Helen Keller Prize Nomination Form

Name of Nominee(s): Joan W. Miller, Patricia A. D'Amore, Anthony Adamis, Lloyd Paul Aiello, Napoleone Ferrara

Affiliation of Nominee(s): Harvard Medical School

Name of Nominator: Jean Bennett, MD, PhD

Any perceived conflict of interest with nominee to report? No

Please summarize in 250 words or less why you are nominating this person for the Helen Keller Prize. Please include significant scientific contributions and the effect on the field of vision research and blindness prevention.

Intraocular vascular diseases are leading causes of vision loss in adults. In developed countries, age-related macular degeneration (AMD) is the leading cause of vision blindness in people over 50. AMD affects 196 million people worldwide — 1 in 4 people over the age of 60, and 1 in 3 over the age of 70. Diabetic retinopathy is the leading cause of blindness in working-age adults, causing an estimated 5 million cases of blindness. With rising global population age and diabetes prevalence, AMD and diabetic retinopathy are significant worldwide health concerns and represent a serious socioeconomic burden.

In both AMD and diabetic retinopathy, vascular growth and leakage have been known for some time to cause vision loss, but until recent years, there were no effective medicines for neovascular ocular diseases. Drs. Joan Miller, Patricia D'Amore, Anthony Adamis, Lloyd Paul Aiello, and Napoleone Ferrara uncovered the mechanisms of ocular neovascularization — leading to the first pharmacological therapies for AMD and diabetic retinopathy. Through collaborations and independent research, they demonstrated VEGF production in the retina, its hypoxic regulation, and its association with ocular neovascularization in primate eyes and in patients with diabetic retinopathy and other retinal disorders. In subsequent preclinical studies, they demonstrated that VEGF inhibition blocks ocular neovascularization. This translational research formed the scientific basis for clinical trials and eventual approval of multiple anti-VEGF agents for intraocular vascular diseases—altering the therapeutic paradigm for the treatment of these diseases and resulting in the most successful applications of anti-angiogenic therapy to date.

Please provide any other supporting documents (a biosketch of the Nominee, an outstanding publication) with this nomination letter for review. The application should not exceed ten pages total, including this one page nomination form.

Center for Advanced Retinal & Ocular Therapeutics
PennCAROT
University of Pennsylvania Perelman School of Medicine

Department of Ophthalmology
Scheie Eye Institute,
F.M. Kirby Center for Molecular Ophthalmology

Jean Bennett, M.D. Ph.D.
F. M. Kirby Professor Emerita of Ophthalmology
Cell & Developmental Biology

January 16, 2024

Helen Keller Foundation
Vision Research Awards Committee
lbeckwith@helenkellerfoundation.org

Re: Nomination of Drs. Joan W. Miller, Patricia A. D'Amore, Anthony P. Adamis, Lloyd Paul Aiello, and Napoleone Ferrara for the 2024 Helen Keller Prize for Vision Research

Dear Members of the Helen Keller Prize for Vision Research Awards Committee:

I am delighted to nominate the team of researchers consisting of Drs. Joan W. Miller, Patricia A. D'Amore, Anthony P. Adamis, Lloyd Paul Aiello, and Napoleone Ferrara (hereafter referred to as the "anti-VEGF group") for the 2024 Helen Keller Prize for Vision Research.

One of the most important breakthroughs in the field of Ophthalmology has been the development of anti-vascular endothelial growth factor (anti-VEGF) drugs, which have revolutionized the treatment of a variety of eye diseases, including neovascular age-related macular degeneration, diabetic retinopathy, and macular edema following retinal vein occlusion. This was nominated by the prestigious journal *Science* as Breakthrough of the Year over a decade ago, and the clinical impact has continued to grow even since then. With this in mind, we can all agree that the clinical development of anti-VEGF drugs would not have been possible without first having identified the molecule, VEGF, as responsible for retinal vascular growth in development and disease.

The search for a target for pathologic ocular neovascularization dates back to at least 1948, when I.C. Michaelson first hypothesized the existence of "Factor X." This factor was thought to affect the growth of vessels in the retina and was associated with the metabolism of retinal tissue. In the early 1970s, Judah Folkman proposed that angiogenesis, or the recruitment and growth of new blood vessels, was required for tumor growth. He further suggested that "anti-angiogenesis" may be used to restrict blood supply to the tumor and induce dormancy. This was the foundation of current treatment modalities for a wide array of ocular conditions characterized by aberrant angiogenesis. In 1983, Harold Dvorak isolated vascular permeability factor (VPF) which was 50,000 times more potent than histamine. Then, in the late 1980s, Napoleone Ferrara cloned, sequenced, and characterized VEGF as a secreted angiogenic factor, regulated by hypoxia, with an important role in cancer. It was subsequently found that VEGF and VPF shard the same cDNA sequence, and were in fact, the same molecule. Excited by these findings, the group began exploring the elucidation of VEGF as Michaelson's "Factor X" and its contribution to retinopathies, in which hypoxia was a known driver of abnormal blood vessel growth in the back of the eye. Their work, while largely independent, was also mutually dependent, with a number of collaborations among the anti-VEGF group.

At Harvard Medical School in the early 1990s, there were two primary groups investigating VEGF and ocular angiogenesis. One was led by Dr. Lloyd Paul Aiello and Dr. George King at Joslin Diabetes Center, who later were joined by Dr. Lois Smith and Dr. Eric Pierce of Boston Children's Hospital. Another group was led by Dr. Patricia D'Amore and her graduate student David Shima, along with Dr. Anthony Adamis, Dr. Joan Miller, and Dr. Evan Gragoudas, at Boston Children's Hospital and Massachusetts Eye and Ear. They also had many collaborators, postdoctoral fellows, and students who were instrumental in carrying out this work. In 1993, Dr. Adamis and Dr. D'Amore worked with Dr. Folkman to show that human retinal cells could indeed express VEGF, the first demonstration that ocular cells made this factor. They also demonstrated that this production was regulated by hypoxia. Dr. Miller worked with the team to show that intraocular levels of VEGF correlated with ocular neovascularization in a primate model of laser-induced retinal ischemia, the first such demonstration in vivo. Drs. Adamis, Miller, and Folkman then showed that patients with proliferative diabetic retinopathy had significantly increased VEGF levels in vitreous samples. This pivotal finding was corroborated by a larger study conducted concomitantly at Boston's Joslin Diabetes Center, where Drs. Aiello, Ferrara, and colleagues showed increased VEGF in the ocular fluid of patients with a number of retinal disorders. Next, Dr. Adamis, Ferrara, D'Amore, and Miller

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showed that VEGF was an essential driver of neovascularization, achieving a complete inhibition of neovascularization in the non-human primate model using intravitreal injection of an anti-VEGF antibody (the precursor to the anti-VEGF agent bevacizumab). Finally, studies by Dr. Miller, Ferrara, and Adamis demonstrated that VEGF injection directly into normal non-human primate eyes led to iris neovascularization and neovascular glaucoma, recapitulating the pathology observed clinically with retina ischemia. VEGF alone was both sufficient and necessary for ocular neovascularization.

The discovery of the pathophysiology of the different neovascular diseases showed that different diseases could be targeted by addressing the same common pathway. The demonstration that VEGF blockade with anti-VEGF antibodies and/or antibody fragments prevented iris and choroidal neovascularization set the stage for clinical trials. Soluble VEGF-receptor fragments and specific oligonucleotides that blocked the effect of VEGF also were shown to be effective therapies. From this early work, many different methods of VEGF blockade have been developed and are now being applied in the clinic. Each of these investigators has developed as an independent leader in this field while maintaining their early ties as collaborators.

Dr. Ferrara and colleagues at Genentech worked to develop an anti-VEGF antibody fragment (a precursor to ranibizumab or Lucentis) and began preclinical and clinical investigations. In parallel, Drs. Adamis, D'Amore, and Miller (in various combinations) conducted critical preclinical studies on the precursor to ranibizumab as well as clinical studies on pegaptanib (Macugen), the first anti-VEGF drug approved by the FDA. The results of these concurrent studies bolstered clinical trials of ranibizumab in various clinical populations with AMD. Following favorable results of Phase III trials, ranibizumab won FDA approval for the treatment of AMD in 2006, and subsequently became a first-line treatment for various neovascular eye diseases. However, prior to ranibizumab's approval, the off-label injection of its full-length antibody precursor (bevacizumab or Avastin) demonstrated clinical effectiveness and became widely used for the treatment of AMD and other ocular diseases. The cumulative work of the anti-VEGF group not only made tremendous strides toward the understanding of numerous blinding neovascular diseases, but made translational advances to multiple successful anti-VEGF treatments.

Prior to the development of anti-VEGF drugs, the natural history of age-related macular degeneration and diabetic macular edema was one of progressive visual decline. In the early 1960s, direct laser photocoagulation was used to treat neovascularization in AMD. However, this treatment often caused extensive retinal scarring, which led to blind spots and decreased vision. For the wet form of AMD, no treatment strategy existed. Diabetic retinopathy was better controlled through panretinal photocoagulation, but still had significant side effects. Treatment for macular edema following retinal vein occlusion was also of limited benefit. Beginning in 2000, photodynamic therapy--an approach borrowed from the field of oncology-- was used to selectively destroy abnormal vessels under the retina. However, success was limited as patients still lost vision.

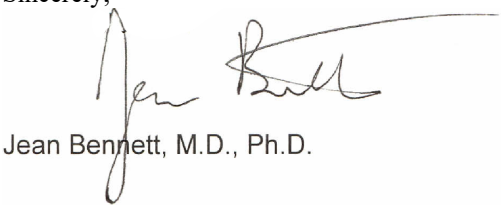
The candidates' work led to a paradigm-shift in the therapeutic options for patients with neovascular eye disease, leading directly to the development of multiple anti-VEGF agents that have replaced verteporfin photodynamic therapy as first-line pharmacotherapies for neovascular AMD. The impact of these vision-saving therapies has been extraordinary—improving quality of life for millions of people worldwide. Based on visual acuity outcomes from phase 3 ranibizumab trials, it is estimated that two years of treatment for neovascular AMD reduces visual impairment by 37% and legal blindness by 72%.

Beyond AMD, anti-VEGF therapy has also become a mainstay of patient care for macular edema associated with diabetes and vein occlusions, with potential for a growing list of indications, including neovascular glaucoma and retinopathy of prematurity, and has been used experimentally to treat over 50 ocular diseases. Indeed, more than a million patients around the world receive anti-VEGF treatments for ocular disease annually. There are currently six FDA-approved agents for neovascular AMD: brolucizumab, aflibercept, ranibizumab, pegaptanib, faricimab, and a novel ranibizumab port delivery system; bevacizumab, a full-length anti-VEGF antibody is also used off-label. These agents are administered to millions of people annually worldwide, with additional therapeutics in development.

The VEGF discovery and the widespread success of anti-VEGF therapy for so many retinal conditions have completely revolutionized the field of ophthalmology, shifting from surgical to pharmacological treatments for retinal diseases and improving vision outcomes and quality of life for millions of people. I hope you will be able to

recognize this most auspicious group of clinicians and scientists for their important and critical contributions, for the development of anti-angiogenic therapy for retinal disease.

Sincerely,



Jean Bennett, M.D., Ph.D.

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R.V. Paul Chan, MD, MSc, MBA, FACS
Professor and Head, Department of Ophthalmology and Visual Sciences
The John H. Panton, MD Professor of Ophthalmology
Director, Pediatric Retina and ROP Service
Illinois Eye and Ear Infirmary
University of Illinois at Chicago

January 16, 2024

Helen Keller Foundation
Vision Research Award Committee
lbeckwith@helenkellerfoundation.org

Re: Nomination of Drs. Joan W. Miller, Patricia A. D'Amore, Anthony P. Adamis, Lloyd Paul Aiello, and Napoleone Ferrara for the 2024 Helen Keller Prize for Vision Research

Members of the Helen Keller Prize for Vision Research Awards Committee:

It is my distinct honor to support the nomination of Drs. Joan W. Miller, Patricia A. D'Amore, Anthony P. Adamis, Lloyd Paul Aiello, and Napoleone Ferrara (the anti-VEGF research team) for the 2024 Helen Keller Prize for Vision Research. Their groundbreaking work, while largely independent, was also mutually dependent, and served as the scientific foundation for the development of anti-VEGF therapies for the treatment of retinal diseases.

One of the greatest achievements in Ophthalmology, the development of anti-vascular endothelial growth factor (anti-VEGF) drugs, revolutionized the treatment of blinding eye diseases, such as neovascular age-related macular degeneration (AMD), diabetic macular edema (DME), and macular edema following retinal vein occlusion (RVO). However, clinical development of these agents would have been impossible without first identifying VEGF as the driver for retinal vascular growth in development and disease.

