Krishnakumar Kizhatil, PhD

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CURRENT ACADEMIC POSITION

March 2024-present Assistant Professor, Department of Ophthalmology and Visual Sciences, The Ohio State University Medical Center, Columbus, OH

PREVIOUS ACADEMIC APPOINTMENTS

November 2017 –February 2024: Research Scientist, The Jackson Laboratory

June 2009 – September 2017: Associate Research Scientist, The Jackson Laboratory

May 2006 - May 2009: Senior Research fellow, Department of Cell Biology, Duke University Medical Center, Durham, North Carolina.

EDUCATION

August 1993 -March 2000: Graduate Teaching Assistant, Department of Microbiology and Immunology, College of Medicine, The University of Tennessee, Memphis Tennessee.

August 1988-August 1992: Bachelor of Pharmacy (Honors, June 1992)- Birla Institute of Technology and Science (BITS), Pilani, Rajasthan, India

TRAINING

April 2000 - May 2006: Postdoctoral Fellow, HHMI and Department of Cell Biology, Duke University Medical Center, Durham, North Carolina.

COMMITTEE ASSIGNMENTS

PhD Thesis Committee of Vinodhini Jayanathan, Kerur Lab DOVS and BSGP Graduate Student

HONORS and AWARDS

Recipient - Barbara and Joseph Cohen Young Investigator Award for 2010, 2015, 2017

Lewis Rudin Glaucoma Prize of the New York Academy of Medicine for 2014 for the most outstanding scholarly article on glaucoma published in a peer-reviewed journal. (Awarded in 2015)
NIEHS paper of the year 2021

FORMAL MENTORING

Thesis committee of BSGP graduate student Vinodhini Jayanathan, The Ohio State University, May 2024-Present

Summer student mentoring program at the Jackson Laboratory- June -August

Madhumitha Gautam, Project "Development of Parasympathetic Innervation in Aqueous Humor Drainage Structures" June-August 2018.

Haelynn Gim, Project "Sympathetic innervation of the developing aqueous humor drainage structures." June-August 2017.

Sherley Collado-Justiniano, Project "Gene mapping of glaucoma related phenotypes in a forward genetics ENU screen." June-August 2016.

Sneha Goswami, Project "Molecular dissection of the role of VEGFA in development of the Schlemm's canal." June- August 2013.

Stephen Henrich, Project "Vascular origins of the Schlemm's canal." June-August 2012.

EDITOR/EDITORIAL BOARD APPOINTMENTS

September 2023-Present: Molecular and Cellular Pathology (specialty section of Frontiers in Cell and Developmental Biology)

MANUSCRIPT REVIEW

2009-Present
Journal of Biological Chemistry
Proceeding of National Academy of Science
Investigative Ophthalmology & Visual Science(IOVS)
Experimental Eye Research (EER)
PlosOne
ELife
Molecular Vision
Survey of Ophthalmology
npj Regenerative Medicine
Communications Biology

PROFESSIONAL MEMBERSHIPS AND ACTIVITIES

2008- Present: Association for Research in Vision and Ophthalmology (ARVO)
2016-Present: International Society for Eye Research (ISER)
Society for Neuroscience (SfN)
American Society for Cell Biology (ASCB)

Session Moderator: Platform Session I: Neurodegeneration, ISER/BrightFocus Glaucoma Symposium, Atlanta, Georgia, October 24, 2019.

Paper session, Animal Models of Opthalmic Disease, ARVO, New Orleans, Louisiana. April 23, 2023

Session Organizer: “Insights into the Schlemm’s Canal Biology” ISER 2024, October 20-24, Buenos Aires, Argentina.

INVITED PRESENTATIONS

1. **K. Kizhatil** “A role for the arginine transporter SLC7A1 in regulating aqueous humor outflow.”, Trabecular Meshwork Study Club, December 8, 2023, Durham, NC, USA.

2. **K. Kizhatil** “Molecular basis of intraocular pressure regulation.” 26 July 2023, Ophthalmology and Visual Sciences Research Center, University of Pittsburgh, Pittsburgh, PA, USA.

3. **K. Kizhatil** " Aqueous humor outflow regulation by FYN." Trabecular Meshwork Study Club, December 2, 2022, Washington D.C., USA.

