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ASIP Centennial Commentary

A Brief History of Anti-VEGF for the Treatment of Ocular Angiogenesis

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In 1994, *The American Journal of Pathology* published a key article reporting that hypoxic retina produces vascular endothelial growth factor (VEGF), suggesting a role for VEGF in ocular neovascularization. Subsequent developments in anti-VEGF treatment for neovascular eye disease have improved visual outcomes and changed the standard of care in retinal medicine and ophthalmology. ***(Am J Pathol 2012, 181: 376–379; http://dx.doi.org/10.1016/j.ajpath.2012.06.006)***

This story starts in the early 1970s with the proposal by Judah Folkman[1] that tumor growth and progression is dependent on the ability of the tumor to recruit and support formation of a vasculature. This concept prompted a significant effort to purify a tumor-derived angiogenic factor, which led to the identification and purification of acidic and basic fibroblast growth factors (FGF-1 and FGF-2, respectively). However, the very wide distribution of the two growth factors, the fact that both molecules lack a conventional signal sequence, and the subsequent finding of very modest phenotypes in mice lacking either FGF-1 or FGF-2 tempered enthusiasm regarding their possible role in tumor angiogenesis.

The publication in 1989 of two back-to-back articles in *Science*[2,3] began a new phase in this chronicle, one that culminated in the relatively recent development of antiangiogenic therapies. One article reported the isolation of an endothelial mitogen from pituitary follicular cells, which the authors termed vascular endothelial cell growth factor (VEGF).[2] The other article described a tumor-derived factor, termed vascular permeability factor (VPF), that was purified on the basis of its ability to induced vascular permeability.[3] Subsequent cloning and sequencing of the genes encoding these factors led to the realization that the two factors are identical. (Under current nomenclature, the recommended name is vascular endothelial growth factor, with vascular permeability factor as an alternative.) To date, antiangiogenesis has had the most dramatic effect in the treatment of neovascular diseases of the eye, which is addressed here in this commentary.

VEGF and Neovascular Eye Disease

It had long been postulated that areas of ischemic retina, which characterize a number of ocular pathologies (most notably diabetic retinopathy and retinopathy of prematurity) would produce an agent, as yet unknown, that stimulates the growth of new blood vessels. In 1956 George Wise wrote, "Pure retinal neovascularization is directly related to a tissue state of relative retinal anoxia. Under such circumstances, an unknown factor *x* develops in this tissue and stimulates new vessel formation, primarily from the capillaries and veins."[4] Early efforts to identify this factor *x* led to the isolation of acidic and basic fibroblast growth factors from retina.[5] At about the same time, however, two studies using the rapidly growing and highly vascularized glioblastoma tumor model demonstrated that the expression of VEGF is associated with new vessel growth and is driven by hypoxia.[6,7] These findings, together with the fact that VEGF not only acts as an angiogenic factor but is also able to induce permeability, made VEGF particularly attractive as a candidate for the long-sought-after factor *x*.

A key demonstration that hypoxic retina produces VEGF was published in *The American Journal of Pathology* in 1994.[8] In that study, the retinas of nonhuman primates were rendered ischemic by laser photocoagulation of the veins. This resulted in neovascularization of the iris (reminiscent of the rubeosis iridis sometimes associated with proliferative diabetic retinopathy), suggesting the presence of a diffusible molecule. Levels of VEGF mRNA and protein were shown to be elevated in a manner that was spatially and temporally consistent with a role for VEGF in the growth of new vessels. In that same year, there was a report of elevated levels of VEGF in ocular fluids from patients with active neovascular ocular disease but not in ocular fluids from patients with no vessel growth.[9] Together, these articles provided intriguing circumstantial evidence of a role for VEGF in ocular neovascularization.