The origin of VEGF as a target for pathologic ocular neovascularization dates back to at least 1948, when IC Michaelson first hypothesized about the existence of "Factor X", a secreted factor released from ischemic retina to drive neovascularization of the retina, optic nerve, and iris. In the early 1970s, Judah Folkman hypothesized that angiogenesis was required for tumor growth, and restriction of such vessels may alter their function and reduce growth. Vascular permeability factor (VPF), discovered by Dr. Harold Dvorak and colleagues in 1983, was named for its ability to make vessels leaky. Its potent angiogenic effects were not appreciated until 1989, when Dr. Napoleone Ferrara and others cloned, sequenced, and characterized VEGF, which proved to be the same molecule as VPF. Excited by these findings, the anti-VEGF research team recognized that VEGF might represent Michaelson's elusive Factor X, and set out to explore the contribution of VEGF to retinopathies.

There were two primary groups investigating VEGF and ocular angiogenesis at Harvard Medical School in the early 1990s: one was led by Drs. Lloyd Paul Aiello and George King at Joslin Diabetes Center; the other by Drs. Patricia A. D'Amore, Anthony P. Adamis, and Joan W. Miller, plus many collaborators including trainees, at Boston Children's Hospital and Massachusetts Eye and Ear. Drs. D'Amore and

Adamis demonstrated that retinal cells express VEGF, and that VEGF protein levels in ocular fluids correlated with ocular neovascularization in a primate model of retinal ischemia. This was the first in vivo demonstration of VEGF's role in ocular neovascularization. Dr. Miller demonstrated that in an animal model of hypoxia, VEGF levels correlated with neovascularization, and with Dr. Adamis, demonstrated that patients with proliferative diabetic retinopathy also had elevated VEGF levels in their ocular fluids. This was confirmed in a much larger study at Joslin by Drs. Aiello, King, and Ferrara. Next, Drs. Adamis, Ferrara, D'Amore, and Miller showed that VEGF was central to the development of neovascularization and that neovascularization could be inhibited with an anti-VEGF antibody given intravitreously in non-human primate model of retinal disease.

These pivotal scientific discoveries directly led to the development of the anti-VEGF therapies, with Dr. Adamis and colleagues developing the drug pegaptanib (Macugen), the first anti-VEGF drug approved by the FDA for the treatment of AMD. Dr. Ferrara, together with his stellar team at Genentech conducted the preclinical studies to develop anti-VEGF antibodies such as bevacizumab and ranibizumab. The successful phase 3 studies resulted in the FDA approval of ranibizumab for the treatment of neovascular AMD, proving to be a true gamechanger in the treatment of blinding diseases.

The development of anti-VEGF agents ushered in an age of pharmacological treatments, transforming the field of retina which was previously primarily surgical. Indeed, millions of people around the world receive anti-VEGF treatments for sight-threatening retinal disease, and these agents have become a mainstay of patient care for neovascular retinal disease. Anti-VEGF drugs do not just stabilize neovascular eye diseases, but enable the average patient to recover vision. With these drugs, more than 90% of patients avoid moderate vision loss, and approximately a third of patients achieve vision of 20/40 or better. Today, there are multiple anti-VEGF agents, all holding potential for a growing list of indications, including neovascular glaucoma, retinopathy of prematurity, and certain cancers.

The impact of this discovery accompanied by the translational research is enormous, with millions of patients benefiting from discovery of VEGF and development of anti-VEGF treatments. For their significant scientific achievements toward the development of anti-VEGF therapies, the anti-VEGF research team received the 2014 António Champalimaud Vision Award, the highest distinction in ophthalmology and visual science.

This research team has conducted discoveries that have led a huge impact on the live of people all over the world. Given the increasing longevity of our world population, the number of patients who are affected by these common ocular conditions will only continue to rise in large numbers. This truly magnifies the importance of these researchers' work which is highly deserving of the 2024 Helen Keller Prize for Vision Research Award.

Sincerely,

R.V. Paul Chan, MD, MSc, MBA, FACS
Professor and Head, Department of Ophthalmology and Visual Sciences
The John H. Panton, MD Professor of Ophthalmology
Director, Pediatric Retina and ROP Service
Illinois Eye and Ear Infirmary
University of Illinois at Chicago

Dr. Joan Miller:

Joan W. Miller, MD, is the David Glendenning Cogan Professor of Ophthalmology and Chair of the Department of Ophthalmology at Harvard Medical School (HMS), as well as Chief of Ophthalmology at both Massachusetts Eye and Ear and Massachusetts General Hospital and Ophthalmologist-in-Chief at Brigham and Women's Hospital. A graduate of Massachusetts Institute of Technology, Dr. Miller earned her MD from HMS and completed her ophthalmology residency and vitreoretinal fellowship at Mass Eye and Ear.

An internationally recognized expert on retinal disorders, Dr. Miller and her colleagues at Mass Eye and Ear/HMS pioneered the development of verteporfin photodynamic therapy (Visudyne®), the first pharmacologic therapy for age-related macular degeneration (AMD). The group also identified the key role of vascular endothelial growth factor (VEGF) in ocular neovascularization, leading to the development of anti-VEGF therapies now administered to millions of people with sight-threatening retinal diseases annually around the world. Dr. Miller's current research investigations focus on the pathogenesis of AMD, including genomics, metabolomics, imaging, and functional measures; strategies for early intervention in AMD; and neuroprotective therapies for retinal disease.

Her scholarly contributions include more than 400 original research investigations, reviews, book chapters, and editorials. Dr. Miller serves on the editorial board for the journals *Ophthalmology* and *Ophthalmology Retina*, and has served as an editor for several textbooks, including the recently published 4th edition (Springer) of Albert and Jakobiec's Principles and Practices of Ophthalmology. Dr. Miller is a member of the National Academy of Medicine, the Academia Ophthalmologica Internationalis, the American Ophthalmological Society, and the Dowling Society, as well as a Gold Fellow of the Association for Research in Vision and Ophthalmology (ARVO). Among her numerous honors, Dr. Miller was a co-recipient of the 2014 António Champalimaud Vision Award, the highest distinction in ophthalmology and visual science. In 2015, Dr. Miller became the first woman to receive the Mildred Weisenfeld Award for Excellence in Ophthalmology from ARVO; in 2018, she became the first woman awarded the Charles L. Schepens Award from American Academy of Ophthalmology (AAO). Additionally, Dr. Miller was awarded the 2018 Lucien Howe Medal from the American Ophthalmological Society and the 2018 Gertrude D. Pyron Award from the American Society of Retinal Specialists.

Dr. Patricia A. D'Amore:

For over 40 years, **Patricia A. D'Amore, PhD, MBA**, has been investigating the pathogenesis of ocular pathologies. One aspect of her early career research was focused on identifying the factor produced by ischemic retina that induced neovascularization that led to her description of acidic FGF as a potent angiogenic factor. Subsequent work conducted in Dr. D'Amore's laboratory, and in collaboration with investigators at Massachusetts Eye and Ear, identified VEGF as the main angiogenic agent and formed the basis for the current use of anti-angiogenic therapies for wet age-related macular degeneration and diabetic macula edema. The group also described essential roles for VEGF in the normal adult eye. Dr. D'Amore's laboratory has also been investigating the pathogenic mechanisms that underlie dry AMD and we documented the

activation of the inflammasome in human retinal pigment epithelial (RPE) cells in vitro and in vivo as well as the ability of oxidized lipids to induce inflammasome activation and cell death. Most recently, Dr. D'Amore's work has reported the identification of a class of hindered phenol molecules that can protect human RPE from oxidized lipoprotein-induced cell death.

Dr. Tony Adamis:

Tony Adamis, MD, is best known for his co-discovery of the central role of vascular endothelial growth factor (VEGF) in two leading causes of blindness: neovascular age-related macular degeneration (nAMD) and diabetic retinopathy. Conducted at Harvard in the 1990s, this research led to Tony's shared receipt of the Antonio Champalimaud Award, the highest honor in vision science, and to his election to the National Academy of Medicine.

Dr. Adamis moved to industry and helped lead the development of the first FDA-approved anti-VEGF drugs for the treatment of nAMD and diabetic retinopathy. With the introduction of anti-VEGF drugs, legal blindness from these two diseases has been reduced by half around the world.

At Genentech/Roche, Dr. Adamis also led the development of the first long-acting delivery technology for an anti-VEGF drug (the ranibizumab port delivery system) and the first bispecific antibody for nAMD and diabetic retinopathy (faricimab). The latter blocks both VEGF and angiopoietin-2 (Ang2) and is rapidly becoming a first line therapy for nAMD and diabetic retinopathy. The role of Ang2 in eye disease was discovered when Dr. Adamis was at Harvard. Both the port delivery system and faricimab have received FDA and worldwide regulatory approval.

Over the course of his career, Dr. Adamis has helped develop 20 medicines across 30 indications, resulting in seven U.S. Food and Drug Administration (FDA) Breakthrough Designations and 25 FDA approvals. Dr. Adamis received his MD from the University of Chicago, his ophthalmology residency training at the University of Michigan, and his fellowship and research training at the Harvard Medical School.

Dr. Lloyd Paul Aiello:

Lloyd Paul Aiello, MD, PhD, FARVO, is Professor of Ophthalmology at Harvard Medical School, Vice Chair Harvard Department of Ophthalmology for Centers of Excellence, Director Beetham Eye Institute at Joslin Diabetes Center, and Founding Chair of the Diabetic Retinopathy Clinical Research Network. Dr. Aiello's contributions to understanding mechanisms underlying diabetic retinopathy, development of novel therapeutics such as VEGF and plasma kallikrein inhibitors, clinical trial design and implementation, telemedicine initiatives and novel retinal imaging modalities have had a global influence on the evaluation and care of diabetic eye disease. He has received over 70 national and international awards and has authored more than 400 publications which have been cited more than 47,000 times with an H-index of 100, and 75 publications ranked over 90% compared to the corpus of NIH-funded papers based on the scientific influence, field- and time-adjusted NIH Relative Citation Ratio (RCR).

Dr. Napoleone Ferrara:

Napoleone Ferrara, MD, is a Distinguished Professor of Pathology and Adjunct Professor of Ophthalmology and Pharmacology at University of California, San Diego. His primary research focuses on angiogenesis, particularly the identification of regulators. In 1989, he discovered, cloned, and named vascular endothelial growth factor (VEGF) and subsequently studied its molecular and biological properties, establishing it as a critical regulator of both normal and pathological angiogenesis.

Dr. Ferrara's research demonstrated that inhibiting VEGF could suppress the growth of various tumors in vivo, leading to the development of bevacizumab, a humanized anti-VEGF monoclonal antibody used in cancer therapy. Bevacizumab has received FDA approval for 12 different indications across multiple cancer types.

Additionally, Dr. Ferrara's work helped reveal the role of VEGF in intraocular neovascular syndromes, resulting in the development of ranibizumab, a humanized anti-VEGF Fab. This drug has been approved for treating neovascular age-related macular degeneration (AMD) and other ocular vascular disorders, offering an effective therapy for vision-threatening conditions. Ranibizumab and other anti-VEGF agents are among the most widely used drugs for older adults. In 2010, Dr. Ferrara received the Lasker-DeBakey Clinical Medical Research Award for his discovery of VEGF and his translational work in the development of a therapy for people suffering from wet AMD.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Adamis, Anthony Peter

eRA COMMONS USER NAME (credential, e.g., agency login): N/A

POSITION TITLE: Lecturer in Ophthalmology

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 *(if applicable)*	Completion Date MM/YYYßY	FIELD OF STUDY
University of Illinois, Urbana	BS	12/1980	Biology
University of Chicago	MD	06/1985	Medicine
University of Michigan		06/1989	Ophthalmology
Harvard Medical School/Mass Eye and Ear		06/1991	Cornea & External Disease
Harvard Medical School/Children's Hospital		06/1995	Vascular Biology

A. Personal Statement

My research is focused on retinal vascular disease mechanisms and long-acting drug delivery. I am best known for the co-discovery of the role of vascular endothelial growth factor (VEGF) in two leading causes of blindness: neovascular age-related macular degeneration (nAMD) and diabetic retinopathy. This research was conducted at Harvard in the 1990s and was supported by multiple NIH R01 grants.

In 2002 I moved to industry and led the development of the first FDA-approved anti-VEGF drugs for the treatment of nAMD and diabetic retinopathy (pegaptanib and ranibizumab). My teams also led the development of the (i) first long-acting delivery technology for an anti-VEGF drug (the ranibizumab port delivery system) and (ii) the first bispecific antibody for nAMD and diabetic retinopathy (faricimab). The latter inhibits both VEGF and angiopoietin-2 (Ang2). The role of Ang2/Tie2 in eye disease was discovered in my laboratory when I was at Harvard. Both the port delivery system and faricimab have received FDA and worldwide regulatory approval. Today, most patients are treated with an anti-VEGF drug as a first line therapy and gain vision. Most recently, I have been involved in the research and development of a novel wnt (FZD4/LRP5) agonist antibody (restoret) for the treatment of DME and nAMD. It is currently in Phase 3, the last stage of development, before FDA approval.

