BIOGRAPHICAL SKETCH

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NAME: Douglas J Rhee, MD

eRA COMMONS USER NAME: DOUGLASRHEE

POSITION TITLE: Professor and Chair, Case Western Reserve University School of Medicine

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Michigan (Ann Arbor, MI)	B.S.	05/1991	Biology / Biomedical Sciences
University of Michigan Medical School (Ann Arbor, MI)	M.D.	06/1995	Medicine
Oakwood Hospital (Dearborn, MI)	Internship	06/1996	Transitional Year
Wills Eye Hospital (Philadelphia, PA)	Residency	07/1999	Ophthalmology
Bascom Palmer Eye Institute (Miami, FL)	Fellowship	07/2000	Glaucoma
National Eye Institute (Bethesda, MD)	Fellowship	08/2001	Molecular Biology

A. Personal Statement

I am a clinician-scientist and have led a basic science laboratory since 2001 that has been funded through federal, foundation, institutional, and corporate sources. My laboratory's most significant scientific contribution was to elucidate the importance of the matricellular protein, SPARC, to the normal physiology of IOP regulation, and its likely critical importance in the pathophysiology of primary open-angle glaucoma. As an active glaucoma clinician, I have been at the forefront of adopting and investigating innovative surgical technologies which has since become known as minimally invasive glaucoma surgery. I have contributed to the understanding of some rare clinical entities; I discovered the previously unrecognized Mendelian inheritance of plateau iris syndrome, was one of the first teams to report topiramate induced acute angle closure glaucoma (TiACG), and discovered the only effective treatment for intractable TiACG.

I have been the site principle investigator of federally funded genetics studies as well as numerous industry-sponsored FDA phase 3 medication and surgical device trials. I have served on data safety monitoring boards of two industry-funded trials. Although I do not have a formal degree in epidemiology/biostatistics, I have built and led the team for the TIME study for nearly 3 years of planning bringing together members who are recognized experts in biostatistics, epidemiology, clinical trials operations, and research pharmacology with decades of experience. Our team includes published experts in cataract surgery and endophthalmitis prophylaxis (ASCRS Research Committee). We have coordinated with the FDA, Veterans Administration (both clinical and clinical trials arms), potential industry partners, university (CWRU), hospital (University Hospitals), and the professional society, American Society of Cataract and Refractive Surgery (ASCRS). We garnered initial seed funding from the ASCRS Foundation. This team has the clinical, scientific, biostatistical, and operational experience to successfully implement the TIME study. The team has successfully published a preliminary safety study of intracameral moxifloxacin and corneal endothelia.

1. Chang DF, Prajna NV, Szczotka-Flynn LB, Benetz BA, Lass JH, O'Brien RC, Menegay HJ, Gardner S, Shekar M, Rajendrababu S, **Rhee DJ**. Comparing corneal endothelial cell toxicity of differing intracameral moxifloxacin doses after phacoemulsification. *J Cataract Refract Surg*. 2020;46:355-359

B. Positions and Honors

Positions

1995 – 1996 Intern, Class Representative; Transitional Year Program; Oakwood Hospital, Oakwood, Michigan

1996 – 1999 Resident and Chief Resident; Department of Ophthalmology; Wills Eye Hospital;

	Thomas Jefferson Medical College, Philadelphia, PA
1999 – 2000	Clinical Fellow and Instructor in Glaucoma; Department of Ophthalmology; Bascom Palmer Eye Institute; University of Miami School of Medicine, Miami, FL
2000 – 2001	Clinical Fellow (Laboratory of Mechanisms of Ocular Disease; Section on Aging & Ocular Disease – Paul Russell, Ph. D) National Eye Institute, National Institutes of Health, Bethesda, Maryland (90% laboratory research)
2001 – 2005	Assistant Professor; Department of Ophthalmology; Wills Eye Hospital; Thomas Jefferson Medical College, Philadelphia, PA
2001 – 2005	Assistant Professor; Department of Pathology, Anatomy, & Cell Biology; Thomas Jefferson Medical College, Philadelphia, PA
2001 – 2005	Clinical Consultant, National Eye Institute, National Institutes of Health
2005 – 2010	Assistant Professor; Department of Ophthalmology; Massachusetts Eye & Ear Infirmary Harvard Medical School, Boston, MA
2010 – 2013	Associate Professor; Department of Ophthalmology; Massachusetts Eye & Ear Infirmary Harvard Medical School, Boston, MA
2013 – Present	Professor; Department of Ophthalmology & Visual Sciences; Case Western Reserve University School of Medicine
	Chair; Dept. of Ophthalmology & Visual Sciences; University Hospitals Eye Institute
2019 – Present	Secretary, American Society of Cataract & Refractive Surgery (Executive Leadership)

