ARC

ASSOCIATED RETINAL CONSULTANTS, P.C.

DISEASES AND SURGERY OF THE RETINA AND VITREOUS

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1939 – 2000

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1933 – 1981

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Tarek S. Hassan, M.D.
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Alan R. Margherio, M.D.
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Tianyu Liu, M.D.
Omar Moinuddin, M.D.
Viet Chau, M.D.
Lydia Sauer, M.D.

Emeritus
Morton S. Cox, Jr., M.D. (1934 - 2013)
Michael T. Trese, M.D. (1946 - 2022)

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January 20, 2025

Helen Keller Award 2026

Dear Helen Keller Award Committee,

I am writing a letter of support for consideration of Mary Elizabeth (ME) Hartnett, M.D. as a recipient of the 2025 Helen Keller Award. As a pediatric retina specialist, I see firsthand the lack of support and resources for our most vulnerable population, infants and children with blinding eye disease. Children with blinding retinal eye disease fall between the cracks for care and management as they have problems that are out of the expertise of the pediatric ophthalmologist and not generally considered part of the vitreoretinal specialty which focuses on adult disease. These children have delayed care as they are bounced between doctors who don't feel comfortable managing their care.

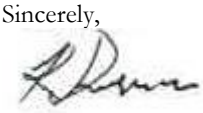
Dr. Hartnett is recognized as a pioneer in our field and has devoted her career to the improved understanding and management of these rare and devastating retinal diseases. Additionally, she has steadfastly worked to promote Pediatric Retina as its own subspecialty. She co-founded the Pediatric Retina Association and has been an active participant in the Association of Pediatric Retinal Surgeons since its inception. Her contributions in basic research have continued to improve the understanding of the developing retina and advance the treatment options for Retinopathy of Prematurity (ROP). Her dedication to advancing the field and thereby improving the outcomes for children around the world are due to her commitment to education, research and clinical practice. She is considered a leader in the research of angiogenesis and has translated this knowledge into improved patient care. She is a true clinician-scientist where her clinical questions are addressed in the laboratory and shared with the pediatric and retinal community.

I have known and worked with Dr. Hartnett for over twenty years. During this time, I have met few people that have had such an impact on Pediatric Retina. She is generous with her time and knowledge and has mentored countless medical students, residents, fellows and researchers over the last two decades. She is respected by her peers and often asked to present her research and collaborate on unique cases due to her unique expertise as both a clinician and scientist.

Dr. Hartnett's background in angiogenesis supported her phenomenal contributions to the understanding and management of ROP. Using a rat model of Oxygen-induced retinopathy (OIR) she uncovered the role of vascular endothelial growth factor (VEGF) in the pathogenesis and how to use the available anti-VEGF therapies to treat ROP in infants. Her work in this area of ROP treatment predates the many anti-VEGF trials and marks her as a true visionary in the pediatric retina world.

The distinguished career and accomplishments that embody the dedication and diligence shown by Dr. ME Harnett merits recognition. In my opinion, Dr. Hartnett is well-deserving of the Helen Keller Award and her continued work for the betterment of children with ROP and similar ischemic retinopathies puts her in a class of rare clinician-scientists. It is my privilege to be able to collaborate with her and be her colleague. I can think of few people whose lifetime work merits such recognition, and I hope you will seriously consider her for the Helen Keller Award.

Sincerely,



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December 9, 2024

Helen Keller Award 2026

Dear Helen Keller Award Committee,

How is a new subspecialty created and validated? And how can we calculate the value to patients who avoid blindness through this subspecialty? These are the questions I ask myself as I write to recommend ME Hartnett, MD, for the 2025 Helen Keller Award. Dr. Hartnett has worked tirelessly to help create and nurture Pediatric Retina as a subspecialty. Children around the world can see because of this.

The subspecialty of Pediatric Retina is fundamentally different than the adult specialty due to the evolving development of the retina and the entire eye-brain network in infants and children, as well as the inability of pediatric patients to give complete histories and cooperation. Pediatric retina began to emerge as a separate field when surgeons like Machemer, Schepens, Hirose and Trese developed novel techniques specific to babies' eyes. But it did not become a truly cohesive field until ME Hartnett, MD, helped create the biannual *Advances in Pediatric Retina* meeting, made the focus of her basic science research the pathophysiology of retinopathy of prematurity, and conceived of and brought to fruition the *Pediatric Retina* textbook. For her roles as a clinician, basic scientist and, most importantly, promoter of Pediatric Retina, ME Hartnett is deserving of the Helen Keller Award.

As a vitreoretinal specialist, Dr. Hartnett's interests in research lie in diseases associated with angiogenesis. Dr. Hartnett is unique in that she developed scientific questions and hypotheses in the clinic, and then actively sought basic science training in order to answer those questions and expand our knowledge, and our ability to treat. To better understand the pathophysiology of retinal diseases and the effects of Mueller and RPE cells on endothelial cells, she performed post-doctoral studies with Patricia D'Amore at Children's Hospital of Boston and Schepens Eye Research Institute while continuing to practice as a vitreoretinal specialist. She later sought another post-doctoral fellowship with Keith Burridge at University of North Carolina in molecular and cell biology also while actively practicing. Her journey as a clinician scientist has been encouraging to other MDs interested in translational research; she has acted as a mentor formally or informally for many throughout the world. She was instrumental in my own academic journey as I attempted to start my translational research laboratory while engaging in a busy academic clinical practice. The opportunity to meet with her one-on-one while she was a visiting professor in my department became an inflection point. Her unflagging confidence in my abilities and the inspirational example of her own career path helped me over several hurdles at a critical time, which led to my research in gene therapy treatments for pediatric inherited retinal diseases.

Dr. Hartnett's greatest research contribution has been her work in basic/translational science on retinopathy of prematurity (ROP). She and her team determined the mechanism for anti-VEGF treatment of ROP and that counterintuitively, an anti-angiogenesis agent not only inhibits pathologic blood vessel growth into the vitreous, but actually promotes normal peripheral angiogenesis, the lack of which is the genesis of ROP. She uses the rat model of oxygen-induced retinopathy (OIR), and noted that the rat model also recapitulates the oxygen fluctuations that occur in human infants with ROP.
She noted that repeated oxygen fluctuations in the rat OIR model increased expression of VEGF164 mRNA, the more prevalent splice variant associated with pathologic angiogenesis, whereas hypoxia only increased the smaller splice variant of the parent VEGFA (VEGF120). *This data on the role of oxygen fluctuation changed clinical practice in the NICU.*

Dr. Hartnett's studies on VEGF in ROP were done prior to clinical trials of ROP treatment with anti-VEGF agents that occurred throughout 2004 to 2009. Hartnett was consulted by Helen Mintz Hittner, a retina specialist conducting clinical trials, who was encouraged that her work did not find persistent avascular retina with VEGF inhibition. At that time the long term outcomes were unknown in humans. Hittner later published the first clinical trial results on anti-VEGF in ROP, the BEAT-ROP study. Unlike other diseases in which treatments are studied in animal models and then slowly rolled out in human clinical trials, the Hartnett lab was studying the underlying mechanisms and effects of anti-VEGF treatment in ROP before, and during, clinician early acceptance of this treatment modality. The stakes are much higher in this type of treatment paradigm shift, and the experimental work coming out of her lab as clinicians sought a treatment for an epidemic of neonatal blindness was vital to its evolution. For me as a pediatric ophthalmologist who treats acute ROP, and who follows the affected children into adulthood, her careful study of the mechanisms, treatment and outcomes, especially of longer term developmental peripheral vascularization, was vital to using this treatment confidently and discussing the data with parents making decisions for their tiny babies.

