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UNIVERSITY

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December 5, 2024

Selection Committee
Helen Keller Prize for Vision Research
The Helen Keller Foundation for Research and Education

Dear Selection Committee members,

It is a pleasure to nominate Dr. Seth Blackshaw, Dr. Joshua Sanes, and Dr. Anand Swaroop for the 2025 Helen Keller Prize for Vision Research. The innovations and discoveries of these three scientists have catapulted the field of retina research from one-gene-at-a-time and whole-tissue approaches to whole-genome and single-cell-resolution approaches to understanding retinal development, function, and disease. The experimental and analytical approaches that they pioneered are now widely used by vision researchers as well as by scientists across all of biomedical research.

By way of introduction, I have been a faculty member at the Johns Hopkins Medical School and an Investigator of the Howard Hughes Medical Institute for the past thirty-six years. I am also a member of the National Academy of Sciences (USA) and the National Academy of Medicine (USA). In 2019, I shared the Helen Keller Prize for Vision Research with Dr. King-Wai Yau.

The paragraphs that follow summarize the contributions of the three nominees. Five relevant publications from each nominee are listed as an addendum to this letter.

As a postdoctoral fellow in Connie Cepko's laboratory in the early 2000s, Dr. Blackshaw was the first person to apply serial analysis of gene expression (SAGE) to eye research. In this method, segments of ~15 bases are sequenced from the 3' end of thousands of mRNAs to generate an atlas of gene expression. Fifteen years later, with the arrival of Next Generation sequencing technology, Dr. Blackshaw generated gene expression profiles and genome-wide maps of accessible chromatin (ATACseq) for the mouse retina across all developmental stages, and used these data to identify NFI family transcription factors as key regulators of cell cycle exit and the generation of late-born retinal bipolar and Müller glia. In more recent experiments, the Blackshaw laboratory has discovered an NFI-dependent pathway for efficient reprogramming of adult mammalian Muller glia to a neuronal cell fate. For the past 7 years, the Blackshaw laboratory has been a leader in the development and analysis of single-cell sequencing and they have used this approach to characterize retinal development and to identify the retina's response to injury and disease in mouse and zebrafish models.

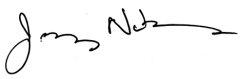
Dr. Sanes has had an extraordinary career in developmental neuroscience, initially focusing on neuromuscular junction development, then transitioning from the analysis of synaptogenesis to synaptic specificity (using the vertebrate retina as his object of study), and most recently pioneering

single-cell RNA sequencing (scRNAseq) technology and applying it to the eye. The last of these is the contribution on which this nomination is based. In 2016, the Sanes laboratory, in collaboration with the laboratory of Aviv Regev, reported that dissociated retinal neurons could be processed in micro-droplets to generate scRNAseq profiles from thousands of individual cells in parallel. This marked the first application of scRNAseq to the visual system and it revealed the extraordinary power of scRNAseq in tissues with complex mixtures of cell types. In a remarkable series of papers (some listed below) the Sanes laboratory has continued to lead the field in generating comprehensive atlases of cell types for the primate retina (including a comprehensive analysis of foveal vs. extra-foveal retina) and anterior ocular structures. Sanes' work on ocular cell types is characterized by detailed immunohistochemical validation and insightful analyses of physiological and disease relevance.

For over 30 years, Dr. Swaroop has been involved in developing and/or using high throughput molecular genetic and genomic strategies to decipher gene regulation in the retina and to elucidate how genetic variants contribute to retinal disease. In the 1980s, Dr. Swaroop used directional cDNA libraries and subtraction cloning to his identify the transcription factor NRL as a master regulator of photoreceptor development. Starting in the 1990s, Dr. Swaroop was one of the first vision scientists to utilize microarray technologies to develop global gene expression profiles of the retina and of purified rods and cones. In the 2000s, he used genome-wide approaches to map binding sites for transcription factors and histone modifications in the mammalian retina. More recently, the Swaroop laboratory produced high resolution genome topology maps of developing and adult human retina. In work that is directly related to human eye disease, the Swaroop laboratory was one of the first groups to use large scale genome-wide association studies (GWAS) for age-related macular degeneration (AMD). The Swaroop laboratory has also performed DNA methylation analyses on hundreds of post-mortem human retina and macula samples, and they have begun to develop a gene-epigenome interaction map that should help in dissecting the contribution of aging and environment to age-associated diseases such as AMD and glaucoma. In sum, by integrating multiple 'omics' datasets (including transcriptome, epigenome, metabolome, and proteome), the Swaroop laboratory is defining the cellular events and networks that lead to retinal disease.

I hope that this brief summary provides a sense of how the research of Drs. Blackshaw, Sanes, and Swaroop has fundamentally advanced vision research. It is now hard to recall the time, only 20-30 years ago, when the field was still groping to understand how different ocular cell types differed at a molecular level and how ophthalmic diseases alter the molecular properties of these cells. The work of these three nominees has fundamentally changed this landscape to the benefit of the entire vision research community and ultimately for the benefit of patients with sight-threatening eye disease.

Sincerely,



Jeremy Nathans, M.D., Ph.D.
Professor of Molecular Biology and Genetics
Professor of Neuroscience
Samuel Theobald Professor of Ophthalmology
Investigator, Howard Hughes Medical Institute
Johns Hopkins Medical School
e-mail: jnathans@jhmi.edu

Dr. Seth Blackshaw - five most relevant publications.

Blackshaw S, Fraioli RE, Furukawa T, Cepko CL. (2001) Comprehensive analysis of photoreceptor gene expression and the identification of candidate retinal disease genes. Cell 107:579-589.

Clark BS, Stein-O'Brien GL, Shiau F, Cannon GH, Davis-Marcisak E, Sherman T, Santiago CP, Hoang TV, Rajaii F, James-Esposito RE, Gronostajski RM, Fertig EJ, Goff LA, **Blackshaw S.** (2019) Single-Cell RNA-Seq Analysis of Retinal Development Identifies NFI Factors as Regulating Mitotic Exit and Late-Born Cell Specification. Neuron 102:1111-1126.e5.

Hoang T, Wang J, Boyd P, Wang F, Santiago C, Jiang L, Yoo S, Lahne M, Todd LJ, Jia M, Saez C, Keuthan C, Palazzo I, Squires N, Campbell WA, Rajaii F, Parayil T, Trinh V, Kim DW, Wang G, Campbell LJ, Ash J, Fischer AJ, Hyde DR, Qian J, **Blackshaw S.** (2020) Gene regulatory networks controlling vertebrate retinal regeneration. Science 370:eabb8598.

Lyu P, Hoang T, Santiago CP, Thomas ED, Timms AE, Appel H, Gimmen M, Le N, Jiang L, Kim DW, Chen S, Espinoza DF, Telger AE, Weir K, Clark BS, Cherry TJ, Qian J, **Blackshaw S.** (2021) Gene regulatory networks controlling temporal patterning, neurogenesis, and cell-fate specification in mammalian retina. Cell Rep 37:109994.

Lyu P, Iribarne M, Serjanov D, Zhai Y, Hoang T, Campbell LJ, Boyd P, Palazzo I, Nagashima M, Silva NJ, Hitchcock PF, Qian J, Hyde DR, **Blackshaw S.** (2023) Common and divergent gene regulatory networks control injury-induced and developmental neurogenesis in zebrafish retina. Nat Commun 14:8477.

Dr. Joshua Sanes - five most relevant publications.

Shekhar K, Lapan SW, Whitney IE, Tran NM, Macosko EZ, Kowalczyk M, Adiconis X, Levin JZ, Nemesh J, Goldman M, McCarroll SA, Cepko CL, Regev A, **Sanes JR**. (2016) Comprehensive Classification of Retinal Bipolar Neurons by Single-Cell Transcriptomics. Cell 166:1308-1323.

Peng YR, Shekhar K, Yan W, Herrmann D, Sappington A, Bryman GS, van Zyl T, Do MTH, Regev A, **Sanes JR.** (2019) Molecular Classification and Comparative Taxonomics of Foveal and Peripheral Cells in Primate Retina. Cell 176:1222-1237.

van Zyl T, Yan W, McAdams A, Peng YR, Shekhar K, Regev A, Juric D, **Sanes JR**. (2020) Cell atlas of aqueous humor outflow pathways in eyes of humans and four model species provides insight into glaucoma pathogenesis. Proc Natl Acad Sci U S A 117:10339-10349.

Yan W, Peng YR, van Zyl T, Regev A, Shekhar K, Juric D, **Sanes JR**. (2020) Cell Atlas of The Human Fovea and Peripheral Retina. Sci Rep 10:9802.

van Zyl T, Yan W, McAdams AM, Monavarfeshani A, Hageman GS, **Sanes JR**. (2022) Cell atlas of the human ocular anterior segment: Tissue-specific and shared cell types. Proc Natl Acad Sci U S A 119:e2200914119.

Dr. Anand Swaroop - five most relevant publications.

Hao H, Kim DS, Klocke B, Johnson KR, Cui K, Gotoh N, Zang C, Gregorski J, Gieser L, Peng W, Fann Y, Seifert M, Zhao K, **Swaroop A**. (2012) Transcriptional regulation of rod photoreceptor homeostasis revealed by in vivo NRL targetome analysis. PLoS Genet 8:e1002649.

Ratnapriya R, Sosina OA, 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**. (2019) Retinal transcriptome and eQTL analyses identify genes associated with age-related macular degeneration. Nat Genet 51:606-610.