Honors and Awards

1999	James S. Shipman Award – 2nd Prize – resident research project, Wills Eye Hospital
1999 – 2000	Heed Ophthalmic Foundation Fellow
2004	American Glaucoma Society - Clinician-Scientist Fellowship 2004
2005	American Glaucoma Society - Clinician-Scientist Fellowship 2005
2006	Norman Knight Leadership Development Award
2007	American Academy of Ophthalmology Achievement Award
2007 – 2020	Best Doctor, Best Doctors (Boston, MA)
2008	Physician Scientist Award, Research to Prevent Blindness
2008	Mid-Career Clinician-Scientist Award, American Glaucoma Society
2013	American Academy of Ophthalmology Senior Achievement Award
2014	American Academy of Ophthalmology Secretariat Award
2016	Power List 2016, *The Ophthalmologist*
2020	Power List 2020, *The Ophthalmologist*

Relevant Experience

2004, 2006	*Ad hoc* Member, Brain Disorders & Clinical Neuroscience (BDCN) F31 Study Section; NIH
2006 – 2008	Member, Scientific Review Committee, American Health Assistance Foundation
2011 – 2014	Member, Research Committee, American Glaucoma Society
2014 – Present	Member, Scientific Review Committee, Glaucoma Research Foundation (San Francisco)
2016 – Present	Chair, Research Committee, American Society of Cataract & Refractive Surgery
2015 – 2020	Member, National Eye Institute Advisory Council

C. Contribution to Science

1. Clinical Trials: I have participated in industry-sponsored surgical device and medication trials which has led to successful FDA approved products – most recently the Hydrus (a surgical drainage device for glaucoma) and durysta (sustained release bimatoprost implant for glaucoma). I have also participated in the NEI funded GLAUGEN, NEIGHBOR, and NEIGHBORHOOD Consortia which have made extensive contributions to understanding the genetic contributions to glaucoma. I am the senior author of the first prospective randomized controlled trial comparing two minimally invasive glaucoma drainage implants (COMPARE Study) as well as the senior author on the translational laboratory study comparing the same two devices. I led the team that developed the consensus guidelines for managing patients with the Cypass (Alcon) device following it's market recall (2018).

1. Samuelson TW, Chang DF, Marquis R, Flowers B, Lim KS, Ahmed IIK, Jampel HD, Aung T, Crandall AS, Singh K; HORIZON Investigators. A Schlemm canal microstent for intraocular pressure reduction in primary open-angle glaucoma and cataract. *Ophthalmology* 2019;126:29-37 (one of the Horizon Investigators)

2. Ahmed IK, Fea A, Au L, Ang R, Harasymowycz P, Jampel H, Samuelson TW, Chang DF, **Rhee DJ**,* COMPARE Investigators. A prospective randomized trial comparing two Schlemm's canal minimally invasive glaucoma surgery implants for standalone treatment of open-angle glaucoma (The COMPARE Study). *Ophthalmology 2019 Apr 26 epub.* *corresponding and senior author
3. Toris CB, Pattabiraman PP, Tye G, Samuelson TW, **Rhee DJ**. Outflow facility effects of 3 Schlemm's canal microinvasive glaucoma surgery devices. *Ophthalmology Glaucoma*. 2020;3:114-121
4. https://ascrs.org/news/ascrs-news/cypass-withdrawl

2. SPARC Regulates IOP by Altering TM ECM: Very few proteins are known to regulate/modulate intraocular pressure (IOP). The mRNA of SPARC was first reported amongst a screen of proteoglycan expression in trabecular meshwork in 1997 by Mary Wirtz and Ted Acott's group. We were first to describe the protein expression pattern within the TM and intracellular location in 2003. We demonstrated that SPARC is an important regulatory node for IOP in human tissue and mice and determined the structural correlations in juxtacanalicular extracellular matrix associated with manipulations of SPARC and subsequent IOP changes. SPARC is now among a very short list of proteins that are known to regulate IOP.

Although, we elucidated several upstream pathways that regulate SPARC, the most important to primary open-angle glaucoma (POAG) is the cytokine/signaling pathway transforming growth factor beta-2 (TGFβ2), which is elevated in the aqueous humor of POAG patients by 2-3 fold. In experimental systems and animal models, TGFβ2 elevates IOP and causes structural changes very similar to POAG. We ascertained the specific signaling pathways (JNK, smad 2/3, and p38) by which TGFβ2 regulates SPARC. When TGFβ2 is overexpressed in SPARC-null mice, the IOP elevation is blunted by over 90%. SPARC-null mice have lower baseline IOP. This transgenic absence of SPARC essentially prevents the pathogenic IOP elevation induced by TGFβ2 indicating that decreasing SPARC may not only lower IOP, but actually interrupt the pathophysiology of POAG, i.e. disease modifying therapy.