Hartnett has now performed a study of human premature infants comparing treatment-warranted type 1 ROP treated with bilateral intravitreal anti-VEGF to the natural history of a gestational age- and birthweight-matched control group of infants with less-than-treatment-warranted ROP. She found that regulation of VEGF signaling with anti-VEGF injection leads to *greater extension of physiologic angiogenesis than the natural history of less severe ROP*. This is important because reducing the area of avascular retina could reduce the elevated risk of retinal detachment that survivors of acute ROP suffer in their teenage years. Hartnett recently received a 2%ile score on her NIH R01 proposal to expand on this exciting research—this score reflects the incredible importance of the work she is doing to prevent blindness in premature infants.

Dr. Hartnett is a clinical leader in therapy of ROP. Her training in surgical pediatric retina was influenced by her mentors, Charles Schepens, Tatsuo Hirose, and Michael Trese. She was the first in Boston to perform lens-sparing vitrectomy, developed by Dr. Trese. She further developed treatment of ROP by contributing to the design of clinical trials.

Dr. Hartnett was the first to suggest that a textbook dedicated to pediatric retina was needed, and in fact was crucial for the further development of the field. She recognized the need for a definitive resource covering diagnosis, treatment and visual rehabilitation in infants and children with retinal disorders that could provide common ground for practitioners of this new specialty. She took it upon herself to create the first comprehensive textbook covering all aspects of pediatric retina. As editor-in-chief, she recruited experts in genetics, medical retina and surgery to be section editors. The book is now in its third edition and is recognized worldwide. Arguably, the creation and evolution of this pediatric retina textbook is what truly made Pediatric Retina its own subspecialty. The textbook has an atlas of images based on phenotype (spots and flecks, hemorrhages, macular conditions, etc.) which enables the reader to find an image similar to their patient's retinal appearance. The image refers the reader to a chapter that includes a comprehensive differential diagnosis and provides insight and guidance for diagnosis and management. In the third edition, the atlas includes multimodal imaging of optical coherence tomography and angiography, as well as a chapter with images of diagnostic patterns of electroretinogram waveforms in inherited retinal disorders.

Hartnett has directed three and co-directed two international meetings on pediatric retina to disseminate knowledge worldwide. The *Advances in Pediatric Retina* (APR) course and meeting strives to address the difficulties in teaching pediatric retina, which comprises many conditions, most of which are rare or recently recognized with the help of genetic investigation. Even a student who spends a year in pediatric retina fellowship after adult retina training will not see many of the conditions that make up pediatric retina. As a result, few conditions are characterized by evidence-based studies with control groups. The APR meeting includes international experts discussing scientific evidence and panels of experts leading discussions on controversial topics. In addition, there are outstanding keynotes who provide wisdom based on experience and science. A hands-on wetlab is included with equipment used in diagnostic imaging and surgery with small group instruction from the faculty. The meeting extends 2.5 days and is an immersive opportunity in which retina and pediatric ophthalmologists, genetic clinicians, scientists, students, and staff participate. The most

recent APR meeting, in August 2023, drew pediatric retina specialists and trainees from 5 continents, numerous countries and 28 states across the USA. This meeting has built a cohesive community of pediatric retina specialists who continue to collaborate and learn from each other in between the in-person events. During the August 2023 meeting, attendees from India, Thailand and Central America went to the microphones asking how to approach specific clinical challenges in ROP during the plenary sessions. Their questions made clear that oxygen monitoring and early treatment, which has markedly improved ROP outcomes in the USA, are not being utilized in many countries. These practitioners received answers and protocols, and connections with colleagues with whom they can communicate to improve treatment of ROP around the world. Creating a community like this is an incredible achievement that is saving vision.

In summary, ME Hartnett has been instrumental in creating the field of Pediatric Retina. She has literally written the book on this young subspecialty and does research and clinical care in its most devastating disease: ROP. Like the incredible past recipients of the Helen Keller Award, she has worked tirelessly, and many children can see because of her work and her care. The value of this can never be fully calculated, but we can and should recognize and reward it.
Sincerely,

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Ronald V. Keech, MD, Professor in Genetic Eye Disease Research
Director, Electrophysiology Service
Department of Ophthalmology and Visual Sciences
Institute for Vision Research

Leonard A. Levin MD, PhD, FRCSC, FCAHS, FARVO
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December 29, 2024

Re: Mary Elizabeth Hartnett, MD, FACS

It is with a great deal of enthusiasm that I write this letter giving my strongest possible recommendation for Mary Elizabeth Hartnett (ME) to be considered for the Helen Keller award. I have known and worked with ME over more than three decades and consider her one of the most brilliant and thoughtful translational visual scientists and clinicians I have known. This letter will explain why I think ME is particularly deserving of the Helen Keller award and how her work in research, education, and writing has greatly enhanced the basic science and clinical application of understanding and treating retinopathy of prematurity (ROP), as well as other retinal diseases.

I first met ME when we were both trainees at the Massachusetts Eye and Ear Infirmary. Over the years we interacted with respect to scientific meetings and study sections. When I was the outgoing chair of the first translational ophthalmology study section at the National Eye Institute (Diseases and Pathophysiology of the Visual System), I thought so highly of ME that I recommended she be brought on as the next chair of the study section. She also took over from me as chair of the ethics committee at ARVO, and this pattern of a shared interest in service to our community continued. As a translational clinician-scientist myself, I have kept up with most of Dr. Hartnett's work, and we are even co-editors on Adler's Physiology of the Eye (just published this year). Because of all of these interactions, I feel comfortable giving a frank assessment of ME's suitability for the Helen Keller award.

I consider "making a difference" in preventing, treating, and curing blindness the critical measure of suitability for an award as meaningful as the Helen Keller. ME has made a difference in three distinct areas, all of which have contributed greatly to saving the vision of children born prematurely, and she will continue to do so. Perhaps the most known to clinical ophthalmologists is her founding work as editor-in-chief of *Pediatric Retina,* the first comprehensive book of the subspecialty. One could argue that pediatric retina was in its adolescence before the main knowledge of the field was compiled in this textbook, now in its third edition. Although founding and nurturing a textbook may seem mundane, it provides accessibility of important information to both clinicians and scientists, and *Pediatric Retina* is the fundamental source for understanding the current state and progress in this area. ME is the engine behind the book, and I cannot imagine how the pediatric retina subspecialty could exist without an equivalent fundamental source.

