Discovering Mechanisms in the Changing and Diverse Pathology of Retinopathy of Prematurity: The Weisenfeld Award Lecture

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Good evening. It is a great honor to receive the Mildred Weisenfeld award. Mildred Weisenfeld, herself suffering blindness from retinitis pigmentosa, had the wisdom to recognize the importance of research to find treatments or cures for blinding eye diseases. She was persistent in establishing the National Council to Combat Blindness, which is now Fight for Sight. Her five research awards in 1947 have grown to over 21 million dollars in research grants (https://www.fightforsight.org, in the public domain) that have helped many in the audience here. It is meaningful to receive this award in honor of Mildred Weisenfeld.

I thank Fight for Sight, ARVO, and the awards committee for the opportunity to speak about some of our work to understand the causes of the features of severe retinopathy of prematurity (ROP) in order to find effective and safe treatments for these fragile, extremely premature infants, who are still undergoing development but in an ex utero environment away from placental support. We cannot experiment on them or their eyes. Therefore, to translate best to infants and children in the clinic, we design experiments using models that best represent human disease.

ROP has been studied by numerous clinicians, scientists, and clinician–scientists over the decades. Many have contributed to our understanding of this complex disease that continues to evolve as ever smaller premature infants survive, and improvements in neonatal care are implemented that change the underlying natural history of ROP. Today, I have focused on work from our lab in understanding the role of VEGF signaling in ROP.

BACKGROUND: FROM ORIGINAL OBSERVATIONS TO CURRENT DAY ROP IN THE UNITED STATES

ROP is a leading cause of childhood blindness worldwide. Currently, severe ROP is diagnosed with longitudinal examinations of the retina in premature infants and is treated when ROP has advanced to a level of severity at which there is increased risk of retinal detachment (for review). Partial retinal detachment is defined as stage 4 ROP and total retinal detachment as stage 5 ROP that can manifest as a white pupil which may represent what we currently know as stage 5 ROP (Fig. 1). When ROP manifested, investigators recreated the conditions premature infants were exposed to and based on experimental studies using oxygen-induced retinopathy (OIR) models in full-term healthy newborn animals, a two-phase hypothesis was developed in which high oxygen injured newly developed capillaries and subsequent technology to regulate oxygen caused ROP to virtually disappear. It is helpful to recognize that these phases of ROP were based on translational experimental studies and were developed approximately 3 decades prior to the clinical classification of ROP by stages, zone, extent, and plus disease used today.

Despite these findings and our improved understanding of the disease, ROP is still prevalent even with regulation of oxygen and avoidance of high oxygen at birth. This is partly due to neonatal advances over the decades that led to the salvation of ever smaller and younger premature infants. Today's premature infants at risk of severe ROP are also less developmentally mature, including that their retinas are not fully vascularized. Other stresses besides high oxygen at birth have been recognized as associated with ROP and, despite numerous studies testing various oxygen saturation targets, there remain no universally accepted standards regarding safe oxygen use in preterm infants other than to avoid high oxygen at birth. However, these other identified stresses have
allowed us to recognize that pathophysiologic processes involved in today’s extremely premature infants with ROP and the appearance of ROP have changed from ROP that manifested in the United States in the 1950s. The original two-phase hypothesis includes not only hyperoxia-induced compromise of physiologic vascularity in some cases, but also a delay in physiologic retinal vascular development in Phase I and intravitreal neovascularization and plus disease, which describes tortuosity and dilation of the major retinal vessels in Phase II. Therefore, we and other labs have experimentally recreated some of these stresses to understand their role in causing ROP features. Some of these include fluctuations in oxygenation, poor postnatal growth, poor infant oxidative reserve under conditions of increased oxidative signaling, and reduced ability to express protective factors to offset events from extreme prematurity.

