BIOGRAPHICAL SKETCH

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NAME: Rex, Tonia S.

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

POSITION TITLE: Associate Professor of Ophthalmology & Visual Sciences

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Oakland University, Rochester, MI	B.S.	05/95	Biochemistry
University of California, Santa Barbara, CA	M.A.	06/97	Molecular, Cellular and Developmental Biology
University of California, Santa Barbara, CA	Ph.D.	05/01	Molecular, Cellular and Developmental Biology
University of Pennsylvania, Philadelphia, PA	Postdoc.	07/07	Retinal Gene Therapy

A. Personal Statement

My laboratory studies mechanisms and neuroprotective strategies in complex neurodegenerations of the visual system including glaucoma and trauma. We have both pre-clinical and clinical studies ongoing. We developed a mouse model of eye blast trauma that induces vision loss in the absence of trauma to the head or trunk of the body. We have discovered that repeat, low-level air-blast exposure induces an indirect traumatic optic neuropathy (ITON) with timing that is similar to that reported in patients. In particular, repeat blast exposure causes loss of 50% of optic nerve axons by 1-month after injury. Our data supports a role of oxidative stress and inflammation in causing this delayed axon degeneration and vision loss. More specifically, we detect activation of the IL-1 pathway and a role of this pathway in the secondary neurodegeneration. We are actively investigating therapeutics to preserve or restore sight after blast-induced ITON using pharmacological, gene therapy, microparticle, and cell replacement therapy approaches.

B. Positions and Honors

Positions and Employment

1992-1995 Undergraduate Research Assistant, Eye Research Institute, Oakland University
1995-2001 Graduate Research Assistant, Neuroscience Research Institute, UCSB
2001-2004 Postdoctoral Fellow, F.M. Kirby Center for Molecular Ophthalmology, U.Penn.
2004-2007 Research Associate, F.M. Kirby Center for Molecular Ophthalmology, U.Penn.
2007-2012 Assistant Professor of Ophthalmology, Hamilton Eye Institute, University of Tennessee Health Science Center
2012-2015 Assistant Professor of Ophthalmology & Visual Sciences, Vanderbilt Eye Institute, Vanderbilt University
2015-Present Associate Professor of Ophthalmology & Visual Sciences, Vanderbilt Eye Institute, Vanderbilt University Medical Center (VUMC)
2019-Present Associate Director for Research, Vanderbilt Eye Institute, VUMC

Other Experiences and Professional Memberships

1997-present Member of Association for Research in Vision and Ophthalmology

2003-present Member of American Society for Gene and Cell Therapy
2009-present Member of the International Society for Eye Research
2013-2015 Chair ARVO Members-in-Training Committee
2014-present VA CDA Study Section, ad hoc reviewer
2016-2018 Member of ASGCT Neurologic & Ophthalmic Gene & Cell Therapy Committee
2016-present Co-Chair ARVO Women Leadership Development Committee
2016-present Member of the National Neurotrauma Society
2016-present Editorial Board Member, Scientific Reports
2016-present NIH DPVS and Special Emphasis Study Sections, ad hoc reviewer
2016-present Department of Defense, ad hoc reviewer
2019 Chair, NIH NEI K08/K23 Study Section

Honors

1997 Association for Research in Vision and Ophthalmology Travel Award
1999 University of California Santa Barbara Neuroscience Excellence in Research Award
1999 University of California Santa Barbara Alumni Research Award
2000 University of California Santa Barbara Graduate Division Travel Award
2000 Ellen Schamberg Burley Graduate Scholarship
2006 XIIth International Symposium on Retinal Degeneration Travel Award
2006 Hope for Vision Young Investigator Award
2010 The University of Tennessee Health Science Center Faculty Research Award
2011 Research Prevent Blindness Career Development Award
2011 Glaucoma Research Foundation Shaffer Prize
2013 NEI Audacious Goals Winner
2017 AAMC Women's Mid-Career Professional Development Seminar Attendee
2018 Silver Fellow, Association for Research in Vision and Ophthalmology

C. Contribution to Science

1. **Understanding mechanisms underlying blindness after neurotrauma.** Background: Warfare has changed in the last decade to include increased use of improvised explosive devices leading to more blast-injured veterans. Due to the development of Kevlar, more military members are surviving blasts and more cases of traumatic brain and eye injury are being seen in military hospitals and in the veteran administration system. Unfortunately, to date there are no medical therapies available to treat vision loss as a result of trauma. Central Findings and Influence of Findings: I developed the first model of ocular blast injury. By directing the overpressure air-wave at the eye while protecting the rest of the mouse we were able to demonstrate for the first time that the primary component of the blast (overpressure air front) can directly damage the eye. We detect damage to the neural retina and optic nerve as well as vision loss similar to that described in patients after blast exposure or blunt trauma. Through a slight modification of this system, we can also induce closed head traumatic brain injury that includes damage to the visual system. Our studies have identified the time course of damage and potential mechanisms underlying the cell death and vision loss that occurs after trauma. This is an important first step towards the development of treatments that will preserve or restore vision in these patients. My Role: I designed and performed or trained others in the performance of the studies, analyzed the results, and wrote the manuscripts.