1. Haddadin RI, Oh DJ, Filipoppopolous T, Gupta M, Michaud N, Sage EH, **Rhee DJ**. SPARC-null mice exhibit lower intraocular pressures. *Invest Ophthalmol Vis Sci.* 2009;50:3771-3777
2. Kang MH, Oh DJ, Kang JH, **Rhee DJ**. Regulation of SPARC by transforming growth factor β-2 in human trabecular meshwork. *Invest Ophthalmol Vis Sci* 2013;54:2523-2532.
3. Oh DJ, Kang MH, Ooi YH, Choi KR, Sage EH, **Rhee DJ**. Overexpression of SPARC in human trabecular meshwork increases intraocular pressure and alters extracellular matrix. *Invest Ophthalmol Vis Sci* 2013;54:3309-3319
4. Swaminathan SS, Oh DJ, Kang MH, Shepard AR, Pang IH, **Rhee DJ**. TGFβ2-mediated ocular hypertension is attenuated in SPARC-null mice. *Invest Ophthalmol Vis Sci* 2014;55:4084-4097

3. Prostanglandin Analogue Medications Mechanism of Action and the Importance of the MMP:TIMP Balance in Regulating ECM and IOP: We demonstrated that similar to other tissues in the body, the balance between the enzymatic degrading enzymes of ECM, matrix metalloproteinases and their kinetic inhibitors, correlates to the effectiveness of IOP lowering agents - prostaglandin analogues and brimonidine – that include enhancing aqueous drainage as part of their mechanism of action. These data more broadly emphasize the importance of extracellular matrix homeostasis on IOP regulation. We also performed what is to date the most comprehensive survey of known MMPs and TIMPs in the outflow tissues of the eye (trabecular meshwork and ciliary body stroma) finding that although the compliment of expressed/not expressed is the same, there are tissue specific responses.

1. Oh DJ, Martin JL, Williams AJ, Peck RE, Pokorny C, Russell P, Birk DE, **Rhee DJ**. Analysis of expression of matrix metalloproteinases and tissue inhibitors of metalloproteinases in human ciliary body following latanoprost. *Invest Ophthalmol Vis Sci.* 2006;47:953-963
2. Oh DJ, Martin JL, Williams AJ, Russell P, Birk DE, **Rhee DJ**. Effect of latanoprost on the expression of matrix metalloproteinases and their tissue inhibitors in human trabecular meshwork cells. *Invest Ophthalmol Vis Sci*. 2006;47:3887-3895.
3. Ooi YH, Oh DJ, **Rhee DJ**. Analysis of alpha-2 adrenergic receptors and effect of brimonidine on matrix metalloproteinases and their inhibitors in human ciliary body. *Invest Ophthalmol Vis Sci* 2009;50:4237-4243
4. Ooi YH, Oh DJ, **Rhee DJ**. Effect of bimatoprost, latanoprost, and unoprostone on matrix metalloproteinases and their inhibitors in human ciliary body smooth muscle cells. *Invest Ophthalmol Vis Sci* 2009;50:5259-5265

4. Helping to Pioneer Minimally Invasive Surgery for Glaucoma: Since 1968, the full-thickness (i.e. creation of a fistula through the eye wall connecting anterior chamber and subconjunctival space) and invasive surgery, trabeculectomy, has been the gold-standard for the surgical management of glaucoma after medical and laser surgery have failed. Trabeculectomy carries significant risk for significant and blinding complications intraoperatively, in the peri-operative period, and even for years in the post-operative period due to the presences of a conjunctival bleb. In the intervening decades, numerous procedures were developed to enhance efficacy and/or safety, but none successfully achieved the goal and were evanescently performed. Originally developed by George Baerveldt, *ab interno* trabeculectomy (i.e. Trabectome; NeoMedix, Tustin, CA), is the first modern angle-based minimally invasive glaucoma surgery. In 2006, I became one of the first 6 surgeons in the world to perform this procedure. I was involved with the early proof of concept case series and led subsequent studies that would ascertain its position within our clinical treatment algorithm – specifically, Trabectome is not as effective as trabeculectomy, but is far superior in terms of safety and recovery. Trabectome is most effective in combination with cataract surgery. If Trabectome fails, laser trabeculoplasty is ineffective and the patient should undergo a trabeculectomy. For that subsequent trabeculectomy, the failed Trabectome, has no effect on the success rates or safety of a subsequent trabeculectomy. Our work has shown that Trabectome is an important addition to our surgical armamentarium and is optimally positioned before trabeculectomy. Today, Trabectome is performed throughout the world and has inspired the next generation of minimally invasive angle-based surgeries and devices. I am actively involved in the early testing of these next generation procedures.

