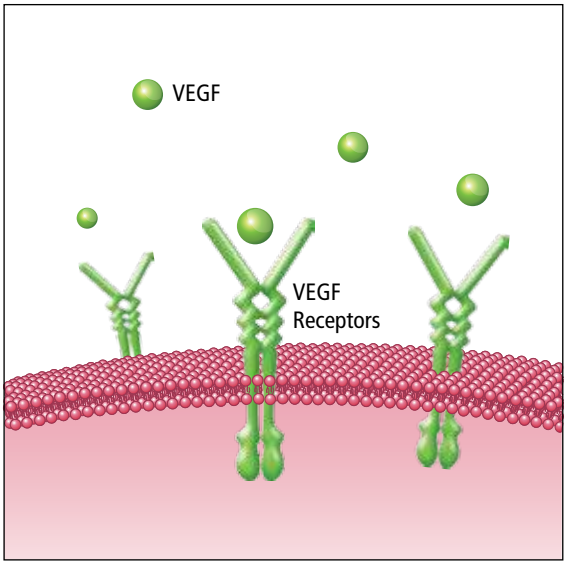
MODULE 9.1
Anti-VEGF Treatments

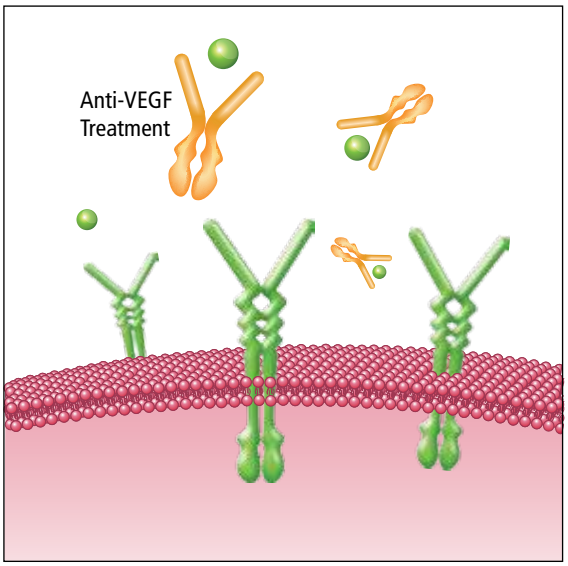
In the early 1970s, Dr. Judah Folkman proposed that tumor growth and progression was dependent on the tumor's ability to recruit and support the formation of a vasculature.[5,6] Two articles published in 1989 reported the isolation of vascular permeability factor or, as it is currently called, vascular endothelial growth factor (VEGF).[7,8] Two studies, using vascularized glioblastoma tumor cells, demonstrated that VEGF expression is induced by hypoxia and associated with new vessel growth.[9,10] A 1994 study in nonhuman primates reported VEGF mRNA and protein were elevated in hypoxic retinas.[11] Injection of VEGF into the eyes of nonhuman primates stimulated growth and increased permeability of new retinal vessels.[12]

The first anti-VEGF agent to be developed was bevacizumab (Avastin), a humanized anti-VEGF antibody.[6,13] The agent was approved in 2004 as an adjunctive treatment with chemotherapy for colon cancer.[6] During the same timeframe that development was taking place with anti-VEGF agents for cancer, VEGF was discovered to play a key role in the pathogenesis of neovascular age-related macular degeneration (NVAMD). The first anti-VEGF drug to be approved for this disease was pegaptanib (Macugen; Eyetech Inc; Palm Beach Gardens, FL) in 2004. Following the approval of bevacizumab (Avastin; Genentech Inc; South San Francisco, CA) for the

Anti-VEGF Therapy

Anti-VEGF agents target and block the glycoprotein VEGF (vascular endothelial growth factor). In DME, VEGF is produced at higher than normal amounts in the retina. Lowering levels of VEGF with anti-VEGF drugs reduces its effects on retinal blood vessels, prompting a reduction in macular edema without risk of developing other major eye conditions.





treatment of cancer, physicians started treating NVAMD patients with the agent using intravitreal injections. Two additional anti-VEGF agents have been approved more recently for the treatment of NVAMD—ranibizumab (Lucentis; Genentech Inc; South San Francisco, CA) in 2006 and aflibercept (Eylea; Regeneron Pharmaceuticals, Inc; Tarrytown, NY) in 2011. Management paradigms for the treatment of diabetic macular edema (DME) are evolving. VEGF is known to play a central role in DME.[4,14] VEGF concentrations are known to be elevated in the eyes of patients with diabetic retinopathy (DR) and DME compared with individuals without these conditions.[15-17] This has driven research efforts in the development of several agents that block the actions of VEGF in the retina. According to one review, "ocular anti-vascular endothelial growth factor (VEGF) therapy represents one of the most significant advances in modern medicine. The introduction and widespread use of ocular anti-VEGF therapy for age-related macular degeneration heralded a new era in the treatment of vascular and exudative diseases of the retina. Its expanding indications now include diabetic macular edema and proliferative diabetic retinopathy, two vision-threatening forms of diabetic retinopathy."[18] The advent of ocular anti-VEGF therapy has shifted the treatment paradigm[18,19] from preventing blindness to improving vision, offering DME patients new hope for saving their vision. Anti-VEGF therapy has emerged in recent years as the first-line therapy for DME, while the future role of focal laser, the prior first-line therapy, now appears somewhat uncertain.

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