Evidence in support of a direct role for VEGF in new vessel growth in the eye came from studies using anti-VEGF anti-

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sera,[10] soluble VEGF receptor,[11] anti-VEGF aptamers,[12] and VEGFR1-neutralizing antisera.[13] Evidence that VEGF is not only necessary but sufficient was provided by the demonstration that injection of VEGF into the eye of a nonhuman primate stimulated the growth and permeability of new vessels on the retina, and also induced neovascular glaucoma.[14]

Anti-VEGF Therapy

Neovascular Age-Related Macular Degeneration

The first treatment developed using a VEGF-neutralizing strategy was bevacizumab (Avastin), a humanized anti-VEGF antibody designed to block all VEGF isoforms. In 1997, Genentech (South San Francisco, CA) initiated phase 1 trials of bevacizumab for the treatment of cancer and established that it had minimal toxicity.[15] A phase 2 trial comparing bevacizumab combined with fluorouracil and leucovorin, against a control arm of fluorouracil and leucovorin alone, revealed a longer median survival time in the combined bevacizumab regimen (21.5 months, compared with 13.8 months for the control).[16] A phase 3 trial indicated that the addition of bevacizumab to control groups receiving a regimen of irinotecan, fluorouracil, and leucovorin increased median survival times.[17] Taken together, these results led to approval by the U.S. Food and Drug Administration (FDA) on February 26, 2004, of bevacizumab for the treatment of colon cancer in combination with chemotherapy.

Concomitant with the development of anti-VEGF therapies for cancer, VEGF was found to play a pivotal role in neovascular age-related macular degeneration (NVAMD). NVAMD, or wet AMD, is the leading cause of blindness in the elderly population. One of the first anti-VEGF therapies for NVAMD was pegaptanib (Macugen), an RNA aptamer that binds and neutralizes VEGF165 (and likely also VEGF188, although this has not been substantiated). This therapy, developed by Eyetech Pharmaceuticals (New York, NY), was shown in two large phase 2 and 3 trials to decrease the progressive loss of vision associated with NVAMD.[18] Pegaptanib was approved by the FDA on December 17, 2004, for the treatment of NVAMD, making it the first antiangiogenic therapeutic approved for ocular neovascularization.

After approval of bevacizumab for cancer therapy and given the suspected role of VEGF in NVAMD, systemic intravenous bevacizumab began to be administered to treat NVAMD, as an off-label use. A small open-label, single-center uncontrolled study showed significant improvement in visual acuity, retinal thickness on optical coherence tomography, and angiographic outcomes; after 12 weeks of therapy, the median and mean visual acuity improved by 8 and 12 letters, respectively.[19] Soon after, ophthalmologists began injecting bevacizumab directly into the vitreous cavity as an off-label use in the treatment of NVAMD. Intravitreal injection of bevacizumab was found to be effective in the treatment of NVAMD, with minimal systemic adverse effects, which led to the first studies to demonstrate an improvement in visual function in patients with NVAMD.[20]

It was initially expected that bevacizumab would not diffuse through the retina efficiently enough to reach the choroid, prompting Genentech to generate an alternative molecule. A truncated and modified variant of bevacizumab, known as ranibizumab (Lucentis), was created by alteration of the complementary domain region of bevacizumab, followed by affinity selection by phage display.[21] Subsequent phase 3 clinical studies determined ranibizumab to be an effective treatment for NVAMD, with a significant improvement in vision. Contrary to the original understanding, full-length anti-VEGF antibody does, in fact, diffuse well in diseased retinas. First, the earlier studies examining antibody diffusibility were not, in fact, conducted with anti-VEGF antibodies, but rather with humanized rhuMAb HER2 antibody, which may bind specifically in the retina.[22] Second, the fact that the diseased retina is not intact likely facilitates diffusion of the antibodies.

The effectiveness of ranibizumab was determined by two pivotal trials: the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA) and the Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR). MARINA and ANCHOR were the first phase 3 trials to show improvement in visual outcomes for all forms of choroidal neovascularization in NVAMD.[23,24] Based on this evidence, ranibizumab was approved by the FDA on June 30, 2006, for the treatment of NVAMD.

Recently, bevacizumab and ranibizumab were compared and found to have equivalent visual outcomes. The Comparison of Age-Related Macular Degeneration Treatment Trials (CATT) revealed equivalent effects on visual acuity after 1 year of monthly administration of either bevacizumab or ranibizumab.[25] Similarly, the two drugs were equivalent when given as needed. The results suggest that these two closely related molecules have equivalent clinical efficacy (as might be expected, given their similar modes of action). The current standard of care in the treatment of NVAMD is the use of anti-VEGF antibodies.

