BIOGRAPHICAL SKETCH

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NAME: Shannon E. Boye

eRA COMMONS USER NAME BOYESH

POSITION TITLE: Associate Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Fairleigh Dickinson University- Madison, NJ	BS	2001	Marine Biology/Chemistry
University of Florida- Gainesville, FL	PhD	2006	Neuroscience
University of Florida- Gainesville, FL	Postdoctoral	2006-2008	Ophthalmology/Gene Therapy

A. Personal Statement

The focus of my research is developing viral vector-based gene therapies for the treatment of inherited ocular disease. My current focus areas are:

1. to develop AAV-based gene therapy approaches for delivery of genes to the outer retina (notably foveal cones)
2. to develop an Adeno associated virus (AAV)-based gene therapy for treatment of autosomal recessive *GUCY2D*-Leber congenital amaurosis-1 (LCA1)
3. to develop dual AAV vector platforms that are capable of delivering large transgenes (> 5kb)
4. to develop a AAV-CRISPR/Cas9-based therapies for dominant inherited retinal disease
5. to develop AAV-based gene therapy approaches for delivery of genes to the trabecular meshwork to address treatments for primary open angle glaucoma

I have extensive experience characterizing animal models of inherited retinal disease, developing novel AAV vectors via both rational design and directed evolution, and testing these vectors for their ability to deliver genes to animal models of retinal disease and normal macaques. The work my team conducted over the last 15 years established that gene replacement restores retinal function/visually guided behavior, and preserves retinal structure over the long term in models of autosomal recessive LCA1. As a result, the FDA recently granted us IND approval to treat patients afflicted with this devastating form of blindness (clinical trials will begin in fall 2019). My record of accomplishment performing longitudinal gene therapy studies, and the outcome measures I routinely employ make me well suited to serve as a major user of the equipment outlined in this proposal. I have three awarded patents, and eight pending patents emanating from my research program and am actively funded by the NIH, private foundations, and pharma. I am the recipient of several major awards including the Foundation Fighting Blindness's Board of Director's Award, the Gund Harrington Scholar Award, the ARVO Foundation/Merck Innovative Ophthalmology Research Award, and the ARVO/Pfizer Carl Camras Translational Research Award. Since 2010, I have given over 60 invited lectures both within and outside the USA. I have served as a member of study sections both for the NIH and the Department of Defense. I was the recipient of the NIH's Loan Repayment Award, currently serve as an LRP ambassador and serve on study sections to review new proposals to this grant mechanism. I perform grant review for various other national and international foundations, serve on the editorial advisory board for multiple journals and perform *ad hoc* peer review for many more. I have participated in workshops including the NIH's Office of Science Policy/Office of Biotechnology Activities "Gene Therapy: Charting a Future Course". Outside of my research, I am actively involved in the teaching mission of the Department of Ophthalmology and College of Medicine at the University of Florida and am passionate about outreach/education outside the University. I routinely provide lab tours for visually impaired patients, host foundation meetings and educate patients about ongoing research being conducted to address treatments for their conditions/provide them with information on how to find out more about their disease.

B. Positions and Honors

Positions

2000-	National Science Foundation REU intern, University of Florida Whitney Marine Lab
2001-2006-	Graduate Research Assistant, Department of Neuroscience, University of Florida
2002-	US Naval intern, SPAWAR, San Diego CA
2004-	Graduate Teaching Assistant, Department of Neuroscience, University of Florida
2006-2008	Postdoctoral fellow, Department of Ophthalmology, University of Florida
2008-2012	Research Assistant Professor, Department of Ophthalmology, University of Florida
2012-present	Assistant Professor, Department of Ophthalmology, University of Florida
2012-present	Assistant Professor, Department of Molecular Genetics and Microbiology, University of Florida
2017-present	Associate Professor, Department of Ophthalmology, University of Florida
2017-present	Associate Professor, Department of Molecular Genetics and Microbiology, University of Florida