A. Bricker-Anthony C, Hines-Beard J, **Rex TS.** (2014) Molecular changes and delayed vision loss in a mouse model of closed-globe blast trauma. *Invest. Ophthalmol. Vis. Sci.* 55: 4853-4862 PMCID: PMC4123895.
B. Bricker-Anthony C, Hines-Beard J, D'Surney L, **Rex TS.** (2014) Exacerbation of blast-induced ocular trauma by an immune response. *J. Neuroinflam.* 11:192. PMCID: PMC4264554
C. Vest V, Bernardo-Colon A, Watkins D, Kim B, **Rex TS**. (2019) Rapid repeat exposure to sub-threshold trauma causes synergistic axonal damage and functional deficits in the visual pathway in a mouse model. *J. Neurotrauma*. 36:1646-1654. PMCID: PMC6531903
D. Bernardo-Colon A, Vest V, Cooper ML, Naguib SA, Calkins DJ, **Rex TS**. (2019) Progression and pathology of traumatic optic neuropathy from repeated primary blast exposure. *Front. Neurosci.* 13:719. PMCID: PMC6637732

2. **Role of redox in retinal health and disease.** Background: The retina is bathed in oxygen from the choroidal blood supply as well as from the inner retinal vasculature while simultaneously being exposed to light, creating the perfect environment for photo-oxidative stress. The photoreceptors are one of the most highly metabolic cells in the body, the outer segments are packed with lipid membranes, and they are bathed in photons and oxygen, making them susceptible to photo-oxidative stress. The axons of the retinal ganglion cells are unmyelinated until they reach the oligodendrocyte populated region of the optic nerve, this results in a high energy demand in these cells such that damage to the mitochondria could be devastating. Long-term exposure to light is thought to contribute to the pathogenesis of age-related macular degeneration and the presence of free radicals are thought to contribute to death of both photoreceptors and retinal ganglion cells in various models of human diseases. Thus it is important to understand oxidative stress in the retina in order to identify potential therapeutic strategies. Central Findings: I performed experiments that showed the essential role of the ascorbate and glutathione redox couple in the antioxidant defenses of the retina. Years later, using a model of photo-oxidative stress I performed gene therapy delivering catalase to the retinal pigment epithelium and demonstrated preservation of the photoreceptors via a bystander effect. In my own lab I demonstrated the important role of antioxidant in protecting against glaucomatous and traumatic neurodegeneration of the retinal ganglion cells. Influence of Findings: This study underscored the role of reactive oxygen species in photoreceptor cell death from bright light exposure and in traumatic optic neuropathy and glaucoma. My Role: My role shifted from performing the experiments to supervising. I also assisted with the analyses, generated figures and either assisted with editing of the manuscripts or wrote them in their entirety.

A. Winkler BS, Orselli SM, and **Rex TS**. (1994) The redox couple between glutathione and ascorbic acid: a chemical and physiological perspective. *Free Radical Biol. & Med.* 17: 333-349.
B. **Rex TS**, Tsui I, Duan D, Maguire AM, Bennett J, Dunaief J. (2004) Adenovirus-mediated delivery of catalase protects the Balb/c mouse retina from light-damage. *Hum. Gene Ther.* 15: 960-967. PMCID: PMC4118285
C. Bernardo-Colon A, Vest V, Clark AF, Cooper M, Calkins DJ, Harrison FE, **Rex TS**. (2018) Antioxidants prevent inflammation and preserve the optic projection and visual function in experimental neurotrauma. *Cell Death & Dis.* 9:1097. PMCID: PMC6203845
D. Hines-Beard J, Bond WS, Backstrom JR, **Rex TS.** (2016) Virus-mediated EpoR76E gene therapy preserves vision in a glaucoma model by modulating neuroinflammation and decreasing oxidative stress. J*. Neuroinflamm.* 13:39. PMCID: PMC4753658

