BIOGRAPHICAL SKETCH

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NAME: Ferrington, Deborah Ann

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POSITION TITLE: Chief Scientific Officer, Stephen J. Ryan- Arnold and Mabel Beckman Foundation Endowed Presidential Chair, Doheny Eye Institute; Professor in Residence, David Geffen School of Medicine at UCLA

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Pittsburgh, PA	B.S.	08/1978	Biological Science/ Scientific Illustration
University of Pittsburgh, PA	M.Ed.	05/1980	Secondary Science Ed
University of Kansas, KS	Ph.D.	05/1997	Biochemistry
University of Kansas, KS	Post-Doc	08/1999	Biochemistry

A. Personal Statement

Research in my laboratory is focused on identifying the molecular changes that occur in the retina with age-related macular degeneration (AMD). My research team has been investigating critical questions driving the field of age-related disease. *What are the cellular changes that occur with aging? What factors "tip the balance" to pathology? How does the cell respond to disease? How can we protect against pathologic changes?*

Since starting my independent position more than 20 years ago, my laboratory has gained considerable expertise in biochemical analysis of tissues and cells, molecular biology, cell biology, and more recently, stem cell biology. Our early investigations of AMD disease mechanism using human eyebank tissue from donors graded for the presence and severity of AMD identified mitochondrial defects as a potential mechanism in AMD pathology. In support of our initial findings, we also showed increased mitochondrial damage in the retinal pigment epithelium (RPE) from a subset of AMD donors harboring the AMD risk SNP for complement factor H (CFH) [A]. In subsequent studies, we initiated research using induced pluripotent stem cell (iPSC)-RPE for use in studying AMD disease mechanism [B] and for large scale [C] and patient-specific drug screening [D]. Of relevance to this proposal, we reported mitochondrial function of iPSC-RPE harboring the CFH high-risk single-nucleotide polymorphisms (SNP) was significantly lower than cells from CFH low risk donors [D]. This discovery supports the use of iPSC-RPE to understand how specific SNPs associated with high risk for advanced AMD influences multiple biological processes in the RPE.

The U01 grant supports research in the Ferrington laboratory as part of a larger consortium of five laboratories, collectively referred to as the "Age-related Macular Degeneration (AMD) Integrative Biology Initiative". The **goal** of the consortium is to determine if patient-derived iPSC-RPE can be used to discover the underlying pathophysiology of AMD. Our studies focus on two SNPs with the highest odds ratio for developing advanced AMD- Age-Related Maculopathy Susceptibility 2/High Temperature Requirement A1 (ARMS2/HTRA1) and CFH. We use the iPSC developed by the NEI and the New York Stem Cell Foundation to differentiate the parent cells and their reciprocal isogenic lines into RPE using the protocol established in the Bharti laboratory. We will **test the hypothesis** that the presence of homozygous risk alleles for either ARMS2/HTRA1 or CFH, independent and in combination, have a negative impact on the RPE stress response. Furthermore, each genetic risk profile will have a unique stress response. Our investigations will include a multidisciplinary team with complementary expertise in iPSC-RPE culturing and experimentation (Ferrington), global protein analysis using label-free mass spectrometry (Dr. Jun Qu, SUNY Buffalo), and targeted metabolomics (Dr. Jianhai Du, West Virginia University). ***Funds from the Reeves Foundation are being requested to purchase equipment needed to process our cell samples for mass spectrometry analysis.***

This analysis will provide new information about the proteins that are altered in the cells with different genetic backgrounds.