4. **K. Kizhatil** “Molecular basis of intraocular pressure regulation.” August 24, 2022, John A. Moran Eye Center, University of Utah, Salt Lake City, UT, USA.

5. **K. Kizhatil** “Innervation of aqueous humor drainage structures and neuronal control of intraocular pressure.**”** Trabecular Meshwork Study Club, December 7, 2018, San Diego, CA, USA.

6. **K. Kizhatil.** “Schlemm’s canal is a unique vessel with a combination of blood vascular and lymphatic phenotypes that forms by a novel developmental process**.”** Lymphangiogenesis, lymphatics and IOP session, ISER, September 29, 2016,Tokyo, Japan.

7. **K. Kizhatil.** “Schlemm’s canal is a unique vessel with a combination of blood vascular and lymphatic phenotypes that forms by a novel developmental process**.”** Rudin glaucoma prize lecture, NYU Ophthalmology Grand Rounds, December 15, 2015, Department of Ophthalmology, NYU Langone Medical Center, New York, NY, USA.

8. **K. Kizhatil.** “Ankyrin-G is required for polarized membrane domain formation in epithelial cells and photoreceptors.” Faculty-Trainee Science Lunch, February 20, 2008, Department of Ophthalmology, Duke University Medical Center, Durham, NC, USA.

9. **K. Kizhatil.** “A new activity of doublecortin in recognition of the phospho-FIGQY tyrosine in the cytoplasmic domain of neurofascin.” UNC NDRC/Neuroscience Center half-day symposium, May 15, 2002, University of North Carolina, Chapel Hill, NC. USA.

GRANTS

Title of grant: Does VECAD at Schlemm canal cell-junctions determine IOP and glaucoma risk?
Funding agency: NIH/NEI
Grant number: R01 EY032062
Award total: $711,715/yr
Dates of funding: 01/01/2021 – 11/30/2025
Role: PI on multi-PI grant
% effort: 15

Title of grant: Selective Targeting of Schlemm's Canal Inner Wall for Next-Generation Glaucoma Drugs.
Funding agency: Bright Focus Foundation
Grant number: BFOCUS CG2020004
Award total: $ $913,300/yr
Dates of funding: 03/31/2021 – 02/29/2024
Role: PI on multi PI grant
% effort: 20

Title of grant: Determining Molecular mechanisms of Human glaucoma genes.
Funding agency: NIH/NEI
Grant number: R01 EY033015
Award total: $ 417,936/yr
Dates of funding: 05/01/2022 –03/31/2026
Role: co-PI

Title of grant: Determining How Lymphatic Molecules Control Conventional Outflow.
Funding agency: NIH/NEI
Grant number: R01 EY028175
Award total: $424,375/yr
Dates of funding: 09/30/2017 –08/31/2022
Role: PI
% effort: 50

Title of grant: Determining How Lymphatic Molecules Control Conventional Outflow.
Funding agency: NIH/NEI
Grant number: R01 EY028175-04S1
Award total: $ $156,158/yr
Dates of funding: 09/30/2021 –08/31/2022
Role: PI

Title of grant: Determining the Neuronal Control of Intraocular Pressure.
Funding agency: Bright Focus Foundation
Grant number: G2017152
Award total: $75,000 /yr
Dates of funding: 07/01/2017 – 06/30/2019
Role: PI

JOURNAL ARTICLES

1. **Kizhatil,** A. Bhandari, G. Clark, D. Sunderland, A. Bhandari, L. Horbal, R. Balasubramanian, and SWM. John. 2023. FYN regulates aqueous humor outflow and IOP through the phosphorylation of VE-cadherin. bioRxiv. doi: https://doi.org/10.1101/2023.09.04.556253.