Over the course of my career, I helped develop 20+ medicines across 30+ indications, resulting in seven 'Breakthrough Designations' and 32 FDA approvals.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments (Academic)

1991-1995 Instructor in Ophthalmology, Harvard Medical School
1995-1997 Assistant Professor of Ophthalmology, Harvard Medical School
1998-2002 Associate Professor of Ophthalmology, Harvard Medical School
2008-2014 Adjunct Professor of Ophthalmology and Visual Sciences, University of Illinois College of Medicine

2010- Lecturer, Department of Ophthalmology, Harvard Medical School

Honors

2014 António Champalimaud Vision Award (shared with Napoleone Ferrara, Joan W. Miller, Evangelos S. Gragoudas, Patricia A. D'Amore, George L. King and Lloyd P. Aiello)
2019 Elected to the National Academy of Medicine

C. Contributions to Science

VEGF in retinal vascular disease

1. Adamis AP, Miller JW, Bernal MT, D'Amico D, Folkman J, Yeo TK, Yeo KT. Increased vascular endothelial growth factor levels in the vitreous of eyes with proliferative diabetic retinopathy. **Am J Ophthalmol** 1994;118:445-450.
2. Adamis AP, Shima D, Tolentino M, Gragoudas ES, Ferrara N, Folkman J, D'Amore PA, Miller JW. Inhibition of vascular endothelial growth factor prevents retinal ischemia- associated iris neovascularization in a non-human primate. **Arch Ophthalmol** 1996; 114:66-71.
3. Tolentino MJ, Miller JW, Gragoudas ES, Moulton R, Chatzistefanou K, Flynn E, Ferrara N, Adamis AP. Vascular endothelial growth factor is sufficient to produce iris neovascularization and neovascular glaucoma in a non-human primate. **Arch Ophthalmol** 1996;114:964-970.
4. Qaum T, Xu Q, Joussen AM, Clemens MW, Qin W, Miyamoto K, Hassessian H, Wiegand SJ, Rudge J, Yancopoulos GD, Adamis AP. VEGF initiated blood-retinal barrier breakdown in early diabetes. **Invest Ophthalmol Vis Sci.**2001**;**42:2408-2413.
5. Gragoudas E, Adamis AP, Cunningham ET, Feinsod M, Guyer DR,; VISION Study Group. Pegaptanib for neovascular age-related macular degeneration. **New Engl J Med.** 2004;351:2805-2816

Ang1/Ang2/Tie2 in retinal vascular disease

6. Joussen AM, Poulaki V, Tsujikawa A, Qin W, Xu Q, Qaum, T, Moromizato Y, Wiegand SJ, Rudge J, Ioffe E, Yancopoulos GD, Adamis AP. Suppression of diabetic retinopathy with angiopoietin-1. **Am J Pathol.** 2002; 160:1683-1693.
7. Wykoff CC, Abreu F, Adamis AP, Basu K, Eichenbaum DA, Haskova Z, Lin H, Loewenstein A, Mohan S, Pearch IA, Sakamoto T, Schlottmann PG, Silverman D, Sun JK, Wells JA, Willis JR, Tadayoni R; Yosemite and Rhine Investigators. Efficacy, durability and safety of intravitreal faricimab with extended dosing up to every 16 weeks in patients with diabetic macular oedema (YOSEMITE and RHINE): two randomized, double-masked Phase 3 trials. **Lancet** 2022;399:741-759.

Long-acting delivery of an anti-VEGF biologic to the retina

8. Ambati J, Gragoudas ES, Miller JW, You TT, Miyamoto K, Adamis AP. Transcleral delivery of bioactive protein to the choroid and retina. **Invest Ophthalmol Vis Sci** 2000;41:1186-1191.
9. Campochiaro PA, Marcus DM, Awh CC, Regillo C, Adamis AP, Bantseev V, Chaing Y, Ehrlich J, Erickson S, Hanley WD, Horvath J, Maass KF, Singh N, Fan T, Barteselli G. The port delivery system with ranibizumab for neovascular age-realted macular degeneration: Results from the randomized phase 2 LADDER clinical trial. **Ophthalmology** 2019;126;1141-1154.
10. Holekamp NM, Campochiaro PA, Chang MA, Miller D. Pieramici D, Adamis AP, Brittain C, Evans E, Kauman D, Maass KF, Patel S, Ranade S, Singh N. Barteselli G, Regillo C, Archway investigators. Archway randomized phase 3 trial of the port delivery system with ranibizumab for neovascular age-related macular degeneration. **Ophthalmology** 2022;129:295-307.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: **Lloyd Paul Aiello, M.D., Ph.D., FARVO**

eRA COMMONS USER NAME (credential, e.g., agency login): LPAiello

POSITION TITLE: Professor & Vice Chair of Ophthalmology, Harvard Medical School; Director, Beetham Eye Institute, Joslin Diabetes Center

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 *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Pennsylvania, Philadelphia, PA	B.A. (cum laude)	06/81	Biochemistry
Boston University School of Medicine, Boston, MA	M.D.	06/88	Medicine
Boston University School of Medicine, Boston, MA	Ph.D.	06/88	Biochemistry

Please refer to the Biographical Sketch sample in order to complete sections A, B, C, and D of the Biographical Sketch.

A. Personal Statement

Dr. Aiello is internationally recognized as an expert in the area of diabetic retinopathy basic and clinical research and has an extensive clinical, biochemical and molecular biological understanding of diabetic eye disease. He was one of the original investigators defining the role of Vascular Endothelial Growth Factor in diabetic retinopathy and other ischemic retinal diseases receiving the prestigious Antonio Champaulimaud Award in 2014 for these efforts (one of his 66 major awards & honors). He was the 2020 Friedenwald Award and the 2022 Lawrence J. Singerman Medal recipient. Dr. Aiello has also pioneered basic studies in protein kinase C and plasma kallikrein in relation to diabetic retinopathy. Dr. Aiello is expert in clinical evaluation and trials. He has been instrumental in major translational approaches to bringing basic studies into the clinical arena for clinical evaluation of diabetic eye disease, including novel assessments of visual function. He has chaired numerous multi-national multicenter randomized controlled clinical trials in treatment of diabetic retinopathy and was the inaugural chair of the NIH-sponsored Diabetic Retinopathy Clinical Research Network. He has extensive experience in diabetic patient evaluation, novel visual function assessment, retinopathy evaluation & treatment, directing clinical trials, telemedicine for diabetic eye disease, diabetes-specific eye research, intraocular fluid acquisition, storage, and analyses. Dr. Aiello is the DCCT/EDIC site PI and overseas all aspects of these studies at the Joslin Diabetes Center..

B. Positions (Selected):

1989-92 Resident in Ophthalmology, Wilmer Ophthalmological Institute, Johns Hopkins University.
1992-94 Research & Clinical Fellow, Joslin Research Laboratories, Joslin Diabetes Center, Boston, MA
1996-2000 Chair, Lions Club International SightFirst Diabetic Retinopathy Research Program Review Panel
1998- Senior Investigator, Joslin Diabetes Center, Harvard Medical School, Boston, MA.
1999- Clinical Affairs Advisory Committee, Juvenile Diabetes Foundation, International.
1999-2002 Chair, Complications Section, Juvenile Diabetes Foundation, Medical Science Review Committee
2002-2006 Chair, Clinical Investigation Section, Juvenile Diabetes Foundation, Medical Sci. Review Committee
2001- Director, Section of Eye Research, Joslin Diabetes Center, Boston, MA
2004- Local Director, Harvard Medical School Residency Program in Ophthalmology.
2005- Director, Beetham Eye Institute & Head, Section of Eye Research, Joslin Diabetes Center, Boston
2003-06 Chair, National Institutes of Health Diabetic Retinopathy Clinical Research Network.

2008 - Vice President of Ophthalmology, Joslin Diabetes Center, Boston, MA.
2008 - Vice Chair, Centers of Excellence. Harvard Department of Ophthalmology, Boston, MA.
2009 -11 Medical Director of Ophthalmology, Brigham and Women's Hospital, Boston, MA.
2010- Professor, Department of Ophthalmology, Harvard University Faculty of Medicine
2011-18 Associate Chief, Massachusetts Eye and Ear at Longwood, Boston, MA.

B. Honors (selected from 74 total honors and awards):

1992-1994 Heed Fellowship & Fellow of the Society of Heed Fellows and Heed/Knapp Fellowship Award.
1993 Pfizer Postdoctoral Fellowship (diabetes & endocrinology), Harvard University, Boston, MA
1994-1996 Capps Scholar in Diabetes, Harvard Medical School, Boston, MA
1994 Marios C. Balodimos, M.D. Award, American Diabetes Association, MA Affiliate.
1996 Alcon Research Institute Award
2002 Richard and Hinda Rosenthal Foundation Award, Macula Society, Cleveland, OH.
2003 Novartis Award in Diabetes – Young Investigator, Novartis, Basil, Switzerland.
2003 Outstanding Foreign Investigator Award, The Japan Society of Diabetic Complications, Kyoto.
2005 Charles Schepens Award in Research and Lecturer, Schepens International Society.
2007 ARVO/Pfizer Ophthalmics Translational Research Award, Rockville, MD.
2007 Award of Merit in Retina Research & the Charles L. Schepens Lecture, Retina Society, Boston, MA.
2007 American Academy of Ophthalmology Senior Achievement Award.
2007 Special Research Scholar Award, Research to Prevent Blindness
2009 Fellow's Silver Medal, Fellow of the Association for Research in Vision and Ophthalmology
2009 Paul Henkind Memorial Lecture. Macula Society. New York, NY.
2010 Lew R. Wasserman Merit Award. Research to Prevent Blindness. New York. NY.
2011 The Montgomery Medal. The Royal College of Surgeons. Dublin, Ireland.
2012 David Rumbough Award for Scientific Excellence. Juvenile Diabetes Research Foundation, NY.
2014 Boston University School of Medicine Distinguished Alumnus Award. Boston, MA.
2014-15 Hong Leong Visiting Professorship, National University of Singapore, Singapore.
2014 António Champalimaud Vision Award, Champalimaud Centre for the Unknown, Lisbon, Portugal
2015 Boston Business Journal 2015 Heathcare Heroes Innovator Award, Boston, MA
2016 The Ernst H. Bárány Prize, International Society for Eye Research, awarded Tokyo, Japan.
2016 Inaugural Kresge Eye Institute Robert N. Frank, MD Clinical Translational Lectureship, Kresge Eye Institute, Wayne State School of Medicine, Detroit, MI.
2017 Edward W. Purnell, MD Distinguished Guest Lecturer, Department of Ophthalmology and Visual Sciences, Case Western Reserve University, Cleveland, OH.
2017 Mary Tyler Moore and S. Robert Levine Excellence in Clinical Research Award, Juvenile Diabetes Research Foundation International, New York, NY.
2018 The Eva Kohner Award, The European Association for the Study of Diabetes (EASD) Eye Complications Study Group, Belfast, Northern Ireland.
2018 Global Achievement Award, Joslin Diabetes Center, Harvard Medical School, Boston, MA.
2020 Friedenwald Achievement Award, Association for Research in Vision and Ophthalmology (ARVO)
2021 Excellence in Mentoring Award Nomination, Harvard Medical School, Boston, MA
2022 Lawrence J. Singerman Medal for outstanding contributions to the advancement of science through Retinal Clinical Trials. Macula Society, Berlin, Germany.
2022 American Academy of Ophthalmology Life Achievement Honor Award2021
2022 Excellence in Mentoring Award Nomination, Harvard Medical School, Boston, MA
2023 Association of American Physicians (AAP) membership J. Donald Gass Lectureship Award. The Retina Society. New York, NY.
2024 Inaugural Douglas Anderson Award for Research in Recognition of Outstanding Research in Ultra-Widefield Retinal Imaging. Seattle, WA.
2024 Melvin Jones Fellow Award. Lions International Foundation highest honor. For dedicated humanitarian services & qualities such as generosity, compassion, & concern for the less fortunate.
2024 The William T. Murphy SIGHT Award. Massachusetts Lions Eye Research Fund. In recognition of outstanding service and dedication to the Massachusetts Lions Eye Research Fund

C. Contribution to Science (from 366 total, Citations=49,994, H-index=101, i10-index=246, iCite 80>90% per Google Scholar 1/23/2025)

1. Initial identification, characterization and clinical correlation of the Vascular Endothelial Growth Factor (VEGF) in diabetic retinopathy, diabetic macular edema and other ischemic retinal disorders. Character-

ized VEGF biochemical effects and receptor, binding and signaling in retinal vascular and nonvascular cells. Demonstrated the presence and activity of VEGF in human ocular samples. These studies were fundamental to the eventual development of antiVEGF agents for the clinic which are now standard care worldwide for several retinal conditions. These contributions led to numerous international recognitions including the António Champalimaud Vision Award, the world's highest honor in vision research.

a. **Aiello LP**, Avery RL, Arrigg PG, Keyt B, Aiello LM, Jampel HD, Shah ST, Pasquale LR, Thieme H, Iwamoto MA, Park JE, Nguyen HV, Ferrara N, King GL. Vascular Endothelial Growth Factor in Ocular Fluids of Patients with Diabetic Retinopathy and Other Retinal Disorders. *New Engl. J. Med*. 1994; **331**:1480-1487.
b. **Aiello LP**, Pierce EA, Foley ED, Takagi H, Chen H, Riddle L, Ferrara N, King GL, Smith LEH. Suppression of Retinal Neovascularization *in Vivo* by Inhibition of Vascular Endothelial Growth Factor (VEGF) using Soluble VEGF-receptor Chimeric Proteins. *Proc. Natl. Acad. Sci.* 1995;**92**(23):10457-10461.
c. **Aiello LP**, George DJ, Cahill MT, Wong JS, Cavallerano JD, Hannah AL, Kaelin WG. Rapid and Durable Recovery of Visual Function in a Patient with von Hippel-Lindau Syndrome Following Systemic Therapy with VEGF Receptor Inhibitor SU5416. *Ophthalmol*. 2002;**109**(9):1745-1751.
d. Jampol LM, Glassman AR, Liu D, **Aiello LP**, Bressler NM, Duh EJ, Quaggin S, Wells JA, Wykoff CC and the Diabetic Retinopathy Clinical Research Network. Plasma Vascular Endothelial Growth Factor Concentrations after Intravitreous Anti-Vascular Endothelial Growth Factor Therapy for Diabetic Macular Edema. *Ophthalmology*. 2018 Jul;125(7):1054-1063.

