BIOGRAPHICAL SKETCH

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NAME: Melinda K. Duncan, Ph.D. FARVO

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

POSITION TITLE: Associate Vice President for Research, Professor of Biological Sciences

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
Lafayette College, Easton, Pennsylvania	BS	5/1987	Chemistry
Rutgers/UMDNJ, Piscataway, New Jersey	Ph.D	5/1992	Biochemistry
National Eye Institute, Bethesda, Maryland	Postdoc	9/1997	Eye development

A. Personal Statement

For the past 35 years, my research has addressed how developmental mechanisms contribute to human disease using animal models to test disease pathogenesis and therapies. These studies have used a diverse set of approaches including transgenic and knockout mice, *ex vivo* and *in vitro* culture models, human cells and tissues, molecular biology techniques, the analysis of cell signaling cascades, molecular modeling, advanced confocal imaging and next generation genomics/informatics.

I established my independent research laboratory in 1997 after training with Joram Piatigorsky on the study of lens development and cataract pathogenesis. I have published over 100 papers and reviews since the beginning of my career, the majority using animal models to elucidate ocular disease pathophysiology. This work has led to fundamental discoveries relevant to the regulation of lens fiber cell differentiation, the pathophysiology of aniridic cataract, the role of the unfolded protein response in cataractogenesis, and the function of the lens capsule. My group's most recent work has focused on studying the molecular mechanisms underlying the major negative sequela of cataract surgery, posterior capsular opacification (PCO). We have developed a robust mouse model for the acute response of lens epithelial cells (LECs) to lens fiber cell removal which has allowed us to use mouse genetic models to study the pathways driving LEC conversion to myofibroblasts following lens injury. This work has led to the discovery of a novel approach to prevent fibrotic PCO and two related patent disclosures for anti-PCO therapeutics which have the potential to improve visual outcomes following cataract surgery, especially in children and those with eye diseases, such as aniridia, which have robust fibrotic research.

Over the past decade, my laboratory has expanded our work to include the use of RNAseq as an unbiased approach to elucidate global disease mechanisms in the lens. The resulting ten publications have led to new insights into lens development, aging and the response of LECs to injury. Notably, we discovered, for the first time, that lens epithelial cells rapidly and robustly contribute to ocular inflammation both following cataract surgery and ocular injury, Thus, I have the expertise in lens pathophysiology, ocular wound healing, and bioinformatics needed to complete the proposed experiments which seek to characterize the gene regulatory network responsible for posterior capsular opacification.

Ongoing and Recent Research Support

RO1 EY015279-18
Duncan (PI)
4/1/14-4/30/26
The Influence of Capsule Composition on Lens Biology

RO1 EY028597-01A1
Duncan (PI)
9/1/18-8/31/23 (in no cost extension)
The mechanisms underlying posterior capsular opacification

Aniridia Foundation International
Duncan (PI)
7/1/20-6/30/22
Runx1 in Aniridia Fibrosis Syndrome

P20 GM103446
Duncan (PI as of 2/1/22)
5/1/14-4/30/24
Delaware INBRE

B. Positions, Scientific Appointments, and Honors

Positions and Employment

2022-present	Associate Vice President for Research, University of Delaware
2018-2022	Associate Director, Center for Biomedical Research Excellence in Molecular Probes and Therapeutic leads, University of Delaware
2017-2022	Director, Education and Professional Development, Delaware INBRE
2015-2020	Guest Professor (unpaid), Xiangya Hospital, Central South University, Changsha, China
2014-2022	Member, Professional Development Committee, DE-MUSC CTR
2012-present	Joint Professor, Department of Chemistry and Biochemistry, University of Delaware, Newark, DE
2008-present	Professor, Department of Biological Sciences, University of Delaware, Newark, DE
2005-2016	Graduate Program Director, Department of Biological Sciences, University of Delaware
2002-2008	Associate Professor, Department of Biological Sciences, University of Delaware, Newark, DE
2000-2005	Track Coordinator, Graduate Program in Molecular Biology and Genetics, U. Delaware
1999-present	Joint Assistant/Associate/Full Professor, Department of Animal and Food Science, U. Delaware
1997-2002	Assistant Professor, Department of Biological Sciences, University of Delaware, Newark, DE
1993-1997	Postdoctoral Fellow, Laboratory of Joram Piatigorsky, Ph.D., LMDB, National Eye Institute
1989-1993	Graduate Assistant and Postdoctoral Fellow, Laboratory of Kiran K. Chada, D. Phil. (OXON), University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School

