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**Harvard Medical School Researchers Awarded Prestigious $1.3M Champalimaud Vision Award**

*World-renowned Scientific Award Recognizes the Groundbreaking Development of Anti-angiogenic Therapy for Blinding Retinal Disease*

**SEPTEMBER 10, 2014 (Lisbon, Portugal)** Six Harvard Medical School (HMS) researchers were among the recipients of the 2014 [António Champalimaud Vision Award](http://www.fchampalimaud.org/en/vision-award/), the highest distinction in ophthalmology and visual science.

The award was given for the development of anti-angiogenic therapy for retinal disease. The researchers include Joan Whitten Miller, M.D., Evangelos S. Gragoudas, M.D., and Patricia A. D’Amore, Ph.D., MBA, of Massachusetts Eye and Ear; Lloyd Paul Aiello, M.D., Ph.D., of Mass. Eye and Ear and Joslin Diabetes Center; George L. King, M.D., of Joslin Diabetes Center; and Anthony P. Adamis, M.D., of Genentech, who is also affiliated with HMS Ophthalmology and Mass. Eye and Ear. Napoleone Ferrara, M.D., of University of California, San Diego School of Medicine and Moores Cancer Center, also received the award.

The 2014 António Champalimaud Vision Laureates were honored on Sept. 10, 2014 during a ceremony held at the [Champalimaud Centre for the Unknown](http://www.fchampalimaud.org/en/the-foundation/champalimaud-centre-unknown/) in Lisbon, Portugal. Presiding at the ceremony was His Excellency Aníbal António Cavaco Silva, President of the Portuguese Republic.

Established by The [Champalimaud Foundation](http://www.fchampalimaud.org/) in 2006, the António Champalimaud Vision Award honors outstanding contributions to the preservation and understanding of sight. In even-numbered years, the award is given for vision research, and in alternate years it recognizes efforts to alleviate visual problems in developing countries or through humanitarian endeavors.

Award recipients are selected by an [international jury panel](http://www.fchampalimaud.org/en/the-foundation/people/vision-award-jury/) that includes two Nobel Laureates and other prominent figures. The Champalimaud Vision Award is often referred to as the “Nobel Prize for Vision” and with its €1 million ($1.3 million USD) purse, it is among the world’s largest scientific and humanitarian prizes.

In the 1990s, the 2014 Champalimaud Award Laureates worked in parallel and in collaboration to identify vascular endothelial growth factor (VEGF) as the major trigger for angiogenesis in the eye. Angiogenesis, or blood vessel growth, underlies the pathology of various blinding retinal disorders, including age-related macular degeneration (AMD) and diabetic retinopathy. Abnormal vascular growth ―a process called neovascularization―above or below the retina allows fluid to leak into the central retina, causing vision loss.

The researchers then demonstrated that blocking VEGF could suppress ocular angiogenesis. This biomedical breakthrough led to a new class of ophthalmic anti-VEGF drugs, which first became available in the United States December 2004 with the introduction of pegaptanib (Macugen®) for the neovascular or “wet” form of AMD. Multiple ophthalmic drugs targeting VEGF activity have since followed, including the widely used ranibizumab (Lucentis®), introduced June 2006, and aflibercept (Eylea®), introduced November 2011. Bevacizumab (Avastin®), an anti-VEGF drug originally developed for cancer and introduced February 2004, is also widely used for treating retinal disease.

The development of anti-VEGF therapy for retinal disease is considered one of the top biomedical advances of the past decade. [In 2006, the development of ranibizumab for neovascular AMD was featured in Breakthrough of the Year](http://www.sciencemag.org/content/314/5807/1850.1.long), a list of the 10 most significant scientific developments compiled annually by the journal [*Science*](http://www.sciencemag.org/).

The global impact of the 2014 Champalimaud Laureate’s work is significant. According to the World Health Organization, AMD is the leading cause of vision loss in industrialized countries and is estimated to cause blindness or severe visual impairment in nearly 9 million people worldwide. Diabetic retinopathy is the leading cause of blindness among working-age adults in industrialized nations and causes an estimated 5 million cases of blindness worldwide.