**Experimental Models of ROP and the Role of VEGF**

Because it would be unethical to experiment on premature infants or their eyes, we use models that represent features of ROP by exposing newborn animals that vascularize their retinas after birth to oxygen stresses representative of those in prematurity. When I started studying ROP, it seemed crucial to use a model that most represented the relevant features in premature infants who developed current severe ROP, which differed from the ROP of the 1940s that occurred in less developmentally premature infants, who were exposed to 100% oxygen. As a result, I chose the rat OIR model, developed by Penn et al., which exposes newborn rat pups to oxygen fluctuations that cause arterial oxygen extremes similar to infants with severe ROP and causes poor postnatal growth. The rat OIR model also reproduces Phase I and Phase II pathologies similar to human ROP. These features can be quantified and analyzed (Fig. 2), and include area of avascular retina as a measure of delayed physiologic retinal vascular development, number of capillary crossings or pixels of fluorescence for compromise of physiologic vascularity in Phase I, and area of intravitreal neovascularization (IVNV) for vasoproliferation and tortuosity index for plus disease in Phase II.

**Increased VEGF Causes Intravitreal Neovascularization (Phase II OIR, Stage 3)**
ROP) But Also Delays Physiologic Retinal Vascular Development

The prevailing hypothesis that hypoxic avascular retina released an angiogenic factor that caused blood vessel growth did not address the question why blood vessels grew into the vitreous instead of into the avascular retina to relieve hypoxia. Perhaps the retina was unable to support vascularization, but from clinical observations, many infants had resolution of intravitreal neovascularization and underwent vascularization of the peripheral avascular retina. Perhaps, the ridge prevented normal vascularization (Fig. 3). Perhaps there were insufficient angiogenic factors or too many angiostatic factors produced during Phase I. We pursued this hypothesis.

At the time, VEGF had been recently recognized as important in adult proliferative angiogenic eye diseases like diabetic retinopathy and AMD. Preclinical data for treatments of these diseases involved the use angiogenic models, including OIR models. Therefore, it seemed logical that too much VEGF might be involved in pathologic intravitreal neovascularization in ROP. But, if that were true and VEGF were inhibited to reduce intravitreal neovascularization, would VEGF inhibition not also inhibit ongoing physiologic retinal vascular development and lead to persistent or increased avascular retina that would then lead to recurrent intravitreal neovascularization? Because we knew that VEGF is increased in hypoxia through hypoxia-inducible transcription factors and over time it was recognized that pigment epithelial-derived factor (PEDF) was an angiogenic inhibitor increased by high oxygen, we decided to address the question by determining the retinal expression of VEGF and PEDF in the rat OIR model, predicting that VEGF/PEDF would be reduced during Phase I and increased during Phase II ROP/OIR. Unexpectedly, there was more retinal VEGF in both Phase I and Phase II compared with room air–raised rat pups. There was little change in PEDF, and as a result the VEGF/PEDF ratio favored angiogenesis in both Phases I and II (Fig. 4).

Next, we used different methods to inhibit VEGF with either intravitreal neutralizing antibodies to rat VEGF or inhibitors to the receptor tyrosine kinase of the angiogenic VEGF receptor 2 (VEGFR2) each compared with its respective control, predicting that inhibition of VEGF would reduce intravitreal neovascularization in Phase II but further delay physiologic retinal vascular development (PRVD), manifesting as increased peripheral avascular area. As predicted, Phase II intravitreal neovascularization was inhibited in association with reduced signaling of VEGFR2. However, peripheral avascular retinal area was not greater and, in some cases, there was a pattern toward improved physiologic retinal vascular development. This was also unexpected (Fig. 4).

Around this time, clinicians were starting to treat infants who had severe ROP with intravitreal injections of anti-VEGF agents that were already being used in adult vasoproliferative diseases, like AMD and diabetic retinopathy. Publications showed that in some infants with severe ROP, anti-VEGF agents injected into the vitreous reduced plus disease and stage 3 ROP or intravitreal neovascularization, which was expected, but also allowed extension of physiologic retinal vascular development. These findings were exciting because they
aligned with results from our animal studies. However, other infants had persistent avascular retina and recurrent stage 3 ROP following anti-VEGF treatment, and this was undesired.