Other Experience and Professional Memberships

2020-present	Chair, Advisory Committee for NIH S10 for Dragonfly and scanning electron microscopes
2020-2021	Vice President, Association for Research in Vision and Ophthalmology
2019	NIH study section evaluating INBRE program grants
2017-2022	Member, University of Delaware Undergraduate Research Council
2016-2021	Trustee (lens), Association for Research in Vision and Ophthalmology
2015-2020	Guest Professor, Xiangya Hospital, South Central University, Changsha, China
2015-2018	Associate Editor, *Investigative Ophthalmology and Visual Sciences*
2014-present	Chair, Advisory Committee for NIH S10, LSM880 confocal microscope, UD
2012, 2013	Two terms of service as Chair of the NEI K99/R00 grant review panel
2011-present	Editorial Board Member, *Molecular Vision*
2010-present	Member of 25 different NIH “Special Emphasis” study sections
2010, 2011	Member S10 Bio-imaging grant review panel, National Center for Research Resources
2009-present	Advisory Committee, Graduate education initiatives, Center for Bioinformatics and Computational Biology, University of Delaware
2008-2017	Ad Hoc member, Fight for Sight grant review panel
2007-present	Editorial Board Member, *Investigative Ophthalmology and Visual Sciences*
2007, 2022	Ad hoc member, Board of Scientific Counselors, National Eye Institute
2006-2010	Permanent member, Anterior Eye Disease panel, Center for Scientific review, NIH.
2005-2007	Permanent member, Fight for Sight grant review panel
2004, 2005	National Science Foundation Graduate Fellowship eligibility review board

2001, 2003 National Science Foundation Graduate Fellowship review board
2000-2006 Center for Scientific Review, 7 rounds *ad hoc* member, VisA and AED panels

Honors

2021 Association for Research in Vision and Ophthalmology Distinguished Service Award
2019 University of Delaware College of Arts and Sciences Excellence in Research Award
2016 Seema S. Sonnad Mentor of the Year Award, IDeA Delaware
2015/18 Fellow (Silver/Gold) of the Association for Research in Vision and Ophthalmology
2015 Elected to the Honor Society of Phi Kappa Phi
2001 Francis P. Allison Young Scholar Award (Currently called Gerald J. Mangone Young Scholars Award) given to the most promising assistant professor at UD for excellence in research and publications
1997 NIH Fellows Award for Research Excellence (FARE)

C. Contributions to Science

Pathogenesis of aniridic eye disease

Pax-6 is a transcription factor best known as a master regulator of eye development. Humans harboring heterozygous Pax6 mutations exhibit a pan-ocular disorder characterized by aniridia, foveal hypoplasia, glaucoma, corneal keratopathy and cataract. Over the past 25 years, I have studied diverse aspects of Pax6 function in the eye. This work has resulted in several publications which demonstrate that Pax6 functions as transcriptional repressor which negatively regulates lens fiber cell differentiation in addition to its better known roles as an activator of ocular cell fates. Current studies, that were initiated at the request of Aniridia Foundation International, a patient advocacy group for those with Aniridia, address the mechanisms underlying aniridia fibrosis syndrome (AFS), a catastrophic pan-ocular fibrotic condition that can lead to blindness in aniridia patients, as well as aniridic cataract and corneal keratopathy. These studies are directly addressing the mechanisms driving the age-related visual decline in patients with aniridia in order to identify potential therapeutics

Melinda K. Duncan, John I. Haynes II, Ales Cvekl and Joram Piatigorsky (1998) Dual roles for Pax-6: a transcriptional repressor of lens fiber cell specific β-crystallin genes. *Molecular and Cellular Biology.* **18,** 5579-5586.

Wenwu Cui, Stanislav I. Tomarev, Joram Piatigorsky, Ana B. Chepelinsky and **Melinda K. Duncan** (2004) Mafs, Prox1 and Pax6 cooperate to direct βB1-crystallin gene expression. *Journal of Biological Chemistry.* **279,** 11088-11095.

Anna Voskresenskaya, Nadezhda Pozdeyeva, Yevgeniy Batkov, Tatyana Vasilyeva, Andrey Marakhonov, Richard A. West, Jeffrey L. Caplan, Ales Cvekl, Yan Wang and **Melinda K. Duncan** (2021) Morphometric analysis of the lens in human aniridia and mouse *Small eye Experimental Eye Research* 203:108371.

