dual-domain arms are used for one VEGF Trap-Eye molecule to mimic the natural receptor pairing necessary for growth factor signaling (right).**


Exhibit 2362
Page 02 of 07

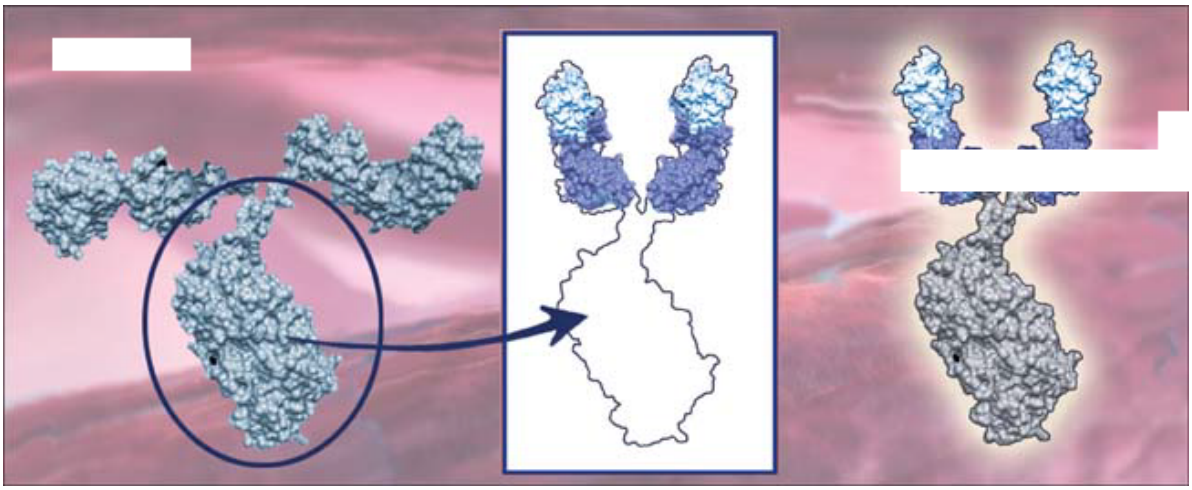

**Figure 2. The Fc portion of IgG1 (left) is fused to the two dual-domain arms (center) resulting in the engineered molecule of VEGF Trap-Eye (right). This exemplifies how a molecule can be designed to possess specific properties of different naturally-occurring molecules with a goal of optimizing therapeutic activity.**

## VEGF TRAP-EYE MECHANISM OF ACTION

VEGF Trap-Eye was developed in an effort to address the unmet need for wet AMD treatments that produce sustainable improvements in visual acuity and/or reduced injection frequency. Based on its unique binding properties (which are distinct from VEGF antibodies/antibody fragments), predictive modeling studies indicate that VEGF Trap-Eye should have a longer duration of activity than currently available treatments.[28,29] Each arm of VEGF Trap-Eye binds to the binding interface on each pole of the active VEGF or PlGF dimer. This forms a stable and inert 1:1 complex with the growth factor,[12] uniquely binding the dimer on both sides. The Trap is aptly named, since the molecule isolates (or traps) the dimer, forming inert complexes with the growth factor[12] that do not interact with more than 1 VEGF Trap molecule. This blocks and effectively arrests the VEGF angiogenesis cascade. It also prevents the creation of multimeric complexes that might aggregate and cause immune responses in body tissues. VEGF Trap-Eye binds VEGF more tightly than native receptors, blocking cell-surface receptor activation.[23] VEGF antibodies and their fragments bind with lower affinity, allowing VEGF dimers to occasionally interact with other molecules, including their receptors.[6,30] VEGF Trap-Eye has undergone phase 1 and phase 2 clinical trials in wet AMD, and is currently in phase 3 testing.

## PHASE 1 STUDY IN WET AMD

CLEAR-IT 1 (CLinical Evaluation of Anti-angiogenesis in the Retina Intravitreal Trial) evaluated safety, tolerability, and biologic activity of intravitreal VEGF Trap-Eye in patients with wet AMD. Safety was the primary endpoint. The primary efficacy measure was the change from baseline in central retinal lesion thickness, determined by an independent optical coherence tomography (OCT) reading center. Best-corrected visual acuity (BCVA), as graded on the Early Treatment Diabetic Retinopathy Study (ETDRS) scale, was conducted using the Electronic Visual Acuity (EVA) system.[31,32]