There are a number of challenges to using intravitreal anti-VEGF agents in premature infant eyes. It is unclear what the concentration of vitreous VEGF is in an individual infant’s eye at a particular pathophysiologic step in ROP, and established anti-VEGF doses and volumes are based on adult formulations, increasing the likelihood of error when adjusting concentrations to small eyes. This difficulty is compounded because differences in injected volumes in the small infant eye could have big differences in individually treated infants. Therefore, the discrepancy among infant outcomes in clinical studies might be due to inaccuracies in doses.
Therefore, we tested different doses of an antirat-neutralizing VEGF antibody in the rat OIR model and analyzed outcomes at Phase II and a later time point when the model naturally experiences regression of pathologic features. Intraocular neovascularization was inhibited at the Phase II time point but later recurred in association with increased retinal VEGF (Fig. 5). This suggested that an effective intravitreal anti-VEGF dose for Phase II vasoproliferation led to recurrent intravitreal neovascularization later. We then wondered if we could optimize the anti-VEGF effect by creating a "physiologic" retinal VEGF level in the rat OIR model by reducing upregulated retinal VEGF in the model to the level of room air–raised rats of the same developmental ages. Would maintaining retinal VEGF at a "physiologic level" inhibit vasoproliferation and extend physiologic retinal vascular development without causing recurrent intravitreal neovascularization?

We determined the expression of retinal VEGF at several time points in the rat OIR model compared with room air–raised pups and found both increased mRNA of the main splice variant, VEGF164, and VEGF protein at day 14 (Fig. 4). We also found that VEGF164 expression was increased by repeated oxygen fluctuations in the rat OIR model whereas other splice variants, VEGF120 and VEGF188, were increased by hypoxia. These findings suggested to us that VEGF164 was particularly important in the pathologic phases that developed in the rat OIR model. Using in situ hybridization to visualize splice variant expression in layers of retina on day 14, we found VEGF164 was expressed in several layers including the inner nuclear layer corresponding to labeled Müller cells that span the retina (Fig. 6A). The anatomic localization of Müller cells allows the cells to sense hypoxia in different retinal layers that are supported by different vascular plexi and respond accordingly. We then focused on methods to reduce Müller cell secretion of VEGF to establish a "physiologic" level.

**FIGURE 6.** Lentiviral driven shRNA with CD44 promoter efficiently targets Müller cell–derived VEGF in the OIR model. (A) In situ hybridization shows that VEGF splice variants expression corresponds to expression of Müller cell marker CRALBP in retinal cryosections of d14 OIR pups. (B) Lentivirus with CD44 promoter and GFP tag. (C) VEGF reporter cell lines demonstrate knockdown of VEGF120 and VEGF164. (D) Micron imaging shows GFP in lentivector-luciferase-shRNA (L-Lucif.shRNA) and L-VEGFA.shRNA-treated retinas, not PBS-treated retinas. (E) Immunohistochemistry (IHC) shows GFP colabeling with CRALBP in retinal cryosection, and (F) ELISA of VEGF protein in the retina from d18 room air (RA) and d18 OIR with subretinal injection of control (PBS), L-Lucif.shRNA, or L-VEGFA.shRNA (**P < 0.001 versus RA control; ††P < 0.01 vs. OIR control). Images reprinted with permission from Wang H, Smith GW, Yang Z, et al. Short hairpin RNA-mediated knockdown of VEGFA in Müller cells reduces intravitreal neovascularization in a rat model of retinopathy of prematurity. *Am J Pathol.* 2013;183:964–974. © 2013 American Society for Investigative Pathology and Yanchao Jiang, Haibo Wang, David Culp, et al. Targeting Müller cell–derived VEGF164 to reduce intravitreal neovascularization in the rat model of retinopathy of prematurity. *Invest Ophthalmol Vis Sci.* 2014;55:824–831. © 2014 Association for Research in Vision and Ophthalmology.
However, cell-specific knockdown of VEGF in the rat model had not yet been done. To tackle this problem, we collaborated with John Flannery, whose lab had developed a lentivirus with a CD44 promoter and green fluorescent protein (GFP) tag that allowed visualization of Müller cells in vivo (Fig. 6B). We developed short hairpin (sh)RNAs to knock down VEGFA and VEGF164 splice variant by screening shRNAs using reporter cell lines expressing VEGF120 or VEGF164 (Fig. 6C). We then embedded the shRNA sequences within a microRNA context to allow its cell-specific expression and generated lentiviral vectors in collaboration with Scott Hammond and Tal Kafri at the University of North Carolina. We performed subretinal injections of the lentiviral vectors in pup eyes at postnatal day 8 and were able to confirm successful transduction by visualizing green Müller cell endfeet in both control luciferase shRNA and VEGFA shRNA lentiviral–treated eyes but not in eyes treated with subretinal PBS (Fig. 6D). A cross-section of retina confirmed colabeling of GFP and cellular retinaldehyde-binding protein (CRALBP) for Müller cells (Fig. 6E). Using the viruses, we were then able to show that retinal VEGF was reduced in the lentiviral VEGF shRNA lentiviral–injected pup eyes to the protein level of room air retinas from pups of the same developmental ages at postnatal day 18 (Fig. 6F). Knocking down VEGF to “physiologic” room air levels significantly inhibited vasoproliferation in Phase II without interfering with physiologic retinal vascular development or causing recurrent intravitreal neovascularization (Fig. 7). This suggested that preserving physiologic vascularity within the already vascularized retina during representative oxygen stresses in the premature infant was important to prevent recurrent intravitreal neovascularization (Fig. 8). This also
VEGF Signaling in Normal and Pathologic Angiogenesis in ROP