Second, the training of future practitioners and scientists is greatly dependent upon the quality of the teacher and the methods by which the teacher transmits the information. In ME's case, she has a long history of superb training of fellows and residents, with the

former being particularly affected by her surgical and nonsurgical skill transfer and mentoring. This one-to-one teaching is individual, and therefore directly trains only small numbers. Her second mode of teaching is her organization of pediatric retina conferences. These are internationally known and are attended by practitioners from all over the world who take care of infants and children with retinopathy of prematurity and other disorders. Another area of education that is meaningful to the care of patients has been her major reviews. For example, ME wrote (with John Penn) the New England Journal of Medicine review of retinopathy of prematurity in 2012, and just this past year published the Annual Reviews of Visual Science review on the subject. Reviews in other high-impact journals such as Progress in Retinal and Eye Research and others make accessible to both scientists and clinicians the information necessary for progress in basic research and to improve medical care.

Third, and most importantly, ME's work on understanding ROP mechanisms and translating that understanding to treatment has been ground-breaking. She was one of the first to examine VEGF in ROP, but it is for her mechanistic work that she is best known. Understanding the changes that occur with anti-VEGF treatment has shed light on the translational aspect of the signaling process. For example, understanding how VEGF stimulates VEGFR2 on endothelial cells affects their ability to continue to divide, and how decreasing this signaling would still allow physiological angiogenesis to continue. This kind of work is the equivalent of sharpening the therapeutic tools by which VEGF modulation can be achieved, all based on mechanistic studies. Another example is related to the fact that VEGF is a survival factor for neurons, an area I personally am very familiar with. Studies of nonspecific inhibition of VEGF may help understand why this mode of treatment could have significant adverse effects, in contrast to ME's work on specific gene therapy targets in the rat oxygen-induced retinopathy model of ROP, which allowed distinction between VEGF isotypes and/or receptors. Along the same lines, she did important work assessing systemic leakage of VEGF from intravitreally-treated neonates and the effects on their development outside of the eye. Another key area that ME has studied relates to comparison between stimulation of VEGF secretion by hypoxia versus stimulation from fluctuations between hypoxia and hypoxia, and the effects on VEGF isoform expression. Understanding the mechanisms for this differential regular regulation could be used not only help decrease the incidence of ROP in the clinical care of premature infants, but also lead to better understanding of the mechanisms that are responsible for the disease itself.

An important area of research in which ME has played a leading role is the role of reactive oxygen species in angiogenesis in retinopathy of prematurity. Reactive oxygen species are generated in endothelial cells and ME has studied this in detail. By understanding the different isoforms of NADPH oxidase, one of the main sources for reactive oxygen species in endothelial cells, she has provided a clear link between VEGF activation of one of the NADPH oxidase isoforms (NOX4) and endothelial cell proliferation, and found that the signaling is through STAT3. This represents a likely translational target for future studies.

ME was also one of the first to study the role of neutralizing antibodies to VEGF in the rat OIR model, and this was one of the bases for the use of anti-VEGF drugs to be used in premature infants, which until then had only been used for adult retinal neovascular

diseases. She also found that even though neutralizing VEGF decreased its levels, it did not increase the amount of a vascularity in the periphery. This led to her studies understanding how increased levels of VEGF could not only cause angiogenesis, but also be responsible for retinal avascularity.

Although ME is most famous for her work in ROP, she has performed highly cited and important work in adult retinal disease. She described one of the first newly recognized retinal circulation neovascular diseases in adults, which was novel because until then the role of the choroid was considered more important. This retinal angiomatous proliferation, now called type 3 neovascularization in AMD, was found by ME to be more common in those with diffuse outer retinal disease. Her work looking at the interplay between choroidal endothelial cells and RPE cells was important for understanding the migration of the former across the latter, and she discovered the role of the small RhoGTPase Rac-1 in this process. She then linked it through VEGF binding to other inflammatory factors such as TNF-alpha, NADPH oxidase, and cholesterol oxidation. Her work in this area has been extensive, and I predict that it will continue to yield seminal scientific fruit for translational applications.

In summary, ME Hartnett's career in retinal surgery and basic research has been transformative in three ways. First, she has solidified the position of pediatric retina as a medical and surgical subspecialty by making the seminal textbook *Pediatric Retina* available to all who work with patients who have pediatric retinal disease. Second, she has trained directly (her trainees) and indirectly (via meetings she organized) multiple practitioners regarding the diagnosis and management of patients with retinopathy of prematurity and related diseases. Third, her work on critical areas of the pathophysiology of retinopathy of prematurity are important not only for clinical trials that have been performed with anti-VEGF drugs for patients, but also in obtaining a better understanding of many of the signaling mechanisms by which pathological and physiological neovascularization occur. This understanding has led, and will continue to lead, to future therapeutic developments. For all these reasons, I truly believe that ME Hartnett has had a gigantic direct and indirect impact on babies with ROP, and is fully deserving of the Helen Keller award.

Sincerely yours.

Leonard A. Levin, MD, PhD, FRCSC, FCAHS, FARVO
Distinguished James McGill Professor of Ophthalmology and Visual Sciences
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December 12, 2024

Dear Awards Committee members,

I would like to submit my nomination for Dr. ME Hartnett, a leading expert in our community, whose career has been dedicated to studying the molecular and biological mechanisms driving retinal angiogenesis and AMD, using her clinical expertise to answer important questions to the entire field. Dr. Hartnett is a uniquely successful clinician-scientist and an inspiring role model in our community, who has had continuous R01 funding. She has maintained 2 parallel long-standing R01's throughout her career, a spectacular feat of great significance, while also running her pediatric retina practice, as a surgeon and clinician. Dr. Hartnett's contributions to our basic and clinical understanding of angiogenesis have provided important insights into age-related macular degeneration as well as ROP, two major causes of blindness in adults and infants respectively. She has had a consistent track-record of high impact, highly insightful publications that continue to illuminate our understanding of the pathophysiology and basic mechanisms in both diseases.

One of her most highly cited studies has radically changed our understanding of the pathophysiology of neovascular AMD. Dr. Hartnett was the first to recognize that the retinal vasculature can participate in the neovascular AMD pathology, at the time this was a radical shift. In 1992 (Graefe's Arch), she initially described and later proposed a hypothesis involving Mueller cells (Ophthalmology, 1996) that clarified the pathogenesis and established the foundation for what is now known as type 3 macular neovascularization. This work shows her unique ability to develop great pathophysiologic insights building on her insightful clinical acumen, a powerful skill that is only shared by only a select few giants in our field. Taking her clinical insights to the lab, she then builds biological systems, where she can test clinically relevant hypothesis, has been her signature, a most fantastic and effective way that allowed her to continuously drive our field forward.

As well, she has made important instrumental contributions to retinal imaging research in the 1990's, even before the use of OCT. In a critical study, she collaborated with Ann Elsner and used infrared imaging of patients with AMD (Ophthalmology, 1996). She characterized the infrared imaging characteristics in eyes with neovascularization beneath the RPE (now type 1 MNV) before the onset of symptoms, as well as characterizing the appearance of lesions that invaded into the outer neural retina (now type 2 MNV). She was driven by the desire to better understand the underlying mechanism that causes choroidal endothelial cells to migrate and invade the neural retina. She reasoned that by identifying the basic mechanisms and then inhibiting these processes, vision might be preserved in neovascular AMD. She also surmised that extending vasculature beneath the RPE might have a beneficial effect by providing nutrition and clearing wastes, simulating a renewed choriocapillaris in eyes with advanced AMD and severely compromised outer retina/Bruch's membrane. These insights were quite astute and well ahead of the times. Her then novel concepts are now finally validated and incorporated in our mainstream with the advances in OCTA imaging.

