ARVO
The Association for Research in Vision and Ophthalmology
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Anti-VEGF Timeline: From Conception to Delivery

1913	A. Carrel et al. hypothesized the existence of growth factors for cellular tissues.[i]
1939	A.G. Ide et al. observed that transplanted tumors induced neovascular growth and postulated a tumor-derived "blood vessel growth stimulating factor".[ii]
1945	G.H. Algire et al. suggested that tumor growth depends on a rich vascular supply.[iii]
1948	I.C. Michaelson suspected that a diffusible angiogenic factor "factor X" existed in the retina.[iv]
1971	J. Folkman published an influential paper on the implications of anti-angiogenesis.[v]
1983	D.R. Senger et al. identified and characterized vascular permeability factor (VPF).[vi]
1989	N. Ferrara et al. cloned, sequenced and characterized VEGF (previously known as VPF).[vii,viii]
1992	Two studies showed that VEGF mRNA expression was induced by hypoxia.[ix,x]
1993	K.J. Kim et al. identified monoclonal antibodies that can target VEGF and inhibit tumor growth.[xi]
1994	J.W. Miller et al. demonstrated in primates that hypoxic retina can produce VEGF and that VEGF is temporally and spatially associated with iris neovascularization.[xii]

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1994	▪ L.P. Aiello et al. reported that patients with active neovascular ocular disease showed increased levels of VEGF in their ocular fluids.[xiii] A paper in the American Journal of Ophthalmology (AJO) by A.P. Adamis et al. showed the same thing (smaller number of patients).[xiv]
1996	▪ Two articles reported the presence of VEGF in choroidal neovascular membranes from patients with wet AMD.[xv,xvi] ▪ Shima et al. cloned an mRNA expression of VEGF in ischemic monkey retina. ▪ Tolentino et al. found VEGF injection was sufficient to produce iris neovascularization and neovascular glaucoma in normal monkey eyes.[xvii] ▪ A.P. Adamis et al. found that anti-VEGF antibodies (precursor of Avastin) suppress iris neovascularization in a primate model.[xviii]
1997	▪ Pournaras et al. showed systemic hyperoxia decreases VEGF gene expression in ischemic monkey retina.[xix] ▪ Phase 1 clinical trial of bevacizumab initiated by Genentech for cancer.
1999	▪ Kim et al. showed constitutive expression of VEGF and VEGF R1 and R2 in normal monkey eyes.[xx] ▪ Y. Chen et al. at Genentech developed a better diffusing variant, ranibizumab, for use in the eye.[xxi]
2000	▪ Genentech initiated the first clinical trial with wet AMD subjects.
2002	▪ Krzystolik et al. showed prevention of experimental CNV with intravitreal anti-VEGF antibody fragment (precursor of reanibuzumab).[xxii]
2004	▪ Pegaptanib received FDA approval for nvAMD.
2006	▪ Two-year results from the MARINA trial of Ranibizumab for neovascular AMD were published by Rosenfeld et al.[xxiii] ▪ Ranibizumab received FDA approval for neovascular AMD.

	▪ Rosenfeld et al. published OCT evidence of the efficacy of bevacizumab in patients with nvAMD.[xxiv]
2010	▪ Ranibizumab received FDA approval for retinal vein occlusion.
2011	▪ Aflibercept received FDA approval for neovascular AMD.
2012	▪ Ranibizumab received FDA approval for diabetic macular edema.
2014	▪ Studies on the effectiveness of ranibizumab and pegaptanib on patients with macular edema from central retinal vein occlusion commenced.
2015	▪ Ranibizumab & aflibercept received FDA approval for treatment of DR in DME patients.
2019	▪ Brolucizumab-dbll received FDA approval for nAMD and DME.
2021	▪ A Lucentis biosimilar was the first to receive FDA approval for nAMD, macular edema following RVO and myopic CNV.
2022	▪ Another biosimilar received FDA approval for nAMD, DR, DME, myopic DNV and macular edema following RVO. ▪ Faricimab-svoa received FDA approval for nAMD and DME.
2023	▪ Higher dose Aflibercept received FDA approval for wet AMD, DME and DR. ▪ Aflibercept received FDA approval for treatment for preterm infants with retinopathy of prematurity. ▪ Faricimab-svoa received FDA approval for the treatment of RVO.

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