translates to what has been published in clinical ROP, in which fluorescein angiograms of infants with severe ROP treated with certain intravitreal anti-VEGF agents developed areas of non-perfused retina within the central vascularized retinas.42,43

The optimal anti-VEGF strategy we designed did not compromise physiologic vascularization, interfere with physiologic retinal vascular development, or lead to recurrent intravitreal neovascularization, but it also did not fully extend physiologic retinal vascular development, and this may be important for development of the visual field. We pursued angiogenic VEGF signaling through its receptors. There are a number of family members of VEGF that signal through several receptors and coreceptors. VEGFR2 is important in angiogenesis and VEGFR3 is important in sensing and signaling of endothelial tip cells to VEGF.44 VEGFR1 is involved in angiogenesis in adults but in development, VEGFR1 binds VEGF and thereby regulates the amount of available VEGF to bind and trigger signaling through VEGFR2.45 We have now worked out a mechanism in which retinal endothelial VEGFR2 causes vasoproliferation by activating the transcription factor, STAT3 in endothelial cells.46 STAT3 is also activated independent of VEGF through signaling involving nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, a leading generator of reactive oxygen species in endothelial cells.47,48 This crosstalk between angiogenic factors and reactive oxygen signaling provides a means to overwhelm homeostatic mechanisms that prevent overactive VEGFR2-initiated intravitreal vasoproliferation. Using a strategy to inhibit STAT3 in endothelial cells reduced vasoproliferation but did not extend physiologic retinal vascular development,49 so we looked for other ways to reduce vasoproliferation but enable physiologic retinal vascular development.

VEGF signaling is difficult to study in vivo, because a single allele knockout of a splice variant or receptor is lethal.50–52 We collaborated with Vicki Bautch at University of North Carolina who had developed an embryonic stem cell model with a GFP tagged to histone 2B driven by a CD31 promoter. This construct allowed us to visualize dividing endothelial cells that became vessel-like structures. By knocking out VEGFR1, encoded by flt-1, we were able to regulate and, therefore, study VEGFR2 signaling. It turns out that the angle between the cleavage planes of dividing endothelial cells and the long axis of the vessel predicts how a vessel will grow: perpendicular angles predict vessel elongation and parallel angles predict vessel widening (Fig. 9A). We measured cleavage angles in the flt1−/− model and found angles were not clustered at 0° or 90° but instead clustered within a number of cleavage angles between the two extremes leading to a pattern of disoriented endothelial growth (Figs. 9B, 9C). This led to a pattern of growth that was similar in appearance to human stage 3 severe ROP53 (Fig. 9D). The disordered mitoses and angiogenesis could be ordered by replacing the VEGFR1 gene, flt-1, providing evidence that excessive VEGF–VEGFR2 signaling caused disordered angiogenesis.53