- **A.** **Ferrington DA**, Kapphahn RJ, Leary MM, Atilano SR, Terluk MR, Karunadharma P, Chen GK, Ratnapriya R, Swaroop A, Montezuma SR, Kenney MC. Increased retinal mtDNA damage in the CFH variant associated with age-related macular degeneration. *Exp Eye Res* 2016; 145: 269-277.
- **B.** Ebeling MC, Geng Z, Kapphahn RJ, Roehrich H, Montezuma SR, Dutton JR, **Ferrington DA**. Impaired mitochondrial function in iPSC-Retinal pigment epithelium with the Complement Factor H polymorphism for Age-Related Macular Degeneration. *Cells* 2021; 10, 789. Doi.org/10.3390/cells10040789.
- **C.** Truong V, Viken K, Geng Z, Barkan S, Johnson B, Ebeling MC, Montezuma SR, **Ferrington DA**, Dutton JR. Automating induced pluripotent stem cell culture and differentiation of iPSC-derived retinal pigment epithelium for personalized drug testing. *SLAS Technol*. 2020 Dec 9:2472630320972110. doi: 10.1177/2472630320972110.
- **D.** Ebeling MC, Geng Z, Stahl MR, et al. Testing Mitochondrial-Targeted Drugs in iPSC-RPE from 490 Patients with Age-Related Macular Degeneration. Pharmaceuticals. 2022;15(1):62. 491 doi:10.3390/ph15010062

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2022-present	Chief Scientific Officer, Doheny Eye Institute
2022-present	Professor, Department of Ophthalmology, David Geffen School of Medicine, UCLA
2017-2022	Director of Research, Department of Ophthalmology and Visual Neurosciences, U Minnesota
2017-2022	Faculty, Stem Cell Institute, University of Minnesota
2015-2022	Professor, Department of Ophthalmology and Visual Neurosciences, U Minnesota
2007-2015	Associate Professor, Department of Ophthalmology and Visual Neurosciences, U Minnesota
1999-2022	Graduate Faculty, Biochemistry, Molecular Biology, & Biophysics Program, U of Minnesota
1999-2006	Assistant Professor, Department of Ophthalmology, University of Minnesota
1997-1999	Postdoctoral Fellow-American Heart Association, Depart. Biochemistry, University of Kansas
1992-1997	Graduate Research/Teaching Assistant, Department of Biochemistry, University of Kansas
1990-1992	Assistant Director, Exercise Physiology Laboratory, University of Kansas
1990-1992	Research/Teaching Assistant, Department of Health, Physical Education & Recreation/ Department of Human Development & Family Life, University of Kansas

Honors

2022	Stephen J. Ryan- Arnold and Mabel Beckman Foundation Endowed Presidential Chair
2022	Professor Emeritus, University of Minnesota
2019	Awarded the Distinguished McKnight University Professorship
2017-2023	Permanent Member, NIH “Biology and development of the eye” Study Section
2017	Borish Distinguished Research Scholar Award, Indiana University- Optometry
	Keynote Speaker, George Kambara Vision Science Symposium, Madison, WI
	Speaker, Distinguished Lectures in Vision Science, U Buffalo, NY
2016	Executive Board Member, Beckman/Ryan Initiative for Macular Research
2015	Visiting Scientist, University of Pierre and Marie Currie, Paris, France
	Chair, Gordon Research Conference Oxidative Stress and Disease, Ventura CA.
	Speaker, Rich Endowed Lecture Series, University of Alabama School of Medicine
2013	Awarded Elaine and Robert Larson Endowed Vision Research Chair
	Speaker, Distinguished Lecture Series, Cole Eye Institute, Cleveland, OH
	Vice Chair Gordon Research Conference Oxidative Stress and Disease, Switzerland
2011	Athlete of Distinction, University of Pittsburgh Varsity Letter Club
2010	Keynote Speaker, Midwest Eye Research Symposium, Iowa City, IA
2003-2004	Fesler-Lampert Chair in Aging Research, Center on Aging, University of Minnesota
2001	Career Development Award, Foundation Fighting Blindness and American Federation for Aging Research
2000	Ellison foundation Grant Candidate, University of Minnesota

Brookdale National Fellowship Candidate, University of Minnesota
1997 Newmark Award for Biochemical Research, University of Kansas
Llewellyn Borgendale JR, Graduate Seminar Award in Biochemistry, University of Kansas
1994 Glenn/AFAR Scholarship-Research in the Biology of Aging, Am. Federation for Aging Research
1993 Ida H. Hyde Scholarship, Division of Biological Sciences, University of Kansas
1981 University Scholar, University of Pittsburgh