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With her biological and basic science research she has invested her entire career since then to study these processes in the lab and characterize these mechanistic processes in greater detail.

Dr. Hartnett used her basic science expertise to develop a novel, physiologic human co-culture of the retinal pigment epithelial cells (RPE) and choroidal endothelial cells (CECs) to study the intricate pathologic processes of neovascular AMD, when CECs make their initial contact with the RPE under controlled conditions. Her research has been instrumental in increasing our understanding of the contribution of inflammation, angiogenesis, aging, and oxidation on the RPE. As well, she has characterized the CEC signaling mechanisms, as well as the RPE-CEC interactions that lead to CEC invasion and RPE barrier compromise in detail. She then tested relevant environmental stresses in AMD on these cell types, critically important research since we know that despite genetic variant associations, the external factors and stresses also play crucial roles in the development of vision-threatening AMD. These processes are highly relevant, especially in a multifactorial disease like AMD, where strong genetic predisposition leads to manifest disease later in life, with the continuous accumulation of these environmental stressors and oxidants.

Using this elegant co-culture system, in a seminal experiment, her recent publication provided new information that describes how exposure to compounds that accumulate in AMD and drusen, including oxidized forms of cholesterol, can incite the relevant chorioretinal cells in AMD to change phenotype into mesenchymal cells (Angiogenesis, 2021). This mesenchymal transition occurs in CECs, Mueller cells and pericytes and causes these cells to initiate the process of fibrosis. Transformed CECs also become more invasive, making them potentially less responsive to anti-VEGF therapies. This important finding that may partly explain the clinically important problem of resistance to anti-VEGF treatment in patients and may provide novel therapeutic avenues to address this clinical hurdle.

Most recently, she has identified a protective compound (Rap1aGTP) that can reduce reactive oxygen signaling in RPE and CECs through NADPH oxidase. This compound results in enhanced RPE barrier integrity in the face of inflammatory stressors, such as TNFalpha. The same compound reduced the activation of CECs and their ability to migrate and invade by activating Rac1GTP. These events are reduced by introducing active Rap1a by gene therapy or activating it pharmacologically. In addition, she identified a role for a multidomain protein, IQGAP1, that binds active Rac1 and sustains pathologic signaling through active Rac1.

In summary, I believe Dr. Hartnett's body of research work, and her dedication to advance our field, improve our understanding of complex pathological processes, involving feed-forward loops, crosstalk in signaling mechanisms and sustained pathologic signaling. Dr. Hartnett's expertise and active research has been highly cited, highly regarded and therefore consistently well-funded by the NEI and NIH.

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She has held many important leadership roles in our societies and volunteers her time generously to advance the field. I believe that Dr. Hartnett's research, Service and tireless contributions are quite deserving to represent the illustrious legacy and important contributions of Helen Keller.

Yours sincerely,

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August 30, 2024

RE: Nomination of Mary Elizabeth Hartnett for Helen Keller award

I join my esteemed colleagues in strongly recommending Dr Mary Elizabeth Hartnett (ME) for the Helen Keller award. As former chair of the awards committee, I believe I have in-depth knowledge of the degree of excellence required by successful nominees, and I can state unequivocally that ME possess that excellence . She is one of those amazing “triple threats” -outstanding as a clinician, educator and researcher, but I will dwell on her substantial contributions to science.

As background, pediatric retina is a very specialized branch of retinal research due to the ongoing development of the child’s eye and the plasticity of the eye-brain network. In infants, angiogenesis is encouraged but at the same time overgrowth must be inhibited, a phenomena well known to researchers in Retinopathy of Prematurity (ROP). ME is such a researcher and her contributions are exceptional.

First, we recognize ME and her team for their work on determining the mechanisms underlying the treatment of ROP with anti-VEGF agents, and specifically the distinction in effects between VEGF isotypes and/or receptors. Notably, her basic research was done prior to the clinical trials using anti-VEGF treatment, and with positive trial results, provided the mechanism for understanding the outcomes. As is understood, ROP is characterized by the lack of normal angiogenesis. She found that such treatment promotes normal angiogenesis in the peripheral retina as well as inhibiting abnormal growth. Using a rat model of oxygen induced retinopathy, she was able to recapitulate the oxygen fluctuations that are seen in infants with ROP. ME found that repeated oxygen fluctuations increased expression of a VEGF variant that is associated with pathologic angiogenesis. Hypoxia only increased expression of another variant. Using neutralizing antibodies, she found that even though neutralizing VEGF decreased its levels, it did not increase the amount of avascularity in the periphery. This led to her studies that clarified how increased levels of VEGF could not only cause angiogenesis, but also cause retinal avascularity. Her detailed findings on specific targets allowed understanding of distinctions between the possible VEGF isotypes/receptors and possible outcomes, both adverse and therapeutic.

ME has taken her research into clinical studies of premature infants , where she compared treatment-warranted type 1 ROP treated with bilateral intravitreal anti-VEGF to the natural history of a matched control group of infants with less-than-treatment-warranted ROP. Her results suggest that regulation of VEGF

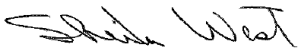
signaling using anti-VEGF injection resulted in less area of avascular retina and larger areas of physiologic angiogenesis than the natural growth in those with ROP where treatment was not warranted. She has received a fundable score of 2% to continue this exciting work which may well have significant consequences for how this disease is treated.

Secondly, ME has conducted critically important research in adult retinal diseases as well. She was one of the first to describe a retinal circulation disease called type 3 neovascular disease. Her extensive work in elucidating the interplay among various retinal cells and the role of inflammatory factors is on track to form the basis for translational applications.

Thirdly, ME virtually singlehandedly took on the creation of the first comprehensive textbook of pediatric retina. As editor-in-chief, she recruited experts in multiple disciplines, including medical retina, surgical retina, and genetics. It is recognized word-wide and is now in its third edition. I note that some professors at my institution were internationally known ONLY for creating the definitive textbook in their specialty, whereas this is just one of many facets of excellence that ME has contributed to our field.

I should add that ME is a tireless mentor and promotor of women in ophthalmology and scientific research. Like many of us, she has her share of glass shards as the result of ceilings she has broken through and serves as an inspiration to our younger colleagues that being a ”triple threat” is possible in a tough academic climate. She is an exceptional nominee for the Helen Keller prize for vision research and I am pleased to offer my strongest support for her application.

Sincerely,



Sheila West, PhD

Institute for Vision Research
Department of Ophthalmology and Visual Sciences
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Iowa City, Iowa 52242
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December 9, 2024

Dear Members of the Selection Committee,

I am delighted to recommend Dr. Mary Elizabeth (ME) Hartnett for the Helen Keller Prize for Vision Research. I have followed Dr. Hartnett's excellent work for several years through her high impact publications and engaging, well received presentations. Dr. Hartnett is an extremely accomplished and talented clinician-scientist who has made, and continues to make, major advances in translational and basic science of angiogenesis, retinopathy of prematurity, and AMD. I fully endorse her for this prestigious award.