We then studied cleavage angles in the rat OIR model. Retinal flat mounts were colabeled with lectin to visualize blood vessels and an antiphosphohistone H3 antibody that labeled dividing cells in anaphase (Fig. 10A). Intravitreal neutralizing antibody to rat VEGF at a dose that inhibited vasoproliferation increased cleavage angles that predicted venous elongation compared with control IgG in which angles predicted widening of veins (Fig. 10B). Anti-VEGF also reduced arteriolar tortuosity compared with control.54 Both dilation and tortuosity are features of plus disease, which is an important feature of severe ROP (Fig. 10). This line of study provided the first evidence that VEGF–VEGFR2 signaling was involved in features of human plus disease.
VEGFR2 is expressed on other cells in the retina and is important to retinal and glial health, so we sought a way to knockdown VEGFR2 only in endothelial cells in the retina, which had not been done before in the rat OIR model. We substituted CD44 in lentiviral vectors for a VE-cadherin (Cdh5) promoter and embedded control luciferase shRNA into the microRNA 30 context. The resulting lentivirus was specific to rat endothelial cells in vitro and in vivo (Fig. 11). We next designed several shRNAs to VEGFR2 and chose the one that had the best knockdown on activated and total VEGFR2, and

![Figure 9](image_url)

**Figure 9.** Increased VEGF receptor 2 signaling in flt-1−/− disoriented mitoses in embryonic stem cell model similar to human stage 3 ROP. (A) Diagram of endothelial cell division in relationship to vessel elongation and dilation; (B) IHC of CD31 (green) and phosphohistone H3 (red) in embryonic stem cell (ES) (wild type and flt-1−/−) cell-derived vessels and (C) representation of endothelial division angles to the vessel long axis diagrammed by the long horizontal lines; (D) infant retina showing IVNV. (A) Reprinted with permission from Hartnett ME. The effects of oxygen stresses on the development of features of severe retinopathy of prematurity: knowledge from the 50/10 OIR model. Doc Ophthalmol. 2010;120:25–39. © Springer-Verlag 2009. (B, C) Reprinted with permission from Zeng G, Taylor SM, McColm JR, et al. Orientation of endothelial cell division is regulated by VEGF signaling during blood vessel formation. Blood. 2007;109:1345–1352. © 2007 by The American Society of Hematology.

![Figure 10](image_url)

**Figure 10.** Neutralizing antibody to rat VEGF reduces venous dilation and arteriolar tortuosity-plus disease. (A) Diagram of cleavage angle in lectin and antiphosphohistone H3 stained retinal flat mount, (B) venous retinal endothelial cell division planes, grouped by degrees from the long axis of the vessel; (C) representative flat mount images, and (D) tortuosity index of retina treated with VEGF antibody (VEGFab) or IgG; and (D) infant retinal image (*P < 0.05 versus IgG). Parts (B–D) reprinted with permission from Hartnett ME, Martinuk D, Byfield G, Geisen P, Zeng G, Bautch VL. Neutralizing VEGF decreases tortuosity and alters endothelial cell division orientation in arterioles and veins in a rat model of ROP: relevance to plus disease. Invest Ophthalmol Vis Sci. 2008;49:3107–3114. © 2008 Association for Research in Vision and Ophthalmology.
embedded this into the endothelial cell specific lentiviral construct. We performed subretinal injections of the lentiviral vectors with endothelial cell-specific VEGFR2 shRNA and found significant inhibition of vasoproliferation and improved physiologic retinal vascular development compared with control luciferase shRNA (Fig. 11). There were no adverse effects on electroretinography, retinal structure, or serum VEGF.59 These data contribute to the hypothesis that over-activated VEGFR2 causes vasoproliferation, plus disease and by disordering endothelial cells, also interferes with physiologic retinal vascular development. Regulation of VEGFR2 signaling in endothelial cells reduces vasoproliferation and plus disease and also extends physiologic retinal vascular development.