1. Francis BA, Minckler D, Dustin L, Kawji S, Yeh J, Sit A, Mosaed S, Johnstone M, and the Trabectome Study Group. Combined cataract extraction and trabeculectomy by the internal approach for coexisting cataract and open-angle glaucoma: Initial results. *J Cataract Refract Surg* 2008;34:1096-1103
2. Jea SY, Mosaed S, Vold SD, **Rhee DJ**. Effect of failed trabectome on subsequent trabeculectomy. *J Glaucoma* 2012;21:71-75.
3. Jea SY, Francis BA, Vakili G, Filipoppolous T, **Rhee DJ**. Ab interno trabeculectomy (Trabectome) versus trabeculectomy for open angle glaucoma. *Ophthalmology* 2012;119:36-42.
4. Töteberg-Harms M, **Rhee DJ**. Limited success of selective laser trabeculoplasty following failed combined phacoemulsification cataract extraction and *ab interno* trabeculectomy (Trabectome). *Am J Ophthalmol.* 2013;156:936-940

5. I discovered the treatment for severe topiramate-induced bilateral acute-angle closure and was one of the first to describe the phenomena and link it to sulfonamide-induced bilateral acute-angle closure. This discovery provided an effective and non-invasive treatment where previously these patients were treated unsuccessfully with invasive surgery.

1. **Rhee DJ**, Goldberg MJ, Parrish RK. Bilateral ciliary body swelling from topomax. *Arch Ophthalmol* 2001;119:1721-1723
2. **Rhee DJ**, Ramos-Esteban, Nipper KS. Rapid resolution of topiramate-induced angle-closure glaucoma with methylprednisolone and mannitol. *Am J Ophthalmol* 2006;141:1133-1134
3. Panday VA, **Rhee DJ**. Review of sulfonamide induced acute myopia and acute bilateral angle-closure glaucoma. *Compr Ophthalmol Update*. 2007;8:271-276

6. I discovered that plateau iris syndrome is familial with an autosomal dominant inheritance pattern in 50% of cases. Plateau iris syndrome is a minority cause of narrow angle glaucoma, but is one of the most aggressive. Despite having been described in 1958, plateau iris had been thought to be sporadic. After our discovery in 2006, the significant risk to family members who had previously gone unscreened was recognized. With increased surveillance and education of those at risk, the condition can be diagnosed earlier with the hopes of preventing damage. The autosomal dominant inheritance pattern implicates a Mendelian-inherited gene defect as the culprit which may be the subject of future investigation.

1. Etter JR, Affel EL, **Rhee DJ**. High prevalence of plateau iris configuration in family members of patients with plateau iris syndrome. *J Glaucoma* 2006;15:394-398

D. Research Support

Current Research Support

NEI, Rhee (PI) RO1 EY 019654-02 (renewal) 2/1/17 – 1/31/21
Title of Project: Matricellular Proteins in Trabecular Meshwork Increase Intraocular Pressure
The major goals: To examine the role of matricellular proteins in regulating extracellular matrix turnover in the trabecular meshwork and IOP, and the potential contributions of dysregulation of matricellular proteins to the pathophysiology of glaucoma.

4/2014 – Ongoing Site PI Ivantis per patient enrollment
Title of Project: The Safety and Effectiveness of the Hydrus Aqueous Implant for Lowering Intraocular Pressure in Glaucoma Patients Undergoing Cataract Surgery: A Prospective, Multicenter, Randomized, Controlled Clinical Trial (Hydrus IV Study) (HORIZON Trial)
The major goals: To determine the efficacy and safety of the Hydrus glaucoma drainage implant, a minimally invasive procedure to lower IOP, as part of the FDA Phase 3 study.

Glaukos, Rhee (Site PI) 12/2014 – 6/15/19
Title of Project: A Prospective, Randomized, Single-Masked, Controlled, Parallel Groups, Multicenter Clinical Investigation of the Glaukos Suprachoroidal Stent Model G3 in Conjunction with Cataract Surgery
The major goals: To determine the efficacy and safety of the G3 suprachoroidal shunt, a minimally invasive procedure to lower IOP, as part of the FDA Phase 3 study.

Completed Research Support in the last 3 years

Merck Rhee (PI) 12/2012 – 06/2016
Effect of Ophthalmic Preservatives on Trabecular Meshwork Outflow Facility
The major goals of this study are to determine the effect of commonly used preservatives found in ophthalmic medications on conventional outflow facility and potential mechanisms any effect may be seen.