C. Contributions to Science

1) *Defining the Molecular Mechanisms of Age-related Macular Degeneration*: My laboratory has been investigating the molecular changes that occur with retinal aging and age-related macular degeneration (AMD), with a major emphasis on understanding how retinal cells respond to stress. Because the anatomical structure of the retina is unique to primates, there are currently no small animal models that can faithfully replicate the retinal conditions associated with AMD. Therefore, the approach for my laboratory has been to use human donor tissue graded for the stage of AMD to study the disease (1). Our experimental approach to investigate AMD pathogenesis has been to study changes in protein expression and in mitochondrial (mt) DNA damage in human donor eyes at progressive stages of AMD using a combination of proteomic and molecular biology techniques. Results from multiple proteomic analysis led to our groundbreaking observation that the mitochondria in the retinal pigment epithelium (RPE) are significantly impacted by the disease (2). To verify that mitochondria are damaged with AMD, a separate study was performed that showed donors with AMD had significantly more mtDNA damage than age-matched controls (3). For my laboraory, this paper was a turning point in that it validated the mitochondria as a molecular target for therapy. Since that time, we have gone from pure discovery-based science asking "What factors tip the balance to pathology?" to developing model systems for testing drugs that can enhance mitochondrial function to answer the question "How can we protect against these pathologic changes?" Our work in AMD is now focused on identifying and testing drugs that counter redox stress and facilitate energy generation in the mitochondria using cultured human RPE cells and murine models of retinal degeneration. Translating this information to the clinic raised the question "Is mtDNA damage limited to the RPE?" To address this question, we compared the extent of mtDNA damage in both the RPE and retina of individual donors and found that the damage was limited to the RPE (4). These results provide a scientific basis for targeting the RPE with therapies that protect mitochondrial function.

1. Decanini AM, Nordgaard CL, Feng X, **Ferrington DA**, Olsen TW, Changes in Select Redox Proteins of the Retinal Pigment Epithelium in Age-Related Macular Degeneration. *Am. J. Ophthalmol,* 2007; 143(4): 607-15. PMCID: PMC2365890
2. Nordgaard CL, Karunadharma PP, Feng X, Olsen TW, **Ferrington DA**, Mitochondrial Proteomics of the Retinal Pigment Epithelium at Progressive Stages of Age-Related Macular Degeneration. *Invest. Ophthalmol. Vis. Sci.* 2008, 49: 2848-55. PMID: 18344451.
3. Karunadharma PP, Nordgaard CL, Olsen TW, **Ferrington DA**, Mitochondrial DNA damage as a potential mechanism fo age-related macular degeneration. *Invest Ophthalmol Vis Sci* 2010; 51: 5470-79. PMCID: PMC3061495.
4. Terluk MR, Kapphahn RJ, Soukup LM, Gong H, Gallardo C, Montezuma SR, **Ferrington DA**, Investigating Mitochondrial as a Target for Treating Age-Related Macular Degeneration. *J Neuroscience* 2015; 35: 7304-11. PMID 25948278

2) Developing effective treatments for patients with dry Age-related Macular Degeneration. One of the major challenges for developing AMD treatments is having a valid model system that can be used (i) to identify the most efficacious targets for intervention and (ii) for testing drugs. To overcome this challenge, we have established two cell culture systems: primary cultures from human donor RPE and induced pluripotent stem cells (iPSC)-derived RPE. Our initial investigations show that primary RPE from donors with AMD exhibit altered bioenergetics and increased resistance to oxidative stress compared with primary RPE from non-diseased donors, suggesting the primary cultures recapitulate important aspects of the AMD disease phenotype (5). The iPSC-RPE displayed a phenotype and gene expression profile that closely matches RPE in vivo. These RPE will provide an inexhaustible source of cells for experiments (6). We are using these primary cultures and iPSC-derived RPE to investigate AMD disease mechanisms and for testing drugs that protect or enhance RPE mt function (7,8).