2. Characterization of VEGF-independent pathways involved in diabetic retinopathy and diabetic macular edema. Numerous studies characterizing pathways other than VEGF that underlie that proportion of retinopathy that does not respond to current antiVEGF inhibitors. These studies have not only defined new pathways, but led to development of inhibitors that have now entered early clinical trials to determine if they are beneficial for the treatment of diabetic macular edema that is unresponsive to antiVEGF treatment.
   a. **Aiello LP**, Sun W, Das A, Gangaputra S, Kiss S, Klein R, Cleary PA, Lachin JM, Nathan DM and The Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group. Intensive Therapy and Ocular Surgery in Type 1 Diabetes. *New Engl. J. Med*. 2015;372:1722-33.
   b. Clermont A, Murugesan N, Zhou Q, Kita T, Robson PA, Rushbrooke LJ, Evans D, **Aiello LP**, Feener EP. Plasma kallikrein mediates vascular endothelial growth factor-induced retinal dysfunction and thickening. *Invest. Ophthalmol. Vis. Sci.* 2016 May;57(6):2390-2399.
   c. Hainsworth DP, Bebu I, **Aiello LP**, Sivitz W, Gubitosi-Klug R, Malone J, White NH, Danis R, Wallia A, Gao X, Barkmeier AJ, Das A, Patel S, Gardner TW, Lachin JM; Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group. Risk Factors for Retinopathy in Type 1 Diabetes: The DCCT/EDIC Study. *Diabetes Care*. 2019 May;42(5):875-882.
   d. Yokomizo H, Maeda Y, Park K, Clermont AC, Hernandez SL, Fickweiler W, Li Q, Wang CH, Paniagua SM, Simao F, Ishikado A, Sun B, Wu IH, Katagiri S, Pober DM, Tinsley LJ, Avery RL, Feener EP, Kern TS, Keenan HA, **Aiello LP**, Sun JK, King GL. Retinol binding protein 3 is increased in the retina of patients with diabetes resistant to diabetic retinopathy. *Sci Transl Med.* 2019 Jul 3;11(499).
3. Founding chair of the Diabetic Retinopathy Clinical Research Network (DRCR.net). The DRCR.net was founded by a cooperative agreement with the National Eye Institute of the National Institutes of Health dedicated to the clinical study of diabetic retinopathy and associated conditions. It has become the premiere national network providing rigorous rapid comprehensive clinical trials focused on the most pressing issues in diabetic retinopathy care. It has twice been cited by the US Congress for excellence. Currently nearly one third of all practicing retinal specialists in this country belong to the network. The network has defined our current state-of-the-art knowledge and our clinical are guidelines for much of contemporary diabetic retinopathy clinical care. Dr Aiello was the founding chair and responsible for guiding its initial development from idea to reality. He has been involved in the networks leadership ever since with permanent positions on the executive and operations committees and other responsibilities.
   a. Wells JA, Glassman AR, Ayala AR, Jampol LM, **Aiello LP**, Antoszyk AN, Arnold-Bush B, Baker CW, Bressler NM, Browning DJ, Elman MJ, Ferris FL, Friedman SM, Melia M, Pieramici DJ, Sun JK, Beck RW, and the Diabetic Retinopathy Clinical Research Network. Comparative Effectiveness Randomized

Clinical Trial of Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema. *New Engl. J. Med*. 2015;372(13)1193-1203.

b. **Aiello LP**, Ayala AR, Antoszyk AN, Arnold-Bush B, Baker C, Bressler NM, Elman MJ, Glassman AR, Jampol LM, Melia M, Nielsen J, Wolpert HA and the Diabetic Retinopathy Clinical Research Network. Assessing the Effect of Personalized Diabetes Risk Assessments During Ophthalmologic Visits on Glycemic Control: A Randomized Clinical Trial. *JAMA Ophthalmol.* 2015 Aug 1;133(8):888-96.

c. Gross JG, Glassman AR, Jampol LM, Inusah S, **Aiello LP**, Antoszyk AN, Baker CW, Berger BB, Bressler NM, Browning D, Elman MJ, Ferris FL 3rd, Friedman SM, Marcus DM, Melia M, Stockdale CR, Sun JK, Beck RW. Panretinal Photocoagulation vs Intravitreous Ranibizumab for Proliferative Diabetic Retinopathy: A Randomized Clinical Trial. *JAMA*. 2015 Nov 24;314(20):2137-46.

d. Baker CW, Glassman AR, Beaulieu WT, Antoszyk AN, Browning DJ, Chalam KV, Grover S, Jampol LM, Jhaveri CD, Melia M, Stockdale CR, Martin DF, Sun JK; **DRCR Retina Network**. Effect of Initial Management With Aflibercept vs Laser Photocoagulation vs Observation on Vision Loss Among Patients With Diabetic Macular Edema Involving the Center of the Macula and Good Visual Acuity: A Randomized Clinical Trial. *JAMA*. 2019;321(19):1880-1894.

4. Global Telemedicine for Diabetic Retinopathy. Development and leadership of the Joslin Vision Network, the most highly published telemedicine program dedicated to diabetic retinopathy. This program has been implemented in academic, private practice, community, government and overseas practices worldwide. The program has helped define the role and possibilities of telemedicine programs in many demographic situations and explored innovative approaches to the field including novel camera validations, point of care image evaluation, ultrawide field imaging and automated analyses.

   a. Cavallerano JD, Silva PS, Tolson AM, Francis T, Tolls D, Patel B, Eagan S, Aiello LM, **Aiello LP**. Imager Evaluation of Diabetic Retinopathy at the Time of Imaging in a Telemedicine Program. *Diabetes Care*, 2012;35:482-484.

   b. Silva PS, Cavallerano JD, Paz-Pacheo E, **Aiello LP**. Diabetic Retinopathy in Southeast Asia: A Call for Ocular Telehealth Programs. *JAFES.* 2012;27(2):176-179.

   c. Silva PS, Cavallerano JD, Tolls D, Omar A, Thakore K, Patel B, Sehizadeh M, Tolson AM, Sun JK, Aiello LM, **Aiello LP**. Potential Efficiency Benefits of Nonmydriatic Ultrawide Field Retinal Imaging in an Ocular Telehealth Diabetic Retinopathy Program. *Diabetes Care* 2014; 37:50-55.

   d. Silva PS, Cavallerano JD, Tolson AM, Rodriguez J, Rodriguez S, Ajlan R, Tolls D, Patel B, Sehizadeh M, Thakore K, Sun JK, **Aiello LP**. Real Time Ultrawide Field Image Evaluation of Retinopathy in a Diabetes Telemedicine Program. *Diabetes Care*. 2015; 38:1643-1649.

5. Novel imaging approaches to diabetic retinopathy. Studies involving the use of new imaging approaches to help improve the care of diabetic eye disease and identify novel biomarkers that predict vision and therapeutic outcomes. Provided field leading investigation of ultrawide field imaging and identification of new risk markers observed by that technique which identity those at particular risk of diabetic retinopathy progression. Also identifying SD-OCT derived biomarkers with greatest predictive agreement with future visual acuity of any reported to date. Additionally, ultrahigh resolution imaging of individual capillaries and cells within the retina using adaptive optics scanning laser ophthalmoscope and response to antiVEGF therapies.

   a. Silva PS, Cavallerano JD, Haddad NM, Kwak H, Dyer KH, Omar AF, Shikari H, Aiello LM, Sun JK, **Aiello LP**. Peripheral Lesions Identified on Ultrawide Field Imaging Predict Increased Risk of Diabetic Retinopathy Progression Over 4 Years of Follow-up. *Ophthalmology* 2015;122(5)969-956.

   b. Sun JK, Radwan S, Soliman AZ, Lammer J, Lin MM, Prager SG, Silva PS, Aiello LB, **Aiello LP**. Neural Retinal Disorganization as a Robust Marker of Visual Acuity in Current and Resolved Diabetic Macular Edema. *Diabetes* 2015; 64:2560–2570.

   c. Gupta A, El-Rami H, Barham R, Fleming A, Hemert JV, Sun JK, Silva PS, **Aiello LP**. Effect of phase-plate adjustment on retinal image sharpness and visible retinal area on ultrawide field imaging". *Eye*. 2019 Apr;33(4):587-591.

   d. **Aiello LP**, Odia I, Glassman AR, Melia M, Jampol LM, Bressler NM, Kiss S, Silva PS, Wykoff CC, Sun JK, 8; for the Diabetic Retinopathy Clinical Research Network. Comparison of Early Treatment Diabetic Retinopathy Study Standard 7-Field Imaging with Ultrawide-Field Imaging for Determining Severity of Diabetic Retinopathy JAMA Ophthalmol. 2019 Jan 1;137(1):65-73.

Complete List of Published Work: https://www.researchgate.net/profile/Lloyd_Aiello/publications

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

Mass Lions Research Fund (Aiello) 08/01/2019-07/31/2020 Role: PD/PI
Diabetic Retinopathy: Pathogenesis, Prediction, and Prevention
Individual Project #1: Regulation of Visual Function by the Kallikrein-Kinin and Complement Pathways in Diabetic Macular Edema (DME)
Individual Project #2: Computational Fluid Dynamics Modeling of the Human Retinal Microvasculature to Predict Outcomes in the Diabetic EyeOcular Biomarkers of Diabetic Retinopathy Progression and of Diabetic Macular Edema Treatment Response
Individual Project #3: Association of Systemic Disease with Predominantly Peripheral Diabetic Retinopathy Lesions Identified on Ultrawide Field Retinal Imaging

R01EY024702 (Sun) NIH/NIDDK 09/01/2014-08/31/2020 Role: Co-Investigator
Predicting Outcomes & Anti-VEGF Response in Diabetic Eyes by Adaptive Optics SLO
The goal of this project is to utilize in vivo, ultra-high resolution, adaptive optics scanning laser ophthalmoscopy (AOSLO) to identify combined characteristics of vascular and neural retina in the human diabetic eye that predict vision loss and response to anti-vascular endothelial growth factor (anti-VEGF) agents.

Completed Research Support (selected)

R01EY026080 (King) NIH/NEI 03/1/16-02/28/2020 Role: Co-Investigator
Identification of retinol-binding protein 3 (RBP3): a protective factor against diabetic retinopathy using retina from people with extreme duration of diabetes
The goal of this project is to substantiate that the target identified in Medalists protected from severe DR despite chronic hyperglycemia can neutralize hyperglycemia's toxic effect on retinal endo cells and pericytes and preserve retinal structure in diabetic rats. It will also determine correlation in ocular fluids and the peripheral system for use as a biomarker of risk, development and treatment of neuro-retinal pathology.

DP3 DK094333 (King) NIH/NIDDK 09/30/2011-06/30/2016 Role: Co-Investigator
Validation of Potential Protective Factors from Diabetic Complications
This study proposes to measure the identified and validated candidates in the plasma and circulating cells in the Medalists and in another unusual group of diabetic patients with ultra-fast progression.

3-SRA-2014-264-M-R (Sun) JDRF 09/01/2014-08/31/2017 Role: Co-Investigator
Molecular and Anatomic Biomarkers of Vision and Response to AntiVEGF in Eyes with Diabetes
The major goals of this project are to elucidate response biomarkers to antiVEGF therapy and define predictive models of future VA in eyes with current DME. These studies will improve our understanding of how retinal vascular and neural tissues interact in the diabetic eye and may identify factors predicting response to antiVEGF therapy.

DP3 DK104438 (Gubitosi-Klug) NIH/NIDDK 09/25/2014-8/31/2017 Role: Subcontract PI
Residual Beta Cell Function in Patients with Long-Term Type 1 Diabetes
1) determine the prevalence and amount of residual beta cell function in participants with long standing T1D; 2) understand the effects of glycemic control during the DCCT (intensive vs conventional) and during DCCT/EDIC on the preservation of beta cell function; 3)identify participant characteristics associated with preserved residual beta cell function in EDIC; 4) determine if the preservation of beta cell function in EDIC correlates with lower HbA1c and lower insulin dose requirements; 5) determine if the preservation of beta cell function in EDIC correlates with less hypoglycemia and less micro and/or macrovascular complications.