Corso-Díaz X, Gentry J, Rebernick R, Jaeger C, Brooks MJ, van Asten F, Kooragayala K, Gieser L, Nellissery J, Covian R, Cogliati T, Mondal AK, Jiang K, **Swaroop A**. (2020) Genome-wide Profiling Identifies DNA Methylation Signatures of Aging in Rod Photoreceptors Associated with Alterations in Energy Metabolism. Cell Rep 31:107525.

Marchal C, Singh N, Batz Z, Advani J, Jaeger C, Corso-Díaz X, **Swaroop A**. (2022) High-resolution genome topology of human retina uncovers super enhancer-promoter interactions at tissue-specific and multifactorial disease loci. Nat Commun 13:5827.

Kwong A, Zawistowski M, Fritsche LG, Zhan X, Bragg-Gresham J, Branham KE, Advani J, Othman M, Ratnapriya R, Teslovich TM, Stambolian D, Chew EY, Abecasis GR, **Swaroop A**. (2023) Whole genome sequencing of 4,787 individuals identifies gene-based rare variants in age-related macular degeneration. Hum Mol Genet 2:ddad189.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Eye Institute
Bethesda, Maryland 20892

December 7, 2024
Selection Committee
Helen Keller Prize for Vision Research
The Helen Keller Foundation for Research and Education
Dear Selection Committee members,

Helen Keller Prize for Vision Research 2025: nomination for Drs. Seth Blackshaw, Anand Swaroop, and Joshua Sanes

Dear Selection Committee,

It is a pleasure to write this letter with the most enthusiastic support for the nomination of Drs. Seth Blackshaw, Anand Swaroop, and Joshua Sanes, for 2025 Helen Keller Prize for Vision Research - *for applying genome scale analyses to the study of ocular development, function, and disease.* I am delighted to attest to Drs. Blackshaw's, Swaroop's, and Sanes' achievements, the scientific impact and importance of those achievements, professional recognition, and training record/impact. Their contributions applying large-scale and single cell 'omics' technologies and creation of publicly available datasets for the vision research community have not only significantly advanced understanding of ocular development and degeneration, but also enabled this research in many labs around the world.

Seth Blackshaw: Dr. Blackshaw completed his bachelor's degree in biology and master's degree in biochemistry from University of Chicago and his PhD in neuroscience with Dr. Solomon Snyder at Hopkins university. During his stay in the Snyder lab, Dr. Blackshaw published an impressive list of 30 papers in neuroscience. His interest in gene regulation of the retina started during his post doc with Dr. Connie Cepko where he published eleven manuscripts in journal such as Cell, PNAS, Plos Biology and Genome Biology and completed one of the first large-scale gene expression analysis of the mouse and human retina using serial analysis of gene expression (SAGE). His work led to the discovery of several candidate retinal disease genes differentially expressed in photoreceptors.

He joined the Johns Hopkins faculty in 2004 as an Assistant Professor and since 2015 has served their faculty as a Full Professor. During this tenure at Hopkins, he went on to publish over 150 publications, most of which are in high profile journals including Cell, Science, Neuron, Nature Neuroscience, Nature Methods, Nature Communications, and Cell Reports. More importantly, he continues to make ground-breaking discoveries utilizing 'omics' to further our understanding of retinal development, biology, and pathology. Some of the most significant achievements of his lab in retina genomics include developing methods to discover gene regulatory network of transcription factors using one-hybrid yeast screening platform, developing methods for analyzing human proteome of the human retina, developing activity-based phosphorylation networks, and methods to purify transcription factors and associated proteins. The work started in Seth's lab has changed the field of genomics of the human retina and has enabled others to further transcriptional and epigenetic research in this space. His own lab continues to study the role of homeodomain transcription factors in retina and brain development using mouse models and in utero gene manipulation techniques that his lab has helped develop and are currently being used by others.

Recently, he developed methods to compare scRNAseq data across multiple species to discover pathways conserved across species that are involved in retinal development and regeneration. This work has led to new areas of research

around regeneration of the human retina – a species is known not to regenerate as compared to the retinas of fish and amphibia that have regenerative capacity. These works were published in journals cells as Science and Developmental Cell. More recently, he combined scRNA-Seq and scATAC-Seq technologies to discover chromatin accessibility difference in age-related macular degeneration (AMD) vs non-AMD retinas revealing heterogeneity that exists in gene expression of different retinal cell populations.

Dr. Blackshaw is a renowned leader in retina genomics. He has given over 200 talks and trained over 35 trainees who have gone on to start their own active research programs. He teaches neuroscience, developmental biology, and genomics courses at Hopkins. His research holds an impressive H-index of 78.

Anand Swaroop: After completing his PhD in Biochemistry at the Indian Institute of Science, Dr. Swaroop completed post-doctoral fellowships in Molecular Biology and Genetics at Yale University. He began his tenure career at the University of Michigan, where he became a full professor. In 2007, he was recruited to serve as the Chief of the Neurobiology-Neurodegeneration and Repair laboratory at the National Eye Institute, NIH.

Dr. Swaroop has served in several national and international leadership roles and elected positions, including a member of the Editorial Boards of Progress in Retinal and Eye Research, PNAS, PLoS Genetics, PLoS One, Molecular Vision, Annals of Science, Cilia, and Investigative Ophthalmology and Visual Science. He has received numerous national and international awards for his contributions to science, including becoming first a Silver, then Gold, ARVO fellow. He received the NEI Director's Diversity Champion Award and the NIH Director's Award. Recently, Dr. Swaroop was named the recipient of the 2024 Friedenwald Award from ARVO for his lifetime of outstanding contributions to vision science and the 2024 Ludwig von Sallmann Prize, the highest honor from the International Society for Eye Research.

Dr. Swaroop has published more than 400 articles in top-tier peer-reviewed journals including Nature, Nature Communications, Communications, Cell Reports, Experimental Eye Research, iScience, eLife, eNeuro, Stem Cell Reports, Human Molecular Genetics, Ophthalmology, Neuron, PLoS Genetics, and Investigative Ophthalmology and Visual Science. He is an established leader in the field of genetic and epigenetic regulation of retinal development and aging, genetics of retinal neurodegeneration and age-related macular degeneration, cilia biogenesis and ciliopathies, and retinal stem cells and organoids. He discovered the basic motif leucine zipper transcription factor NRL (Cell 1991) that controls the fate of rod versus cone photoreceptors and identified several retinal disease genes including CEP290, RPGR - associated with ciliopathies. He discovered RPE- and retina-specific genes using expressed sequence tag libraries. In 2002, his was one of the first groups to perform microarray analysis of aging human retina. His extensive work helped build a network between transcription factors CRX, NRL, NR2E2 (published in journals such as Human Molecular Genetics and J. Biol. Chem). His work using genome-wide associate studies (GWAS) and meta-analysis of genomes led to the discovery of single nucleotide polymorphisms (SNPs) associated with the risk for AMD (Nature Genetics, 2006). His recent work has focused on epigenetic control of developing and degenerating retina (Prog Retin Eye Res, 2018; Cell Reports 2023) and on eQTLs linked to AMD risk (Nat Comm 2023).

Dr. Swaroop has mentored 16 graduate students, and over 50 post-doctoral fellows, many of whom have gone on successful scientific careers. Just in the last 3 years, three women scientists from his lab have obtained tenure-track faculty positions. He has actively promoted equity, diversity and inclusion, and students and fellows born in as many as 25 countries and from 6 continents have studied in his laboratory. Dr. Swaroop is an outstanding vision scientist who has contributed significantly to our understanding of the molecular and cellular mechanisms responsible for photoreceptor degeneration. His work has been cited over 46,000 times in Scopus and has an H-index of 108.

Joshua Sanes: Dr. Sanes completed his BA degree from Yale and his Ph.D. from Harvard. He began his tenure career at Washington University School of Medicine where he eventually became a full professor. In 2004, he moved to Harvard as the Director of Center for Brain Science. Dr. Sanes has spent his career studying synaptogenesis and understanding mechanism that regulate synapse formation during development and how they are regulated in disease states. During the initial 15 years of his scientific career, he discovered several pre- and post-synaptic elements and analyzed the role of over 40 genes involved in formation, maturation, maintenance, and degeneration of synapses and published over 200 papers, in journals such a Cell, Nature, Neuron.

Dr. Sanes transitioned from the brain to the retina in the early 2000s, to study synaptic specificity - a process by which axons choose their synaptic partner neuron. His work led to the discovery of several axonal specificity molecules such as Sidekick, Dscam, Contactin, and type II cadherin. Several high-profile publications came out of this work. His work showed how individual identity is conferred on neurons and how they distinguish their own processes from that of other neurons. Furthermore, he demonstrated evolutionary conservation of synaptic specificity from vertebrates to flies. To make this approach of cell identity unbiased, Dr. Sanes helped develop the first high throughput single cell RNA seq called DropSeq (Cell, 2015). This manuscript was a game changer in the field and enabled many groups to start research in this space. Dr. Sanes went on to show that gene groups could define neuronal types (Cell, 2016), and went on to generate the first complete atlas of retinal cell types. This work provided the first comprehensive set of markers for synaptic specificity and retinal cell diversity. He has most recently applied this method to generate a primate retinal atlas (Cell, 2019) and a human "whole eye" atlas (PNAS, 2023), and to analyze critical issues of neuronal development, disease, injury and evolution (Neuron, 2019; Neuron, 2022; eLife, 2022; Nature 2023).