Part 1 (N=21) was a single, ascending-dose 6-week study. One intravitreal VEGF Trap-Eye injection was given (0.05, 0.15, 0.5. 1, 2, or 4 mg), which reduced retinal thickness and improved visual acuity for the combined experimental groups vs baseline. BCVA scores improved by a mean of 4.4 letters and central retinal lesion thickness diminished by 78.8 µm. The effects of VEGF Trap-Eye appeared durable; patients averaged >5 months before retreatment was necessary in an extension study, with a mean time to retreatment of 166 days.[31,32] Part 2 was a parallel-group, randomized, 8-week trial (N=28), examining 1 intravitreal VEGF Trap-Eye injection (0.15 or 4 mg). Both doses diminished retinal thickness at 2 weeks, with a significantly greater reduction in retinal thickness


Exhibit 2362
Page 03 of 07

in the 4-mg group at weeks 4 and 8. The 4-mg dose significantly improved visual acuity at 4, 6, and 8 weeks. In both parts of this study, intravitreal injection of up to 4 mg of VEGF Trap-Eye was well tolerated, with no clinically significant intraocular inflammation.[31,32] In part 1, no inflammation or endophthalmitis was observed. No serious ocular adverse events occurred, ocular adverse events were mild to moderate in severity, and only 1 ocular adverse event was related to the study drug.[32] Most adverse events in Part 2 were related to the injection procedure. No ocular inflammation was evident. In subjects with increased intraocular pressure, none exceeded 30 mm Hg.[31]

## PHASE 2 STUDY IN WET AMD

CLEAR-IT 2[33] was designed based upon results of CLEAR-IT 1. This was a randomized, controlled, doseand interval-ranging study of intravitreal VEGF Trap-Eye in patients with wet AMD. Patients were randomized into 5 groups (N=159 randomized, N=157 treated) and treated with VEGF Trap-Eye in the study eye at 0.5 mg and 2.0 mg q4 weeks, and 0.5, 2.0, and 4.0 mg q12 weeks for 12 weeks, followed by as-needed (prn) dosing through week 52. Retinal thickness, visual acuity, and safety were measured. The primary endpoint was change in central retinal lesion thickness as determined from Stratus OCT scans read at an independent reading center.

Treatment with VEGF Trap-Eye induced clinically meaningful and durable vision improvement over 1 year. At 12 weeks, VEGF Trap-Eye significantly improved visual acuity, with a mean of +5.7 letters gained for all groups combined. At 12 weeks there was also significantly reduced retinal thickness, with a mean reduction of 119 µm for all groups combined. There was a 5.3 mean letter gain in visual acuity vs baseline (P<.0001) and a mean decrease in retinal thickness of 130 µm vs baseline (P<.0001) for all dose-groups combined at week 52. During the prn dosing period from week 12 to week 52, patients from all dose groups combined received, on average, only 2 additional injections.

Patients receiving 4 monthly doses of VEGF Trap-Eye, either 2.0 or 0.5 mg, for 12 weeks followed by prn dosing thereafter, achieved mean improvements in visual acuity vs baseline of 9.0 letters (P<.0001) and 5.4 letters (P=.085), respectively, and mean decreases in retinal thickness vs baseline of 143 µm (P<.0001) and 125 µm (P<0.0001) at week 52, respectively. During the subsequent prn dosing phase, patients initially dosed on a 2.0 mg monthly schedule received, on average, only 1.6 additional injections, and those initially dosed on a 0.5 mg monthly schedule received, on average, 2.5 injections.

While prn dosing following a fixed quarterly dosing regimen (with dosing at baseline and week 12) also yielded improvements in visual acuity and retinal thickness vs baseline at week 52, the results generally were not as robust as those obtained with initial fixed monthly dosing.

On fluorescein angiography, VEGF Trap-Eye was associated with a reduction in the size of the total active choroidal neovascularization. In addition, all groups showed either stabilization or a reduction in total lesion size, with the 2.0 mg q4 week group reaching a statistically significant reduction.

VEGF Trap-Eye was generally well tolerated and there were no drug-related serious adverse events. There was 1 reported case of culture-negative endophthalmitis/uveitis in the study eye and 1 arterial thrombotic event, neither of which was deemed to be drug-related. The most common adverse events were those typically associated with intravitreal injections.