2. R. Balasubramanian*, **K.Kizhatil*,** T. Li, N.Tolman, A. Bhandari, G. Clark, V. Bupp-Chickering, S. Zhou, J. Peregrin, M Simon, C Montgomery, J. Qian and SWM. John. 2023. Transcriptomic profiling of Schlemm's canal cells reveals a lymphatic-biased identity and three major cell states. bioRxiv. doi: https://doi.org/10.1101/2023.08.31.555823. ***Co first author**

3. C M. McDowell, **K. Kizhatil**, M H. Elliott, D R. Overby, J van Batenburg-Sherwood, J C. Millar, M H. Kuehn, G. Zode, T S. Acott, M G. Anderson, S K. Bhattacharya, J A. Bertrand, T. Borras, D E. Bovenkamp, L. Cheng, J. Danias, M L. De Ieso, Y. Du, J A. Faralli, R. Fuchshofer, P S. Ganapathy, H. Gong, S Herberg, H. Hernandez, P. Humphries, S.W.M John, P L. Kaufman, K

E. Keller, M J. Kelley, R A. Kelly, D. Krizaj, A. Kumar, B C. Leonard, R L. Lieberman, P. Liton, Y. Liu, K C. Liu, N N. Lopez, W. Mao, T. Mavlyutov, F. McDonnell, G J. McLellan, P. Mzyk, A. Nartey, L R. Pasquale, G C. Patel, P P. Pattabiraman, D M. Peters, V. Raghunathan, P V. Rao, N. Rayana, U. Raychaudhuri, E. Reina-Torres, R. Ren, D. Rhee, U R. Chowdhury, J R. Samples, E G. Samples, J S. Schuman, V C. Sheffield, C H. Stevenson, A Soundararajan, P Subramanian, C K. Sugali. Y Sun, C B. Toris, K Y. Torrejon, A. Vahabikashi, J A. Vranka, T. Wang, C E. Willoughby, C. Xin, H. Yun, H F. Zhang, M P. Fautsch, E R. Tamm, A F. Clark, C. R Ethier and W. D Stamer. 2022. Consensus Recommendation for Mouse Models of Ocular Hypertension to study 2 aqueous humor outflow and its mechanisms. Inves. Ophthalmol and Vis Sci. 63:12. Pubmed

4. K. S. Nair, C. Srivastava, R. Brown, S. Koli, H. Choquet, H. S Kang, Y-M Kuo, S. Grimm, C. Sutherland, A. Badea, G. A Johnson, Y. Zhao, J. Yin, K. Okamoto, G. Clark, T. Borras , G. Zode, **K. Kizhatil,** S. Chakrabarti, S. John, E. Jorgenson and A. Jetten. 2021. GLIS1 regulates trabecular meshwork function and intraocular pressure and is associated with glaucoma in humans. Nat. Comm. 12 (1) 4877. Pubmed

5. N. G. Tolman, D. .G Macalinao, A.L Kearney, K. H MacNicoll, W. N de Vries, I. J Jackson, S. H Cross, **K Kizhatil**, K. S Nair, S. W. M John. 2020. Genetic background modifies vulnerability to glaucoma related phenotypes in *Lmx1b* mutant mice. Dis Model Mech. 14 (2): dmm046953. Pubmed

6. P. A. Williams, C. E Braine, **K Kizhatil**, N. E Foxworth, N. G Tolman, J. M Harder, R. A Scott, G. L Sousa, A. Pantich, G. R Howell, and S. W. M John. 2019. Inhibition of monocyte-like cell extravasation protects from neurodegeneration in DBA/2J glaucoma. Mol Degeneration. 14: 6. Pubmed

7. B. R. Thomson, T. Souma, S. W. Tompson, T. Onay, **K. Kizhatil**, O. M. Siggs, L. Feng, KN. Whisenhunt, T. L. Yanovitch, L. Kalaydjieva, D. N. Azmanov, S. Finzi, CE. Tanna, A. W. Hewitt, D. A. Mackey, Y. S. Bradfield, E. Souzeau, S. Javadiyan, J. L. Wiggs, F. Pasutto, X. Liu, S. W. John, J. E. Craig, J. Jin, T. L. Young and S. E. Quaggin. 2017. Angiopoietin-1 is required for Schlemm's canal development in mice and humans. J Clin. Invest.127:4421-4436. Pubmed

8. **K. Kizhatil**, A. Chlebowski, N. G. Tolman, N. F. Freeburg, M. M. Ryan, N. N. Shaw, A. D. M. Kokini, J. K. Marchant and S.W.M. John. 2016. An *in vitro* perfusion system to enhance outflow studies in mouse eyes. Inves. Ophthalmol and Vis Sci. 57:5207-5215. Pubmed