Honors

2001	Cum Laude graduation honors from Fairleigh Dickinson University
2001-2005	Alumni Fellowship from University of Florida's College of Medicine
2002	Office of Naval Research Enterprise Fellowship
2006	Department of Ophthalmology Training Grant
2008	National Institute of Health Pediatric Loan Repayment Award
2010	National Institute of Health Pediatric Loan Repayment Award Renewal
2012	Acceptance into the NIH Early Career Reviewer (ECR) Program
2013	ARVO Foundation/Merck Innovative Ophthalmology Research Award in Gene Therapy and Eye Disease Prize
2013	"Exceptionally Good Review" ranking from *IOVS*
2014	Travel Fellowship for XVIth International Symposium on Retinal Degenerations
2014	Exemplary Teacher Award, University of Florida College of Medicine
2014	Technology Innovator Award from University of Florida Office of Tech Licensing
2015	Foundation Fighting Blindness Board of Director's Award
2015	Nominated to speak at 2015 IDP Commencement Ceremony
2016	UF nominee for Life Sciences Category for The Blavatnik Awards for Young Scientists
2016	MOMs for Sight Visionary Award
2017	Gund Harrington Scholar Award
2017	University of Florida Term Professorship
2017	Exemplary Teacher Award, University of Florida College of Medicine
2018	ARVO Foundation/Pfizer Carl Camras Translational Research Award
2018	Exemplary Teacher Award, University of Florida College of Medicine
2019	University of Florida Research Foundation Professorship

C. Contribution to Science

My overarching contribution to science has been to advance the field of retinal gene therapy. Major contributions thus far are listed below:

1. **Developing a gene therapy for *GUCY2D*-Leber congenital amaurosis (LCA1) which is now slated for clinical application**. My doctoral research at the University of Florida was to develop a gene therapy for a devastating form of pediatric blindness- *GUCY2D* LCA1. I continued to focus on this disease as a postdoc in the Department of Ophthalmology under the mentorship of Dr. William Hauswirth. It was during that time that I discovered the necessary components (viral vector, capsid and transgene cassette) that efficiently conferred therapy. I have now successfully restored retinal function and useful vision over the long term in 3 different mouse models of LCA1. Results were summarized in 5 manuscripts. In 2014 I partnered with Genzyme/Sanofi to conduct the final pre-clinical studies necessary to file an IND and bring a gene therapy

for LCA1 into the clinic. This will be one of the first gene therapies targeted to retinal photoreceptors. A press release from Genzyme and a story on ABC news highlight this work.

- http://abc30.com/health/gene-therapy-hope-for-the-blind/551753/
- Samuel G. Jacobson, Artur V. Cideciyan, Alexander Sumaroka, Alejandro J. Roman, Jason Charng, Monica Lu, Shreyasi Choudhury, Sharon B. Schwartz, Elise Heon, Gerald A. Fishman and Shannon E. Boye. Defining Outcomes for Clinical Trials of Leber Congenital Amaurosis caused by GUCY2D Mutations. *American Journal of Ophthalmology*. 2017 May;177:44-57. doi: 10.1016/j.ajo.2017.02.003
- US patent # 9,816,108 "rAAV- Guanylate Cyclase Compositions and Methods for Treating Leber's Congenital Amaurosis"- Licensed to Genzyme/Sanofi in December, 2017

2. **Evaluating gene therapy vectors in a clinically relevant species**. Proof of concept work to develop AAV gene therapies for inherited retinal disease has been done primarily in rodent models. An emerging question is how these AAV vectors will perform in a species with ocular characteristics most similar to man. In collaboration with Paul Gamlin, Ph.D., C. Douglas Witherspoon, M.D., and Steve Breaud, M.D. at UAB, I have evaluated the transduction profile of various AAV serotypes being considered for clinical application in non-human primate (NHP), a novel surgical technique to increase transduction of retinal neurons by AAV, and developed a method for generating NHPs with sortable photoreceptors and ganglion cells that may be used to screen novel capsid libraries. One such study informed the choice of vector serotype for the clinical treatment of LCA1 (see below). For this study, I was awarded the ARVO Foundation/Merck Innovative Ophthalmology Research Award and the cover image in *Human Gene Therapy*. This type of research is essential as more gene therapies for inherited retinal disease advance to the clinic. For this reason, I am currently funded via multiple grant mechanisms to evaluate novel AAV capsid variants and surgical approaches for targeting genes to NHP neural retina. A major goal is to develop a novel AAV serotype via rational design and/or directed evolution with the capability of transducing photoreceptors following intravitreal injection.