With the aging population and global diabetes rates on the rise, AMD and diabetic retinopathy are becoming significant worldwide socioeconomic concerns.

Results of Phase III trials of Lucentis®, first published in 2006, showed remarkable results: two years of monthly eye injections preserved vision for nearly 95% of treated patients, and visual acuity improved for nearly one-third.

Based on these trials, [it is estimated that two years of Lucentis® treatment reduces visual impairment in neovascular AMD by 37% and legal blindness by 72%](http://www.ncbi.nlm.nih.gov/pubmed/21670337). By 2010, global annual use of Lucentis® reached more than 3 million injections, translating to approximately 500,000 patients treated per year worldwide.

Eylea® has since become the predominant approved therapy for neovascular AMD, treating 26% of patients (surpassing patient share of 21% for Lucentis® or ranibizumab), while Avastin® continues to be the most widely used off-label treatment for wet AMD.

Extrapolating from these data and December 2013 estimates of U.S. sales, one can conclude that over 500,000 ophthalmic patients in the United States and more 1 million worldwide are treated annually with all anti-VEGF agents combined.

Anti-VEGF therapy is now a mainstay of patient care for neovascular AMD, diabetic macular edema (swelling of the central retina, a complication of diabetic retinopathy) and macular edema following retinal vein occlusion. VEGF inhibitors hold potential for a growing list of indications, including neovascular glaucoma and retinopathy of prematurity. Moreover, VEGF inhibitors have been used experimentally to treat over 50 ocular diseases.

“The work of the nominees has had a tremendous impact on the work of my faculty colleagues—both in the clinic and in the laboratory,” says Paul Lichter, M.D., Chair of Ophthalmology and Visual Sciences from 1978 to 2012 and Founding Director of the Kellogg Eye Center at University of Michigan. “Anti-VEGF therapy ranks at the top of the list of pharmacological treatments that have been developed for retinal disease, and have helped masses of people in my long career as an ophthalmologist.”

“To one degree or another, AMD affects nearly 70% of people over age 75 in Europe and the United States. This group's body of work has fundamentally changed the world for millions of citizens worldwide,” says David W. Parke II, MD, Executive Vice President and CEO of the American Academy of Ophthalmology. “I am a retina subspecialist, and for the first twenty years of my clinical career, I had nothing to offer my elderly patients who were robbed of vision, of independence, and of enjoyment of life by neovascular AMD. I can now tell them that, with newer medications spawned by the work of the Champalimaud Award Laureates, ophthalmologists have a very high likelihood of arresting disease progression and a reasonable chance of recovering some lost sight.”

Jeffrey S. Flier, M.D., Dean of the Faculty of Medicine at Harvard Medical School, praised the collaborative nature of the research that spanned academia and industry to translate scientific discovery to clinical reality. “These scientists’ triumphs show what can happen when fertile minds meet, brainstorm and combine ideas in alliances that cross institutional and academic boundaries,” said Dr. Flier. “Their discoveries remind us why medicine must begin with exploring science at the basic level—shedding light on pathological mechanisms and pinpointing the root causes of human disease.”

The researchers will use the funds from the award to further their research efforts to cure blindness.

“It is a great honor to be recognized as a group for our translational work in the field of angiogenesis,” said Dr. Miller. “We are thrilled to receive this wonderful award, and remain inspired to continue our investigations, pursuing our passion to improve the lives of patients around the world, so that children born today may see throughout their lives.”

**About** [**Massachusetts Eye and Ear**](http://www.masseyeandear.org/)Mass. Eye and Ear clinicians and scientists are driven by a mission to find cures for blindness, deafness and diseases of the head and neck. Led by the Eaton-Peabody Laboratory in Otology, the Howe Laboratory in Ophthalmology, the Berman-Gund Laboratories for Retinal Degenerations, and Schepens Eye Research Institute, Mass. Eye and Ear in Boston is the world's largest vision and hearing research center, offering hope and healing to patients everywhere through discovery and innovation. Mass. Eye and Ear is a Harvard Medical School teaching hospital and trains future medical leaders in ophthalmology and otolaryngology, through residency as well as clinical and research fellowships. Internationally acclaimed since its founding in 1824, Mass. Eye and Ear employs full-time, board-certified physicians who offer high-quality and affordable specialty care that ranges from the routine to the very complex. *U.S. News & World Report’s* “Best Hospitals Survey” has consistently ranked the Mass. Eye and Ear Departments of Otolaryngology and Ophthalmology as among the top hospitals in the nation.