3. **Erythropoietin as a neuroprotective agent.** Background: Erythropoietin (EPO) is neuroprotective in addition to its role in increasing red blood cell production by blocking apoptosis of progenitor cells. It is currently in clinical trials for a myriad of neurodegenerative conditions. Central Findings and Influence of Findings: I initiated a gene therapy study on EPO while I was a post-doctoral fellow. In that study we were the first to show that systemic, but not intraocular, gene delivery of EPO protected the photoreceptors in two models of photoreceptor cell death. One model, light damage, causes cell death as a result of increased oxidative stress (as shown by my previous paper using catalase gene therapy). This suggests that EPO may also block oxidative stress and, in fact, others have shown that it can increase expression of antioxidant enzymes. My following research demonstrated that the lack of efficacy of intraocular gene delivery of EPO was due to dose and not due to improper processing of the protein or lack of increased hematocrit. My laboratory has developed a mutated form of EPO (EPO-R76E) with attenuated erythropoietic activity while preserving its neuroprotective action. Finally, we have shown that systemic delivery of rAAV.EpoR76E is non-toxic and that neither EPO nor EPO-R76E induces proliferation of human microvascular retinal endothelial cells suggesting that they are not angiogenic in the healthy retina. My Role: In the first study, I designed and performed the studies, analyzed the results and edited the manuscript. In the following studies, I designed and performed or trained others in the performance of the studies, analyzed the results, and wrote the manuscripts.

A. **Rex TS,** Allocca M, Domenici L, Surace EM, Maguire AM, Lyubarsky A, Cellerino A, Bennett J, Auricchio A. (2004) Systemic but not intraocular Epo gene transfer protects the retina from light- and genetic-induced degeneration. *Mol. Ther.* 10:855-861.
B. **Rex TS**, Wong Y, Kodali K, Merry S. (2009). Neuroprotection of photoreceptors by direct delivery of erythropoietin to the retina of the retinal degeneration slow mouse. *Exp. Eye Res*. 89: 735-740. PMCID: PMC2757459
C. Bond WS, Hines-Beard J, GoldenMerry YL, Farooque A, Davis M, Sappington RM, Calkins DJ, **Rex TS.** (2016) Virus-mediated EpoR76E therapy slows optic nerve axonopathy in experimental glaucoma. *Mol Ther.* 24:230-239. PMCID: PMC4817814
D. Hines-Beard J, Bond WS, Backstrom JR, **Rex TS.** (2016) Virus-mediated EpoR76E gene therapy preserves

vision in a glaucoma model by modulating neuroinflammation and decreasing oxidative stress. J. *Neuroinflamm.* 13:39. PMCID: PMC4753658

4. **Differential effect of retinal detachment on the rod and cone photoreceptors.** Background: A common injury in trauma patients is rhegmatogenous retinal detachment, i.e. a separation of the neural retina from the back of the eye involving a hole or tear in the retina. This separation of the photoreceptors from the choroidal blood supply causes a hypoxic and hypoglycemic environment around the highly metabolically active photoreceptors. Reattachment surgery can lead to formation of epiretinal membranes. These membranes prevent further reattachment and lead to permanent vision loss. Central Findings: My research on rhegmatogenous retinal detachment uncovered a significant difference in the response of rod and cone photoreceptors to this injury. My data showed that while the rods begin to die soon after retinal detachment, the cones survive longer but decrease expression of proteins involved in phototransduction. In so doing they may decrease their energy output allowing them to survive longer under this hypoxic condition. I also identified proteins that were increased in the cones after retinal detachment suggesting that they may play a protective role. Influence of Findings: Since the cones are responsible for central vision, they are the most critical to preserve. My research showed the phosducin is a potential protective protein for these cells. It also provided support for the use of oxygen therapy, which is now standard of care for retinal detachment patients prior to reattachment surgery. My Role: I performed the experiments, assisted with the analyses, and assisted with writing and editing of the manuscripts.

A. Linberg KA, Lewis GP, Shaaw CL, **Rex TS**, and Fisher SK. (2001) The distribution of S and M/L cones in normal and experimentally detached cat retina. *J. Comp. Neurol.* 430: 343-356.
B. **Rex TS**, Fariss RN, Lewis GP, Linberg KA, Sokal I, and Fisher SK. (2002) A survey of molecular expression by photoreceptors after experimental retinal detachment. *Invest. Ophthalmol. Vis. Sci.* 43: 1234-1247.
C. **Rex TS**, Lewis GP, Geller SF, and Fisher SK. (2002) Differential expression of rod and cone opsin mRNA levels following experimental retinal detachment and reattachment. *Mol. Vis*. 8: 114-118.