9. T. Souma, S. W. Tompson, B. R. Thomson, O. M. Stiggs, **K. Kizhatil**, S. Yamaguchi, L. Feng, V. Limivipuvadh, K. N. Whisenhunt, S. Maurer-Stroh, T. L. Yanovitch, L. Kalaydjieva, D. N. Azmanov, S. Finzi, L. Mauri, S. Javadiyan, E. Souzeau, T. Zhou, A. W. Hewitt, B. Kloss, K. P. Burdon, DA. Mackey, K. F. Allen, J. B. Ruddle, S-H. Lim, S. Rozen, K-N. Tran-Viet, X. Liu, S. John, J. L. Wiggs, F. Pasutto, J. E. Craig, J. Jin, S. E. Quaggin and T. L. Young. 2016. Mutations in the angiopoietin receptor TEK cause primary congenital glaucoma with variable expressivity. J Clin. Invest. 126:2575-2587. Pubmed

10. I. Martinez-Corral , M. H. Ulvmar, L. Stanczuk, F. Tatin, **K. Kizhatil**, S. W. John, K. Alitalo, S.Ortega and T. Makinen. 2015. Nonvenous origin of dermal lymphatic vasculature. Circulation Research 116:1649-1654. Pubmed

11. **K. Kizhatil**, M. Ryan, J. K. Marchant, S. Henrich, and S.W. M. John. 2014. Schlemm's canal is a unique vessel with a combination of blood vascular and lymphatic phenotypes that forms by a novel developmental process. PLoS Biology **12:**e1001912. Pubmed

12. G. Ayalon, J. D. Hostettler, J. Hoffman, **K**. **Kizhatil,** J. Q. Davis, and V. Bennett. 2011. Ankyrin-B interactions with spectrin and dynactin-4 are required for dystrophin-based protection of skeletal muscle from injury. Journal of Biological Chemistry 286**:**7370-7378. PubMed

13. **K. Kizhatil**, S. Baker, V. Arshavsky, and V. Bennett. 2009. Ankyrin-G promotes cyclic nucleotide-gated channel transport to rod photoreceptor sensory cilia. Science 323**:**1614-1617. PubMed

14. **K. Kizhatil**, N. Sandhu, N. Peachey, and V. Bennett. 2009. Ankyrin-B coordinates assembly of beta-2 spectrin, the Na/K ATPase and the Na/Ca exchanger in the inner segment of rod photoreceptors. Experimental Eye Research 88**:**57-64. PubMed

15. **K. Kizhatil**, J. Q. Davis, L. Davis, J. Hoffman, B. L. Hogan, and V. Bennett. 2007. Ankyrin-G is a molecular partner of E-cadherin in epithelial cells and early embryos. Journal of Biological Chemistry 282**:**26552-26561. PubMed

16. **K. Kizhatil,** W. Yoon, P. J. Mohler, L. H. Davis, J. A. Hoffman, and V. Bennett. 2007. Ankyrin-G and beta2-spectrin collaborate in biogenesis of lateral membrane of human bronchial epithelial cells. Journal of Biological Chemistry 282**:**2029-2037. PubMed

17. **K. Kizhatil**, and V. Bennett. 2004. Lateral membrane biogenesis in human bronchial epithelial cells requires 190-kDa ankyrin-G. Journal of Biological Chemistry **279:**16706-16714. PubMed

18. **K. Kizhatil**, Y. X. Wu, A. Sen, and V. Bennett. 2002. A new activity of doublecortin in recognition of the phospho-FIGQY tyrosine in the cytoplasmic domain of neurofascin. Journal of Neuroscience 22**:**7948-7958. PubMed

19. **K. Kizhatil** and L. M. Albritton. 2002. System y+ localizes to different membrane subdomains in the basolateral plasma membrane of epithelial cells. American Journal of Physiology Cell Physiology 283**:**C1784-1794. PubMed