Over the last several years Sanes has developed single cell atlases of – chick retina (elife 2021), mouse retina (J. Neuroscience 2020), human ocular anterior segment (PNAS 2022), human fovea and peripheral retina (Sci. Report 20220), aqueous humor outflow pathways (PNAS 2020), and mouse ganglion cell (Cell Reports 2022, eLife 2022). Dr. Sanes has published over 400 papers and received numerous awards, including from National Academy of Science and AAAS, and as per Web of Science, his work has an H-index of 134.

I hope my letter provides sufficient evidence that Drs. Blackshaw, Swaroop, and Sanes are pioneers in the field of *genome scale analyses to the study of ocular development, function, and disease*, and continue to be leaders in this space. Their work has started new areas of research in analyzing and defining ocular cell types at a genomic level. They continue to train the next generation of scientist in this cutting-edge field who will take this technology to the next frontier. I most enthusiastically support their nomination for the 2025 Helen Keller Prize in Vision Research.

Sincerely,

Kapil Bharti,
Director, Division of Intramural Research,
Chief Ocular and Stem Cell Translational Research Section, National Eye Institute (NEI),
Adjunct Faculty National Center for Advancing Translational Sciences (NCATS)
Adjunct Faculty Center for Biomedical Engineering Technology Acceleration (βETA)
National Institute of Biomedical Imaging and Bioengineering (NIBIB)
National Institutes of Health
E-mail: Kapil.bharti@nih.gov

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Seth Blackshaw

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

POSITION TITLE: Professor of Neuroscience

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
University of Chicago	B.S.	1987-1991	Biology
University of Chicago	M.S.	1990-1991	Biochemistry
Johns Hopkins University School of Medicine	Ph.D.	1991-1997	Neuroscience

A. Personal Statement:

My research program seeks to identify gene regulatory networks that control specification of cell identity in the developing nervous system, and to eventually use this information to replace specific cell types lost to degenerative disease, as well as to gain understanding of neuronal circuitry controlling innate behaviors by selectively targeting individual neuronal cell types. Our studies have focused on two structures derived from the embryonic ventral forebrain: the retina, which is tractable and relatively simple system for learning basic mechanisms that guide neural cell types, and the hypothalamus, which is a central regulator of a broad range of medicially relevant and experimentally tractable innate behaviors.

Since my postdoctoral training, I have used high-throughput approaches to identify evolutionarily-conserved and species-specific gene regulatory networks that control cell fate specification in first the developing retina, and later the developing hypothalamus. Using comparative single-cell multiomic analysis combined with *in vivo* gain and loss of function studies of differentially expressed genes, we identified both evolutionarily conserved and species-specific mechanisms controlling temporal patterning, neurogenesis and cell fate specification in a range of vertebrate species. We have extended these studies to identify molecular mechanisms that control the ability of retinal glial cells to undergo injury-induced reprogramming in zebrafish, identifying NFI family factors and other genes as key negative regulators of neurogenic competence in Muller glia, and to re-examine spectacular claims of rapid and efficient glia-to-neuron conversion induced by knockdown of *Ptbp1*. More recently, we have also used similar approaches to identify aging-regulated gene regulatory networks in zebrafish and mouse retina. In addition to our work on analyzing hypothalamic patterning, neurogenesis and cell fate specification using first large-scale *in situ* hybridization and later scRNA-Seq, we have demostrated that shown mammalian tanycytes function as neural progenitors in the early postnatal hypothalamus, and generate neurons that regulate body weight. These studies have also allowed us to use intersectional genetic approaches to identify genes that guide the development of the core circadian oscillator, and to identify Lhx6-expressing neurons of the zona incerta as key sensors and signals of sleep pressure.

Ongoing research projects that I would like to highlight:
R01MH126676
Blackshaw (PI)
4/01/21 – 3/31/26
Development and function of hypothalamic Lhx6-positive neurons.

R01 EY031685
Blackshaw (PI)

7/01/20 – 6/30/24
Identification of gene regulatory networks that control proliferative and neurogenic competence in mammalian Muller glia

Milky Way Research Foundation Award for Rejuvenation Research
Blackshaw (PI)
11/01/21 – 10/31/24
Milky Way Research Foundation
Identification of gene regulatory networks controlling retinal aging.

KEY CITATIONS:
a. Liu K, Kim J, Kim DW, Zhang S, Denaxa M, Bao H, Lim SA, Kim E, Liu C, Wickersham IR, Pachinis V, Hattar S, Song J, Brown SR, and **Blackshaw S**. Lhx6-positive GABAergic neurons of the zona incerta promote sleep. *Nature* (2017) 548:582-587.
b. Clark BS, Stein-O'Brien GL, Shiau F, Cannon GH, Davis E, Sherman T, Rajaii F, James-Esposito RE, Gronostajski RM, Fertig EJ, Goff LA, and **Blackshaw S.** Comprehensive analysis of retinal development at single cell resolution identifies NFI factors as essential for mitotic exit and specification of late-born cells. *Neuron* (2019) 102:1111-1126.
c. Hoang T, Wang J, Boyd P, Wang F, Santiago C, Jiang L, Lahne M, Todd LJ, Saez C, Yoo S, Keuthan C, Palazzo I, Squires N, Campbell WA , Jia M, Rajaii F, Payail T, Wang G , Ash J, Fischer AJ, Hyde DR, Qian J, and **Blackshaw S**. Cross-species transcriptomic and epigenomic analysis reveals key regulators of injury response and neuronal regeneration in vertebrate retinas. *Science* (2020), 370(6519):eabb8598.
d. Hoang T, Kim DW, Appel H, Ozawa M, Zheng S, Kim J, and **Blackshaw S**. *Ptbp1* deletion does not induce astrocyte-to-neuron conversion in adult mouse brain. *Nature* (2023), 618:E1-7.

B. Positions, Scientific Appointments, and Honors

2015-present Professor of Neuroscience, Johns Hopkins University School of Medicine
2011-2015 Associate Professor of Neuroscience, Johns Hopkins University School of Medicine
2004-2011 Assistant Professor of Neuroscience, Johns Hopkins University School of Medicine
1999-2004 Postdoctoral Fellow, laboratory of Constance Cepko, Department of Genetics, Harvard Medical School
1997-1999 Postdoctoral Fellow, laboratory of Solomon Snyder, Department of Neuroscience, Johns Hopkins University School of Medicine

Professional Societies and Activities:

2022 Chair, Visual Systems Neuroscience Gordon Research Conference
2021-present Member, Scientific Advisory Board, Hearing Health Foundation
2019-present Member, Biology and Medicine Panel, Research Grants Council of Hong Kong
2018 Vice-chair for Visual Systems Neuroscience Gordon Research Conference
2014-present Member, Scientific Advisory Board, Foundation Fighting Blindness Canada
2014, 2020-22 Special emphasis study section member, NIH BRAIN Initiative.
2014 Ad hoc reviewer for Medical Research Council, United Kingdom
2013-2019 Regular study section member, NIH BVS Biology of the Visual System.
2012 Ad hoc study section member, NIH CMBG Cellular and Molecular Biology of Glia.
2011-12 Ad hoc study section member, NIH BVS Biology of the Visual System.
2005 Reviewer, Silvio O. Conte Center Grant study section, NIMH
2004- Society for Developmental Biology
2004- Society for Neuroscience

Honors and Awards:

2021 Milky Way Research Foundation Inaugural Awardee for Research on Rejuvenation
2019 Research to Prevent Blindness Stein Innovation Award
2007 Ruth and Milton Steinbach Fund Award for Research in Macular Degeneration
2007 NARSAD Young Investigator Award
2006 W. M. Keck Foundation Distinguished Young Scholar in Medical Research Award
2006 Esther A. and Joseph Klingenstein Fellowship in the Neurosciences

2006 NARSAD Young Investigator Award (award declined)
2006 Basil O'Connor Starter Scholar Award, March of Dimes
2005 Whitehall Foundation Research Grant
2005 Sloan Foundation Research Fellowship
1999 Howard Hughes Medical Institute Fellow of the Life Sciences Research Foundation
1991 Howard Hughes Medical Institute Predoctoral Fellow

Invited reviewer for the following journals: *Science*, *Nature, eLife, Neuron, Nature Neuroscience, Nature Cell Biology, Nature Biotechnology, Nature Communications, Developmental Cell, Cancer Cell*, *Cell Genomics, Science Signaling, Science Advances*, *PNAS, Genes and Development, Current Biology, Cell Reports, PLoS Genetics*, *Nature Metabolism*, *EMBO Journal, Journal of Neuroscience, Development, Genetics, Genome Research, Genome Biology, Neuroscience, Molecular and Cellular Neuroscience, Human Molecular Genetics, Journal of Comparative Neurology, Trends in Neuroscience, Trends in Pharmacology and Therapeutics, Trends in Endocrinology and Metabolism, Trends in Genetics, European Journal of Human Genetics, Journal of Neuroendocrinology, Molecular Endocrinology, PLoS Computational Biology, Developmental Dynamics, Investigative Ophthalmology and Visual Science, Experimental Eye Research, Cerebral Cortex, Developmental Neurobiology, Biomolecules, Frontiers in Neuroscience, Molecular Vision, Molecular Evolution, Journal of Biological Rhythms, BMC Developmental Biology, BMC Bioinformatics, Psychoneuroendocrinology, Physiology and Behavior, Disease Models and Mechanisms, Disease Models and Mechanisms, WIRES Systems Biology and Medicine, Gene Expression Patterns, Brain Research, PLoS ONE, Brain Structure and Function, International Journal of Developmental Neuroscience, Frontiers in Neuroscience, Frontiers in Genetics, Frontiers in Psychiatry, and Biotechniques.* Section editor for *Brain Research.* Reviewing editor for *eLife*, *Biomolecules* and *Frontiers in Neuroscience.* Guest editor for *PNAS* and *PLoS Genetics*.