R01 EY019029 (Aiello) NIH/NEI 04/01/2014-03/31/2018 Role: Co-Investigator
Role of the kallikrein-kinin system in diabetic retinopathy
The major goals are 1) to characterize and compare the bradykinin receptor-dependent and independent effects of Pkal on retinal edema in diabetic mice, 2) to compare Pkal and VEGF-induced retinal edema and investigate interactions between these pathways, and 3) characterize the roles of nitric oxide synthase and calpain-mediated intermediate filament degradation/remodeling in retina edema.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Patricia A. D'Amore

eRA COMMONS USER NAME (credential, e.g., agency login): pdamore

POSITION TITLE: Professor of Ophthalmology & Pathology

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 *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Regis College, Weston, MA	BA	1973	Biology
Boston University, Boston, MA	PhD	1977	Cell Biology
John Hopkins Univ. Sch. Med., Baltimore, MD	Postdoctoral Fellow	1987	Ophthal & Physiol Chem
Northeastern University, Boston, Ma	MBA	1987	Finance

A. Personal Statement

For over 40 years, I have been investigating the pathogenesis of retinopathies. The work conducted in my laboratory and in collaboration with investigators at Massachusetts Eye and Ear, formed the basis for the current use of anti-angiogenic therapies for diabetic retinopathy. Throughout my career, I have also been committed to the training of students and fellows and have mentored over 80 trainees in my laboratory. Seven of these trainees are now full Professors at universities. Several of my former trainees are Senior Scientists at companies such as Biogen and Novartis. I have been the Chair of the Training Committee at the Schepens Eye Research Institute (SERI) for more than fifteen years. I am a recipient of the A. Clifford Barger Excellence in Mentoring Award, the Everett Mendelsohn Excellence in Mentoring Award from Harvard Medical School, the American Medical Association Women Physicians Sector Mentorship Award, and the William Silen Lifetime Achievement Award in Mentoring. Currently, my lab is conducting two lines of research. In the first we are examining the contribution of the vascular glycocalyx in the regulation of endothelial function. Specifically, we are investigating the role of endomucin, an endothelial-specific mucin, in the regulation of vascular inflammation and angiogenesis. The second project is the pathogenesis of dry AMD, with a focus on the mechanism of lipid-induced damage to the RPE. This program has identified a small molecular that protects RPE from ox-LDL induced damage and aims to determine the mechanism of its protective action.

Ongoing and recently completed projects:
R01EY026539 (D'Amore, PI) 02/01/2017-07/31/2025
NIH/NEI $262,895 total direct annually
Investigation of endomucin as a novel regulator of angiogenesis

P30 EY03790-42 (D'Amore, PI) 08/02/97- 08/31/2027
NEI/NIH $500,000 total direct annually
The major goal of this project is to provide support for four core modules available for all SERI investigators. The four modules are Morphology, Animal Resources, Laboratory Computer Applications and Flow Cytometry

2T32EY007145-21 (D'Amore, PI) 02/01/1997- 05/31/2028
NIH/NEI
Training

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2023 - 2024	President, Association for Research in Vision and Ophthalmology
2020 - 2021	President, American Society for Investigative Pathology
2019 - 2024	RC Section Representative, ARVO Board of Trustees
2019 - present	Executive Committee Member, Ryan Initiative for Macular Research
2015 - 2020	Elected Associate Council Member, Association for University Professors of Ophthalmology
2015 - present	Member, Vision Academy, Bayer Healthcare
2014 - present	Associate Chief of Basic and Translational Research, MEE, Boston, MA
2014 - present	Director, Howe Laboratory, MEE, Boston, MA
2013 - present	Professor of Pathology, HMS, Boston, MA
2013 - present	Grant Review & Awards Committee, Global Ophthalmology Awards Program
2012 - present	Director of Research, SERI, Mass Eye and Ear (MEE), Boston, MA
2012 - present	Charles L. Schepens Professor of Ophthalmology, SERI, Boston, MA
2009 - present	Vice Chair of Basic and Translational Research, Depart. of Ophthalmology, HMS, Boston, MA
2009 - 2013	Member, Biology and Diseases of the Posterior Eye Study Section, NIH, CSR
2006 - 2020	Editor-in-Chief, Microvascular Research
2002 - present	Ankeny Scholar of Retinal Molecular Biology, SERI, Boston, MA
1998 - 2003	Professorship, Jules and Doris Stein Research to Prevent Blindness
1998 - present	Senior Scientist, Schepens Eye Research Institute (SERI), Boston, MA
1983 - present	Faculty of the Cell & Developmental Biology, Biological & Biomedical Sciences Program, HMS,
1981 - 2000	Research Associate, Surgery, The Children's Hospital, Boston, MA

Honors

2024	Research to Prevent Blindness David F. Weeks Award for Outstanding Vision Research
2023	Gabor Kaley Memorial Lectureship Award, American Physiological Society (APS) and The Microcirculatory Society
2021	Ramzi S. Cotran, M.D. Lecturer/Visiting Professor
2021	Jay McDonald Memorial Lecture, ASIP PISA meeting
2020	Roger Johnson Award in Macular Degeneration Research, Univ. of Washington, Seattle, WA
2020	Earl Benditt Award, North American Vascular Biology Organization
2019	Program Award for a Culture of Excellence in Mentoring, Harvard Medical School Co-Director with Dr. David Hunter
2018	Fellow of American Academy of Arts & Sciences, Medical Sciences, Clinical Medicine, and Public Health Section
2018	Barbara J. McNeil Faculty Award for Exceptional Institutional Service, Harvard Medical School and Harvard School of Dental Medicine
2018	Distinguished Alumni Award for Professional Achievement, Department of Biology, Boston University
2018	RC Section Representative, ARVO Board of Trustees
2016	William Silen Lifetime Achievement in Mentoring Award, Harvard Medical School
2015	Proctor Medal, Association for Research & Vision Ophthalmology
2014	Endre A. Balazs Prize, International Society for Eye Research
2014	Laureate, Antonio Champalimaud Award
2013	Everett Mendelsohn Mentoring Award, Harvard University
2013	American Medical Association Women Physicians Sector Mentorship Award
2012	Rous-Whipple Award, American Society of Investigative Pathology
2010	5th Annual Jeffrey M. Isner, M.D. Endowed Memorial Lectureship
2010	Distinguished Lecturer in Vision Science, State University of New York, Buffalo, NY
2009	Gold Fellow, Association for Research in Vision and Ophthalmology

2007	A. Clifford Barger Excellence in Mentoring Award, Harvard Medical School
2006	Senior Scientific Investigator Award, Research to Prevent Blindness
2006	First Annual David Shepro Lecture, Boston, University
2005	Excellence Award, Schepens Eye Research Institute
2004 - 2015	Member, The Academy at Harvard Medical School
1994	Alcon Research Institute Award
1993	Cogan Award, Association for Research in Vision and Ophthalmology
1986	American Heart Association Established Investigatorship
1979	Myers Honor Award for Research in Ophthalmology, Baltimore, MD

C. Contributions to Science

1. Pericyte-endothelial cell interactions

   Capillaries are composed of endothelial cells (EC) and pericytes. Little was known about the nature of the interactions, if any, between these two cells; however, loss of pericytes during background retinopathy pointed to a role in the regulation of vessel integrity and stabilization. We demonstrated that EC recruits pericytes (or their precursors) via the release of PDGFB, which also stimulates the proliferation of pericytes/smooth muscle. We showed that the association between EC and pericytes leads to the inhibition of endothelial proliferation, to the induction of pericyte differentiation, and to the production of VEGF by pericytes, all processes that are mediated by the contact-dependent activation of TGFß1. Our work paved the way for the understanding that pericyte association with capillary endothelium mediates vessel stabilization and maturation.

   a. Orlidge A, **D'Amore PA**. Inhibition of capillary endothelial cell growth by pericytes and smooth muscle cells. J Cell Biol. 1987 Sep;105(3):1455-62. PubMed PMID: 3654761; PMCID: PMC2114828

   b. Antonelli-Orlidge A, Saunders KB, Smith SR, **D'Amore PA**. An activated form of transforming growth factor beta is produced by cocultures of endothelial cells and pericytes. Proc Natl Acad Sci U S A. 1989 Jun;86(12):4544-8. PubMed PMID: 2734305; PMCID: PMC287307

   c. Hirschi KK, Rohovsky SA, **D'Amore PA**. PDGF, TGF-beta, and heterotypic cell-cell interactions mediate endothelial cell-induced recruitment of 10T1/2 cells and their differentiation to a smooth muscle fate. J Cell Biol. 1998 May 4;141(3):805-14. PubMed PMID: 9566978; PMCID: PMC2132737

   d. Darland DC, Massingham LJ, Smith SR, Piek E, Saint-Geniez M, **D'Amore PA**. Pericyte production of cell-associated VEGF is differentiation-dependent and is associated with endothelial survival. Dev Biol. 2003 Dec 1;264(1):275-88. PubMed PMID: 14623248

2. Role of VEGF in ischemic retinal neovascularization

   Clinical observations have suggested that ischemic retinal tissue was a source of an angiogenic activity, that more than 65 years ago was referred to as "factor x." Working with my clinical colleagues, Drs. Anthony Adamis and Joan Miller, my laboratory demonstrated that this factor was VEGF. Using non-human primates, we showed that rendering the retina ischemic led to neovascularization that was associated with increases in VEGF mRNA and protein, and that neutralization of VEGF blocked the new vessel growth. This work formed a major portion of the basic work that led to the use of anti-VEGF therapies for the treatment of age-related macular degeneration and diabetic macular edema, treatments that have revolutionized their management.

   a. Miller JW, Adamis AP, Shima DT, **D'Amore PA**, Moulton RS, et al. Vascular endothelial growth factor/vascular permeability factor is temporally and spatially correlated with ocular angiogenesis in a primate model. Am J Pathol. 1994 Sep;145(3):574-84. PubMed PMID: 7521577; PMCID: PMC1890317

   b. Shima DT, Adamis AP, Ferrara N, Yeo KT, Yeo TK, Allende R, Folkman J, **D'Amore PA**. Hypoxic induction of endothelial cell growth factors in retinal cells: identification and characterization of vascular endothelial growth factor (VEGF) as the mitogen. Mol Med. 1995 Jan;1(2):182-93. PubMed PMID: 8529097; PMCID: PMC2229943

   c. Shima DT, Deutsch U, **D'Amore PA**. Hypoxic induction of vascular endothelial growth factor (VEGF) in human epithelial cells is mediated by increases in mRNA stability. FEBS Lett. 1995 Aug 21;370(3):203-8. PubMed PMID: 7656977

d. Adamis AP, Shima DT, Tolentino MJ, Gragoudas ES, Ferrara N, Folkman J, **D'Amore PA**, Miller JW. Inhibition of vascular endothelial growth factor prevents retinal ischemia-associated iris neovascularization in a nonhuman primate. Arch Ophthalmol. 1996 Jan;114(1):66-71. PubMed PMID: 8540853

3. Role of VEGF and VEGF isoforms in the adult

   VEGF proteins are encoded by a single gene that is alternatively spliced to generate multiple isoforms (three in mice). Whether the isoforms served different functions was unknown. In addition, early studies demonstrated a critical role for VEGF in vascular development and pathology, but there was little consideration of a possible role for VEGF in the adult. Our observation that virtually all adult tissues expressed VEGF mRNA, in the absence of active angiogenesis, led us to hypothesize a physiologic role for VEGF. Using in vivo and in vitro models we showed that VEGF was produced by a subset of cells in all tissues examined. In addition, we noted that the profile of VEGF isoforms varied widely among adult tissues. We demonstrated that neutralization of VEGF or that lack of specific VEGF isoforms in the normal adult led to tissue dysfunction and degeneration. Finally, we reported that VEGF acts as a survival factor not only for vascular endothelial but also for a wide variety of non-vascular cells.

   a. Stalmans I, Ng YS, Rohan R, Fruttiger M, Bouché A, Yuce A, Fujisawa H, Hermans B, Shani M, Jansen S, Hicklin D, Anderson DJ, Gardiner T, Hammes HP, Moons L, Dewerchin M, Collen D, Carmeliet P, **D'Amore PA**. Arteriolar and venular patterning in retinas of mice selectively expressing VEGF isoforms. J Clin Invest. 2002 Feb;109(3):327-36. PubMed PMID: 11827992; PMCID: PMC150858

   b. Saint-Geniez M, Maharaj AS, Walshe TE, Tucker BA, Sekiyama E, Kurihara T, Darland DC, Young MJ, **D'Amore PA**. Endogenous VEGF is required for visual function: evidence for a survival role on Müller cells and photoreceptors. PLoS One. 2008;3(11):e3554. PubMed PMID: 18978936; PMCID: PMC2571983

   c. Maharaj AS, Walshe TE, Saint-Geniez M, Venkatesha S, Maldonado AE, Himes NC, Matharu KS, Karumanchi SA, **D'Amore PA**. VEGF and TGF-beta are required for the maintenance of the choroid plexus and ependyma. J Exp Med. 2008 Feb 18;205(2):491-501. PubMed PMID: 18268040; PMCID: PMC2271023

   d. dela Paz NG, Walshe TE, Leach LL, Saint-Geniez M**, D'Amore PA**. Role of shear-stress-induced VEGF expression in endothelial cell survival. J Cell Sci. 2012 Feb 15;125(Pt 4):831-43. PubMed PMID: 22399811; PMCID: PMC3311927