**About** [**Harvard Medical School**](http://www.hms.harvard.edu)
Harvard Medical School (hms.harvard.edu) has more than 7,500 full-time faculty working in 11 academic departments located at the School’s Boston campus or in one of 47 hospital-based clinical departments at 16 Harvard-affiliated teaching hospitals and research institutes. Those affiliates include Beth Israel Deaconess Medical Center, Brigham and Women’s Hospital, Cambridge Health Alliance, Boston Children’s Hospital, Dana-Farber Cancer Institute, Harvard Pilgrim Health Care, Hebrew Senior Life, Joslin Diabetes Center, Judge Baker Children’s Center, Massachusetts Eye and Ear Infirmary, Massachusetts General Hospital, McLean Hospital, Mount Auburn Hospital, Schepens Eye Research Institute, Spaulding Rehabilitation Hospital and VA Boston Healthcare System.

**About the** [**Champalimaud Foundation**](http://www.fchampalimaud.org/)

The Champalimaud Foundation, created in 2005 by the last will and testament of António de Sommer Champalimaud, focuses on cutting-edge research and strives to stimulate new discoveries and knowledge which can improve the health and well-being of people around the world. The Champalimaud Centre for the Unknown, based in Lisbon, Portugal, hosts the Foundation’s activities in the fields of Neuroscience and Oncology by means of research programmes and the provision of clinical care of excellence. The fight against blindness is also supported through a focused outreach programme. In seeking to achieve significant advances in biomedical science the Champalimaud Foundation has adopted a translational methodology, which establishes a direct link between research carried out in the laboratory and the diagnosis and treatment offered in the clinic. This connection and interdependency is at the core of the Foundation’s mission to bring the benefits of biomedical science to those most in need. More than anything, the Champalimaud Foundation works to improve the health and well-being of humanity by actively searching for solutions which can alleviate the burden of disease in individuals and in society as a whole. On October 5th 2010 the Champalimaud Foundation inaugurated an innovative research facility to contribute to its objective of developing biomedical research activities in Portugal.

**Vision Award:** The Champalimaud Vision Award is given in alternate years for contributions to overall vision research (even numbered years) and contributions to the alleviation of visual problems, primarily in developing countries (odd numbered years). The recipients of the award are productive laboratories/organizations or collaborative efforts and this may involve groups from more than one institution or discipline. The Award does not focus only on the largest global organizations but on organizations of any size that can demonstrate high impact achievements. These could be on a local, national, regional or international level. The jury of the award consists of a distinguished panel of leading international scientists and of exceptional public figures involved in meeting the needs of the developing world. The award may be used in any way that furthers the outstanding contribution of the recipients. The António Champalimaud Vision Award has the support of Vision 2020 – The Right To Sight, a global initiative for the prevention of blindness launched in association with the World Health Organization and the International Agency for the Prevention of Blindness.

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**Background**

**The Search for Factor X: Clues from Cancer Biology**

Angiogenesis is a normal developmental process, but in adults it is usually restricted to wound healing or to the female reproductive system. Outside of these physiological processes, angiogenesis is typically pathological, and occurs in many cancers and eye diseases.

In 1948, ophthalmologist I. C. Michaelson proposed that the eye secretes a growth factor that causes blood vessel growth and leakage in eye disease. However, this growth factor, coined “angiogenic factor” by Michaelson and later referred to as “Factor X” in ophthalmology, remained unidentified for nearly half a century.