C. Contributions to Science (190 total peer-reviewed publications)

1. **Molecular mechanisms controlling retinal neurogenesis, cell fate specification, and regeneration:** As a postdoc, I used SAGE-based analysis to generate a comprehensive temporal profile of gene expression during retinal neurogenesis. This identified dozens of transcription factors that are dynamically expressed in developing retina and demonstrated an important role for long noncoding RNAs in retinal cell fate specification. We have shown that the homeodomain factor Lhx2 plays a central role in both retinal gliogenesis and Notch signaling in late-stage retinal progenitors. We have also shown that in mature retinal glia, Lhx2 represses hypertrophic gliosis in the resting state and is also essential for expression of glial-derived neuroprotective factors following injury. We have also shown that Lhx2 controls expression of multiple FGF genes in neuroretina, which are in turn both necessary and sufficient for development of lens fiber cells and shown that Atoh7 is necessary to regulate survival and differentiation, but not specification, of retinal ganglion cells. Most recently, we have used integrated scRNA-Seq and scATAC-Seq to comprehensively map gene regulatory networks controlling neurogenesis and cell fate specification in the developing mouse and human retina. In parallel, we have used these same approaches to molecular mechanisms that control the ability of retinal glial cells to undergo injury-induced reprogramming in zebrafish, identifying NFI family factors and other genes as key negative regulators of neurogenic competence in Muller glia. Finally, we have used genetic cell lineage analysis to investigate and debunk recent claims that *Ptbp1* loss of function induces glia-to-neuron conversion in retina.
a. **Blackshaw S,** Harpavat S, Trimarchi J, Cai L, Huang H, Kuo WP, Weber G, Lee K, Fraioli RE, Cho S-H, Yung R, Asch E, Wong, WH, and Cepko CL. Genomic analysis of mouse retinal development. *PLoS Biol*. (2004) 2:E247. PMC439783.
b. Lyu P, Hoang T, Santiago CP, Thomas ED, Timms AE, Appel H, Gimmen M, Le N, Jiang L, Kim DW, Chen S, Espinoza D, Telger AE, Weir K, Clark BS, Cherry TJ, Qian J, and **Blackshaw S**. Gene regulatory networks controlling temporal patterning, neurogenesis and cell fate specification in the mammalian retina. *Cell Reports* (2021) 37:109994.
c. Brodie-Kommit J, Brian S. Clark BS, Shi Q, Shiau F, Kim DW, Langel J, Sheely C, Schmidt T, Badea T, Glaser T, Zhao H, Singer J, **Blackshaw S***, and Hattar S* (*indicates corresponding author). Atoh7-independent specification of retinal ganglion cell identity. *Sci Advances* (2021) 7:eabe4983.
d. Hoang T, Kim DW, Appel H, Panullo N, Leavey P, Ozawa M, Zheng S, Yu M, Peachey P, Kim J, and **Blackshaw S**. *Ptbp1* deletion does not induce glia-to-neuron conversion in adult mouse retina. *Cell Reports* (2022) 11:110849.

2. **Identification of hypothalamic tanycytes as diet and hormone-regulated neural progenitors in postnatal hypothalamus**: Our gene expression atlas revealed that hypothalamic tanycytes express many molecular markers of neural stem and progenitor cells. Using genetic lineage analysis and focal irradiation, we demonstrated that tanycyte-derived neurogenesis in the ventrobasal hypothalamus plays a critical role in controlling body weight and activity levels. Later studies from our group showed that this occurs more strongly in females. We have also identified Lhx2 and Rax as critical for specifying hypothalamic tanycyte identity. We have also developed genetic tools to selectively enhance and disrupt tanycyte-derived neurogenesis, have identified NFI factors as essential regulators of neurogenic competence in hypothalamic tanycytes, and are conducting detailed analysis of the identity and fate of tanycyte-derived neurons.
a. Lee DA, Bedont JL, Pak T, Wang H, Song J, Miranda-Angulo A, Takiar V, Charubhumi V, Balordi F, Takebayashi H, Ford E, Fishell G, and **Blackshaw S.** Tanycytes of the Hypothalamic Median Eminence Form a Diet-Responsive Neurogenic Niche. *Nat Neurosci* (2012) 15:700-2.
b. Yoo S, Cha D, Kim DW, Hoang T, and **Blackshaw S**. Tanycyte-independent regulation of leptin signaling. *Frontiers in Neuroscience* (2019) https://doi.org/10.3389/fnins.2019.00240.
c. Yoo S, Cha D, Kim S, Jiang L, Adebesin M, Wolfe A, Riddle R, Aja S, and **Blackshaw S**. Ablation of tanycytes of the arcuate nucleus and median eminence increases visceral adiposity and decreases insulin sensitivity in male mice. *Glia* (2020), doi:10.1002/glia.23817.
d. Yoo S, Kim J, Lyu P, Hoang TV, Ma A, Trinh V, Dai W, Jiang L, Leavy P, Won JK, Park SH, Qian J, Brown SP, and **Blackshaw S**. Control of neurogenic competence in mammalian hypothalamic tanycytes. *Science Advances* (2021) 7:eabg3777.

3. **Specification of hypothalamic cell identity, with a focus on neural circuitry controlling sleep and circadian timing**: The hypothalamus regulates many homeostatic and appetitive behaviors, but the molecular mechanisms controlling hypothalamic neuronal specification are little understood. To address this, we conducted an unbiased screen of gene expression in the developing mouse hypothalamus, which in combination with a large-scale *in situ* hybridization screen of candidate genes resulted in the first large-scale gene expression atlas of the developing hypothalamus. This identified a standardized set of molecular markers for the developing hypothalamus, along with dozens of genes that are candidates for controlling hypothalamic cell specification. This identified Lhx1 as a master regulator of neuropeptide expression in the body's master circadian clock in the suprachiasmatic nucleus and demonstrated an unexpected role of the SCN in acute light-dependent regulation of sleep and demonstrated an essential role for neuropeptide signaling in the SCN in resistance to temperature-induced shifts in the phase of the master clock. Most recently, we identified Lhx6-expressing GABAergic neurons of the zona incerta as a novel subtype of sleep-promoting neurons that induce NREM by inhibition of hypocretin neurons and induce REM through hypocretin-independent mechanisms. Finally, we have recently applied scRNA-Seq analysis to developing mouse and chick hypothalamus to identify molecular mechanisms controlling regionalization, neurogenesis, and cell fate specification.
a. Liu K, Kim J, Kim DW, Zhang S, Denaxa M, Bao H, Lim SA, Kim E, Liu C, Wickersham IR, Pachinis V, Hattar S, Song J, Brown SR, and **Blackshaw S**. Lhx6-positive GABAergic neurons of the zona incerta promote sleep. *Nature* (2017) 548:582-587.
b. Kim DW, Washington PW, Wang ZQ, Lin S, Sun C, Jiang L, and **Blackshaw S**. The cellular and molecular landscape of hypothalamic patterning and differentiation from embryonic to late postnatal development. *Nat Comm* (2020) 11:4360.
c. Kim DW, Liu K, Wang ZQ, Zhang YS, Bathini A, Brown MP, Lin SH, Washington PW, Sun C, Lindtner S, Lee B, Wang H, Shimogori T, Rubenstein JLR, and **Blackshaw S**. Gene regulatory networks controlling differentiation, survival, and diversification of hypothalamic Lhx6 neurons. *Comm Bio* (2021) 4:95.
d. Kim DW, Place E, Chinnaiya K, Manning E, Sun C, Dai W, Burbridge S, Placzek M, and **Blackshaw S**. Single cell analysis of early hypothalamic regionalization and neurogenesis in chick. *Cell Reports* (2022) 38:110251.

4. **Control of mammalian photoreceptor specification and survival**: Photoreceptor degeneration is the main cause of hereditary blindness, and many genes mutated in Mendelian photoreceptor dystrophies are selectively expressed in photoreceptors. In my postdoctoral work, I performed SAGE-based expression profiling to generate a comprehensive catalog of photoreceptor-enriched genes, prospectively pinpointed at least a dozen novel disease genes, as well as previously uncharacterized regulators of photoreceptor differentiation. As an

independent PI, my group showed that the E3 SUMO ligase Pias3 plays a dual role in promoting differentiation of rods and M-cones while also repressing S-cone identity and does this by site-specific SUMOylation of photoreceptor-enriched nuclear hormone receptors. Furthermore, we demonstrated that the orphan nuclear hormone ERRbeta is essential for rod photoreceptor survival. Most recently, we have demonstrated that the progression of age-related macular degeneration is associated with a reduction in regions of accessible chromatin in both photoreceptors and retinal pigment epithelium, have identified molecular mechanisms that regulate photoreceptor-specific alternative splicing, and used scRNA-Seq analysis to characterize human retinal organoid-derived cells following subretinal transplantation in immunocompromised host mice.

a. Onishi A, Peng GH, Chen S, **Blackshaw S.** Pias3-dependent SUMOylation controls mammalian cone photoreceptor differentiation. *Nat Neurosci* (2010) 13:1059-65.

b. Wang J, Zibetti C, Shang P, Sripathi SR, Zhang P, Cano M, Ji H, Merbs SL, Zack DJ, Handa J, Sinha D, **Blackshaw S*** and Qian J*. A widespread decrease in chromatin accessibility in age-related macular degeneration. *Nature Communications* (2018) 9:1364 (* indicates co-corresponding author).

c. Ling JP, Wilks C, Charles R, Ghosh D, Jiang L, Santiago CP, Pang B, Venkataraman A, Clark BS, Nellore A, Langmead B, and **Blackshaw S**. ASCOT identifies key regulators of neuronal subtype-specific RNA splicing. *Nat Comm* (2020), 11:37.

d. Liu YV, Santiago CP, Sogunro A, Konar GK, Hu MW, McNally MM, Lu Y, Li Z, Agakishiev D, Hussey K, Hadyniak S, Teng D, Creamer TJ, Orzolek LD, Qian J, Jiang Z, Johnston RJ Jr. *, **Blackshaw S*,** Singh MS* (*indicates corresponding author). Single-cell transcriptomic analysis of xenotransplanted human retinal organoids defines two migratory cell populations of nonretinal origin. *Stem Cell Reports* (2023) 5:1138-54.