20. S. M. Jenkins, **K. Kizhatil**, N. R. Kramarcy, A. Sen, R. Sealock, and V. Bennett 2001. FIGQY phosphorylation defines discrete populations of L1 cell adhesion molecules at sites of cell-cell contact and in migrating neurons. Journal of Cell Science 114**:**3823-3835. PubMed

21. **K. Kizhatil,** A. Gromley, and L. M. Albritton. 2001. Two point mutations produce infectious retrovirus bearing a green fluorescent protein-SU fusion protein. Journal of Virology 75**:**11881-11885. PubMed

22. M. Chung, **K. Kizhatil**, L. M. Albritton, and G. N. Gaulton. 1999. Induction of syncytia by neuropathogenic murine leukemia viruses depends on receptor density, host cell determinants, and the intrinsic fusion potential of envelope protein. Journal of Virology 73**:**9377-9385. PubMed

23. **K. Kizhatil** and L. M. Albritton. 1997. Requirements for different components of the host cell cytoskeleton distinguish ecotropic murine leukemia virus entry via endocytosis from entry via surface fusion. Journal of Virology **71:**7145-7156. PubMed

24. **K. K. Kumar,** R. Srivastava, V. B. Sinha, J. Michalski, J. B. Kaper, and B. S. Srivastava. 1994. recA mutations reduce adherence and colonization by classical and El Tor strains of Vibrio cholerae. Microbiology 140 (Pt 5)**:**1217-1222. PubMed

ABSTRACTS

Platform Presentations

Presented by K. Kizhatil.

1. **K. Kizhatil** and G. Clark" Primary cilia and aqueous humor outflow" Outflow and aqueous humor dynamics II, May 8, ARVO 2024, Seattle, WA, USA. IOVS June 2024, Vol.65, 4261.

2. **K. Kizhatil** and G. Clark "A role for the arginine transporter SLC7A1 in regulating aqueous humor outflow." Aqueous humor dynamics, trabecular meshwork and ciliary body II. April 27th ARVO 2023, New Orleans, LA, USA. IOVS, June 2023, Vol.64, 5078.

3. **K. Kizhatil**, A. Kokini, G. Clark and S. John "Neuronal control of IOP". Invited speaker, Molecular pathways involved in outflow changes in glaucoma, October 25-29, ISER 2020. Buenos Aires, Argentina. (Cancelled due to COVID19 pandemic).

4. **K. Kizhatil** , D. Sunderland, G. Clark and S. John "Permeability of cell junctions in the Schlemm's canal correlates with pressure-dependent phosphorylation of VE-CADHERIN" May 1, ARVO2019, Vancouver, Canada. IOVS July 2019, Vol.60, 5211.

5. **K. Kizhatil**, A. Kokini, G. Clark and S. John "Neuronal control of intraocular pressure through innervation of the Schlemm's canal." Schlemm's canal and beyond, novel targets for glaucoma, September 10, ISER 2018. Belfast, N. Ireland.

6. **K. Kizhatil.** "Schlemm's canal is a unique vessel with a combination of blood vascular and lymphatic phenotypes that forms by a novel developmental process**." Invited speaker**, Lymphangiogenesis, lymphatics and IOP session, September 29, ISER 2016.Tokyo, Japan.

7. **K. Kizhatil**, J. Q. Davis, W. Yoon, B. L. M. Hogan, and V. Bennett. "Polarized targeting of E-cadherin to sites of cell-cell contact in early embryos and epithelial cells requires ankyrin-G and beta-2-spectrin." Minisymposium: Cytoskeleton, adhesion and disease, December 9-13, 2006, ASCB Annual Meeting. San Diego, CA, USA.

Presented by other investigators.

1. **M. L De Ieso,** K. Kizhatil, S. W. John, O. Bankole; M.H Elliott, and W. D. Stamer "Selective Knockout of Caveolin-1 in the Trabecular Meshwork Elevates Intraocular Pressure and Reduces Outflow Facility in Mice." Aqueous humor dynamics, trabecular meshwork and ciliary body II. April 27th ARVO 2023, New Orleans, LA, USA. IOVS, June 2023, Vol.64, 1887.

2. **A.D.M. Kokini**, K. Kizhatil and S. John "Determining Neuronal Elements of IOP Regulation Using Mice" May 5, ARVO2017, Baltimore, MD, USA. IOVS July 2017, Vol.58, 1600.