Alejandra Daruich, **Melinda K. Duncan**, Matthieu P. Robert, Neil Lagali, Elena V. Semina, Daniel Aberdam, Stefano Ferrari, Vito Romano, Cyril Burin des Roziers, Rabia Benkortebi, Nathalie De Vergnes, Michel Polak, Frederic Chiambaretta, Ken K. Nischal, Francine Behar-Cohen, Sophie Valleix, Dominique Bremond-Gignac (2022) Congenital aniridia beyond black eyes: from phenotype and novel genetic mechanisms to innovative therapeutic approaches *Progress in Retinal and Eye Research* in press.

Discovery of mechanisms responsible for Posterior Capsular Opacification (PCO)

Cataracts are historically the most common cause of visual disability but are now treated by extracapsular lens extraction where the central anterior lens capsule and lens fibers are removed, followed by implantation of an artificial intraocular lens. While this is very effective, significant numbers of patients develop PCO, due to proliferation and migration of remaining lens epithelial cells (LECs) to the posterior capsule and their differentiation/transdifferentiation into either aberrant lens fiber cells or myofibroblasts. My laboratory has discovered several important features of this wound healing response. Using a mouse model of wound healing after cataract surgery, we have found that immediate early gene expression upregulates directly after surgery and this expression is likely necessary for lens driven post-surgical inflammation and the initial fibrotic response (ongoing studies). This is followed by the upregulation of the hyaluronic acid binding protein, CD44, just prior to the conversion of LECs to a fibrotic phenotype. The upregulation of αV-integrins is required for the

onset of the fibrotic phenotype, likely due to the ability of αVβ8-integrin to activate latent TGFβ. Ongoing studies seek to elucidate the gene regulatory network underlying PCO and and have recently found that new small molecular therapeutics can prevent LEC fibrosis following lens injury.

Samuel G. Novo, Adam P. Faranda, Mahbubul H. Shihan, Yan Wang, Ananya Garg, and **Melinda K. Duncan** (2022) The immediate early response of lens epithelial cells to lens injury *Cells* 11(21):3456. doi: 10.3390/cells11213456

Jian Jiang, Mahbubul Shihan, Yan Wang and **Melinda K. Duncan** (2018) Lens epithelial cells initiate the inflammatory response following cataract surgery. *Investigative Ophthalmology and Visual Sciences.* ***Denoted a "hot topic" in ophthalmology at the 2018 ARVO meeting*** **59,** 4986-4997

Mahbubul H. Shihan, Mallika Pathania, Yan Wang, Erin E. Jackson, Adam B. Pater-Faranda, and **Melinda K. Duncan** (2020) Fibronectin has multifunctional roles in posterior capsular opacification (PCO) *Matrix biology* **90,** 79-108

Mahbubul H. Shihan, Yan Wang, Dean Sheppard, Amha Atakili, Thomas D. Arnold, Nicole M. Rossi, Adam P. Faranda, and Melinda K. Duncan (2021) αVβ8 integrin- a potential druggable target to prevent posterior capsular opacification (PCO) *Journal of Clinical Investigation Insight* 8;6(21). doi: 10.1172/jci.insight.145715

Understanding the molecular mechanisms of underlying lens development:
The transition of head ectoderm into the ocular lens has long been a classical model to study tissue induction and cellular differentiation, while defects in this process result in a wide variety of ocular disorders ranging in severity from anophthalmia to cataracts. Over the past 25 years, I have investigated numerous aspects of this process, with an emphasis on the mechanisms controlling the lens epithelial to fiber cell transition. As a postdoctoral fellow, I was involved in the initial discovery that Prox1 is a highly evolutionarily conserved protein expressed in the ocular lens and my research group later described its high level expression in lens fibers. My group later discovered that Prox1 can directly bind to the lens fiber cell preferred βB1-crystallin promoter, regulating its expression. We also created mice that lack Prox1 specifically in the lens, and found that that in addition to crystallins, Prox1 also regulates the expression of three different fibroblast growth factor receptors, setting up a feed-forward loop between FGF signaling and Prox1 function which drives lens fiber cell differentiation. We have also described a novel function for the ZEB family transcription factor, Sip1, in the lens, and found that this factor drives the loss of head ectoderm specific gene expression as the lens differentiates. Most recently, we have expanded our work on lens development to include aging, leading to a new understanding of how aging and sex affect lens biology at the transcriptional level.

Abby L. Manthey, Salil A. Lachke, Paul G. FitzGerald, Robert W. Mason, David A. Scheiblin, John H. McDonald, and **Melinda K. Duncan** (2014) Loss of Sip1 leads to migration defects and retention of ectodermal markers during lens development *Mechanisms of Development,* **131,** 86-110.