5. **Development of new techniques for functional proteomics and cell-specific expression of AAV-based vectors**:

We have co-developed the HuProt protein microarray that contains over 20,000 full-length human proteins, representing over 13,000 full-length genes. We used this to characterize the DNA binding specificity of over one-third of human transcription factors, and unexpectedly identified many novel proteins, including the kinase ERK2, as transcription factors. We have also used it to identify monoclonal antibodies to human transcription factors that are truly monospecific, and do not cross-react with any other proteins, and have used HuProt arrays in collaborations with over 50 different research groups. Most recently, we have used cell type-specific alternative splicing, to generate a new class of cell type-specific AAV-based expression vectors for functional manipulation of defined neuronal subtypes that substantially improve on conventional minipromoter-based designs.

a. Hu S, Xie Z, Onishi A, Jiang L, Wang H, He X, Rho H-S, Woodard C, Yu X, Lin J, Long S, **Blackshaw S***, Qian J*, and Zhu H*. Profiling the human protein-DNA interactome reveals ERK2 as a transcriptional repressor of interferon signaling. *Cell* (2009) 139:610-22. PMC2774939 (*indicates corresponding author).

b. Jeong JS, Jiang L, Albino E, Marrero J, Rho HS, Hu S, Woodard C, Vera C, Bayron-Poueymirou D, Rivera-Pacheco ZA, Ramos L, Torres-Castro C, Bonaventura J, Boeke JD, Pino I, Eichinger DJ, Zhu H and **Blackshaw S**. A human proteome microarray-based pipeline for efficient production of monospecific monoclonal antibodies. *Mol Cell Proteomics* (2012) 6;O111.016253.

c. Venkataraman A, Yang K, Irizarry J, Mackiewicz M, Mita P, Kuang K Xue L, Ghosh D, Liu S, Ramos P, Hu S, Bayron D, Keegan S, Saul R, Colantonio S, Zhang H, Behn FP, Song G, Albino E, Asencio L, Ramos L, Lugo L, Morell G, Rivera J, Ruiz K, Almodovar R, Nazario L, Murphy K, Vargas I, Rivera-Pacheco ZA, Rosa C, Vargas M, McDade J, Clark BS, Yoo S, Khambadkone SG, de Melo J, Stevanovic M, Jiang L, Li Y, Yap WY, Jones B, Tandon A, Campbell E, Anderson S, Myers RM, Boeke JD, Fenyo D, Whiteley G, JS, Pino I, Eichinger DJ, Zhu H, and **Blackshaw S**. A toolbox of immunoprecipitation-grade monoclonal antibodies against human transcription factors. *Nat Methods* (2018) 15:330-338.

d. Ling J, Bygrave A, Santiago CP, Trinh V, Carmen R, Yu M, Li Y, Han J, Taneja K, Liu Y, Dongmo R, Babola T, Parker P, Jiang L, Leavey P, Smith J, Vistein R, Gimmen M, Dubner B, Teodorescu P, Kanold P, Bergles D, Langmead B, Sun S, Nielsen K, Peachey N, Singh M, Dalton W, Rajaii F, Huganir R, and **Blackshaw S**. Cell-specific regulation of gene expression using splicing-dependent frameshifting. *Nature Communications* (2022) 13:5773.

Complete List of Published Work in MyBibliography:

https://www.ncbi.nlm.nih.gov/myncbi/seth.blackshaw.1/bibliography/public/

Joshua R. Sanes

Place of Birth: Buffalo, New York

Citizenship: United States

Office Address: Department of Molecular and Cellular Biology
Harvard University, Cambridge, MA 02138

EDUCATION AND TRAINING

Yale College, New Haven, CT	B.A.	l970	Biochemistry and Psychology
Harvard University, Boston, MA	MA, Ph.D.	l976	Neurobiology

ACADEMIC POSITIONS/EMPLOYMENT

2013-2023	Biogen	Visiting Scientist (Interim head of ophthalmology research, 2020-2021)
2008	Trinity College, University of Cambridge	Visiting Fellow
2004-	Department of Molecular and Cellular Biology, Harvard University	Jeff C. Tarr Professor
2004-2020	Center for Brain Science Harvard University	Paul J. Finnegan Director
1999-2004	Department of Anatomy and Neurobiology Washington University School of Medicine	Alumni Endowed Professor of Neurobiology
1999	Molecular Biology of Development Institute (IDBM), University of Marseille	Sabbatical with Chris Henderson
1993	Division of Biology California Institute of Technology	Cornelius Wiersma Visiting Professor; Sabbatical with Kai Zinn
1989-99	Department of Anatomy and Neurobiology Washington University School of Medicine	Professor of Neurobiology
1985-89	Department of Anatomy and Neurobiology Washington University School of Medicine	Associate Professor of Neurobiology
1985-86	Laboratory of Molecular Biology Institut Pasteur, Paris, France	Sabbatical with Francois Jacob
1980-85	Department of Physiology Washington University School of Medicine	Assistant Professor of Physiology and Biophysics
1978-79	Department of Physiology University of California, San Francisco	Postdoctoral study with Dr. Zach Hall
1977	Department of Neurobiology Harvard Medical School	Postdoctoral study with Dr. U.J. McMahan
1976	Office of Technology Assessment, US Congress	Professional Staff Member
1970-75	Department of Neurobiology Harvard Medical School	Predoctoral thesis research with Dr. John Hildebrand
1969-70	Department of Pharmacology Yale Medical School	Undergraduate thesis research with Dr. Paul Greengard

SCHOLARSHIPS AND HONORS

Yale National Scholar, 1966
Scholar of the House, Yale College, 1969-1970
Phi Beta Kappa, 1970

Andelot Fellow in Cell Biology, Harvard, 1970-1971
Sigma Xi, 1974
Fellow, Muscular Dystrophy Association, 1977-1979
Sloan Fellow, 1980-1982
Established Investigator, American Heart Association, 1981-1986
Member, Javits Center of Excellence in Neuroscience, 1985-1990
Francis McNaughton Lecturer, Montreal Neurological Institute, 1987
McKnight Neuroscience Development Award, 1988-1990
Javits Neuroscience Investigator Award, NIH (first award), 1989-1995
F.E. Bennett Lecture, American Neurological Association, 1991
Fellow of the American Association for the Advancement of Science, 1992
Dana Alliance for Brain Initiatives, 1993
Clinton Woolsey Lecturer, University of Wisconsin, 1996
Stephen Kuffler Lecturer, Harvard Medical School, 1996
Keynote Speaker, Gordon Conference on Neural Plasticity, 1997
McKnight Senior Investigator Award, 1998-2000
Richard Bunge Lecturer, University of Miami, 1998
Alden Spencer Award, Columbia University 2000
National Academy of Sciences, USA, 2002
Visiting Professorship, College de France, Paris, 2004
Viktor Hamburger Lecturer (U. Wurzburg), 2004
Picower Lecturer (MIT), 2005
Liu Lecturer (U. Penn), 2005
Javits Neuroscience Investigator Award, NIH (second award), 2005-2011
American Academy of Arts and Sciences, 2006
Keynote speaker, Gordon Conference on Synaptic Transmission, 2008
Grass Lecture, Society for Neuroscience, 2008
Sager Lecturer (Friday night lecture), Woods Hole, 2009
Bishop Lecturer, Washington University, 2010
Keynote speaker, Gordon Conference on Molecular and Cellular Neuroscience, 2010
Rachford Lecturer, U Cincinnati, 2011
Rush Record Award and Lecture, Baylor Medical Center. 2011
Keynote speaker, Gordon Conference on Dendrites, 2011
Eckert Lecturer, German Neuroscience Society, 2011
Stadtler Lecturer, M.D. Anderson Medical Center, 2011
Javits Neuroscience Investigator Award, NIH (third award), 2012
Keynote Speaker, Gordon Conference on Visual System Development, 2012
Harvey Lecture, New York, 2012
Beams Lecture (Iowa), 2013
Schmitt Lecture (MIT), 2013
Elected Member-at-Large, Section on Neuroscience, AAAS, 2013-2016
Agranoff Lecture (University of Michigan), 2014
Keynote speaker, FASEB Conference on Retinal Neurobiology and Visual Processing, 2014
Elected Chair, Section 24, National Academy of Sciences, 2014
Keynote speaker, EMBO Symposium on Neuronal Remodeling, 2016
Arnold M. Clark Memorial Lecture, University of Delaware, 2017
Vernon Mountcastle Lecture, Johns Hopkins University, 2017
Gruber Prize in Neuroscience, Society for Neuroscience, 2017
Keynote speaker, FENS/Brain Conference on Cell Types for Brain Function, 2018
Perl-UNC Neuroscience Prize, 2019
Maxwell Cowan Award in Developmental Neuroscience, 2019
Scolnick Prize in Neuroscience, 2020
Honorary Doctoral Degree, Hebrew University of Jerusalem, 2020 (conferred 2022)