Another anti-VEGF strategy, developed by Regeneron Pharmaceuticals (Tarrytown, NY), consists of a chimeric fusion protein comprising the second immunoglobulin domain of VEGF receptor 1, the third immunoglobulin domain of VEGF receptor 2, and the Fc portion of human IgG1.[26] This so-called VEGF-trap (aflibercept) functions as a decoy receptor to sequester VEGF, thereby blocking its biological effects. Aflibercept was developed to improve the pharmacokinetics of VEGF binding. Aflibercept exhibits a binding affinity near 0.5 pmol/L, compared with 50 pmol/L for ranibizumab or bevacizumab, which represents a 100-fold increase in binding affinity. In addition, the intravitreal half-life of aflibercept is 4.8 days, compared with 3.2 days and 5.6 days for ranibizumab and bevacizumab, respectively.[27] The improved pharmacokinetics of aflibercept is thought to decrease the frequency of dosing in patients, with similar efficacy as anti-VEGF antibodies. Phase 3 results from the VIEW trials (VEGF Trap: Investigation of Efficacy and Safety in Wet AMD) revealed that 2 mg of aflibercept dosed every 2 months was not inferior to ranibizumab dosed monthly. Based on these studies, aflibercept was approved by the FDA on November 18, 2011.

Diabetic Retinopathy

In addition to its role in NVAMD, VEGF plays a critical role in diabetic retinopathy and contributes to the development of diabetic macular edema (DME). DME is the leading cause of

vision loss in the working-age population in developed countries. Analogous to the use of anti-VEGF treatment in NVAMD, bevacizumab, ranibizumab, and aflibercept have all been shown to have some efficacy in the treatment of DME. However, given the relatively rapid improvement of macular edema with anti-VEGF treatment, anti-VEGF therapy for DME is likely mediated by modulating VEGF-induced vascular permeability. To date, the FDA has not approved the use of any of the anti-VEGF agents for the treatment of DME. However, ranibizumab has been approved for the treatment of DME in Europe and Australia.

The treatment of DME with bevacizumab has been evaluated in a variety of trials. One of the larger trials investigated intravitreal bevacizumab alone or in combination with intravitreal triamcinolone versus macular laser photocoagulation.[28] The results of the 2-year study showed superiority of visual improvement in the bevacizumab-alone group at the 6-month time point, and these findings were sustained over the 24-month study period. Intravitreal bevacizumab demonstrated only slight superiority in visual acuity over either intravitreal bevacizumab combined with intravitreal triamcinolone or macular laser photocoagulation.

The efficacy and safety of intravitreal ranibizumab was evaluated in the Ranibizumab Injection in Subjects With Clinically Significant Macular Edema With Center Involvement Secondary to Diabetes Mellitus (RISE and RIDE) trials. These parallel studies evaluated monthly intravitreal ranibizumab injections at 0.5 or 0.3 mg versus sham injections in the treatment of DME, with macular laser photocoagulation available according to protocol guidelines. These studies revealed significant improvement in visual acuity (in approximately 63% of patients), decreased macular edema, decreased worsening of retinopathy, and increased likelihood of improvement with laser therapy in the ranibizumab-treated groups. A significant proportion of patients exhibited persistently poor vision despite resolution of macular edema, suggesting that anti-VEGF therapy does not restore damaged retinal tissue. Ocular safety was similar to that in previous ranibizumab studies.[29]

A phase 2 study of aflibercept for the treatment of DME assessed different doses of aflibercept versus macular laser photocoagulation. In general, aflibercept therapy was well tolerated in the eye and resulted in statistically significant visual gains and reduction in macular thickness. One-third of the aflibercept patients gained 15 or more letters from baseline, compared with only 21% in the laser-treated patients. Mean reductions in macular thickness ranged from 127.3 to 194.5 μm, compared with only 67.9 μm in the laser-treated group.