3. **LM Albritton** and K Kizhatil "Retroviruses subvert the host cell cytoskeleton during early events in infection." December 9-13, 2000, ASCB Annual Meeting. San Francisco, CA, USA.

Posters

1. **K. Kizhatil,** G. Clark, D. Sunderland, A.Bhandari, L. Horbal and S. John "FYN Regulates Aqueous Humor Outflow and IOP through the Phosphorylation of VE-cadherin." February17-23, 2023, ISER, Gold Coast, Queensland, Australia.
2. N. G Tolman, S. Kneeland, K. MacNicoll, S. Cross, **K Kizhatil,** and S. John. "Genetic studies towards determining disease mechanisms in *Lmx1b* mutant mice", May 1, ARVO 2019, Vancouver, Canada. IOVS June 2019 Vol 60, 4251.

3. M. Xuyi, D. Wu, **K. Kizhatil**, S.W.M John, C.L Cepko, and W. Xiong. "AAV-mediated overexpression of nuclear SRBP1/2 induces buphthalmous and retinal degeneration in mice", May 2, ARVO 2018, Honolulu, Hawaii, USA. IOVS 2018, Vol 59, 4497.

4. **K. Kizhatil**, H. Gim, G. Clark and SWM. John " Sympathetic innervation of developing aqueous humor drainage structures", May 2, ARVO 2018, Honolulu, Hawaii, USA. IOVS July 2018, Vol 59,4700.

5. N. Tolman, K. H. MacNicoll, **K. Kizhatil**, S. Nair, S. H. Cross, R. S. Smith and S.W. John "Strain dependent differences modulating ocular phenotypes in Lmx1b mutant mice" May 2, ARVO 2018, Honolulu, HI, USA. IOVS July 2018, Vol.59, 5158.

6. B. R. Thomson, I. Carota, T. Souma, **K. Kizhatil**, L. Feng, Xi. Liu, S. W. John, T. L. Young, and S. E. Quaggin "Defects in Angiopoietin-Tie2 signaling lead to dose-dependent glaucoma in mice" May 1, ARVO 2016, Seattle, WA USA. IOVS July 2016, Vol.57.

7. **K. Kizhatil**, S. Baker, V. Arshavsky and V. Bennett "CNG Channels Require Ankyrin-G for Transport to Outer Segments of Rod Photoreceptors" May 3, ARVO 2009, Ft. Lauderdale, FL, USA. IOVS April 2009, Vol.50, 2721.

8. K. Abdi, J. Q. Davis, **K. Kizhatil**, and V. Bennett "Ankyrin-G and Beta 2-spectrin coordinate cargo recognition and basolateral trafficking in polarized epithelial cells." December 13-17, 2008, ASCB Annual Meeting. San Francisco, CA, USA.

9. **K. Kizhatil**, H. Li, and V. Bennett "The Ankyrin-G adaptor hypothesis and basolateral targeting of membrane proteins in epithelial cells." December 1-5, 2007, ASCB Annual Meeting. Washington D.C., USA.

10. **K. Kizhatil**, P. J. Mohler, W. Yoon, and V. Bennett "Ankyrin-G and assembly of specialized membrane domains." December 10-14, 2005, ASCB Annual Meeting. San Francisco, CA, USA.

11. **K. Kizhatil**, W. Yoon, and V. Bennett "Interaction between 190 kDa ankyrin-G and β-2-spectrin is required for the formation of the lateral membrane domain in human bronchial epithelial cells." December 4-8, 2004, ASCB Annual Meeting. Washington D.C., USA.

12. **K. Kizhatil**, Y.X. Wu, A. Sen, and V. Bennett "Neuronal migration and cell surface signaling: Doublecortin binds to a phospho-FIGQY-tyrosine motif conserved in the cytoplasmic domains of L1 family of cell adhesion molecules." December 8-12, 2001, ASCB Annual Meeting. Washington D.C., USA.

13. **K. Kizhatil**, A. Sen, and V. Bennett "Doublecortin is a SH2/PTB independent phosphotyrosine specific adapter for L1 family cell adhesion molecules." December 9-13, 2000, ASCB Annual Meeting. Washington D.C., USA.