I have briefly outlined below my overall enthusiasm and assessment of Dr. Hartnett's research program and contributions. Dr. Hartnett is a very well-respected expert in both benchtop and bedside aspects of retinal diseases whose work is highly appreciated internationally.

Dr. Hartnett's CV to me represents one of true success. She is consistently effective in raising extramural support for her elegant research program, which is highly productive and consists of both independent, very high-profile and high-impact basic research into the biology and pathophysiology of RPE and choroidal endothelial cells, as well as clinical research into sociological areas of medicine. Her work is characterized by careful, thoughtful experimentation, translational importance, creativity, and attention to detail. She publishes in prestigious journals and her work is highly regarded and highly cited. The fact that top tier journals show such interest in her work shows the universal and broad impact and interest —even outside of ophthalmology—her groundbreaking studies engender.

Of specific importance to the Helen Keller prize, she is a world leading expert in angiogenesis, and her detailed knowledge in ROP brings powerful insight to her elegant studies on vascular endothelial cell biology in retinal diseases. Whereas most of the studies performed to date on attempting to model AMD in vitro have relied on solitary

cell types, Dr. Hartnett's work recognizes the complex set of interactions that drive the health of the macula. To address this she uses ingenious co-culture approaches to determine the interactions between the RPE, choriocapillaris, environmental challenges such as 7-keto-cholesterol, and signaling pathways. Her work beautifully synthesizes the events in the aging macula and has begun to pinpoint molecular actors (such as the RAP1-RAC1 axis) that are intriguing potential targets in devising new treatments for AMD.

On a personal level, Dr. Hartnett is a wonderful, caring and positive person who I know would be a fantastic ambassador for the award. The times that I have been fortunate to work with her on study sections or ARVO committees, I have constantly been impressed by her fair, calm, insightful leadership. Her commitment to others is further reflected in her leadership in addressing gender and racial disparities in ophthalmic health care, in addition to her being a world expert clinician scientist.

In summary, I strongly recommend Dr. ME Hartnett, a truly exceptional clinician-scientist and scholar, to be the recipient of the Helen Keller Prize for Vision Research.

If you require any additional information, please do not hesitate to contact me.

Sincerely,

Robert F. Mullins, PhD, FARVO
Martin Carver Chair in Ocular Cell Biology
Professor of Ophthalmology and Visual Sciences
The University of Iowa Institute for Vision Research

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person.

NAME: Mary Elizabeth Ruth Hartnett

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

Institution and Location	Degree/Position	Completion Date	Area of Study
Rensselaer Polytechnic Institute, Troy, NY (*6-year BS-MD)	BS	05/82*	Biology
Albany Medical College, Albany, NY	MD	05/83*	Medicine
University Hospitals of Cleveland, OH	Intern	05/84	Medicine
University Hospitals of Cleveland, OH	Resident	06/87	Ophthalmology
Mass Eye and Ear/Schepens Retina Assoc.	Fellow	07/89	Retina
Mass Eye and Ear/Schepens Retina Assoc.	Fellow	07/90	Pediatric Retina
Harvard Medical/Schepens Eye Res. Inst.	training with P. D'Amore	11/1999	Cell/molec biology
University of North Carolina	training with K. Burridge	5/2010	Developmental biology, GTPases, signaling

Personal Statement

I am a clinician scientist studying diseases of the retina and choroid that are associated with abnormal angiogenesis. As a scientist, my lab has focused on understanding mechanisms leading to abnormal blood vessel growth as well as homeostatic mechanisms that maintain the health of the retina and the vasculatures supporting it. Specifically, I seek to understand what stimuli cause endothelial cells to become activated to migrate, proliferate and grow into the wrong compartments of the eye and to prevent this abnormal growth, rather than to inhibit or destroy blood vessels. The goal is to restore or contain vasculature in normal compartments within retina or choroid in order to support vision. I've sought treatments to preserve retinal health and vision in patients or to prevent disease. I also treat patients to restore vision through prevention of disease and vitreoretinal surgery to restore vision.

In retinopathy of prematurity (ROP), I studied the question why blood vessels pathologically grow into the vitreous rather than into the retina, in order to extend developmental angiogenesis and prevent pathologic angiogenesis in treatment-warranted ROP. My laboratory-based experimental work provided the proof of concept that inhibition of an angiogenic signaling pathway, specifically VEGF receptor 2 in retinal endothelial cells, can extend developmental angiogenesis as well as inhibit intravitreal growth of blood vessels. (This property is not present in adult retinovascular diseases, such as diabetic retinopathy). We identified a mechanism whereby abnormal signaling through VEGF receptor 2 in retinal endothelial cells disorders the cleavage planes of dividing endothelial cells allowing them to grow on top of one another into the vitreous rather than as ordered linear vessels to extend developmental angiogenesis to the ora serrata. We also found clinical evidence that intravitreal anti-VEGF causes greater developmental angiogenesis than the natural history of less severe treatment-warranted ROP in a carefuly designed study in a single institution. De-identified images were reviewed by a masked analyst who developed a method to measure the lengths from optic nerve to peripheral temporal extent in pixels. Infants with severe ROP (type 1) treated with the same dosage of anti-VEGF had greater peripheral extension of developmental angiogenesis than prematurity-matched, untreated infants with less severe ROP. Our experimental work predated clinical trials testing anti-VEGF agents in ROP. Additionally, my work in ROP has included clinical trial design and the testing of different anti-VEGF agents and dosages. More work is needed to assess visual field and long-term follow up clinically. We continue studies into mechanisms at the VEGF receptor 2 level to distinguish angiogenesis that would be physiologic (i.e., extending peripheral vascularization) vs. pathologic (intravitreal growth).

In age-related macular degeneration (AMD), my basic research is to understand how external factors, associated with environmental risk factors, can mechanistically influence the pathophysiology of different vision-threatening features in AMD. I am interested in understanding the mechanisms that lead to vision-threatening invasion of choroidal endothelial cells into the neural retina, in order to prevent these processes without inhibiting angiogenesis that may be supportive to the outer retina if contained beneath the RPE. We found factors (e.g., VEGF, TNFalpha, oxidative compounds) activated the common small GTPase, Rac1, and

that activated Rac1 was essential to choroidal endothelial cell transmigration of the RPE, a key step in choroidal endothelial cell invasion of the neural retina. Another GTPase, Rap1a, reduced the effect of Rac1. My lab has found that oxidized forms of cholesterol that form in the retina and that are predominant in human drusen cause choroidal endothelial cells and pericytes to become fibroblastic and undergo mesenchymal transition. At the same time, retinal pigment epithelial cells (RPE) adopt a senescence associated secretory phenotype releasing factors that attract choroidal endothelial cells to migrate to the drusen beneath RPE and encounter the oxidized cholesterol forms. We are studying these processes with a goal to prevent fibrosis, currently an untreatable cause of vision loss in AMD.

I have also performed diabetic retinopathy research, including identifying oxidative compounds as biomarkers of retinopathy severity and treatment trials involving anti-VEGF agents. I have led and served on the American Diabetes Association (ADA) research council for 3 years, and reviewed grants for the ADA for 8 years. I led the group that published basic science biomarkers in diabetic eye disease as part of the Mary Tyler Moore consortium for diabetic retinopathy.