Retinal Vein Occlusions

VEGF neutralization has also been found to be effective in the treatment of macular edema associated with vein occlusions. Retinal vein occlusion is the second most common retinal vascular disease after diabetic retinopathy. Results from the Ranibizumab for the Treatment of Macular Edema following Branch Retinal Vein Occlusion (BRAVO) trial found that ranibizumab at doses of 0.3 and 0.5 mg resulted in a higher proportion of subjects who gained 15 or more letters at the 6-month time point. Specifically, 55.2% (0.3 mg) and 61.1% (0.5 mg) of patients in the ranibizumab groups and 28.8% in the sham group gained 15 or more letters at 6 months. The ranibizumab group also had a statistically significant decrease in retinal thickness, compared with the control group.[30]

Central retinal vein occlusions are also amenable to ranibizumab therapy. The Ranibizumab for the Treatment of Macular Edema after Central Retinal Vein Occlusion Study (CRUISE) trial yielded similar results. The proportion of patients who gained 15 or more letters in visual acuity at 6 months was 46.2% (0.3 mg) and 47.7% (0.5 mg) in the ranibizumab groups and 16.9% in the sham injection group. Similar to findings from other trials, central foveal thickness as determined by optical coherence tomography was significantly reduced in the ranibizumab groups.

Summary

Other significant findings relevant to understanding the role of VEGF in the eye have appeared in the pages of *The American Journal of Pathology*. Insight into the mechanisms of VEGF up-regulation came from studies demonstrating that the inhibition of NAD(P)H oxidase could block ischemia-induced VEGF up-regulation.[31] Consistent with a known role for VEGF in vascular development, retinal pigment epithelial cell-derived VEGF has been shown to play a critical role for in the formation of the choriocapillaris,[32] whereas overexpression of VEGF leads to choroidal neovascularization.[33] The fact that virtually every adult tissue expresses VEGF in a cell type-specific fashion points to a postdevelopmental role for VEGF.[34,35] Consistent with this idea, evidence indicates VEGF is a survival factor and neuroprotectant for retinal neurons,[36–38] observations that have led some to raise concerns regarding chronic VEGF neutralization in patients. One of the efforts to improve the efficacy of anti-VEGF therapy involves the simultaneous blockade of PDGF-B signaling.[39,40]

The progress in scientific development and in treatment of diseases caused by pathological ocular angiogenesis highlights the importance of basic research dedicated to improving patient care. The use of anti-VEGF therapies has introduced a paradigm shift in the treatment of a wide array of ocular diseases, including NVAMD, diabetic retinopathy, and retinal vein occlusions. Before the development of anti-VEGF therapies, these conditions were most often treated with a combination of ablative and nonspecific laser treatment or were simply given careful observation and monitoring, with a universal decline in vision. The current use of anti-VEGF treatment has resulted in improvement of visual outcomes and has changed the standard of care in retinal medicine and ophthalmology.

References

1. Folkman J: Tumor angiogenesis: therapeutic implications. N Engl J Med 1971, 285:1182–1186
2. Leung DW, Cachianes G, Kuang WJ, Goeddel DV, Ferrara N: Vascular endothelial growth factor is a secreted angiogenic mitogen. Science, 1989, 246:1306–1309
3. Keck PJ, Hauser SD, Krivi G, Sanzo K, Warren T, Feder J, Connolly DT: Vascular permeability factor, an endothelial cell mitogen related to PDGF. Science, 1989, 246:1309–1312
4. Wise GN: Retinal neovascularization. Trans Am Ophthalmol Soc 1956, 54:729–826
5. D'Amore PA, Klagsbrun M: Endothelial cell mitogens derived from retina and hypothalamus: biochemical and biological similarities. J Cell Biol 1984, 99:1545–1549