5. **Ferrington DA**, Ebeling MC, Kapphahn RJ, Terluk MR, Fisher CR, Polanco JR, Roehrich H, Leary MM, Geng Z, Dutton JR, Montezuma SR, Altered bioenergetics and enhanced resistance to oxidative stress in human retinal pigment epithelial cells from donors with age-related macular degeneration. *Redox Biology* 2017; 13: 255-265.
6. Geng Z, Walsh PJ, Truong V, Hill C, Ebeling M, Kapphahn RJ, Montezuma SR, Yuan C, Roehrich H, **Ferrington DA**, Dutton JR, Generation of retinal pigmented epithelium from iPSCs derived from the conjunctiva of donors with and without age-related macular degeneration. *PLOS One* 2017; DOI: 10.1371
7. Ebeling MC, Polanco JR, Qu J, Tu C, Montezuma SR, **Ferrington DA.** Improving retinal mitochondrial function as a treatment for age-related macular degeneration. *Redox Biol*. 2020 Jul;34:101552. doi: 10.1016/j.redox.2020.101552.
8. Terluk MR, Ebeling MC, Fisher CR, Kapphahn RJ, Yuan C, Kartha RV, Montezuma SR, **Ferrington DA.** N-Acetyl-L-Cysteine protects human retinal pigment epithelial cells from oxidative damage: Implications for age-related macular degeneration. *Oxid Med Cell Longev*. 2019 Aug 14;2019:5174957. doi: 10.1155/2019/5174957

3) *Mechanistic investigations in AMD pathology*.
I collaborate with multiple research groups both within and outside of my institute to investigate the mechanistic basis for AMD pathogenesis and progression. In addition to my intellectual contribution in developing the question and approach, I provide research tissue from human donor eye that have been graded for the presence and severity of AMD using the Minnesota Grading System for evaluating Eye Bank eyes. This collaborative work has helped advance the field by testing multiple hypotheses about specific pathways or mechanisms [9,10] and using investigative tools (Mass Spectrometry to determine mtDNA damage [11,] RNA seq to identify novel genes linked to AMD [12]) that are complementary to the Ferrington laboratory.

9. Ghosh S, Shang P, Yazdankhah M, Bhutto I, Hose S, Montezuma SR, Luo T, Chattopadhyay S, Qian J, Lutty GA, **Ferrington DA**, Zigler JS, Sinha D. Activating the AKT2-nuclear factor –kB-lipocalin axis elicits an inflammatory response in age-related macular degeneration. *J. Pathology*. 2017 Apr; 241(5):583-588. Doi.10.1002/path.4870.
10. Ratnapriya R, Sosina K, Starostik MR, Kwicklis M, Kapphahn RJ, Fritsche LG,Walton A, Arvanitis M, Gieser L, Pietraszkiewicz A, Montezuma SR, Chew EY, Battle A, Abecasis GR, **Ferrington DA**, Chatterjee N, Swaroop A. Genetic variants regulating retinal transcriptome (GREx) identify genes underlying age-related macular degeneration. *Nature Genetics*. 2019, Apr; 51(4):606-610. Doi: 10.1038/s41588-091-0351.
11. Schultz H, Song Y, Baumann BH, Kapphahn RJ, Montezuma SR, **Ferrington DA**, Dunaief JL. Increased serum proteins in non-exudative AMD retinas. *Exp Eye Res.* 2019. Sep; 186: 107686. Doi. 10.1016/j.exer.2019.05.026.
12. Ma B, Jing M, Villalta PW, Kapphahn RJ**,** Montezuma SR, **Ferrington DA**, Stepanov I. Simultaneous determination of 8-oxo-2'-deoxyguanosine in human retinal DNA by liquid chromatography nanoelectrospray-tandem mass spectrometry. *Science Report.* 2016 Mar 16; 6:22375. Doi: 10.1038/srep22375.

Complete List of Published work
http://www.ncbi.nlm.nih.gov/sites/myncbi/deborah.ferrington.1/bibliography/41145105/public/?sort=date&direction=descending