My lab uses molecular techniques in cells, in human heterotypic coculture models that represent human disease, and in genetically modified rodent models to determine the effect of relevant stresses and stimuli on triggering pathologic signaling pathways in human diseases. I have the leadership capabilities and training to design experiments and oversee and supervise staff, review protocols, and assure integrity in data synthesis and analysis. I have brought together teams in leadership roles as chair of scientific advisory boards for several international groups, including ARVO, and in group grants including planning grants as the PI for a future MPI grant. I have also worked in PEDIG and DRCR.net to develop protocols and Manuals of Procedures/Protocols for clinical trials.

I have chaired study sections at NIH (including DPVS), the Macula Society and the Jack McGovern Coats' Disease Foundation, and served on grant reviews for the ADA and the Knights Templar Eye Foundation. I have mentored clinicians, scientists, graduate and post-doctoral students, clinician-scientists, students (including high school and undergraduate), faculty, residents and fellow as well as laboratory members for about 20 years of NIH support for my lab. I also work with industry in clinical trial design, implementation and analysis interpretation. I have created the first textbook on Pediatric Retina and have led educational courses to teach about pediatric retina diseases, including the Advances in Pediatric Retina international Course and meeting and intiated efforts there to highlight new research, including basic science. Recent high school trainees have been involved in creating programs to encourage science interest in high school through ARVO.

Ongoing NIH grants:

R01 EY015130 (NEI/NIH) Hartnett, ME (PI) 12/02/2004–08/31/2029
Mechanisms of Angiogenesis in Retinopathy of Prematurity renewal application received 2 percentile
Major Goals: The objectives of the grant are to determine mechanisms of intravitreous neovascularization and those of vascularization of previously avascular retina with focus on signaling of VEGF pathways.
Role: Principal Investigator

R01 EY017011 (NEI/NIH) Hartnett, ME (PI) 04/01/2007–5/01/2026
Endothelial Transmigration in Neovascular Age-related Macular Degeneration (renewal submitted)
Major goals: To study mechanisms involved in choroidal endothelial cell transmigration into the neurosensory retina as it relates to age-related macular degeneration.
Role: Principal Investigator

R01 EY034975 (NEI/NIH) Zhu, Weiquan and Hartnett, ME 07/01/2023-06//30/2028
Inhibiting neovascularization and subretinal fibrosis in neovascular age-related macular degeneration
Major Goals: To study the role of GTPases, particularly Arf6, involved in RPE and endothelial cell mesenchymal transition and fibrosis.
Role: multi-Principal Investigator

R21 EY033579-01 Bernstein, Paul and Hartnett, ME (Co-PIs) 05/01/2022-04/30/2024
A Pilot Study of the Value of Pre-symptomatic Genetic Risk Assessment for Age-Related Macular Degeneration
Major Goals: To study whether individuals who are informed of a high risk of eventual AMD will be more likely to make sustained changes in behavior associated with decreased incidence of AMD later in life such as smoking cessation, weight loss, decreased light exposure, and diets rich in carotenoids relative to subjects who have deferred testing or who are informed of low risk.
Role: Co-Principal Investigator

R13EY035179 (NIH) Hartnett ME (PI) 07/01/2022- 5/31/2024
Fourth Advances in Pediatric Retina International Meeting
Major Goals: To provide funding to support students presenting research at the 4th International Advances in Pediatric Retina meeting and course September 7-9, 2023 in Santa Clara, CA.
Role: Principal Investigator

R01EY019474 Campbell, J. Peter (PI). 07/11/2021-5/31/2024
Oregon Health and Science University | NEI/NIH
Clinical and Genetic Analysis of Retinopathy of Prematurity
Major Goals: To develop quantitative models relating the clinical, imaging, and genetic features of retinopathy of prematurity, and to examine genotype-phenotype correlations.
Role: PI subaward

3353 Hartnett ME (PI) 04/01/2023-03/31/2028
Jaeb Center for Health Research | NIH
Laboratory Analysis Agreement for PEDIG ROP3 and ROP4 studies
Major Goals: To perform laboratory ELISA testing for human infants enrooled in clinical studies, ROP 3 and ROP 4.
Role: Principal Investigator

1R34EY034969-01 Dammann, Olaf (PI) 03/01/2023-03/01/2025
Tufts
VICTORY
Major Goals: To review and develop a study to analyze risk factors for ROP and visual loss related to ROP and prematurity
Role: Site Principal Investigator

1. Wang H, Ramshekar A, Kunz E, **Hartnett ME**. 7-ketocholesterol induces endothelial-mesenchymal transition and promotes fibrosis: implications in neovascular age-related macular degeneration and treatment. *Angiogenesis* 2021, Aug;24(3):583-595. PMC8865553.
2. Ramshekar A, Wang H, Kunz E, Pappas C, Hageman GS, Chaqour B, Sacks DB, **Hartnett ME**. Active Rap1-mediated inhibition of choroidal neovascularization requires interactions with IQGAP1 in choroidal endothelial cells. FASEB J. 2021 Jul;35(7):e21642. PMC8238370.
3. Peterson LJ, Wittchen ES, Geisen P, Burridge K, **Hartnett ME**. Heterotypic RPE-choroidal endothelial cell contact increases choroidal endothelial cell transmigration via PI 3-kinase and Rac1. *Exp Eye Res*, 2007 84(4), 737-44. PMID: 1792356
4. Wang H, Ramshekar A, Kunz E, Sacks DB, **Hartnett ME.** IQGAP1 causes choroidal neovascularization by sustaining VEGFR2-mediated Rac1 activation. *Angiogenesis*. 2020, 23:685-698. PMC7530064
5. **Hartnett ME**, Stratton RD, Browne RW, Rosner BA, Lanham RJ, Armstrong D. Serum markers of oxidative stress and severity of diabetic retinopathy. Diabetes Care. 2000 Feb;23(2):234-40. PMID: 10868837.
6. Sauer L, Chandler M, **Hartnett ME**. Extending Peripheral Retinal Vascularization in Retinopathy of Prematurity (ROP) through Regulation of VEGF Signaling. Am J Ophthalmol. 2024 Apr;260:190-199. PMC10981561
7. Hartnett ME. Pathophysiology of Retinopathy of Prematurity. Annu Rev Vis Sci. 2023 Sep 15;9:39-70. PMID: 37164029.