6. Plate KH, Breier G, Weich HA, Risau W: Vascular endothelial growth factor is a potential tumour angiogenesis factor in human gliomas in vivo. Nature 1992, 359:845–848
7. Shweiki D, Itin A, Soffer D, Keshet E: Vascular endothelial growth factor induced by hypoxia may mediate hypoxia-initiated angiogenesis. Nature 1992, 359:843–845
8. Miller JW, Adamis AP, Shima DT, D'Amore PA, Moulton RS, O'Reilly MS, Folkman J, Dvorak HF, Brown LF, Berse B, Yeo TK, Yeo KT: Vascular endothelial growth factor/vascular permeability factor is temporally and spatially correlated with ocular angiogenesis in a primate model. Am J Pathol 1994, 145:574–584
9. Aiello LP, Avery RL, Arrigg PG, Keyt BA, Jampel HD, Shah ST, Pasquale LR, Thieme H, Iwamoto MA, Park JE, Nguyen HV, Aiello LM, Ferrara N, King GL: Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. N Engl J Med 1994, 331:1480–1487
10. Adamis AP, Shima DT, Tolentino MJ, Gragoudas ES, Ferrara N, Folkman J, D'Amore PA, Miller JW: Inhibition of vascular endothelial growth factor prevents retinal ischemia-associated iris neovascularization in a nonhuman primate. Arch Ophthalmol 1996, 114:66–71
11. Aiello LP, Pierce EA, Foley ED, Takagi H, Chen H, Riddle L, Ferrara N, King GL, Smith LE: Suppression of retinal neovascularization in vivo by inhibition of vascular endothelial growth factor (VEGF) using soluble VEGF-receptor chimeric proteins. Proc Natl Acad Sci USA 1995, 92:10457–10461
12. Robinson GS, Pierce EA, Rook SL, Foley E, Webb R, Smith LE: Oligodeoxynucleotides inhibit retinal neovascularization in a murine model of proliferative retinopathy. Proc Natl Acad Sci USA 1996, 93:4851–4856
13. Ozaki H, Seo MS, Ozaki K, Yamada H, Yamada E, Okamoto N, Hofmann F, Wood JM, Campochiaro PA: Blockade of vascular endothelial cell growth factor receptor signaling is sufficient to completely prevent retinal neovascularization. Am J Pathol 2000, 156:697–707
14. Tolentino MJ, Miller JW, Gragoudas ES, Chatzistefanou K, Ferrara N, Adamis AP: Vascular endothelial growth factor is sufficient to produce iris neovascularization and neovascular glaucoma in a nonhuman primate. Arch Ophthalmol 1996, 114:964–970
15. Gordon MS, Margolin K, Talpaz M, Sledge GW Jr, Holmgren E, Benjamin R, Stalter S, Shak S, Adelman D: Phase I safety and pharmacokinetic study of recombinant human anti-vascular endothelial growth factor in patients with advanced cancer. J Clin Oncol 2001, 19:843–850
16. Kabbinavar F, Hurwitz HI, Fehrenbacher L, Meropol NJ, Novotny WF, Lieberman G, Griffing S, Bergsland E: Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. J Clin Oncol 2003, 21:60–65
17. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N, Fyfe G, Rogers B, Ross R, Kabbinavar F: Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004, 350:2335–2342
18. Gragoudas ES, Adamis AP, Cunningham ET Jr, Feinsod M, Guyer DR; VEGF Inhibition Study in Ocular Neovascularization Clinical Trial Group. Pegaptanib for neovascular age-related macular degeneration. N Engl J Med 2004, 351:2805–2816
19. Michels S, Rosenfeld PJ, Puliafito CA, Marcus EN, Venkatraman AS: Systemic bevacizumab (Avastin) therapy for neovascular age-related macular degeneration: twelve-week results of an uncontrolled open-label clinical study. Ophthalmology 2005, 112:1035–1047
20. Rosenfeld PJ, Moshfeghi AA, Puliafito CA: Optical coherence tomography findings after an intravitreal injection of bevacizumab (Avastin) for neovascular age-related macular degeneration. Ophthalmic Surg Lasers Imaging 2005, 36:331–335
21. Chen Y, Wiesmann C, Fuh G, Li B, Christinger HW, McKay P, de Vos AM, Lowman HB: Selection and analysis of an optimized anti-VEGF antibody: crystal structure of an affinity-matured Fab in complex with antigen. J Mol Biol 1999, 293:865–881
22. Mordenti J, Cuthbertson RA, Ferrara N, Thomsen K, Berleau L, Licko V, Allen PC, Valverde CR, Meng YG, Fei DT, Fourre KM, Ryan AM: Comparisons of the intraocular tissue distribution, pharmacokinetics, and safety of 125I-labeled full-length and Fab antibodies in rhesus monkeys following intravitreal administration. Toxicol Pathol 1999, 27:536–544
23. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, Kim RY; MARINA Study Group: Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006, 355:1419–1431
24. Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, Sy JP, Schneider S; ANCHOR Study Group: Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med 2006, 355:1432–1444
25. CATT Research Group, Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL, Jaffe GJ: Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med 2011, 364:1897–1908
26. Holash J, Davis S, Papadopoulos N, Croll SD, Ho L, Russell M, Boland P, Leidich R, Hylton D, Burova E, Ioffe E, Huang T, Radziejewski C, Bailey K, Fandl JP, Daly T, Wiegand SJ, Yancopoulos GD, Rudge JS: VEGF-Trap: a VEGF blocker with potent antitumor effects. Proc Natl Acad Sci USA 2002, 99:11393–11398
27. Stewart MW, Rosenfeld PJ, Penha FM, Wang F, Yehoshua Z, Bueno-Lopez E, Lopez PF: Pharmacokinetic rationale for dosing every 2 weeks versus 4 weeks with intravitreal ranibizumab, bevacizumab, and aflibercept (vascular endothelial growth factor Trap-eye). Retina 2012, 32:434–457
28. Soheilian M, Garfami KH, Ramezani A, Yaseri M, Peyman GA: Two-year results of a randomized trial of intravitreal bevacizumab alone or combined with triamcinolone versus laser in diabetic macular edema. Retina 2012, 32:314–321
29. Nguyen QD, Brown DM, Marcus DM, Boyer DS, Patel S, Feiner L, Gibson A, Sy J, Rundle AC, Hopkins JJ, Rubio RG, Ehrlich JS; RISE and RIDE Research Group: Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology 2012, 119:789–801
30. Campochiaro PA, Heier JS, Feiner L, Gray S, Saroj N, Rundle AC, Murahashi WY, Rubio RG; BRAVO Investigators: Ranibizumab for macular edema following branch retinal vein occlusion: six-month primary end point results of a phase III study. Ophthalmology 2010, 117:1102–1112.e1
31. Al-Shabrawey M, Bartoli M, El-Remessy AB, Platt DH, Matragoon S, Behzadian MA, Caldwell RW, Caldwell RB: Inhibition of NAD(P)H oxidase activity blocks vascular endothelial growth factor overexpression and neovascularization during ischemic retinopathy. Am J Pathol 2005, 167:599–607
32. Marneros AG, Fan J, Yokoyama Y, Gerber HP, Ferrara N, Crouch RK, Olsen BR: Vascular endothelial growth factor expression in the retinal pigment epithelium is essential for choriocapillaris development and visual function. Am J Pathol 2005, 167:1451–1459
33. Spilsbury K, Garrett KL, Shen WY, Constable IJ, Rakoczy PE: Overexpression of vascular endothelial growth factor (VEGF) in the retinal pigment epithelium leads to the development of choroidal neovascularization [Erratum appeared in Am J Pathol 2000, 157:1413]. Am J Pathol 2000, 157:135–144
34. Maharaj ASR, Saint-Geniez M, Maldonado AE, D'Amore PA: Vascular endothelial growth factor localization in the adult. Am J Pathol 2006, 168:639–648
35. Maharaj ASR, D'Amore PA: Roles for VEGF in the adult. Microvasc Res 2007, 74:100–113
36. Nishijima K, Ng YS, Zhong L, Bradley J, Schubert W, Jo N, Akita J, Samuelsson SJ, Robinson GS, Adamis AP, Shima DT: Vascular endothelial growth factor-A is a survival factor for retinal neurons and a critical neuroprotectant during the adaptive response to ischemic injury. Am J Pathol 2007, 171:53–67
37. Saint-Geniez M, Maharaj AS, Walshe TE, Tucker BA, Sekiyama E, Kurihara T, Darland DC, Young MJ, D'Amore PA: Endogenous VEGF is required for visual function: evidence for a survival role on Müller cells and photoreceptors. PLoS One 2008, 3:e3554
38. Gerhardinger C, Brown LF, Roy S, Mizutani M, Zucker CL, Lorenzi M: Expression of vascular endothelial growth factor in the human retina and in nonproliferative diabetic retinopathy. Am J Pathol 1998, 152:1453–1462
39. Jo N, Mailhos C, Ju M, Cheung E, Bradley J, Nishijima K, Robinson GS, Adamis AP, Shima DT: Inhibition of platelet-derived growth factor B signaling enhances the efficacy of anti-vascular endothelial growth factor therapy in multiple models of ocular neovascularization. Am J Pathol 2006, 168:2036–2053
40. Wilkinson-Berka JL, Babic S, De Gooyer T, Stitt AW, Jaworski K, Ong LG, Kelly DJ, Gilbert RE: Inhibition of platelet-derived growth factor promotes pericyte loss and angiogenesis in ischemic retinopathy. Am J Pathol 2004, 164:1263–1273