PATENTS AND TECHNOLOGY TRANSFER

DEVICES AND METHODS FOR CREATING INTRACELLULAR PORES filed June 2, 2023

BIOGRAPHICAL NARRATIVE

1. Discovery that Schlemm's canal is a unique vessel that forms through a unique sequence of vascular development (Research Scientist-Simon John Lab). Schlemm's canal (SC) plays central roles in aqueous humor drainage (AQH) and ocular physiology. Improper function of the AQH drainage system results in elevated IOP, a key risk factor for glaucoma. The Simon John lab had previously characterized the anatomy of mouse AQH drainage structures including SC, demonstrating that they are remarkably similar to those in humans using conventional two dimensional tissue sectioning methods. On this basis the mouse was exploited to identify key genes and pathways that affected the drainage structures in ocular developmental abnormalities and glaucoma. SC function was proposed to depend on the molecular phenotypes of SC endothelial cells (SECs). However, the nature of SEC phenotype and also the details of SC development remained poorly defined when I joined the John lab. To allow a modern and extensive analysis of SC and its origins, I developed a new whole-mount procedure to visualize its development in the context of surrounding tissues and then applied genetic lineage tracing, specific-fluorescent reporter genes, immunofluorescence, high-resolution confocal microscopy, and three-dimensional (3D) rendering to study SC. Using these techniques, I and my colleagues showed that SECs had a unique phenotype that is a blend of both blood and lymphatic endothelial cell phenotypes. We showed that SC develops from blood vessels through a newly discovered process that we name "canalogenesis". Canalogenesis has features of vasculogenesis, angiogenesis and lymphangiogenesis and is thus a newly discovered blend of vascular developmental programs. These advances defined SC as a unique vessel with a combination of blood vascular and lymphatic phenotypes and will be important for dissecting its functions that are essential for ocular health and normal vision. This study also provided a new paradigm of studying lymphatic molecules as key in SC development, aqueous humor drainage and glaucoma treatment. In collaboration with Dr. Sue Quaggin we showed a critical role for TEK/ANGPT1 system in SC development in both mice and humans. A recent collabotration with Dr. Sai Nair has yielded mechanistic insights into the role of GLIS1 a glaucoma ssociated gene. We also developed a mouse eye perfusion device to measure outflow facility in the mouse. This device has a great potential for organ culture and live imaging of SC function. Recently found that FYN kinase is required for regulation of AQH outflow by phosphorylation of VE-CADHERIN in the SC. Also identifiedthat SC cells exists in three states using a multimodal transcriptome approach.
K. Kizhatil, M. Ryan, J. K. Marchant, S. Henrich, and S.W. M. John. 2014. Schlemm's canal is a unique vessel with a combination of blood vascular and lymphatic phenotypes that forms by a novel developmental process. PLoS Biology 12:e1001912. Pubmed

T. Souma, S. W. Tompson, B. R. Thomson, O. M. Stiggs, K. Kizhatil, S. Yamaguchi, L. Feng, V. Limivipuvadh, K. N. Whisenhunt, S. Maurer-Stroh, T. L. Yanovitch, L. Kalaydjieva, D. N. Azmanov, S. Finzi, L. Mauri, S. Javadiyan, E. Souzeau, T. Zhou, A. W. Hewitt, B. Kloss, K. P. Burdon, DA. Mackey, K. F. Allen, J. B. Ruddle, S-H. Lim, S. Rozen, K-N. Tran-Viet, X. Liu, S. John, J. L. Wiggs, F. Pasutto, J. E. Craig, J. Jin, S. E. Quaggin and T. L. Young. 2016. Mutations in the angiopoietin receptor TEK cause primary congenital glaucoma with variable expressivity. J Clin. Invest. 126:2575-2587. Pubmed

K. Kizhatil, A. Chlebowski, N. G. Tolman, N. F. Freeburg, M. M. Ryan, N. N. Shaw, A. D. M. Kokini, J. K. Marchant and S.W.M. John. 2016. An in vitro perfusion system to enhance outflow studies in mouse eyes. Inves. Ophthalmol and Vis Sci. 57:5207-5215. Pubmed