A. Positions, Scientific Appointments, and Honors

Positions in Societies, and Service and Scientific Appointments

2022-present	Professor of Ophthalmology, Stanford University
2022-present	Member of the American Ophthalmological Society Council
2021-present	Member ARVO Foundation
2021-2024	Chair, Research Committee, Macula Society
2019-2023	Member of the National Advisory Eye Council, NEI/National Institutes of Health
2019-2021	Chair, Publications Committee, ARVO
2023-present	Adjunct Professor of Ophthalmology, University of Utah
2018-2023	Co-Director of President's Committee on the Status of Women, University of Utah
2015-2016	Co-Director of MD-PhD program, University of Utah

2014-2015	Chair, Program committee for Retinal Cell Biology, AMPC ARVO
2013-2015	Chair, Ethics and Regulations in Human Research Committee, ARVO
2013-present	Member of Scientific Advisory Board, Knights Templar Eye Foundation
2012-2023	Adjunct Professor of Neurobiology and Anatomy, University of Utah, Salt Lake City, UT
2011-2015	Member (2010-2015) and Chair (2013-2015) DPVS study section: NIH
2009-2013	American Diabetes Association National Research Committee
2007-2011	NIH BDPE R01 study section
2010-2023	Adjunct Professor of Pediatrics, University of Utah, Salt Lake City, UT
2010-2023	Professor of Ophthalmology with tenure, University of Utah, Salt Lake City, UT
2008-2010	Professor of Ophthalmology with tenure, University of North Carolina, Chapel Hill, NC.
2005,2013,2021	*PEDIATRIC RETINA,* **Hartnett ME,** Editor-in-Chief, Wolters- Kluwer/Lippincott Williams & Wilkins, Philadelphia, PA (2021 third edition)
2006-2009	American Diabetes Association study section
2003-2008	Associate Professor of Ophthalmology with tenure, UNC, Chapel Hill, NC.
2001-2019	NIH ad hoc study sections: Clinical Science study sections, K-, T-,F-awards, R21
2000-2003	Associate Professor of Ophthalmology, Director, Retina Service, LSU Eye Center, Louisiana State University Health Sciences Center, New Orleans, LA.
1999-2000	Assistant Clinical Professor of Ophthalmology, Harvard University, Cambridge, MA
1997-2009	NIH study section for Small Business Innovation Research (SBIR) Grants. National Institutes of Health, Washington, DC
1996-2000	Clinical Associate in Surgery, Massachusetts General Hospital, Boston, MA
1995-2000	Assistant Clinical Scientist, The Schepens Eye Research Institute, Boston, MA
1995-99	Consultant, Children's Hospital, Boston, MA
1994-2000	Associate in Ophthalmology, Massachusetts Eye and Ear Infirmary, Boston, MA
1993-1999	Clinical Instructor, Harvard University, Cambridge, MA
1990-93	Assistant Professor, Retina Service, State University of New York, Buffalo, NY
1989-90	Senior Research Fellow in Ophthalmology, Harvard University, Boston, MA
1988-89	Chief Fellow, Schepens Retina Associates, Boston, MA

<u>Honors</u>

2024	Inducted into American Society of Clinical Investigation as Honorary member
2023	Michael F. Marmor, M.D., Professor of Retinal Science and Disease, endowed professor
2023	Bradley R. Straatsma Lecture, UCLA
2023	Constance West Lecture, University of Cincinnati
2022	Research to Prevent Blindness 2022 for IRIS Registry Research
2022	Distinguished Research Award for Pediatrics and Ophthalmology, University of Utah
2022	27th Annual Gertrude D. Pyron Award, American Society of Retina Specialists
2021	Suzanne Verroneau Troutman Award from Women in Ophthalmology
2020	Senior Honor Award, American Academy of Ophthalmology
2019-	Distinguished Professor of Ophthalmology, University of Utah, Salt Lake City, UT
2019	Paul Kayser/Retinal Research Foundation Global Award
2019	Arnall Patz Medal, Macula Society
2018	Future Vision Foundation Laureate
2018	Calvin S. and JeNeal N. Hatch Presidential Endowed Chair, University of Utah
2018	Mildred Weisenfeld Award from ARVO
2016	Paul Henkind Memorial Award and Lecture, Macula Society
2015	Distinguished Visiting Lecturer, Dept. of Ophthalmology, State University of NY, Buffalo
2015	Gold Fellow of ARVO
2014	Medical College of Wisconsin Vision Science Distinguished Lecture
2014	Kresge Eye Institute Vision Workshop Keynote Speaker
2014	Annual Lecture in Honor of Raniya Ramadan at University of Oklahoma
2014	WIO Scientific Contribution Award
2014	Honorary Lecture Award, Women in Ophthalmology International meeting
2008-2015	Research Committee appointee for National American Diabetes Association
2006	Finalist: Burroughs Wellcome Fund Clinical Scientist Awards, Translational Research
2005-present	“Best Doctors in America”
2004	Physician Scientist Merit Award, Research to Prevent Blindness

2000	Prince Abdul Aziz Bin Ahmed Bin Abdul Aziz Al Saud Professor, LSU LA
1998	Honor Award, American Academy of Ophthalmology, San Francisco, CA
1993-present	Fellow of the American College of Surgeons
1988-89	Chief Fellow, Retina Associates, Boston, MA
1988-89	Charles de Gunzburg Fellowship in Clinical Retina Research, Schepens Eye Research Institute, Boston, MA
1983	Arthur W. Wright Award, Albany Medical College, Albany, NY
1982-83	Alpha Omega Alpha Honor Society, Albany Medical College, Albany, NY
1982	Graduated summa cum laude, Rensselaer Polytechnic Institute, Troy, NY
1981	Perrin Oncology Fellowship in Research, University of Pittsburgh, Pittsburgh, PA

Patents:
10,214,741 (US) – Targeting endothelial induced STAT3 inhibits severe retinopathy of prematurity
62/905,880 (provisional) Gene therapy to restore homeostasis and reduce macular disease

B. Contributions to Science

1. We developed a method to study molecular mechanisms in the most representative model of human ROP, the rat oxygen-induced retinopathy model using gene therapy approaches. In order to specifically knockdown proteins or receptors we used cell specific promoters and developed a method to embed them within a miR30 context in order to drive expression of shRNAs in vivo. We were then the first to use this method to knockdown expression of VEGF receptor 2 specifically in retinal endothelial cells in the rat OIR model. This adapted model provided proof of concept that regulation of retinal endothelial VEGFR2 extended developmental angiogenesis as well as inhibit intravitreal angiogenesis. This translates to anti-VEGF treatment for ROP.

a. Simmons AB, Bretz CA, Wang H, Kunz E, Hajj K, Kennedy C, Yang Z, Suwanmanee T, Kafri T, **Hartnett ME** (2018). Gene therapy knockdown of VEGFR2 in retinal endothelial cells to treat retinopathy. *Angiogenesis*, 21(4):751-764 PMC6203654.
b. Wang H, Smith GW, Yang Z, Jiang Y, McCloskey M, Greenberg K, Geisen P, Culp WD, Flannery J, Kafri T, Hammond S, **Hartnett ME**. (2013). Short hairpin RNA mediated knockdown of VEGFA in Müller cells reduces intravitreal neovascularization in a rat model of ROP. *Am Journal of Path* 183(3):964-74 PMC3763762.
c. Jiang Y, Wang H, Culp D, Yang Z, Fotheringham L, Flannery J, Hammond S, Kafri T, **Hartnett ME**. (2014). Targeting Muller cell-derived VEGF 164 to reduce intravitreal neovascularization in the rat model of retinopathy of prematurity. *Invest Ophthalmol Vis Sci*, 55(2), 824-31 PMC3920823.
d. Yang Z, Wang H, Jiang Y, **Hartnett ME**. (2014). VEGFA Activates Erythropoietin Receptor and Enhances VEGFR2-mediated Pathological Angiogenesis. *Am J Pathol*, 184(4), 1230-9 PMC3969997