   - Shannon E. Boye, Alexander JJ, Boye SL, Witherspoon CD, Sandefer KJ, Conlon TJ, Erger K, Sun J, Ryals R, Chiodo VA, Clark ME, Girkin CA, Hauswirth WW, Gamlin PD: "Evaluating the human GRK1 promoter in conjunction with AAV5 as a means of photoreceptor specific expression in primate retina," *Hum Gene Ther*. 2012 Oct;23(10):1101-15. http://www.ncbi.nlm.nih.gov/pubmed/22845794
   - Shannon E. Boye, John J. Alexander, C. Douglas Witherspoon, Sanford L. Boye, James J. Peterson, Mark E. Clark, Kristen J. Sandefer, Chris A. Girkin, William W. Hauswirth, Paul D. Gamlin. Highly Efficient Delivery of AAV vectors to the Primate Retina. *Human Gene Therapy* 2016. Aug;27(8):580-97. https://www.ncbi.nlm.nih.gov/pubmed/27439313
   - Shreyasi Choudhury, Christianne E. Strang, John J. Alexander, Miranda L. Scalabrino, Julie Lynch Hill, Daniel T. Kasuga, C. Douglas Witherspoon, Sanford L. Boye, Paul D. Gamlin, and Shannon E. Boye. Novel Methodology for Creating Macaque Retinas with Sortable Cell Populations. *Frontiers Neuroscience*, 2016 Dec 1;10:551. eCollection 2016. https://www.ncbi.nlm.nih.gov/pubmed/27990105

3. **Developing treatments for inherited retinal disease associated with mutations in large genes**. Another major hurdle in the field of retinal gene therapy is how to efficiently deliver large therapeutic genes to photoreceptors. A limitation of AAV is its relatively modest genetic payload capacity. Despite this, it is to date the only viral (and non-viral) vector capable of efficiently transducing photoreceptors. To overcome the size limitation, I have developed dual AAV vector platforms wherein the therapeutic gene is split in half and delivered via two different, matched vectors. Once inside the cell, the matching halves recombine to form full length gene. I recently validated the safety of this approach by evaluating sequence fidelity in the area of recombination. I am currently funded to use dual AAV vectors to develop a gene therapy for a severe deaf-blinding condition, Ushers syndrome 1B.

   - Frank M. Dyka, Sanford L. Boye, Vince A. Chiodo, William W. Hauswirth, Shannon E. Boye. Dual adeno-associated virus vectors result in efficient in vitro and in vivo expression of an oversized

gene, MYO7A. *Hum Gene Ther Methods*. 2014 Apr;25(2):166-77. http://www.ncbi.nlm.nih.gov/pubmed/24568220

- Vanda Lopes*, Shannon E. Boye**, Carrie M. Louie, Sanford Boye, Frank Dyka, Vince Chiodo, William W. Hauswirth, and D. S. Williams. 2013. Retinal gene therapy with a large MYO7A cDNA using adeno-associated virus. *Gene Therapy.* 20/8: 824-33.
  *equal contribution
  http://www.ncbi.nlm.nih.gov/pubmed/23344065

For my contributions to the discipline, I was selected as one of two retinal gene therapists in the country to attend the NIH workshop, "Gene Therapy: Charting a Future Course" in 2013. My talk, entitled, "Ocular Gene Therapy: an update and what's on the horizon" summarized the major hurdles we continue to face in the field and how best to overcome them. Relevant topics included how to treat diseases associated with mutations in large genes, how to safely target foveal cones without losing visual acuity and, importantly, how to expedite the approval process/path to clinical application. With my input, ideas for funding and policy initiatives were generated to help transition the field of gene therapy into its next phase- mainstream medical practice.

D. Additional Information: Research Support and/or Scholastic Performance:

Peer reviewed manuscripts: (52 total, h-index 25)
https://www.ncbi.nlm.nih.gov/myncbi/shannon.boye.1/bibliography/public/

Research Support:

Ongoing Research Support:

1. Title: R01 EY024280 "Developing Efficient AAV Vectors for Photoreceptor Targeting via the Vitreous"
   Funding Agency: National Eye Institute
   Role: **PI**
   Effective Dates: 6/1/2014-5/31/2019
   The major goal of this research is to develop novel AAV variants via both rational design and directed evolution that are optimized for retinal transduction following intravitreal injection.