B. R. Thomson, T. Souma, S. W. Tompson, T. Onay, K. Kizhatil, O. M. Siggs, L. Feng, KN. Whisenhunt, T. L. Yanovitch, L. Kalaydjieva, D. N. Azmanov, S. Finzi, CE. Tanna, A. W. Hewitt, D. A. Mackey, Y. S. Bradfield, E. Souzeau, S. Javadiyan, J. L. Wiggs, F. Pasutto, X. Liu, S. W. John, J. E. Craig, J. Jin, T. L. Young and S. E. Quaggin. 2017. Angiopoietin-1 is required for Schlemm's canal development in mice and humans. J Clin. Invest.127:4421-4436. Pubmed

N. G. Tolman, D. .G Macalinao, A.L Kearney, K. H MacNicoll, W. N de Vries, I. J Jackson, S. H Cross, K Kizhatil, K. S Nair, S. W. M John. 2020. Genetic background modifies vulnerability to glaucoma related phenotypes in Lmx1b mutant mice. Dis Model Mech. 14 (2): dmm046953.

K. S. Nair, C. Srivastava, R. Brown, S. Koli, H. Choquet, H. S Kang, Y-M Kuo, S. Grimm, C. Sutherland, A. Badea, G. A Johnson, Y. Zhao, J. Yin, K. Okamoto, G. Clark, T. Borras , G. Zode, K. Kizhatil, S. Chakrabarti, S. John, E. Jorgenson and A. Jetten. 2021. GLIS1 regulates trabecular meshwork function and intraocular pressure and is associated with glaucoma in humans. Nat. Comm. 12 (1) 4877.

2. Discovered a novel role for Ankyrin adaptor proteins in formation of specialized membrane domains in cells (Postdoctoral fellowship). Ankyrins are membrane skeleton associated adaptor proteins that help localize channels, transporters and adhesion molecules to specialized membrane domains. Historically, these proteins were not thought to have any role besides linking membrane proteins to the spectrin-actin membrane skeleton. In a series of papers, I demonstrated a novel role for the ankyrin proteins in definition of entire membrane domains. I showed that in epithelial cells ankyrin-G was required for lateral membrane biogenesis Ankyrin-G collaborated with beta-2-spectrin in this process. I then went on to identify E-cadherin as a new molecular partner of ankyrin-G in epithelial cells and early embryos. I also showed ankyrin-G was required for post Golgi trafficking of E-cadherin. These initial findings have since been validated in mice by Vann Bennett's laboratory at Duke University Medical Center. I next showed that ankyrins were required for defining the inner and outer segments of rod photoreceptors. Ankyrin-B was required for coordinated expression of beta-2-spectrin, Na/K ATPase and Na/Ca exchanger in the inner segment of photoreceptors. Ankyrin-G was required for the transport of cyclic nucleotide gated channels to the outer segment and required for formation of the outer segment. Together these papers established a novel role for ankyrins in the morphogenesis of specialized membrane domains in vertebrate cells.
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3. Discovered a role for the cellular cytoskeleton in retrovirus entry (PhD thesis project). At the initiation of the project, the host cell factors that mediated retrovirus entry were largely unknown. Using murine ecotropic retrovirus (MLV-E) as a model virus, under the supervision of Dr. Lorraine Albritton, I demonstrated a requirement for the cellular cytoskeleton in virus entry. At the beginning of the work it was known that the virus entered cells using a common receptor but the site of virus fusion (cell surface or endosome) differed based on cell type. Clustering of the virus receptor on surface of cells suggested an interaction with the cytoskeleton. Based on this observation, we tested the requirement of the cytoskeleton in virus entry. An early critical requirement for the actin network prior to internalization of virus was discovered that was common to both modes of virus entry based on

sites of virus fusion. Disruption of microtubules before and shortly after virus internalization markedly reduced entry in the case of endosomal virus fusion, while entry mediated by cell surface fusion remained efficient. These data suggested that intact microtubules are required in a post-penetration step unique to efficient virus entry via endocytosis. Following this work, other groups showed a requirement of the cellular cytoskeleton for HIV entry and amphotrophic retrovirus entry.

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