2. We identified factors ($VEGF_{189}$ splice variant, eotaxins [CCl11, CCl24, CCl26]) were overexpressed in age and by oxidative signaling in the retinal pigment epithelium (RPE) and that RPE- generated factors activated choroidal endothelial cells having translational importance in neovascular AMD.

a. Geisen P, McColm JR, **Hartnett ME**. (2006). Choroidal endothelial cells transmigrate across the retinal pigment epithelium but do not proliferate in response to soluble vascular endothelial growth factor. *Exp Eye Res, 82*(4), 608-19. PMID: 16259980.
b. Takeda A, Baffi JZ, Kleinman ME, Cho WG, Nozaki M, Yamada K, Kaneko H, Albuquerque RJ, Dridi S, Saito K, Raisler BJ, Budd SJ, Geisen P, Munitz A, Ambati BK, Green MG, Ishibashi T, Wright JD, Humbles AA, Gerard CJ, Ogura Y, Pan Y, Smith JR, Grisanti S, **Hartnett ME**, Rothenberg ME, Ambati J. (2009). CCR3 is a target for age-related macular degeneration diagnosis and therapy. *Nature*, *460*(7252), 225-30. PMC2712122
c. Wang H, Geisen P, Wittchen ES, King B, Burridge K, D'Amore PA, **Hartnett ME**. (2011). The role of RPE cell-associated VEGF in choroidal endothelial cell transmigration across the RPE. *Invest Ophthalmol Vis Sci*, *52*(1), 570-8. PMC3053298
d. Wang H, Wittchen ES, Jiang Y, Ambati B, Grossniklaus HE, **Hartnett ME**. (2011). Upregulation of CCR3 by Age-Related Stresses Promotes Choroidal Endothelial Cell Migration via VEGF-Dependent and Independent Signaling. *Invest Ophthalmol Vis Sci*, *52*(11), 8271-7. PMC3208059

3. We determined that activation of NADPH oxidase (also important in cardiovascular biology and disease) is a cause of neovascular AMD through the breakdown of the RPE barrier integrity. Competitively inhibiting subunit

p22phox by activation of the GTPase, Rap1a, maintains RPE barrier integrity and has translational potential.

a. Wang H, Han X, Bretz CA, Becker S, Gambhir D, Smith GW, Samulski RJ, Wittchen ES, Quilliam LA, Chrzanowska-Wodnicka M, **Hartnett ME.** Retinal pigment epithelial cell expression of active Rap 1a by scAAV2 inhibits choroidal neovascularization. Mol Ther Methods Clin Dev. 2016 Aug 24;3:16056. PMC4996131.

b. Monaghan-Benson E, Hartmann J, Vendrov AE, Budd S, Byfield G, Parker A, Ahmad F, Huang W, Runge M, Burridge K, Madamanchi N, **Hartnett ME**. (2010). The role of vascular endothelial growth factor-induced activation of NADPH oxidase in choroidal endothelial cells and choroidal neovascularization. *Am J Pathol*, *177*(4), 2091-102. PMC2947302

c. Wittchen ES, Nishimura E, McCloskey M, Wang H, Quilliam LA, Chrzanowska-Wodnicka M, and **Hartnett ME**. (2013). Rap1 GTPase activation and barrier enhancement in RPE inhibits choroidal neovascularization in vivo. *PLOS ONE* Sep 10;8(9):e73070 PMC3769400

d. Wang H, Jiang Y, Shi D, Quilliam LA, Chrzanowska-Wodnicka M, Wittchen ES, Li DY, **Hartnett ME**. (2014). Activiation of Rap1 inhibits NADPH oxidase-dependent ROS generation in retinal pigment epithelium and reduces choroidal neovascularization. *FASEB J*. 28(1):265-74 PMC3868836

4. I was involved in early studies clinically and experimentally on the role of oxidative signaling in pathologic and physiologic angiogenesis involving the retina. This led to my initial study of the role of STAT3 in intravitreal neovascularization and some of my early studies demonstrating the role of NOX4 in VEGF-induced intravitreal neovascularization as seen in retinopathy of prematurity.

a. Saito Y, Uppal A, Byfield G, Budd S, **Hartnett ME**. (2008). Activated NAD(P)H oxidase from supplemental oxygen induces neovascularization independent of VEGF in retinopathy of prematurity model. *Invest Ophthalmol Vis Sci*, *49*(4), 1591-8. PMC2362384

b. Byfield G, Budd S, **Hartnett ME**. (2009). The role of supplemental oxygen and JAK/STAT signaling in intravitreous neovascularization in a ROP rat model. *Invest Ophthalmol Vis Sci*, *50*(7), 3360-5.PMC3682836

c. Wang, H, Zhang SX, **Hartnett ME**. (2013). Signaling pathways triggered by oxidative stress that mediate features of severe retinopathy of prematurity. *JAMA Ophthalmol,* 131(1), 80-5. PMC3703446

d. Wang H, Yang Z, Jiang Y, **Hartnett, ME**. (2014). Endothelial NADPH oxidase 4 mediates vascular endothelial growth factor receptor 2-induced intravitreal neovascularization in a rat model of retinopathy of prematurity. *Mol Vis*, 20, 231-41. PMC3945806

5. Results from my lab, showed that VEGF signaling not only has a role in aberrant intravitreal angiogenesis but also in disorienting dividing endothelial cells in order to gain access to the vitreous rather than the retina, thus contributing to avascular retina. VEGF-induced STAT3 downregulated erythropoietin in Mueller cells to contribute to avascular retina. Our lab was among the first to identify mechanisms leading to avascular retina from oxygen stresses in ROP. We have also redefined the hypothesis of the phases of ROP based on current knowledge now used in clinical work.

a. Wang H, Byfield G, Jiang Y, Smith GW, McCloskey M, **Hartnett ME**. (2012). VEGF-mediated STAT3 activation inhibits retinal vascularization by down-regulating local erythropoietin expression. *Am J Pathol*, *180*(3), 1243-53. PMC3349887

b. Fung C, Cung T, Nelson C, Wang H, Bretz C, Ramshekar A, Brown A, Stoddard GJ, **Hartnett ME** (2023). Retinopathy of prematurity protection conferred by uteroplacental insufficiency through erythropoietin signaling in an experimental murine model. *Pediatr Res*, *94*(3):950-955.

c. Zeng G, Taylor SM, McColm JR, Kappas NC, Kearney JB, Williams LH, **Hartnett ME**, Bautch VL. (2007). Orientation of endothelial cell division is regulated by VEGF signaling during blood vessel formation. [This was a plenary paper with a commentary]. *Blood*, *109*(4), 1345-52. PMC1794069

d. **Hartnett ME**, Martiniuk D, Byfield G, Geisen P, Zeng G, Bautch VL. (2008). 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*, *49*(7), 3107-14. PMC2459334

e. **Hartnett ME**, Penn JS. (2012). Mechanisms and management of retinopathy of prematurity. *N Engl J Med, 367*(26), 15-26. PMC3695731

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https://www.ncbi.nlm.nih.gov/sites/myncbi/1zUZedvU5xoQd/bibliography/43786285/public/?sort=date&direction=descending