## PHASE 3 STUDIES IN WET AMD

Two identical, noninferiority Phase 3 studies called VIEW 1 and VIEW 2 (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD)[34] are currently under way to examine the effects of VEGF Trap-Eye in wet AMD. These trials have been designed to evaluate VEGF Trap-Eye vs the standard dosing schedule for the monoclonal antibody fragment ranibizumab, 0.5 mg monthly. Four treatment groups will be followed for 52 weeks: 3 VEGF


Exhibit 2362
Page 04 of 07

Trap-Eye treatment groups, 0.5 mg q 4 weeks, 2.0 mg q 4 weeks, and 2.0 mg q 8 weeks will be compared with ranibizumab 0.5 mg q 4 weeks. VIEW 1 and 2 are randomized, double-masked, active-controlled efficacy and safety studies with a primary endpoint of the prevention of moderate vision loss at the end of 1 year. Visual acuity will be assessed using total number of letters read correctly on the ETDRS chart.

## SUMMARY AND KEY POINTS

VEGF Trap-Eye is a promising investigational compound in development for the treatment of eye diseases characterized by the pathologic production of VEGF, including wet AMD and diabetic macular edema. It is a fully human fusion protein of VEGFR1 and VEGFR2. It uniquely blocks all forms of VEGF-A, as well as PlGF, each arm binding to each pole of an active growth factor dimer. This forms a stable and inert 1:1 complex. Its high affinity allows it to bind growth factors more tightly than naturally occurring VEGF receptors or antibodies, perhaps leading to more complete blockade of VEGF signaling and potentially an increased duration of efficacy. To date, VEGF Trap-Eye has demonstrated encouraging efficacy and safety in phase 1 and 2 clinical trials in the treatment of wet AMD and in a phase 1 study for diabetic macular edema.[35] A phase 2 dose-ranging study comparing various doses of VEGF Trap-Eye for DME administered at various dosing intervals to focal laser treatment is currently ongoing (the DA VINCI study).[34] Phase 3 studies for the treatment of exudative AMD (VIEW1 and VIEW2) are currently in progress and will further explore whether VEGF Trap-Eye will provide a sustainable improvement in clinical effect with prolonged dosing intervals. **RP**

## REFERENCES


1. Gehrs KM, Anderson DH, Johnson LV, Hageman GS. Age-related macular degeneration—emerging pathogenetic and therapeutic concepts. *Ann Med.* 2006;38:450-471.
2. Schmier JK, Jones ML, Halpern MT. The burden of age-related macular degeneration. *Pharmacoeconomics.* 2006;24:319-334.
3. AMDAllianceInternational. Impact of AMD-Overview. http://www.amdalliance.org/professionals/impactofamd/overview.php. Accessed Feb 19, 2009, 2009.
4. Kleinman ME, Ambati J. Molecular Mechanisms of Neovascularization in AMD. *Retinal Physician.* Feb 7, 2009; http://www.retinalphysician.com/article.aspx?article=101897.
5. Lotery A, Trump D. Progress in defining the molecular biology of age related macular degeneration. *Hum Genet.* 2007;122:219-236.
6. Chappelow AV, Kaiser PK. Neovascular age-related macular degeneration: potential therapies. *Drugs.* 2008;68:1029-1036.
7. van Wijngaarden P, Qureshi SH. Inhibitors of vascular endothelial growth factor (VEGF) in the management of neovascular age-related macular degeneration: a review of current practice. *Clin Exp Optom.* 2008;91:427-437.
8. Emerson MV, Lauer AK. Emerging therapies for the treatment of neovascular age-related macular degeneration and diabetic macular edema. *BioDrugs.* 2007;21:245-257.
9. Breen EC. VEGF in biological control. *J Cell Biochem.* 2007;102:1358-1367.
10. Olsson AK, Dimberg A, Kreuger J, Claesson-Welsh L. VEGF receptor signalling- in control of vascular function. *Nat Rev Mol Cell Biol.* 2006;7:359-371.
11. Holash J, Davis S, Papadopoulos N, et al. VEGF Trap: a VEGF blocker with potent antitumor effects. *Proc Natl Acad Sci U S A.* 2002;99:11393-11398.
12. Rudge JS, Holash J, Hylton D, et al. Inaugural Article: VEGF Trap complex formation measures production rates of VEGF, providing a biomarker for predicting efficacious angiogenic blockade. *Proc Natl Acad Sci U S A.* 2007;104:18363-18370.
13. Gerber HP, Hillan KJ, Ryan AM, et al. VEGF is required for growth and survival in neonatal mice. *Development.* 1999;126:1149-1159.