4. Role and regulation of inflammation in ocular pathogenesis

   It is widely believed that chronic low-level inflammation (often termed para-inflammation) is a major contributor to most degenerative pathologies such as AMD and diabetic retinopathy. In spite of this, little is known about the mechanisms that underlie the pathogenesis. We have been studying the role of inflammation at the level of both the vasculature and the retinal pigment epithelium. The vascular is the site of leukocyte extravasation into tissue, and as such, represents a rate-limiting step in the process. We have shown that two factors, VEGF and TGFß, which are both involved in microvascular stabilization participate in maintaining a non-inflammatory endothelium. We are also examining the role of innate immunity in the pathogenesis of geographic atrophy and have reported NLRP3 activation in RPE of donor eye with AMD, but not in age-matched controls, and have demonstrated NLPR3 activation in human RPE in vitro.

   a. Tseng WA, Thein T, Kinnunen K, Lashkari K, Gregory MS, ***D'Amore PA**, *Ksander BR (co-corresponding authors). NLRP3 inflammasome activation in retinal pigment epithelial cells by lysosomal destabilization: implications for age-related macular degeneration. Invest Ophthalmol Vis Sci. 2013 Jan 7; 54:110-120. PMC3544415

   b. Gnanaguru G, Choi AR, Amarnani D, **D'Amore PA**. Oxidized lipoprotein uptake through the CD36 receptor activates the NLRP3 inflammasome in human retinal pigment epithelial cells. Invest Ophthalmol Vis Sci. 2016 Sep 1;57(11):4704-12. doi: 10.1167/iovs.15-18663. PMC5024668

   c. Gnanaguru G, Wagschal A, Oh J, Saez-Torres KL, Li, Temel RE, Kleinman ME, Näär AM, **D'Amore PA**. Targeting of miR-33 ameliorates phenotypes linked to age-related macular degeneration. Molecular Therapy, 2021, https://doi.org/10.1016/j.ymthe.2021.03.014

d. Gnanaguru G, Mackey A, Choi EY, Arta A, Rossato FA, Gero TW, Urquhart AJ, Scott DA, ***D'Amore PA**, *Ng YS. (co-corresponding authors). Discovery of sterically-hindered phenol compounds with potent cytoprotective activities against ox-LDL–induced retinal pigment epithelial cell death as a potential pharmacotherapy. *Free Radic. Biol. Med*. 2022. 2022 Jan;178:360-368. doi: 10.1016/j.freeradbiomed.2021.11.026. Epub 2021 Nov 27. https://doi.org/10.1016/j.freeradbiomed.2021.11.026

5. Role of the endothelial glycocalyx in regulation of vascular inflammation and angiogenesis

   We identified endomucin as a molecule that was significantly downregulated in cystic embryonic bodies that we generated from VEGF-null murine embryonic stem cells. Knowing by endomucin's non-adhesive characteristics and its apical localization on venous and capillary, but not by arterial, endothelium we examined its role in leukocyte-endothelial cells and showed that it prevents leukocyte adhesion under quiescent conditions. Moreover, activation of endothelial cells by inflammatory cytokines leads to the cleavage of cell surface endomucin, facilitating interaction between circulating inflammatory cells and the endothelium. Motivated by the fact that VEGF-deficient embryoid bodies generated endothelial cells but not capillaries, we investigated the role of endomucin in VEGF-stimulated endothelial cell functions. We showed that endomucin depletion from capillary endothelial cells blocked VEGF-induced proliferation, migration, and tube formation in tissue culture and impaired developmental retinal vascularization in vivo. Recent observations indicate that endomucin is essential for VEGF- induced VEGFR2 internalization.

   a. Zahr A, Alcaide P, Yang J, Jones A, Gregory M, dela Paz NG, Patel-Hett S, Nevers T. Luscinskas FW, Saint-Geniez M, Ksander B, * **D'Amore PA**,* Argueso P (co-corresponding authors). Endomucin prevents leukocyte–endothelial cell adhesion and has a critical role under resting and inflammatory conditions. Nat Commun. 2016. PMC4740757

   b. LeBlanc ME, Saez-Torres KL, Cano I, Hu Z, Saint-Geniez M, Ng YS, **D'Amore PA**. Glycocalyx regulation of vascular endothelial growth factor receptor 2 activity. FASEB J. 2019 May 29:fj201900011R. PubMed PMID: 31141406.

   c. Hu Z, Cano I, Saez-Torres KL, LeBlanc ME, Saint-Geniez M, Ng YS, Argüeso P, **D'Amore PA.** Elements of the endomucin extracellular domain essential for VEGF-induced VEGFR2 activity. MPDI Cells. 2020 Jun 5;9(6):1413. doi: 10.3390/cells9061413

   d. Cano I, Wild M, Gupta U, Chaudhary S, Ng YSE, Saint-Geniez M, **D'Amore* PA**, Hu* Z. Endomucin selectively regulates vascular endothelial growth factor-2 through its interaction with AP2. Cell Commun Signal. 2024 Apr 11;22(1):225. doi: 10.1186/s12964-024-01606-w. (co-corresponding authors)

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/myncbi/patricia.d'amore.1/bibliography/41153600/public/?sort=date&direction=ascending

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Ferrara, Napoleone

eRA COMMONS USER NAME (credential, e.g., agency login): NFERRARA

POSITION TITLE: Distinguished Professor of Pathology, Hildyard Endowed Chair in Eye Disease

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 *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Catania Medical School Catania, Italy	M.D.	04/1981	Medical School
University of California, San Francisco	Postdoctoral	06/1985	Reproductive Endocrinology
University of California, San Francisco	Postdoctoral	06/1988	Cancer Research

A. Personal Statement

The main research interests of my laboratory are the biology of angiogenesis and the identification of its regulators. It was about thirty years ago that we reported the isolation and cDNA cloning of vascular endothelial growth factor (VEGF) and proposed that this molecule plays a unique role in the regulation of angiogenesis. My laboratory focused on the investigation of the molecular and biological properties of VEGF. In 1993, we reported that inhibition of VEGF by specific monoclonal antibodies results in suppression of growth of a variety of tumors in vivo. These studies led to the development of a humanized anti-VEGF monoclonal antibody (bevacizumab) as a cancer therapy. Bevacizumab has been approved by the FDA for the treatment of several malignancies. Also, we reported that VEGF is an important mediator of angiogenesis associated with intraocular neovascular syndromes. These studies resulted in the clinical development of a humanized anti-VEGF Fab (ranibizumab), which has been approved by the FDA as therapy for neovascular age-related macular degeneration and retinal vein occlusion. We are presently investigating mechanisms of angiogenesis alternative to VEGF, including the identification of novel angiogenic pathways.

B. Positions and Employment

2020-Pres Hildyard Endowed Chair in Eye Disease
2015-Pres Adjunct Professor of Pharmacology
2012-Pres Senior Deputy Director for Basic Sciences UC San Diego Moores Cancer Center
2012-Pres Adjunct Professor of Ophthalmology
2012-Pres Distinguished Professor of Pathology
2002-2012 Genentech Fellow, Genentech, Inc.
1997-2002 Staff Scientist, Dept. of Molecular Oncology, Genentech, Inc.
1993-1997 Senior Scientist, Dept. of Cardiovascular Research, Genentech, Inc.
1988-1993 Scientist, Dept. of Cardiovascular Research, Genentech, Inc.
1986-1988 Postdoctoral Research Fellow, Cancer Research Institute, UCSF
1985-1986 Intern, Dept. of Obstetrics and Gynecology, Oregon Health Sciences University
1983-1985 Postdoctoral Research Fellow, Reproductive Endocrinology Center, UCSF

Other Experience and Professional Memberships

2015-Present Member, National Academy of Medicine
2014-2018 Member, "Consiglio Superiore di Sanita' " (Health Advisory Council) of Italy.
2006-Present Member, National Academy of Science

Honors and Awards

2023 Prince Mahidol Award in Medicine
Keio Medical Sciences Prize
2022 Weinman Award in Cancer Research, Univ. of Hawaii
2020 Named Hildyard Endowed Chair in Eye Disease
G.B. Bietti Medal. Italian Society of Ophthalmology
2018 25th Annual John F. Enders Lecture. Harvard Medical School, Boston MA
2015 Leslie Dana Gold Medal. Washington Univ.
Elected Member. National Academy of Medicine, USA
2014 Canada Gairdner International Award
A. Champalimaud Vision Award
2013 Breakthrough Prize in Life Sciences
Elected Fellow, AACR Academy
2012 The Economist Innovation Award (Bioscience)
2011 Dr. Paul Janssen Award for Biomedical Research
2010 Macula Society-Michaelson Award
Lasker-DeBakey Clinical Medical Research Award
Jules Gonin Lecture. Retina Research Foundation
2009 Pezcoller Foundation-AACR International Award
2008 Macula Society-Arnall Patz Award
2007 ASCO Science of Oncology Award
2006 Elected Member. National Academy of Sciences, USA
Passano Foundation Research Award
General Motors Cancer Research Award
2005 AACR Bruce F. Cain Memorial Award
Lefoulon-Delalande Institut-de-France Scientific Prize
2004 American-Italian Cancer Foundation Prize
Italian Assoc. for Res. and Cure of Ocular Disorders (A.I.R.C.M.O.) Prize

C. Contribution to Science

1. **Cloning and biochemical characterization of VEGF and receptors**
A key limiting factor in harnessing the scientific and therapeutic potential of angiogenesis was the identification of the key regulators of this process. By the mid-1980s, several molecules had been characterized as angiogenic factors in some bioassays (e.g. aFGF, bFGF, angiogenin, etc), but none had been shown to function as an endogenous regulator. Our contribution to the field was the identification, isolation and cDNA cloning of vascular endothelial growth factor (VEGF), an endothelial cell specific mitogen. Together with our collaborators, we also identified the first VEGF tyrosine kinase receptor, known as Flt-1 or VEGFR-1.
   a. Leung DW, Cachianes G, Kuang WJ, Goeddel DV, **Ferrara N**. Vascular endothelial growth factor is a secreted angiogenic mitogen. Science. 1989 Dec 8;246(4935):1306-9. doi: 10.1126/science.2479986. PMID: 2479986.
   b. de Vries C, Escobedo JA, Ueno H, Houck K, **Ferrara N**, Williams LT. The fms-like tyrosine kinase, a receptor for vascular endothelial growth factor. Science. 1992 Feb 21;255(5047):989-91. doi: 10.1126/science.1312256. PMID: 1312256; Not PMCID eligible.
   c. Houck KA, Leung DW, Rowland AM, Winer J, **Ferrara N**. Dual regulation of vascular endothelial growth factor bioavailability by genetic and proteolytic mechanisms. J Biol Chem. 1992 Dec 25;267(36):26031-7. PMID: 1464614.
   d. Xin H, Zhong C, Nudleman E, **Ferrara N**. Evidence for Pro-angiogenic Functions of VEGF-Ax. Cell. 2016 Sep 22;167(1):275-284.e6. doi: 10.1016/j.cell.2016.08.054. PubMed PMID: 27662093;

NIHMSID:NIHMS27662093.

2. Discovery of the role of VEGF and other angiogenic pathways in angiogenesis

After the discovery of VEGF, it was essential to establish whether or not this molecule played an important role the regulation of angiogenesis. As above noted, a problem in the field was the lack of correlation between angiogenic activity in bioassays and a true physiological role. For example, knockout of the *bFGF* gene in mice was not associated with any defect in vascular development. Utilizing a variety of genetic and pharmacological approaches, we were able to demonstrate the essential role of VEGF in developmental and physiological angiogenesis such as that occurring in the ovary and reproductive organs. In particular, inactivation of a single *vegf* allele in mice was shown by our group to result in embryonic lethality in mice. Further work from our laboratory resulted in the identification of more specialized angiogenic molecules such as EG-VEGF and Bv8, respectively implicated in endocrine gland- and in myeloid cell-dependent angiogenesis. Most recently, we reported that glycosylation inhibitors can stimulate endothelial cell growth and angiogenesis through activation of stress pathways.

a. **Ferrara N**, Carver-Moore K, Chen H, Dowd M, Lu L, O'Shea KS, Powell-Braxton L, Hillan KJ, Moore MW. Heterozygous embryonic lethality induced by targeted inactivation of the VEGF gene. Nature. 1996 Apr 4;380(6573) : 439-42. doi: 0.1038/380439a0. PMID: 8602242; No PMCID.

b. LeCouter J, Moritz, D, Li, B, Phillips, GL, Liang, XH, Gerber, HP, Hillan, KJ, **Ferrara N.** Angiogenesis-independent endothelial protection of liver: Role of VEGFR-1. Science. 2003 Feb 7;299(5608):890-3. doi: 10.1126/science.1079562.PMID: 12574630

c. Zhong C, Li P, Argade S, Liu L, Chilla' A, Liang, W, Xin H, Eliceiri B, Choudhury B, **Ferrara, N**. Inhibition of protein glycosylation, is a novel pro-angiogenic strategy that acts through activation of stress pathways. Nat. Commun. 2020 Dec 10;11(1):6330. doi: 10.1038/s41467-020-20108-0. PMID: 33303737.