2. Title: "Cas9 mediated gene editing therapy for CORD6 cone rod dystrophy"
   Funding Agency: Editas
   Role: **PI**
   Effective Dates: 11/1/2017-12/31/2019
   The major goals of this project are to identify the appropriate dose of Cas9 and evaluate efficacy of gene editing in mouse.

3. Title: R01 EY025752 "Therapy development in canine models of open angle glaucoma"
   Funding Agency: National Eye Institute
   Role: **Subproject PI** (PI- Komaromy)
   Effective Dates- 5/1/2017-4/30/2022
   The major goals of this project are to design AAVs optimized for transduction of trabecular meshwork and to correct the phenotype of the ADAMTS10 dog model of primary open angle glaucoma.

4. Title: R01 NS102624 "Optimizing AAV Vectors for Central Nervous System Transduction"
   Funding Agency: NINDS
   Role: **Collaborator** (PI- Heldermon)
   Effective Dates: 08/01/2017 – 05/31/2022
   The major goal of this research is to improve upon current CNS-directed gene therapy approaches for Sanfilippo Syndrome and neurodegenerative disease.

5. R01 EY027767 "Vascular Gene Delivery and Early Disease Biomarkers in Diabetic Retinopathy"
   Funding Agency: National Eye Institute
   Role: **Subproject PI** (PI- Daniel Lipinski, Ph.D.)

Dates: 9/30/2018-8/31/2023
The major goal of this project is develop AAV vectors targeted to vascular endothelial cells of the retina. This in in collaboration with Daniel Lipinski at MCW who is investigating therapeutic approaches for diabetic retinopathy.

Completed Research Support (Role- PI)

1. Title: "Gene Therapy for LCA1"
   Funding Agency: Genzyme/Sanofi
   Role: **PI**
   Effective Dates: 3/1/2014-12/31/2018
   The major goal of this research is to obtain IND approval for clinical application of a gene therapy for GUCY2D LCA1.

2. Title: "AAV- mediated optogenetic gene therapy in bipolar cells"
   Funding Agency: Applied Genetics Technology Corporation (AGTC, Inc.)
   Role: **PI**
   Effective Dates: 2/1/16-1/31/18
   The major goal of this project was to develop an optogentic mediated gene therapy targeted to bipolar cells for the treatment of patients with advanced photoreceptor degeneration.

3. Title: "Cas9 mediated in vivo gene editing of photoreceptors in the nonhuman primate and in a mouse model of cone rod dystrophy"
   Funding Agency: Editas Medicine
   Role: **PI**
   Effective Dates: 2/1/2016-3/31/2017
   The major goal of this project was to establish proof of concept for Crispr-Cas9 mediated gene editing in mouse and non-human primate retina

4. Title: "Dual AAV vector-mediated therapy for Myosin7a Usher syndrome (USH1B)"
   Funding Agency: Foundation Fighting Blindness (FFB)
   Role: **PI**
   Effective dates: 6/2014-2/2017
   The major goals of this project were to 1) evaluate the efficacy of dual AAV vector platforms for their ability to drive MYO7A expression and rescue the phenotype of a mouse model of Usher syndrome 1B and 2) evaluate vectors in NHP to identify the best dual vector platform for clinical application.

5. Title: "Targeting Foveal Cones Using Novel Delivery Methods and Novel AAV Serotypes"
   Funding Agency: Foundation Fighting Blindness (FFB)
   Role: **PI**
   Effective Dates: 6/30/2012-6/29/2015
   Preliminary data obtained with this funding was used in a successful R01 application

6. Title: "Non-human primate studies in support of RPGR-XLRP"
   Funding Agency: Applied Genetics Technology Corporation (AGTC, Inc.)
   Role: **PI**
   Effective dates: 10/1/14-9/30/15
   This research provided confirmation of promoter activity in NHP and ultimately informed design of clinical AAV vector for treatment of RPGR XLRP.