Exhibit 2362

Page 05 of 07

14. Wiegand SJ, Zimmer E, Nork TM, et al. VEGF Trap both prevents experimental choroidal neovascularization and causes regression of established lesions in non-human primates. Invest. *Ophthalmol Vis Sci.* 2005;46:(E-Abstr. 1411).
15. Jain RK, Xu L. alphaPlGF: a new kid on the antiangiogenesis block. *Cell.* 2007;131:443-445.
16. Odorisio T, Cianfarani F, Failla CM, Zambruno G. The placenta growth factor in skin angiogenesis. *J Dermatol Sci.* 2006;41:11-19.
17. Carmeliet P, Moons L, Luttun A, et al. Synergism between vascular endothelial growth factor and placental growth factor contributes to angiogenesis and plasma extravasation in pathological conditions. *Nat Med.* 2001;7:575-583.
18. Ziche M, Maglione D, Ribatti D, et al. Placenta growth factor-1 is chemotactic, mitogenic, and angiogenic. *Lab Invest.* 1997;76:517-531.
19. Rakic JM, Lambert V, Devy L, et al. Placental growth factor, a member of the VEGF family, contributes to the development of choroidal neovascularization. *Invest Ophthalmol Vis Sci.* 2003;44:3186-3193.
20. Khaliq A, Foreman D, Ahmed A, et al. Increased expression of placenta growth factor in proliferative diabetic retinopathy. *Lab Invest.* 1998;78:109-116.
21. Mitamura Y, Tashimo A, Ohtsuka K, Mizue Y, Nishihira J. Placenta growth factor and vascular endothelial growth factor in the vitreous of patients with proliferative vitreoretinopathy. *Clin Experiment Ophthalmol.* 2005;33:226-227.
22. Economides AN, Carpenter LR, Rudge JS, et al. Cytokine traps: multi-component, high-affinity blockers of cytokine action. *Nat Med.* 2003;9:47-52.
23. Rudge JS, Thurston G, Davis S, et al. 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. *Cold Spring Harbor Symp Quant Biol.* 2005;70:411-418.
24. Kaiser PK. Antivascular endothelial growth factor agents and their development: therapeutic implications in ocular diseases. *Am J Ophthalmol.* 2006;142:660-668.
25. Konner J, Dupont J. Use of soluble recombinant decoy receptor vascular endothelial growth factor trap (VEGF Trap) to inhibit vascular endothelial growth factor activity. *Clin Colorectal Cancer.* 2004;4(Suppl 2):S81-S85.
26. Regeneron/Bayer. Data on file. 2008.
27. Cursiefen C, Chen L, Borges LP, et al. VEGF-A stimulates lymphangiogenesis and hemangiogenesis in inflammatory neovascularization via macrophage recruitment. *J Clin Invest.* 2004;113:1040-1050.
28. Stewart MW. Predicted biologic activity of intravitreal bevacizumab. *Retina.* 2007;27:1196-1200.
29. Stewart MW, Rosenfeld PJ. Predicted biological activity of intravitreal VEGF Trap. *Br J Ophthalmol.* 2008;92:667-668.
30. Lowe J, Araujo J, Yang J, et al. Ranibizumab inhibits multiple forms of biologically active vascular endothelial growth factor in vitro and in vivo. *Exp Eye Res.* 2007;85:425-430.
31. Nguyen QD, Hariprasad S, Browning DJ, et al. Interim results from a Phase 1, safety, tolerability, and bioactivity study of intravitreal VEGF trap in patients with neovascular age-related macular degeneration: the CLEAR-IT 1 study. Paper presented at: Annu Meet Assoc Res Vision Ophthalmol (ARVO), 2007; Fort Lauderdale, FL.
32. Nguyen QD, Shah SM, Browning DJ, et al. Results of a phase I, dose-escalation, safety, tolerability, and bioactivity study of intravitreous VEGF Trap in patients with neovascular age-related macular degeneration. Paper presented at: Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO); April 30-May 4, 2006; Fort Lauderdale, FL.
33. Heier J. VEGF Trap-Eye for exudative AMD. Paper presented at: Macula 2009; January 16-17, 2009; New York, NY.
34. Regeneron/Bayer. Data on File. 2009.
35. Do DV, Nguyen QD, Browning DJ, et al. An exploratory study of the safety, tolerability and biological effect of a single intravitreal administration of VEGF trap in patients with diabetic macular edema. Paper presented



Exhibit 2362

Page 06 of 07

at: Association for Research in Vision and Ophthalmology (ARVO); May 6-10, 2007; Fort Lauderdale, FL.

*Retinal Physician*, Issue: April 2009
Table of Contents
Archives

Copyright © 2022, **PentaVision, Inc**. All rights reserved. Privacy Policy


Exhibit 2362