Dylan S. Audette, Deepti Anand, Tammy So, Troy B. Rubenstein, Salil A. Lachke, Frank J. Lovicu and **Melinda K. Duncan** (2016) Prox1 and fibroblast growth factor receptors form a novel regulatory loop controlling lens fiber differentiation and gene expression *Development* **143,** 318-328.

Adam P. Faranda, Mahbubul H. Shihan, Yan Wang, and **Melinda K. Duncan** (2021) The aging mouse lens transcriptome *Experimental eye research.* 209:108663 doi: 10.1016/j.exer.2021.108663

Adam P. Faranda, Mahbubul H. Shihan, Yan Wang, and **Melinda K. Duncan** (2021) The effect of sex on the mouse lens transcriptome *Experimental eye research.* 209:108676. doi: 10.1016/j.exer.2021.108676

Endoplasmic reticulum stress (unfolded protein response, UPR) as a mechanism underlying cataract
While many extracellular matrix disorders have associated cataracts, the mechanisms underlying this observation were not known. We discovered that overexpression of unfoldable collagen IV chains in the lens results in cataract development associated with translational attenuation of lens differentiation markers and a great expansion of endoplasmic reticulum in lens fibers. My laboratory discovered that phenomena was due to a massive induction of the endoplasmic reticulum stress response pathway (UPR) which greatly

reprogrammed lens cell biology. Since that initial discovery, we found that UPR is activated as part of normal lens differentiation in embryos, while it is also a feature of cataracts arising from mutation of collagen IV, connexin 50, and other cellular stresses. Our initial finding has been followed up by numerous other laboratories who have found the ER stress response to be induced in a diverse array of other cataract models where it is likely to contribute to cataract, especially in patients harboring mutations in genes encoding proteins which must transit the ER during their synthesis..

Zeynep Firtina, Brian P. Danysh, Xiaoyang Bai, Douglas B. Gould, Takehiro Kobayashi, and **Melinda K. Duncan** (2009) Abnormal expression of collagen IV in lens activates the unfolded protein response resulting in cataract. *Journal of Biological Chemistry* **284,** 35872-35884

Zeynep Firtina and **Melinda K. Duncan** (2011) Unfolded Protein Response (UPR) is activated during normal lens development *Mechanisms of Development- Gene Expression Patterns* **11,** 135-143

Lei Lyu, Shuhong Jiang, Min-Lee Chang, Yumei Gu, **Melinda K. Duncan**, Ales Cvekl, Wei-Lin Wang, Saima Limi, Lixing W. Reneker, Linfang Du, Fu Shang, Elizabeth A. Whitcomb, Allen Taylor (2016) p27 stabilization due to an unfolded protein response interferes with lens fiber denucleation and causes cataract *Faseb Journal* **30,** 1087-1095.

Elucidation of the composition and function of the lens capsule and lens-derived fibrotic ECM
The lens capsule is a thickened basement membrane surrounding the lens. My laboratory investigates diverse aspects of the capsule including its structure and influence on lens cell biology. We discovered that the capsule is a semi-permeable filter that limits communication between the lens and the ocular environment, while alterations in the lens capsule destabilize its structure and activate the unfolded protein response. Our investigations also revealed that lens integrin function varies during development, with β1-integrin loss from the lens vesicle resulting in premature differentiation of LECs to lens fibers, while later integrin deletion results in LEC fibrosis/apoptosis and β1 integrin deletion from elongating lens fibers destabilizes the actin cytoskeleton and abnormalities in cell structure and lens circulation. Most recently we have been studying how the balance between normal and fibrotic ECM production changes the phenotype of lens cells in both normal and pathological situations.

Brian P. Danysh, Tapan P. Patel, Kirk J. Czymmek, David A. Edwards, Liyun Wang, Jayanti Pande, and **Melinda K. Duncan** (2010) Characterizing Molecular Diffusion in the Lens Capsule. *Matrix Biol.* **29,** 228-236

Mallika Pathania, Yan Wang, Vladimir N. Simirskii, and **Melinda K. Duncan** (2016) β1-integrin controls cell fate specification in early lens development *Differentiation,* **92,** 133-147.

Yichen Wang, Anne M. Terrell, Brittany A. Riggio, Deepti Anand, Salil A. Lachke, and **Melinda K. Duncan** (2017) β1-integrin deletion from lens activates cellular stress responses leading to fibrosis and apoptosis. Investigative Ophthalmology and Visual Sciences, **58,** 3896-3922.

Complete List of Published Work in MyBibliography (Total of 101):
https://www.ncbi.nlm.nih.gov/myncbi/1NAoK7xmgp2Ao/bibliography/public/