3. Development of VEGF inhibitors for therapy

Given the important role of VEGF in developmental angiogenesis as assessed by genetic targeting studies, we sought to develop reagents eventually suitable for clinical trials. One of these was a murine VEGF neutralizing antibody. In view of the strong immunogenicity of mouse antibodies in humans, we "humanized" this antibody, employing protein engineering techniques. The amino acid sequences of the humanized antibody are about 93% human and 7% murine. This antibody is known today as bevacizumab, a widely used anti-cancer agent. Another class of inhibitors that our laboratory pioneered is the high affinity soluble receptor or "VEGF-traps", based on structure-function studies, which led to the discovery that the second immunoglobulin-like domain in VEGFR1 is the key binding element for VEGF. This discovery was instrumental to the development of aflibercept, a molecule which has been FDA-approved for multiple indications.

a. Presta LG, Chen H, O'Connor SJ, Chisholm V, Meng YG, Krummen L, Winkler M, **Ferrara N**. Humanization of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders. Cancer Res. 1997 Oct 15;57(20):4593-9. PMID: 9377574; No PMCID.

b. Davis-Smyth T, Chen H, Park J, Presta LG, **Ferrara N**. The second immunoglobulin-like domain of the VEGF tyrosine kinase receptor Flt-1 determines ligand binding and may initiate a signal transduction cascade. EMBO J. 1996 Sep 16;15(18):4919-27. PMID: 8890165; PMCID: PMC452229.

c. Xin H, Biswas N, Li P, Zhong C, Chan TC, Nudleman E, **Ferrara, N.** Heparin-binding VEGFR1 variants as long-acting VEGF inhibitors for treatment of intraocular neovascular disorders. Proc Natl Acad Sci USA. 2021 May 25;118(21):e1921252118. doi: 10.1073/pnas.1921252118. PMID: 34006633 PMCID: PMC816614

4. Elucidation of the VEGF role in cancer

The hypothesis that blocking angiogenesis may inhibit tumor growth was proposed decades ago, but the key tumor angiogenesis factors were unknown. As above noted, we developed an anti-VEGF antibody in the early 1990s. We demonstrated that administration of such antibody substantially reduced tumor angiogenesis and growth in a variety of models. Clinical trials with the anti-VEGF humanized antibody (bevacizumab) began in 1997, and the drug was first approved by the FDA as therapy of metastatic colorectal cancer in 2004. This approval was followed by approval for other indications, including renal cell carcinoma, non-small cell lung cancer, cervical cancer and ovarian cancer. Bevacizumab and other VEGF inhibitors today are standard of therapy for multiple malignancies. Our laboratory sought to

elucidate the mechanisms of resistance to VEGF inhibitors and identified multiple pathways that can potentially bypass VEGF signaling.

a. Kim KJ, Li B, Winer J, Armanini M, Gillett N, Phillips HS, **Ferrara N**. Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumour growth in vivo. Nature. 1993 Apr 29;362(6423):841-4. doi:10.1038/362841a0. PMID: 7683111; No PMCID.
b. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, **Ferrara N**, Fyfe G, Rogers B, Ross R, Kabbinavar F. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med. 2004 Jun 3;350(23):2335-42. doi:10.1056/NEJMoa032691. PMID: 15175435; No PMCID.
c. Itatani Y, Yamamoto T, Zhong C, Molinolo AA, Ruppel J, Hegde P, Taketo M, **Ferrara N**. Suppressing neutrophil-dependent angiogenesis abrogates resistance to anti-VEGF antibody in a genetic model of colorectal cancer. Proc Natl Acad Sci U S A. 2020 Sep 1;117(35):21598-21608. doi: 10.1073/pnas.2008112117. Epub 2020 Aug 19. PubMed PMID: 32817421; PubMed Central PMCID: PMC7474657.

5. Elucidation of the role of VEGF and other regulators in intraocular neovascular disorders

The hypothesis that angiogenic factors may be responsible for intraocular neovascularization was initially proposed in 1948. However, identifying such molecules proved very challenging. The identification of VEGF as a key angiogenic molecule in multiple biological contexts and the demonstration that anti-VEGF antibody can inhibit tumor growth in 1993 generated much interest in the possibility that VEGF may be also implicated in ocular angiogenesis. Work with our collaborators led to the demonstration that the VEGF levels in eye fluids are strongly correlated with proliferative retinopathy in humans. VEGF inhibitors were shown to inhibit angiogenesis in animal models of retinal and choroidal neovascularization. These findings led to the clinical trials of VEGF inhibitors in multiple intraocular neovascular disorders. VEGF inhibitors now represent standard of therapy and have dramatically changed the outcome for disorders that until recently were associated with severe vision loss.

a. Aiello LP, Avery RL, Arrigg PG, Keyt BA, Jampel HD, Shah ST, Pasquale LR, Thieme H, Iwamoto MA, Park JE, Nguyen HV, Aiello LM, **Ferrara N,** King GL. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. N Engl J Med. 1994 Dec 1;331(22):1480-7. doi: 10.1056/NEJM199412013312203. PMID:7526212; No PMCID.
b. Aiello LP, Pierce EA, Foley ED, Takagi H, Chen H, Riddle L, **Ferrara N**, King GL, Smith LE. Suppression of retinal neovascularization in vivo by inhibition of vascular endothelial growth factor (VEGF) using soluble VEGF-receptor chimeric proteins. Proc Natl Acad Sci USA.1995 Nov 7;92(23):10457-61. doi:10.1073/pnas.92.23.10457. PMID: 7479819; PMCID: PMC40630.
c. Adamis AP, Shima DT, Tolentino MJ, Gragoudas ES, **Ferrara N**, Folkman J, D'Amore PA, Miller JW. Inhibition of vascular endothelial growth factor prevents retinal ischemia-associated iris neovascularization in a nonhuman primate. Arch Ophthalmol.1996 Jan;114(1):66-71.doi: 10.1001/archopht.1996.01100130062010. PMID: 8540853; No PMCID.
d. **Ferrara N**. Vascular endothelial growth factor and age-related macular degeneration: from basic science to therapy. Nat Med. 2010 Oct;16(10):1107-11.doi: 10.1038/nm1010-1107. PMID: 20930754; No PMCID.
e. Li, P, Li, Q, Biswas, N, Xin, H, Diemer, T, Liu, L, Perez Gutierrez, L, Paternostro, G, Piermarocchi, C, Domanskyi, S, Wang, RK, **Ferrara, N**. LIF, a mitogen for choroidal endothelial cells, protects the choriocapillaris: Implications for prevention of geographic atrophy. EMBO Mol. Med**.** e14511, 2022. PMID: 34779136
f. Biswas, N, Mori, T, Kumar Chetty Nagaraj, K, Xin, H, Diemer, T, Li, P, Su, Y, Piermarocchi, C, **Ferrara, N**. Adenosine diphosphate stimulates VEGF-independent choroidal endothelial cell. proliferation: A potential escape from anti-VEGF therapy. Proc. Natl. Acad. Sci. USA. In press

Complete List of Published Work in Google Scholar

https://scholar.google.com/citations?user=WPJnV70AAAAJ&hl=en&oi=ao

Total citations: >209,000; h-index: 187

BIOGRAPHICAL SKETCH

NAME: Miller, Joan W.

eRA COMMONS USER NAME (credential, e.g., agency login): JWMILLER33

POSITION TITLE: David Glendenning Cogan Professor of Ophthalmology and Chair of Ophthalmology, Harvard Medical School; Chief of Ophthalmology, Massachusetts Eye and Ear, Massachusetts General Hospital; Ophthalmologist-in-Chief, Brigham and Women's Hospital

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 *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Massachusetts Institute of Technology, Cambridge, MA	S.B.	06/1980	Life Sciences
Harvard Medical School, Boston, MA	M.D.	06/1985	Medicine
Newton Wellesley Hospital, Newton, MA	Internship	06/1986	Medicine
Massachusetts Eye and Ear, Harvard Medical School, Boston, MA	Residency	06/1989	Ophthalmology
Massachusetts Eye and Ear, Harvard Medical School, Boston, MA	Fellowship	06/1991	Vitreoretinal Surgery

A. Personal Statement

As an ophthalmologist with subspecialty expertise in retina, I am committed to understanding the molecular mechanisms of retinal disease and developing innovative therapeutic interventions. I pursue these objectives using a combination of laboratory and clinical research, clinical care, teaching, and administrative leadership. These activities take place primarily at Massachusetts Eye and Ear—the flagship academic center for the Harvard Medical School Department of Ophthalmology—and extend worldwide through international collaborations and partnerships. My research interests focus on diseases of the retina and choroid, particularly age-related macular degeneration (AMD) and diabetic retinopathy. My work has led to two major advances: the first pharmacologic therapy for AMD, and the identification of a prominent therapeutic target in neovascular retinal disease. The first endeavor comprised the development of verteporfin photodynamic therapy (PDT), from preclinical studies to clinical trials to FDA approval, for the treatment of choroidal neovascularization. A parallel line of investigation identified the key role of vascular endothelial growth factor (VEGF) in pathological retinal and choroidal neovascularization. Several drugs targeting VEGF have since been developed and approved by health authorities worldwide. For the development of anti-angiogenic therapy for retinal disease, I was a co-recipient of the 2014 António Champalimaud Vision Award, the highest distinction in ophthalmology and visual science. Current research investigations focus on the pathogenesis of AMD, including genomics, metabolomics, imaging, and functional measures, strategies for early intervention in AMD, and neuroprotective therapies for retinal disease. My clinical practice at Mass Eye and Ear also focuses on retinal disease, with special emphasis on AMD. Clinical effort is divided between office visits, outpatient treatments, laser procedures, and associated teaching of medical trainees. Patients are generally referred by ophthalmologists throughout the world, and typically require special expertise in diagnosis and/or therapy. Additionally, I have served as a principal investigator or co-investigator in numerous clinical trials of AMD therapies.

Ongoing and recently completed projects that I would like to highlight include:

1R01EY030088-01A1
Husain (PI); Role: Co-investigator
03/01/2020-02/28/2025
Metabolomics a Novel Tool for Investigating the Pathogenesis of Age-Related Macular Degeneration

Research to Prevent Blindness Unrestricted Grant
Miller (PI)

01/01/2021-12/31/2025
As Chair of the HMS Department of Ophthalmology, I allocate funds to active research programs within the department. I do not receive support for my research program from this grant.

Citations:

1. **Miller JW**. Age-related macular degeneration revisited--piecing the puzzle: the LXIX Edward Jackson memorial lecture. Am J Ophthalmol. 2013 Jan;155(1):1-35.e13. PMID: 23245386
2. **Miller JW**. VEGF: From Discovery to Therapy: The Champalimaud Award Lecture. Transl Vis Sci Technol. 2016 Mar 11;5(2):9. Mar. PMID: 26981331; PMCID: PMC4790434.
3. **Miller JW**. Beyond VEGF: The Weisenfeld Lecture. Invest Ophthalmol Vis Sci. 2016 Dec 1:57(15):6911-6918. PMID: 28027565.
4. **Miller JW.** Developing Therapies for Age-related Macular Degeneration: The Art and Science of Problem-solving: The 2018 Charles L. Schepens, MD, Lecture. Ophthalmol Retina 2019 Oct;3(10):900-909. PMID: 31585712.