Clues to the identity of Factor X came from the field of cancer research. Just as in eye disease, angiogenesis was known to occur in tumors, and in the late 1960s scientists hypothesized that tumors secrete substances that stimulate and attract new blood vessels. Judah Folkman, a medical scientist at Harvard Medical School and Boston Children’s Hospital, realized that angiogenesis could fuel the growth of tumors and facilitate the spread of cancer. In 1971, [Dr. Folkman published his seminal theory](http://www.ncbi.nlm.nih.gov/pubmed/4938153) that angiogenesis inhibitors could be used to treat cancer and other angiogenesis-dependent diseases such as diabetic retinopathy. Although initially met with skepticism, this theory formed the basis of the field of tumor angiogenesis, as well as the award-winning research of the 2014 Champalimaud Vision Award Laureates in ophthalmology.

In 1989, working at the biotechnology giant Genentech, Dr. Ferrara [isolated and characterized VEGF](http://www.ncbi.nlm.nih.gov/pubmed/2479986). The same molecule had been [isolated a few years earlier as “vascular permeability factor”](http://www.ncbi.nlm.nih.gov/pubmed/6823562) by Harvard Medical School’s Harold Dvorak and Donald Senger, who described its ability to make blood vessels leaky. However, Dr. Ferrara and colleagues additionally demonstrated VEGF’s potent angiogenic effects. VEGF quickly became a major research focus for anti-angiogenic cancer therapy.

Many angiogenic factors are produced by the body, and in the decades that followed Michaelson’s hypothesis, several candidates for Factor X were isolated. However, VEGF is unique among angiogenic factors because it not only stimulates blood vessel growth, but also causes vascular leakage, which is also a feature of various eye diseases (including neovascular AMD and diabetic retinopathy). Moreover, VEGF is stimulated by hypoxia (lack of oxygen), another condition known to induce angiogenesis in the retina. Thus, at Folkman’s suggestion, several researchers from Harvard Medical School explored VEGF as a potential Factor X in ocular disease.

**Mutually Synergistic Research Spanning Academia and Industry**

In the 1990s, the 2014 Champalimaud Award Laureates embarked on a series of scientific and clinical studies that were alternately collaborative and parallel—but always mutually interdependent and ultimately implicating VEGF in ocular disease.

Working with Dr. Folkman at Boston Children’s Hospital and Harvard Medical School, Drs. Adamis and D’Amore [showed that retinal cells produce VEGF](http://www.ncbi.nlm.nih.gov/pubmed/8512562), and together with Dr. Ferrara, [demonstrated its regulation by hypoxia](http://www.ncbi.nlm.nih.gov/pubmed/8529097). In a subsequent study, Dr. Aiello [demonstrated in retinal cells that hypoxia stimulates VEGF, which in turn stimulates the proliferation of endothelial cells](http://www.ncbi.nlm.nih.gov/pubmed/7487623) (the cell type that forms the lining of blood vessels).

Together with Dr. Miller of Mass. Eye and Ear, Drs. Adamis, D’Amore, and Folkman then [associated VEGF with ocular angiogenesis in an experimental model of laser-induced retinal ischemia and ocular neovascularization](http://www.ncbi.nlm.nih.gov/pubmed/7521577). This was the first study to link VEGF with angiogenesis in a living organism.

In 1994, Dr. Adamis, Miller, and Folkman (working at Mass. Eye and Ear) published the [first article describing increased VEGF in diabetic retinopathy](http://www.ncbi.nlm.nih.gov/pubmed/7943121). Shortly thereafter, Drs. Aiello, King, and Ferrara (in a larger study conducted between Joslin Diabetes Center and Genentech) [found increased levels of VEGF in patients with angiogenic retinal disorders, including proliferative diabetic retinopathy](http://www.ncbi.nlm.nih.gov/pubmed/7526212).

The following year, Drs. Aiello, Ferrara, and King [demonstrated that VEGF inhibition using soluble VEGF receptors could suppress oxygen-induced retinal neovascularization](http://www.ncbi.nlm.nih.gov/pubmed/7479819). Then, in 1996, Adamis, Gragoudas, Ferrara, Folkman, D’Amore, and Miller [demonstrated suppression of laser-induced ocular neovascularization with anti-VEGF antibody](http://www.ncbi.nlm.nih.gov/pubmed/8540853), which was the precursor to bevacizumab (Avastin®).