PROFESSIONAL SERVICE

Editorial Board, Journal of Neuroscience, 1984-1989, 1995-2000
Editorial Board, Journal of Neurocytology, 1986-2000
Editorial Board, Neuron, 1987-
Member, NIH Neurology C Study Section, 1988-1992

Editorial Board, Current Opinions in Neurobiology, 1990-2014
Councilor, Society for Neuroscience, 1990-1994
Associate Editor, Developmental Dynamics, 1991-1994
Scientific Advisory Committee, Muscular Dystrophy Association, 1991-1999
Editorial Board, Cell, 1992-2013
Board of Scientific Counselors, NINDS, NIH, 1993-1998
Publications Committee, Society for Neuroscience, 1993-1998
Editorial Board, Development, 1994-1998
Program Committee, International Society for Neurochemistry, 1994
Program Committee, International Congress for Cell Biology, 1994-1996
Gordon Conference on Neural Development, Co-Chair, 1994; Chair, 1996
Editorial Board, Molecular and Cellular Neurosciences, 1995-2015
Editorial Board, Developmental Biology, 1995-2005
Editorial Board (Monitoring Editor), Journal of Cell Biology, 1995-2013
Board of Scientific Overseers, Jackson Laboratory, 1998-2004
Neuroscience Advisory Committee, Klingenstein Simons Fund, 1998-
National Advisory, Council, NINDS, NIH, 1999 – 2003
Editorial Board, Physiological Reviews, 1999-2005
Keystone Symposium on Synapse Formation, Co-organizer, 2000
Chair, Neuroscience Program Review Committee, U. Pennsylvania, 2000
External Review Committee, Neuroscience Program, St. Jude Research Institute, 2000
Section Head for Neurodevelopment, Faculty of 1000, 2000 –2017
Co-Chair, NINDS Workshop on Spinal Cord Regeneration, 2001
Visiting Committee, Duke Neurobiology Department, 2003
Editorial Board, Cell Communication and Adhesion, 2001-2005
Editorial Board, Physiological Genomics, 2001-2003
Chair, New York State Spinal Cord Injury Board Scientific Advisory Committee, 2001
External Advisory Committee, Neuroscience Program, Hunter College (CCNY), 2001– 2002
External Advisory Committee, Neuroscience Program, Meharry Medical College, 2001–2006; chair, 2002-2006
Public Affairs Committee, Society of Neuroscience, 2001 – 2005
Councilor, American Society for Matrix Biology, 2001–2004
Scientific Advisory Board, Max-Planck Institute for Neurobiology, 2001–2012; chair, 2000-2012
Alumni Advisory Board, MBL, Woods Hole, 2001–
Scientific Initiatives Committee, ALS Association, 2001-; Steering committee, 2003-2010
Editorial Board, BMC Biology, 2002-2019
Reviewing Editor, Journal of Neuroscience, 2002– 2004
Advisory Board, Searle Scholars Program, 2003-2006; Chair, 2005, 2006
Editorial Board, Public Library of Science, Biology, 2003-2005
Scientific Advisory Board, Ataxia-Telangiectasa Children's Project, 2003-2015
Scientific Advisory Board, Howard Hughes Medical Institute, 2004-2021
Cold Spring Harbor Meeting on Axon Guidance and Neural Plasticity, Co-organizer, 2004
Chair, Visiting Committee, Tufts Neurobiology Graduate Program, 2005
Program Committee, International Brain Research Organization (IBRO), 2005
Cold Spring Harbor Meeting on Neural Imaging, Co-Organizer, 2005
Champalimaud Foundation Award Committee, 2006-
Advisory Board, Institute of Neuroscience, Shanghai, China, 2006-2012
Human Embryonic Stem Cell Research Advisory Committee, National Academy of Sciences, 2006-2010
Scientific Advisory Board, Stowers Institute, 2006-2023
Co-Editor-in-Chief, Neural Development, 2006-2015
NINDS/NIH Strategic Planning Steering Committee, 2007-2008
Scientific Advisory Board, Centre for Developmental Neurobiology, King's College London, 2007-2010
Co-organizer, Center for Developmental Biology (Kobe, Japan) Symposium on Neural Development, 2008
Scientific Review Board, Charles A. King Trust, 2009-2013
Cold Spring Harbor/Asia Crick Symposium in Neuroscience, co-organizer, 2009
Advisory Board, Neuroscience Research Unit, McGill and Montreal General Hospital, 2009-
Editorial Board, Journal of Comparative Neurology, 2009-2012
Visiting Committee, Tufts Neurobiology Graduate Program, 2009
Steering Committee, Edmund and Lily Safra Center for Brain Science, Jerusalem, 2009-; Chair, 2013-
Editorial Board, Skeletal Muscle, 2010-2015

Harvard-MIT Joint Research Grants in Neuroscience, Review Committee, 2010-
Visiting Committee, Duke Neurobiology Department, 2010
Publication Committee, National Academy of Sciences, 2010-2014
Editorial Board, Neuroscience Bulletin (Chinese Academy of Science), 2011-
NIH Workshop in "Molecular Anatomy: The Next Decade." Chair, 2011
Science/AAAS Workshop on Publications in Developmental Biology, 2012
Wellcome Trust Science Funding Selection Panel, 2012-2016
NINDS Leadership Review Committee, 2012
AAAS Neuroscience Section Committee, elected member, 2012-2016
Neuroscience Peer Review Consortium, Co-chair, 2012-2014
External Advisory Board, McGovern Institute, 2013-
NIH Advisory Committee on BRAIN Initiative, 2013-2014
Advisory Committee, Neuroscience Institute, Morehouse School of Medicine, 2013-
Montreal Neurological Institute, External Review Committee, 2013
World Economic Forum Global Agenda Council on Brain Research, 2013-2017
Search Committee, Director, NINDS, NIH, 2014
Section Chair, National Academy of Sciences, Section 24, 2014-2018
Advisory Committee, Audacious Goals Program, NEI, NIH, 2014-2020
National Academy of Sciences, Committee on Science, Technology, and Law, 2015-, executive committee, 2016-
Advisory Editor, Neural Computation, 2015-
Rosensteil Prize Jury, 2015-
Spectrum, Simons Foundation, Advisory Board, 2016-2017
External Scientific Advisory Panel, BJC Investigator Program, Washington University, 2016-
Visiting Committee, Cambridge Neuroscience, University of Cambridge, UK, 2016
Search Committee, BRAIN Initiative Director, NIH, 2016
NEI Leadership Review Committee, NIH, 2016
Officer Nominating Committee, National Academy of Sciences, 2016
Scientific Review Board, Smith Family Awards, 2016-
Search Committee, Director, Neuroscience Institute, Morehouse School of Medicine, 2017-2018
Scientific Advisory Board, Gurdon Institute, Cambridge, 2017-2018
Scientific Advisory Board, St. Jude Children's Research Hospital, 2018-2023
Chair, Review Committee, Canada-Israel Joint Research Program, 2018
National Academy of Science, Neuroscience Prize Jury, 2018
American Academy of Arts and Sciences, Section II:3 Membership Committee, 2018-2021
Scientific Advisory Board, Chinese Institute for Brain Research, Beijing, 2018-
Gruber Foundation, Neuroscience Prize Jury, 2019-2022 and 2024-
National Academy of Sciences, Committee on Neural Organoids and Chimeras, co-chair, 2020-2021
Scientific Advisory Board, Max-Planck Institute for Brain Research, Frankfort - Vice-chair, 2020; Chair, 2023
Visiting Committee, VIB-Leuven Center for Brain & Disease Research, Chair, 2020
Scientific Advisory Board, K. Lisa Yang and Hock E. Tan Center for Molecular Therapeutics at MIT, 2022-
National Academy of Sciences and Dana Foundation Workshop on Neuroethics, chair, 2022
Transmitter, Simons Foundation, Contributing Editor, 2023-

UNIVERSITY COMMITTEES

Washington University
Neuroscience Steering Committee 1982-2003
Anatomy and Neurobiology - Faculty Search Committees - 1993-2003
Molecular Biology and Pharmacology - Faculty Search Committee - 1996
Neuroscience Program Admissions Committee 1982-1985
Hamburger Lecture Organizing Committee 1986-1997
Research Support Assessment Steering Committee, 1998
Director, Neuroscience Graduate Program, Washington University, 1997-2002
Seminar Committees, Department of Anatomy and Neurobiology, and Neurobiology Program, 1997-2004
Director, Neuroscience Transgenic Mouse Core, Washington University, 1998-2000
Co-organizer, Brain Awareness Week Coordinating Committee, Washington University, 1997-2001
Governance Committee, Center for Development Biology, 2000-2002
Committee on the Future of Fundamental Research, 2000
Director, Mouse Genetics Core Facility, Washington University, 2000-2004
Co-chair, Organizing Committee, Sesquecentennial Symposium on Neuroscience, 2003