B. Positions and Honors

Positions and Employment

2019- Ophthalmologist-in-Chief, Brigham and Women's Hospital
2017- David Glendenning Cogan Professor of Ophthalmology, Harvard Medical School
2009- Chief of Ophthalmology, Massachusetts General Hospital, now Chair of Ophthalmology
2003- Chief of Ophthalmology, Massachusetts Eye and Ear, now Chair of Ophthalmology
2003- Chair of Ophthalmology, Harvard Medical School
2003-2017 Henry Willard Williams Professor of Ophthalmology, Harvard Medical School
2002- Professor of Ophthalmology, Harvard Medical School
1998-2002 Associate Professor of Ophthalmology, Harvard Medical School
1994-1998 Assistant Professor of Ophthalmology, Harvard Medical School
1991- Assistant Surgeon - Surgeon, Department of Ophthalmology, Massachusetts Eye and Ear
1991-1994 Instructor in Ophthalmology, Harvard Medical School
1991 Assistant Professor of Ophthalmology, Tufts University School of Medicine

Other Experience and Professional Memberships

2015- National Academy of Medicine (formerly Institute of Medicine)
2013- Academia Ophthalmologica Internationalis
2012-2021 Heed Ophthalmic Foundation (Board of Directors)
2009- Women in Eye and Vision Research
2008- American Ophthalmological Society
2007- Women in Retina
2005- American Society of Retinal Specialists
2004- Association of University Professors of Ophthalmology (Board of Trustees 2017-2021, President-Elect 2021-2022; President 2022-2023)
1998- Club Jules Gonin
1995- Macula Society (Treasurer 2016-2017, Secretary 2017-2018, President- Elect 2018-2019, President 2019-2020, Past-President 2020-2021, Award Committee Chair 2021-2022)
1995- Retina Society
1994- New England Ophthalmological Society (Vice President 2011–2012, President 2013–2014)
1993- Research to Prevent Blindness
1992- American Association for the Advancement of Science
1992- American Academy of Ophthalmology
1991- American Board of Ophthalmology
1989- Association for Research in Vision and Ophthalmology (Silver Fellow 2010, Gold Fellow 2015)
1987- American Medical Association

Select Honors and Awards

2018 Lucien Howe Medal, American Ophthalmological Society
2018 Charles L. Schepens Award, AAO, Retina Research Foundation, and Schepens International Society
2018 Gertrude D. Pyron Award, Retina Research Foundation and ASRS
2015 Mildred Weisenfeld Award for Excellence in Ophthalmology, ARVO
2014 António Champalimaud Vision Award, Champalimaud Foundation

2014 Cless Best of the Best Award, University of Illinois at Chicago Department of Ophthalmology
2013 ARVO Foundation Honoree
2012 Edward Jackson Memorial Lectureship, American Academy of Ophthalmology
2011 Senior Achievement Award, American Academy of Ophthalmology
2011 Life Sciences Award, Health Resources in Action
2011 Paul Henkind Memorial Award, Macula Society
2010 Suzanne Veronneau-Troutman Award (Women in Ophthalmology)
2010 Joseph B. Martin Dean's Leadership Award for the Advancement of Women Faculty, HMS.
2010 Founders Award, American Society of Retina Specialists
2009 J. Donald Gass Medal for outstanding contributions in the study of macular diseases (Macula Society)
2006 ARVO/Pfizer Ophthalmics Translational Research Award (ARVO)
2004 John Milton McLean Medal, Weill Cornell Medical College
2003 American Academy of Ophthalmology Achievement Award
2002 Alcon Research Institute Award for "outstanding contributors to ophthalmic research"
2002 Jules Gonin Lecturer of the Retina Research Foundation (Club Jules Gonin)
2000 Top Products of 2000 Award (Business Week) – Awarded for Visudyne®
2000 Best of What's New Award (Popular Science Magazine) – Awarded for Visudyne®
2000 Research to Prevent Blindness Physician-Scientist Award
1999 Rosenthal Award, The Macula Society

C. Contribution to Science

Background: My research interests focus on diseases of the retina and choroid, including age-related macular degeneration (AMD) and diabetic retinopathy. Abnormal vascular growth (neovascularization) above or below the retina allows fluid to leak into the central retina, causing vision loss. AMD is the leading cause of vision loss in older adults in industrialized countries, with the number of people living with AMD expected to reach 196 million people worldwide by 2020. My most significant contributions to the field of ophthalmology are summarized below.

1) **Photodynamic therapy (PDT) with verteporfin (Visudyne®)**: Along with Evangelos Gragoudas, MD, I am credited with the translational development of Visudyne® from preclinical studies to clinical trials. Visudyne® is the first pharmacologic AMD treatment approved by the US Food and Drug Administration and international drug regulatory agencies, and has been used to treat well over one million patients worldwide. This work initiated the pharmacologic era of AMD therapy.

   Selected publications (*member of the investigative team cited in the appendix of the manuscript):
   a) **Miller JW**, Walsh AW, Kramer M, Hasan T, Michaud N, Flotte TJ, Haimovici R, Gragoudas ES. Photodynamic therapy of experimental choroidal neovascularization using lipoprotein-delivered benzoporphyrin. Arch Ophthalmol. 1995 Jun; 113 (6) :810-8. PMID:7540388.
   b) **Miller JW**, Schmidt-Erfurth U, Sickenberg M, Pournaras CJ, Laqua H, Barbazetto I, Zografos L, Piguet B, Donati G, Lane AM, Birngruber R, van den Berg H, Strong A, Manjuris U, Gray T, Fsadni M, Bressler NM, Gragoudas ES. Photodynamic therapy with verteporfin for choroidal neovascularization caused by age-related macular degeneration: results of a single treatment in a phase 1 and 2 study. Arch Ophthalmol. 1999 Sep;117(9):1161-73. PMID: 10496388.
   c) Bressler NM; **Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group**.* Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: two-year results of 2 randomized clinical trials-tap report 2. Arch Ophthalmol. 2001 Feb;119(2):198-207. PMID: 11176980.

2) **Establishing basis for anti-VEGF therapy for ophthalmic disease:** Concomitant with the development of Visudyne®, a parallel line of investigation identified the key role of vascular endothelial growth factor (VEGF) in pathological retinal and choroidal neovascularization. This work demonstrated the first *in vivo* correlation of VEGF with pathological ocular neovascularization, and established preclinical proof-of-concept that VEGF inhibition prevents pathological ocular neovascularization. This work formed the scientific basis of the anti-VEGF class of ophthalmic drugs, which have become front-line therapies for neovascular AMD, diabetic retinopathy, macular edema following retinal vein occlusion, and for eyes with choroidal neovascularization secondary to pathologic myopia, with millions of patients treated annually worldwide.

   Selected publications:

a) **Miller JW**, Adamis AP, Shima DT, D'Amore PA, Moulton RS, O'Reilly MS, Folkman J, Dvorak HF, Brown LF, Berse B, Yeo TK, Yeo KT. Vascular endothelial growth factor/vascular permeability factor is temporally and spatially correlated with ocular angiogenesis in a primate model. Am J Pathol. 1994;145(3):574-84. PMID: 7521577; PMCID: PMC1890317.
b) Adamis AP, **Miller JW**, Bernal MT, D'Amico DJ, Folkman J, Yeo TK, Yeo KT. Increased vascular endothelial growth factor levels in the vitreous of eyes with proliferative diabetic retinopathy. Am J Ophthalmol. 1994;118(4):445-50. PMID: 7943121.
c) Adamis AP, Shima DT, Tolentino MJ, Gragoudas ES, Ferrara N, Folkman J, D'Amore PA, **Miller JW**. Inhibition of vascular endothelial growth factor prevents retinal ischemia-associated iris neovascularization in a nonhuman primate. Arch Ophthalmol. 1996;114(1):66-71. PMID: 8540853.
d) Krzystolik MG, Afshari MA, Adamis AP, Gaudreault J, Gragoudas ES, Michaud NA, Li W, Connolly E, O'Neill CA, **Miller JW**. Prevention of experimental choroidal neovascularization with intravitreal anti-vascular endothelial growth factor antibody fragment. Arch Ophthalmol. 2002;120(3):338-46. PMID: 11879138.

3) **Genetic and environmental risk factors for retinal degenerative disorders:** I have worked with numerous collaborators to identify genetic and environmental risk factors for AMD and related ocular neurodegenerative disorders. Earlier studies identified genetic and environmental risk factors for AMD using novel approaches in genetic epidemiology, Systems biology-based approaches have implicated additional novel pathways in AMD pathogenesis. My Jackson Memorial Lecture (delivered to the American Academy of Ophthalmology in 2012 and published in 2013) is considered an authoritative summary of AMD pathogenesis, including the role of genetics.

Selected publications:

a) DeAngelis MM, Lane AM, Shah CP, Ott J, Dryja TP, **Miller JW**. Extremely discordant sib-pair study design to determine risk factors for neovascular age-related macular degeneration. Arch Ophthalmol. 2004 Apr;122(4):575-80. PMID: 15078676.
b) Morrison MA, Silveira AC, Huynh N, Jun G, Smith SE, Zacharaki F, Sato H, Loomis S, Andreoli MT, Adams SM, Radeke MJ, Jelcick AS, Yuan Y, Tsiloulis AN, Chatzoulis DZ, Silvestri G, Kotoula MG, Tsironi EE, Hollis BW, Chen R, Haider NB, **Miller JW**, Farrer LA, Hageman GS, Kim IK, Schaumberg DA, DeAngelis MM. Systems biology-based analysis implicates a novel role for vitamin D metabolism in the pathogenesis of age-related macular degeneration. Hum Genomics. 2011 Oct;5(6):538-68. PMID: 22155603; PMCID: PMC3525248.
c) **Miller JW**. Age-related macular degeneration revisited--piecing the puzzle: the LXIX Edward Jackson memorial lecture. Am J Ophthalmol. 2013 Jan;155(1):1-35.e13. PMID: 23245386.

4) **Characterization and Treatment of Early and Intermediate AMD:** My current lines of research are aimed at addressing the significant unmet need for improved phenotyping and treatments for early and intermediate AMD. My work has expanded our knowledge of structure-function correlation and prediction of progression in retinal disease by describing new methodology to measure contrast sensitivity for better detection of early visual deficits, and identified systemic and imaging biomarkers capable of distinguishing subjects with AMD. Additionally, research efforts have identified statins as a possible treatment for early/intermediate AMD, as patients treated with high-dose Atorvastatin had an observed regression of drusen with vision gain, no atrophy, and did not progress to neovascular AMD.

Selected publications:

a) Vavvas DG, Daniels AB, Kapsala ZG, Goldfarb JW, Ganotakis E, Loewenstein JI, Young LH, Gragoudas ES, Eliott D, Kim IK, Tsilimbaris MK, **Miller JW**. Regression of some high-risk features of age-related macular degeneration (AMD) in patients receiving intensive statin treatment. EBioMedicine. 2016 Feb 4;5:198-203. PMID: 27077128.
b) Vingopoulos F, Bannerman A, Zhou P, Koch P, Wescott HE, Kim L, Vavvas DG, **Miller JW**, Miller JB. Toward the validation of quantitative contrast sensitivity as a clinical endpoint: correlations with vision-related quality of life in bilateral AMD. Br J Ophthalmol 2024 May 21;108(6):846-851. PMID: 37857454
c) Laíns I, Kelly RS, Miller JB, Silva R, Vavvas DG, Kim IK, Murta JN, Lasky-Su J, **Miller JW**, Husain D. Human Plasma Study across All Stages of Age-Related Macular Degeneration Identifies Potential Lipid Biomarkers. Ophthalmology. 2018 Feb;125(2):245-254. PMID: 28916333.
d) Laíns I, Gantner M, Murinello S, Lasky-Su JA, **Miller JW**, Friendlander M, Husain D. Metabolomics in the study of retinal health and disease. Prog Retin Eye Res. 2019 Mar;69:57-79. Review. PMID: 30423446.

5) **Neuroprotection:** Different retinal diseases have different origins, but many converge on cellular pathways that lead to photoreceptor death—the ultimate cause of vision loss in many retinal diseases. These pathways have become a major focus of my research, which aims to identify new strategies for preserving vision through neuroprotection. This endeavor has elucidated the mechanisms of photoreceptor cell death and identified potential therapeutic targets through genetic, molecular, and cellular studies.

Selected publications:

a) Murakami Y, Matsumoto H, Roh M, Suzuki J, Hisatomi T, Ikeda Y, **Miller JW**, Vavvas DG. Receptor interacting protein kinase mediates necrotic cone but not rod cell death in a mouse model of inherited degeneration. Proc Natl Acad Sci U S A. 2012 Sep 4;109(36):14598-603. PMID: 22908283.

b) Murakami Y, Matsumoto H, Roh M, Giani A, Kataoka K, Morizane Y, Kayama M, Thanos A, Nakatake S, Notomi S, Hisatomi T, Ikeda Y, Ishibashi T, Connor KM, **Miller JW**, Vavvas DG. Programmed necrosis, not apoptosis, is a key mediator of cell loss and DAMP-mediated inflammation in dsRNA-induced retinal degeneration. Cell Death Differ. 2013 Aug 16. PMID: 23954861.

c) Kataoka K, Matsumoto H, Kaneko H, Notomi S, Takeuchi K, Sweigard JH, Atik A, Murakami Y, Connor KM, Terasaki H, **Miller JW**, Vavvas DG. Macrophage- and RIP3-dependent inflammasome activation exacerbates retinal detachment-induced photoreceptor cell death. Cell Death Dis. 2015 Apr 23;6:e1731. PMID: 25906154.

d) Ueta T, Ishihara K, Notomi S, Lee JJ, Maidana DE, Efstathiou NE, Murakami Y, Hasegawa E, Azuma K, Toyono T, Paschalis EI, Aihara M, **Miller JW**, Vavvas DG. RIP1 kinase mediates angiogenesis by modulating macrophages in experimental neovascularization. Proc Natl Acad Sci USA. 2019 Nov 19;116(47): 23724-23734. PMID: 31699817.

Complete List of Published Work in PubMed:
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