At Genentech, Dr. Ferrara and colleagues [performed experimental intraocular injections with full-length anti-VEGF antibodies and antibody fragments](http://www.ncbi.nlm.nih.gov/pubmed/10528633), and finding that the antibody fragments could rapidly penetrate the retina, they proceeded to test the anti-VEGF antibody fragment (Lucentis®) in patients with neovascular AMD.

At Mass. Eye and Ear, Drs. Adamis, Gragoudas, and Miller [tested Genentech’s anti-VEGF antibody fragment in a preclinical model](http://www.ncbi.nlm.nih.gov/pubmed/11879138) and showed that it safely prevented choroidal neovascularization—the type of blood vessel growth that occurs in wet AMD—and decreased the leakiness of existing choroidal neovascularization. This provided proof of principle to support the ongoing clinical trials of Lucentis®.

Drs. Gragoudas, Miller and Adamis also [examined the ocular delivery of anti-VEGF RNA aptamers](http://www.ncbi.nlm.nih.gov/pubmed/12506087) and [oversaw clinical trials of the aptamer pegaptanib (Macugen®) for neovascular AMD](http://www.ncbi.nlm.nih.gov/pubmed/15625332), which would form the basis of FDA approval of Macugen® as the first anti-VEGF ophthalmic drug in 2004.

Then, in 2006, Lucentis® [demonstrated remarkable results in phase III multicenter randomized controlled trial for neovascular AMD](http://www.ncbi.nlm.nih.gov/pubmed/17021318), leading to its regulatory approval for the treatment of neovascular AMD.

ADDITIONAL LINKS

**National Eye Institute: Eye Health Information** <http://www.nei.nih.gov/health/>

**Nature Focus: Angiogenesis** <http://www.nature.com/focus/angiogenesis>

**NOVA ScienceNow Profile: Judah Folkman** <http://www.pbs.org/wgbh/nova/body/judah-folkman.html>

**World Health Organization: Priority Eye Diseases** <http://www.who.int/blindness/causes/priority/en/index1.html>

**About the 2014 Champalimaud Laureates**

Besides co-discovering the role of VEGF in eye disease, the 2014 Champalimaud Laureates have made additional noteworthy biomedical contributions and currently oversee active research groups.

Concurrent with his collaborations with the 2014 Champalimaud Laureates, **Dr. Ferrara** developed monoclonal antibodies that suppressed the growth of a variety of cancers by preventing the growth of new blood vessels into solid tumors. These findings led to development of the anti-angiogenesis drug bevacizumab (Avastin®), which has become standard therapy for a variety of cancers. Dr. Ferrara has won many awards for his achievements, including the 2010 [Lasker-DeBakey Clinical Medical Research Award](http://www.laskerfoundation.org/awards/), which frequently precedes the Nobel Prize.

Dr. Adamis co-founded Eyetech Pharmaceuticals in 2000, where he helped lead the development of pegaptanib (Macugen®) as the first anti-VEGF drug in ophthalmology. While at Eyetech, he also initiated the development of the first anti-PDGF-B drug in ophthalmology, a therapy that is used in conjunction with anti-VEGF therapy to further improve vision. The drug combination is currently in Phase III trials. After moving to Genentech/Roche, Dr. Adamis helped lead the team that obtained FDA approval for ranibizumab (Lucentis®) for diabetic macular edema and retinal vein occlusion.

Besides identifying VEGF’s role in eye disease, the **Dr. Gragoudas** and **Dr. Miller** are also credited with the development of photodynamic therapy with verteporfin (Visudyne®) from [preclinical studies](http://www.ncbi.nlm.nih.gov/pubmed/7540388) to [clinical trials](http://www.ncbi.nlm.nih.gov/pubmed?term=Verteporfin%20In%20Photodynamic%20Therapy%20Study%20Group%5BCorporate%20Author%5D) to agency approval for the treatment of neovascular AMD. A light-activated drug, Visudyne® destroys abnormal blood vessels under the retina and stops their leakage. As the first AMD treatment approved by the FDA (in 2000) and international drug regulatory agencies, Visudyne® opened the pharmacologic era of retinal disease therapy and was a first-line treatment for wet AMD before the advent of anti-VEGF therapy.