Harvard University
Center for Brain Science, Paul J. Finnegan Director, 2004-2020
Graduate Program in Neuroscience, 2004-
Northwest Building Oversight Committee, Co-chair, 2004-2010
Molecular and Cellular Biology Faculty Search Committee, 2004-2012 (several)
Center for Brain Science Faculty Search Committee, 2005-2018 (several)
Mind-Brain-Behavior Standing Committee, 2004-
Harvard Intergrated Life Science (HILS) Program Coordinating Committee, 2004-2018
Molecular and Cellular Biology, Executive Committee, 2005-2010
Faculty of Arts and Sciences, Resource Committee, 2005-2009
Life Science Executive Committee, (renamed Science Council) 2005-2012
Harvard Center for Neurodegeneration and Repair Scientific Advisory Committee, 2005
Harvard University-wide Neuroscience Coordinating Committee, Co-chair, 2006-2009
Neurobiology Concentration Standing Committee, 2006-
Graduate Program in Neuroscience Steering Committee, 2007-2018
Hoopes Prize Committee, 2009-
Scientific Advisory Board, Center for Regenerative Medicine, MGH, 2009-
eProtocol coordinating committee, 2011-2013
Mind-Brain-Behavior Steering Committee, 2011-
Harvard Brain Initiative, Co-director, 2013-2020
University Committee on Rights and Responsibilities, 2015-

TEACHING

Washington University
Introduction to Neurobiology (undergraduate course, initially with D. Purves, later solo) 1980-1985
Neuroscience (first year medical students, lectures) 1980-1999
Scientific Ethics (graduate students, multiple years)
Developmental Neurobiology (first year graduate students, designed course and served as coursemaster or co- coursemaster) 1988-1997
Oral Presentation (second year graduate students, designed course and served as co-coursemaster) 1995-1997
Cellular and Molecular Neuroscience (first year graduate students, section on development) 1999-2003
Occasional lectures in graduate courses in Cell Biology, Matrix Biology, Cellular Neuroscience, and Developmental Biology

Harvard University
HST 130 /Neuro 200. Introduction to Neuroscience. Lecturer. 2004-2007
MCB 210. Interesting Questions in Modern Biology. Module leader. 2005
OEB 174r. Topics in Behavioral Ecology. Assistant director (Naomi Pierce, director) 2005
BS 80. Behavioral Neuroscience. 2006. Co-director; gave ½ of lectures. (160 undergraduate students)
MCB 80. Behavioral Neuroscience. 2007-2016. Co-director; gave ½ of lectures. (150-300 undergraduate students)
MCB 292. Cell, Developmental and Neurobiology. 2018-present; Co-director. (overview course for first year graduate students)
NB311. Classics in Visual Neuroscience. 2019 Lecturer. (upper level graduate course)
MCB143. Neurobiology of Vision and Blindness. 2019-present. Sole teacher. (upper level undergraduate course)

Other
Summer courses at Cold Spring Harbor and/or Woods Hole, annually, 1982-2010, 2013-2015
PhD Program in Biomedicine, Gulbenkian Institute, Lisbon, Portugal, 2002
Co-director (with Ben Barres), Developmental Neurobiology, Cold Spring Harbor, 2003

PUBLICATIONS

1. Kuo JF, Krueger BK, Sanes JR and Greengard P: Cyclic nucleotide dependent protein kinases--V. Preparation and properties of adenosine 3',5'-monophosphate dependent protein kinase from various bovine tissues. Biochem. Biophys. Acta 1970; 212:79-91.

2. Kuo JF, Sanes J and Greengard P: Guanosine 3',5'-monophosphate-dependent protein kinases. Federation Proceedings 1970; 29:601.

3. Krueger B and Sanes J: Cyclic AMP and information transfer. Yale Scientific 1970; 44:2-6.

4. Sanes JR and Zigler E: Premorbid social competence in schizophrenia. J. Abnormal Psych. 1971; 78:140-144.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: SWAROOP, ANAND

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

POSITION TITLE: Senior Investigator and Chief, Neurobiology, Neurodegeneration & Repair Laboratory

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
G.B. Pant University, Pantnagar, India	M.Sc.	06/1977	Biochemistry
Indian Institute of Science, Bangalore, India	Ph.D.	06/1982	Biochemistry (laboratory of Prof. T. Ramasarma)
Dept. of Molecular Biophysics & Biochemistry, Yale University, New Haven, CT	Post-doc	06/1986	Biochemistry (laboratory of Prof. Alan Garen)
Dept. of Human Genetics, Yale University School of Medicine, New Haven, CT	Assoc. Res. Scientist	07/1987	Laboratory of Prof. Uta Francke
Dept. of Human Genetics, Yale University School of Medicine, New Haven, CT	NRSA Postdoc	08/1988	Laboratory of Prof. Sherman M. Weissman
Dept. of Human Genetics, Yale University School of Medicine, New Haven, CT	Assoc. Res. Scientist	09/1989	Laboratory of Prof. Sherman M. Weissman

A. Research Statement

The studies in my laboratory have focused primarily on (i) genetic and epigenetic regulation of retinal photoreceptor development, evolution, and aging, (ii) genetic defects and mechanisms of photoreceptor dysfunction in retinal neurodegeneration, especially focusing on retinitis pigmentosa and Leber congenital amaurosis, (iii) genetics and biology of age-related macular degeneration, and (iv) design of new therapeutic paradigms using cell, gene or small molecule-based approaches.

Total Publications: 407. Scopus – *h*-index, 86; citations, 39,625; as of 11/08/2023
Google Scholar – *h*-index: 100; *i10* index: 322; citations: 41,915. Since 2018: 19,221
A complete list of publications can be obtained at https://pubmed.ncbi.nlm.nih.gov/?term=swaroop+a

B. Positions and Employment

1990-96	Assistant Professor, Department of Ophthalmology, University of Michigan, Ann Arbor, MI.
1990-98	Assistant Professor, Department of Human Genetics, University of Michigan, Ann Arbor, MI.
1991-2007	Faculty Member, Graduate Program in Cellular & Molecular Biology.
1996-2000	Associate Professor, Department of Ophthalmology & Visual Sciences.
1996-2007	Faculty Member, Neuroscience Graduate Program.
1998-2002	Associate Professor, Department of Human Genetics
2000-2007	Professor, Department of Ophthalmology and Visual Sciences
2000-2000	Scientist (on sabbatical for 6 months), Laboratory of Genetics, Salk Institute, La Jolla, CA
2001-2007	Coordinator/Director, Center for Retinal and Macular Degeneration, University of Michigan
2002-2007	Professor, Department of Human Genetics
2003-2007	Harold F. Falls Collegiate Professor of Ophthalmology & Visual Sciences
Sept 2007–	Senior Investigator and Chief, Neurobiology-Neurodegeneration and Repair Laboratory (N-NRL), National Eye Institute, National Institutes of Health, Bethesda, MD.
2015–2016	Distinguishing Medical Scientist (visiting) for Prof. P.N. Chhuttani Chair, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India.

Select Scientific Activities

- Chair, Appointments and Promotions Committee at UM Ophthalmology & Visual Sciences, 2005–2007.
- Member, UM Med SchAdvisory Committee for Appointments, Promotions and Tenure, 2006–2007.
- Chair, Organizing Committee, NEI 40th Anniversary Symposia on "Genetics and Genomics in Vision", April 16-17, 2009; "Neuroscience and Vision", November 19-20, 2009; "Focus on Glaucoma", February 18-19, 2010; "Translational Research and Vision", June 24-25, 2010; Search Committee for Basic Science Tenure Track Investigator(s), NINDS. 2010; Review Committee for NiPSCC, NIH. 2010; Search Committee for NEI Clinical Tenure Track position, 2010-11. Scientific Advisory Board and Selection Committee of the Institut de la Vision, Paris, France. 2011. Genetics of Health and Disease study section, 2012. Reviewer for NIH Director's Challenge Awards, 2012. The Thiel Foundation, 2012. Federal Panel for NEI Audacious Goals Initiative, 2012-13. International Advisory Committee, Asia-ARVO in New Delhi, India, 2013. Genetics Advisory Committee, The Diabetic Retinopathy Clinical Research Network (DRCR.net). Scientific Advisory Board, GenSight Biologics, Paris, France. 2014. NEI-IRP Planning Committee 2014. Scientific Advisory Board, FFB Usher Syndrome therapy, 2014.
- Co-Editor with Dr. Emily Chew for Age-related Macular Degeneration: From Clinic to Genes and Back to Patient Management. Advances in Experimental Medicine and Biology, volume 1256. Springer. 2021
- Reviewer of 25-30 papers every year for several journals, including Cell journals, PLoS journals, Nature journals, Science, AJHG, IOVS, HMG, JBC, PNAS, JCI, J. Neurosci, NEJM, among others
- Editorial Boards. *IOVS*, June 2002–Dec 2007. *Molecular Vision*, 1995– . *Cilia*, 2011 – . PLoS One, 2012-. Advisory Board Member, *EBioMedicine*, 2017– **;** Guest Editor, Special Issue on Vision and Novel Therapeutics, *Clinical Genetics*, Wiley. August 2013. Guest Editor for manuscripts: *PNAS*, *PLoS Genetics.* Member, Editorial Advisory Board, *Progress in Retinal and Eye Research, March 2018 – .*
- Reviewer of grants for numerous foundations: The Foundation Fighting Blindness; The Wellcome Trust, U.K.; Comitato Promotore Telethon, Italy; The South Africa Retinitis Pigmentosa Foundation; The Medical Research Council of Canada; Canadian Foundation Fighting Blindness; ANR-BBSRC, UK; Juvenile Diabetes Research Foundation, National Science Foundation; Austrian Science Fund; ANR/ French National Research Agency, France. Deutsche Forschungsgemeinschaft (DFG), Germany; Action Medical Research for Children, U.K.; Medical Research Council, UK.; Swiss National Science Foundation, Switzerland; Israel Science Foundation, Israel; Netherlands Organisation for Scientific Research, Netherlands; Medical Research Council, UK; Macula Society, UK
- Since 2019, Grants Review Panels for Deutsche Forschungsgemeinschaft (DFG), Germany. Austrian Science Fund. Wellcome Trust-DBT India Alliance, Medical Research Council, UK. Israel Ministry of Science & Technology. Israel Science Foundation. Retina, UK. Swiss National Science Foundation, Bern, Switzerland. Transformative Res Awards Panel, Fighting Blindness Canada, Toronto, Canada.
- Federal Evaluator, "Follow that Cell" Challenge. NIH Common Fund, NIH. 3D Retina Organoid Challenge, 2017, NEI/NIH. Co-Chair, 2020 Stadtman Investigator Neurodevelopment search committee. Quad Review Committee, 2021**.** Member, 2021 NIH Stadtman Investigator Neurodevelop-ment Search Committee. Member, Genes to Disease Mechanisms workgroup for 2021 NEI Strategic Plan. Member, Search Committee for Senior Scientist and Director of the Translational Bioengineering Program (TBP), Early Translation Branch, NCATS, NIH. 2022. Scientific Advisory Committee, Institut de la Vision, Paris, 2023. Co-Chair, Stadtman Investigator Search Committee on Stem Cells, 2023.
- Member (Current and Past): AAAS, ASHG, SFN, Association for Research in Vision and Ophthalmology, American Society for Biochemistry and Molecular Biology**,** Indian Institute of Science Alumni Association of North America, Alumni Almamater Advancement Association, Pantnagar, India**,** Society for Redox Biology and Medicine
- Senior Advisory Group founder/member, NIH India. Member, Federation of AANHPI Networks (FAN).
- Many patents and disclosures.
- *329 invited talks* at institutions & conferences, including many named and keynote lectures since 1991.
- *Mentored over 300 undergraduate/masters students and residents, 15 graduate students, 50+ post-doctoral fellows and scientists. A vast majority are now clinicians and scientists worldwide.*