**VEGF Provides Protection for Neural and Glial Cells**

Regulating VEGFR2 in endothelial cells extended physiologic vascular development to a degree, whereas knocking down VEGF to “physiologic” levels by targeting Müller cell VEGF production did not. Knocking down Müller cell expressed VEGF reduces the amount of VEGF available to multiple cells in the retina, not only endothelial cells. This led us to wonder if other cells were affected by reduced VEGF during OIR and if VEGF could be protective of retinal cells under oxygen stresses.

To address this, we looked at long-term effects of lentiviral-delivered Müller cell–specific VEGF knockdown on neural retinal structure and function. We tested lentiviral vectors delivering VEGFA shRNA or VEGF164 shRNA, which would permit some secreted VEGF to the retina.56 Both shRNAs reduced vasoproliferation compared with control luciferase shRNA without recurrent intravitreal neovascularization or delay in physiologic retinal vascular development. However, knocking down full-length VEGFA thinned the outer nuclear layer suggesting photoreceptor damage. Despite thinning, photoreceptor a-waves were not affected in full-field ERGs, and b-waves were actually higher than control. Probing further, we found that neuroprotective factors were increased in the retinas transduced with lentiviral VEGFA shRNA, potentially to compensate for loss of some forms of VEGFA, but not in those transduced with lentiviral VEGF164 shRNA56 (Fig. 12).

These data add to the literature that VEGF is neuroprotective and are unique in showing the importance of secreted VEGF to the developing retina under oxygen stresses similar to those in human ROP. Even optimal anti-VEGF strategies altered retinal structure and stimulated neuroprotective factor expression in the full-term rat OIR model. Translating to the human, it might be good to have neuroprotective factors released following short-term anti-VEGF treatment, but we do not know what happens in the premature, incompletely developed infant retina stressed by other external factors besides oxygen stress. Also, it would be unsafe to create a similar optimal anti-VEGF strategy using subretinal gene therapy in the premature
human infant retina. Intravitreal anti-VEGF in infants with only mild ROP or too high a dose of anti-VEGF may be harmful to the retina and to physiologic vascularity, potentially stimulating recurrent intravitreal neovascularization. These data provide insight into the observation that not all extremely premature infants, those born less than 1000 g birth weight or under 28 weeks gestational age, develop severe ROP, and it may be that some infants are able to induce protective mechanisms for survival and to avoid severe ROP.21,57

CONCLUSIONS
In summary, models of OIR have been modified to represent current ROP in which there is both a delay in physiologic retinal vascular development and compromise of physiologic vascularity that lead to intravitreal vasoproliferation. Regulation but not total inhibition of overactive VEGF–VEGFR2 in endothelial cells is necessary to extend physiologic retinal vascular development and to inhibit intravitreal neovascularization. Overactive VEGF–VEGFR2 signaling causes plus disease. Intravitreal neovascularization recurs after high anti-VEGF doses that compromise existing capillaries in oxygen-stressed retina. VEGF is neuroprotective in oxygen stresses. In translating to human ROP, these data support the concern that intravitreal anti-VEGF in mild ROP or in high doses may harm existing capillaries, lead to recurrent intravitreal neovascularization, or harm neural retina. Further studies are needed to extend physiologic retinal vascular development and protect developing neural retina and vasculature, including studies to adapt existing models to identify and test protective mechanisms in the developing retina that is stressed by external factors similar to those in extreme prematurity.

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Disclosure: M.E. Hartnett, P

Biographical Note
Mary Elizabeth Hartnett holds the Calvin S. and JeNeal N. Hatch Presidential Endowed Chair in Ophthalmology and Visual Sciences at the University of Utah and is Professor of Ophthalmology and Visual Sciences and Adjunct Professor of Neurobiology and Anatomy and Pediatrics. After ophthalmology residency training at Case Western/University Hospitals of Cleveland, Dr. Hartnett completed adult and pediatric vitreoretinal fellowships at Schepens Retina Associates and Schepens Eye Research Institute of Harvard Medical School. She is Director of Pediatric Retina at the John A. Moran Eye Center and one of a few pediatric retina specialists internationally trained to diagnose and treat pediatric retina disorders. Dr. Hartnett is Principal Investigator of an
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