Dr. Gragoudas additionally [pioneered the development of proton beam therapy for uveal melanoma](http://www.ncbi.nlm.nih.gov/pubmed/17065472), a potentially lethal cancer of the eye. He is Charles Edward Whitten Professor of Ophthalmology at Harvard Medical School and Director of the Retina Service at Mass. Eye and Ear.

Dr. Miller currently serves as Chair and Henry Willard Williams Professor of Ophthalmology at Harvard Medical School, and Chief of Ophthalmology at Mass. Eye and Ear and Massachusetts General Hospital. Dr. Gragoudas is the Charles Edward Whitten Professor of Ophthalmology at Harvard Medical School and Director of the Retina Service at Mass. Eye and Ear. They co-direct the Angiogenesis Laboratory at Mass. Eye and Ear and have both received numerous awards, including the [Mildred Weisenfeld Award for Excellence in Ophthalmology](http://www.arvo.org/awards/#weisenfeld), one of the highest individual distinctions awarded by the [Association for Research in Vision and Ophthalmology (ARVO)](http://www.arvo.org/).

Dr. D’Amore is noted for her scientific contributions to the understanding of VEGF biology and angiogenesis. She [isolated and characterized the murine VEGF gene](http://www.ncbi.nlm.nih.gov/pubmed/8632007) and [developed a widely used model of oxygen-induced retinopathy](http://www.ncbi.nlm.nih.gov/pubmed/7507904). Both systems have served as the cornerstone of numerous scientific studies and preclinical studies of therapies targeting angiogenesis, and the report describing the oxygen-induced retinopathy model is the [most-cited article ever](http://www.iovs.org/reports/most-cited) in the journal [*Investigative Ophthalmology and Visual Science*](http://www.iovs.org/)*.* She is Professor of Pathology and Charles L. Schepens Professor of Ophthalmology at Harvard Medical School, and serves as Director of the Howe Laboratory at Mass. Eye and Ear and Director of Research at Schepens Eye Research Institute of Mass. Eye and Ear.

Dr. Aiello and Dr. King have made significant progress toward understanding, manipulating and inhibiting the expression, regulation, and signaling functions of VEGF and its receptors. In 1989 Dr. King proposed that activation of protein kinase C (PKC) is the major mechanism by which hyperglycemia disrupts the retina, kidney, and cardiovascular systems in diabetes. Drs. Aiello and King subsequently published the first evidence that PKC is involved in vascular leakage in diabetic retinopathy in part mediating the VEGF pathway. They went on to develop and evaluate an orally administered PKC-beta inhibitor for diabetic macular edema —thus opening a new therapeutic avenue for diabetic and other retinopathies.

Dr. Aiello helped found and then served as the inaugural chair of the Diabetic Retinopathy Clinical Research Network (DRCR.net), a national collaborative network funded by the National Eye Institute. The DRCR.net performed the first large randomized controlled clinical trial proving the benefit of VEGF inhibition for the treatment of diabetic macular edema. Dr. Aiello is Professor of Ophthalmology at Harvard Medical School, and at Joslin Diabetes Center, he serves as Vice President of Ophthalmology, Head of the Section on Eye Research, and Director of the Beetham Eye Institute.

Dr. King is Professor of Medicine at Harvard Medical School and at Joslin Diabetes Center he is Director of Research and Head of the Section on Vascular Cell Biology. He leads the Medalist Study, a comprehensive study to identify protective factors in a large group of type 1 diabetic patients with diabetes duration over 50 years. His numerous honors include the [Cogan Award](http://www.arvo.org/awards/#cogan), one of the highest individual distinctions awarded by [ARVO](http://www.arvo.org/).