Select Honors and Awards

- The Foundation Fighting Blindness Board of Directors Award in recognition of outstanding research achievements, January 26, 2007.

- Distinguished Faculty Lectureship Award, 2007. The highest honor bestowed by the Univ of Michigan Medical School on a scientist/faculty member.
- Bireswar Chakrabarti Memorial Oration, awarded by Indian Eye Research Group at their 17th annual meeting in Madurai, India. July 26-27, 2008.
- Inducted in the inaugural class of ARVO Fellows, ARVO Silver Fellow, 2009. ARVO Gold Fellow, 2012.
- Director's Award, National Eye Institute, 2010.
- Alcon Research Institute Award, 2011.
- NIH Director's Ruth L. Kirschstein Award "For exemplary performance while demonstrating significant leadership, skill and ability in serving as a mentor," June 2013.
- Distinguished Medical Scientist (visiting), Prof. P.N. Chhuttani Chair, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India. July 2015, Feb-Mar 2016.
- The 2019 Outstanding Alumnus of College of Basic Sciences & Humanities, G.B. Pant University of Agriculture & Technology, Pantnagar, India. November 2019.
- The 2020 National Eye Institute Director's Diversity Champion Award "in recognition of a long-standing commitment to diversity, equity and inclusion."
- The 2022 NEI Director's Award "in recognition of trans-institute collaboration and exemplary teamwork to distill, prioritize, and translate the NEI Strategic Plan into concrete implementable actions."
- The 2024 ARVO Friedenwald Award for outstanding contributions to vision science. To be presented at ARVO annual meeting in May 2024, in Seattle, USA.
- The 2024 Ludwig von Sallman Prize. To be conferred at the XXVI Biennial Meeting of the International Society for Eye Research (ISER) in October, 2024, in Buenos Aires, Argentina.

C. Contributions to Science

1. Genetic and Epigenetic Regulation of Retinal Development, Aging and Evolution

Our goals are to elucidate gene regulatory networks that guide differentiation of photoreceptor subtypes in the mouse and human retina and in retinal organoids derived from embryonic or induced pluripotent stem cells (iPSCs). We are investigating transcriptional, epigenetic as well as post-transcriptional regulation of retinal development, aging and evolution. NRL, discovered in my laboratory, is a critical determinant of photoreceptor cell fate; its loss results in complete lack of rods with concomitant gain of S-cones, and ectopic expression of NRL generates rods from photoreceptor precursors. Disruption of gene networks mediated by NRL and it's interactor CRX leads to vision impairment and blindness. We have developed conceptual framework for evolution of rods from S-cones and examining the evolution of nocturnality using large scale RNA-seq data analysis.

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4. **Swaroop A**, Kim D, Forrest D: Transcriptional regulation of photoreceptor development and homeostasis in the mammalian retina. *Nat Rev Neurosci*. 11:563-576, 2010. PMID: 20648062
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10. Qu Z, Batz Z, Singh N, Marchal C, **Swaroop A**: Stage-specific reorganization of genome topology shapes transcriptional neighborhoods in developing human retinal organoids. *Cell Rep*. Accepted.
11. Corso Diaz X, Liang X, Dandewad V, Preston K, Nellissery J, **Swaroop A**: Cell type-specific Maf-family bZIP transcription factor NRL modulates R-loop dynamics through interactions with ubiquitously expressed RNA binding proteins.

2. Inherited retinal degeneration, development of pre-clinical models and therapies

My scientific career in the retina began with research on X-linked forms of retinitis pigmentosa (RP) and later expanded to other inherited diseases such as Leber congenital amaurosis (LCA) and ciliopathies with photoreceptor death as a highly penetrant phenotype. Over the years, my laboratory (in collaboration with clinicians worldwide) has identified mutations in two genes - *RPGR* and *RP2* - in hundreds of RP patients and discovered that mutated *RPGR* constitute the most common cause of RP, accounting for 15-20% of all patients. We developed several mouse models for *RPGR* and *RP2* disease and demonstrated successful AAV-based gene replacement therapy for both forms in preclinical models. My group has also been involved in discovering several RP and LCA genes. In collaborative studies, we have identified mutations in genes including *NRL*, *NR2E3*, *CRX*, *CEP290*, *NPHP5*, *RD3*, *RD11, CERKL, GUCY2D*, *EYS*, *ALMS1*, *IDH3A*, *CEP78*, among others.

Primary cilium acts as the sensory organelle in most cells and altered biogenesis or function of cilium can lead to pleiotropic phenotypes. My lab identified a cilia-centrosomal gene *CEP290* by studying the retinal degeneration (rd) 16 mouse model and as a cause of Joubert syndrome. CEP290 has turned out to be a very important protein that is likely involved in ciliary gating during photoreceptor outer segment biogenesis. Mutations in *CEP290* account for 20-25% of LCA and many other syndromic ciliopathies. We have also been involved in elucidating how mutations in several ciliopathy genes (specifically *CEP290*, *NPHP5* and *CC2D2A*) cause defects in cilia biogenesis using animal models and stem cell derived organoids and suggested novel insights for developing therapy.

Our focus has also been on developing gene-independent therapy paradigms by identifying common cellular pathways that are induced in early stages of retinal degeneration and targeting specific nodal proteins for drug discovery. Given that rod photoreceptors are more vulnerable to genetic insult and many RP genes are highly expressed in rods, our lab used AAV-delivered CRISPR-CAS9 to knockdown the master regulator NRL in rods and demonstrated rescue of cone function in different mouse models. We have identifying novel targets for drug discovery to rescue photoreceptor cell death in inherited retinal degeneration by network analysis and machine learning.

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3. Genetic architecture of age-related macular degeneration

In late 1990s, our group was among the first to identify genetic loci for advanced AMD by high-resolution genome scan (2004), the association of Complement Factor H (Y402H), and even larger

contribution of non-coding variants to disease (2005-2006). In 2010, we reported a large genome-wide association study (GWAS) identifying several additional AMD susceptibility loci. We hypothesized that most associated variants impact AMD progression and pathology through their effect on context- or tissue-specific gene regulation. Our group generated transcriptomes of over 400 human donor retinas from healthy and disease individuals and performed eQTL analysis to uncover the role of non-coding variants in regulating the expression of retinal genes (2019). Integrating this data with AMD GWAS helped in identifying the target genes at six loci. We developed the largest resource of transcriptome and eQTLs from human retina and identified genes and pathways associated with AMD. We have identified retinal mQTLs and sQTLs and their relationship to AMD target genes. We have constructed a comprehensive high resolution genome topology map and transcriptional regulatory networks of the adult human retina and of developing human retinal organoids, with a goal to identify how genetic variants modify or cause healthy and disease retinal phenotypes (focusing on AMD and glaucoma).

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4. Stem Cell based modeling and therapies of retinal diseases

My laboratory has been developing therapies for LCA caused by *CEP290*, *NPHP5* and *CRX* using stem cell-based approaches combined with gene therapy and small molecule screening. For dominant *CRX*-LCA, we established AAV gene therapy approach for which a patent application has been filed by NEI.

Organoid-derived photoreceptors have been employed for high throughput screening to rescue *CEP290*-LCA phenotypes in retinal organoids. A multiplex screening platform was designed for selecting drug candidates that maintain photoreceptor survival (in collaboration with NCATS). Four different molecules including Reserpine that survived multiple screening assays are good candidates for potential therapeutic intervention and are part of a patent application submitted by NEI. We have used Reserpine and other molecules to preserve photoreceptor function in P23H rhodopsin rat model of ADRP. Our goal is to identify small molecules that can be used for treatment of retinal degeneration in a gene-agnostic manner and deliver these by eye drop formulations.

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