5. **Retinal gene therapy for monogenic diseases.** Background: Inherited retinal degenerations cause permanent blindness in approximately 100,000 individuals in the U.S. Until recently, there was no treatment available for these patients. However, in the last two decades many of the causative genes mutated in patients have been identified, simultaneously, the field of gene therapy was developing. Central Findings and Influence of Findings: I participated in gene therapy studies that led to the first successful gene therapy clinical trial for the treatment of an inherited retinal degeneration (Leber congenital amaurosis, now in Phase III). I also contributed to the understanding of transduction efficacy of different recombinant adeno-associated viral vector (rAAV) serotypes in the retina and to the determination of the efficacy of congenital delivery of rAAV for therapeutic intervention. My Role: I performed the experiments, assisted with the analyses, and participated in writing the manuscripts.

A. Bennicelli J, Wright JF, Jacobs J, Komaromy A, Hauck B, Zelenaia O, Mingozzi F, Hui D, Chung, D, **Rex TS**, Wei Z, Zeiss C, Arruda VR, Pugh EN Jr, Acland GM, Dell'Osso LF, High KA, Maguire AM, Bennett J. (2008) Reversal of Blindness in Animal Models of Leber Congenital Amaurosis Using Optimized AAV2-mediated Gene Transfer. *Mol. Ther.* 16: 458-465. PMCID: PMC2842085
B. Allocca M, Doria M, Petrillo M, Colella P, Garcia-Hoyos M, Gibbs D, Maguire A, **Rex TS**, Di Vicino U, Cutillo L, Sparrow JR, Williams DS, Bennett J, Auricchio A. (2008) Serotype-dependent packaging of large genes in adeno-associated viral vectors results in effective gene delivery in mice. *J. Clin. Invest.* 118: 1955-1964. PMCID: PMC2298836
C. Surace EM, Auricchio A, Reich SJ, **Rex T,** Glover E, Pineles S, Tang W, O'Connor E, Lyubarsky A, Savchenko A, Pugh Jr EN, Maguire AM, Wilson JM, Bennett J. (2003) Delivery of Adeno-associated virus vectors to the fetal retina: Impact of viral capsid proteins on retinal neuronal progenitor transduction. *J. Virol.* 77(14): 7957-7963.
D. Dejneka NS, Surace EM, Aleman TS, Cideciyan AV, Lyubarsky A, Savchenko A, Redmond TM, Tang W, Wei Z, **Rex TS**, Glover E, Maguire AM, Pugh EN Jr, Jacobson SG, Bennett J. (2004) *In utero* gene therapy rescues vision in a murine model of congenital blindness. *Mol. Ther.* 9(2): 182-188.

The full list of published work is available at the following URL:
http://www.ncbi.nlm.nih.gov/sites/myncbi/tonia.rex.1/bibliography/45475154/public/?sort=date&direction=descending

D. Research Support

Recently Completed:

DoD CDMRP W81XWH-13-1-0048
Role: PI 2015-2016
Dietary approaches to protect against eye blast-induced oxidative stress and vision loss.
The major goal of this project is to determine if vision can be preserved after eye trauma by treatment with antioxidants and/or a ketogenic diet. We hypothesize that delayed vision loss from trauma is due oxidative stress-induced neuronal damage that can be blocked by the proposed therapeutic interventions. My responsibilities were to design the study, train students and staff, analyze data, and write/edit the manuscripts.

NIH NEI R01 EY022349
Role: PI 2012-2017
Novel Therapy and Mechanisms in Glaucoma
The major goals of this project are to determine if EPO-R76E protects the retinal ganglion cell bodies and axons by acting on the complement pathway in the neural retina and by decreasing Aquaporin 4 on the astrocytes of the optic nerve head, thus preventing swelling and pressure on the axons. We will test delayed and long-term therapy with EPO-R76E in multiple mouse models of inherited glaucoma that represent different subforms of glaucoma. My responsibilities were to design the study, train students and staff, analyze data, and write/edit the manuscripts.

DoD CDMRP W81XWH-15-1-0096
Role: PI 2015-2018
Neuroprotective strategies for the treatment of blast-induced optic neuropathy
The goals of the project are to: 1) Investigate the role of the inflammasome in retinal cell dysfunction and optic nerve degeneration after blast; 2) Determine the efficacy of galantamine to prevent optic nerve damage and vision loss after blast; and 3) Determine the efficacy of intraocular rAAV.EpoR76E to prevent optic nerve damage and vision loss after blast. My responsibilities were to design the study, train students and staff, analyze data, and write/edit the manuscripts.

Ongoing:

DoD CDMRP W81XWH-17-2-0055
Role: PI 2017-2020
Quantitative Evaluation of Visual and Auditory Dysfunction and Multi-Sensory Integration in Complex TBI Patients
The goal of this study is to identify objective, and quantitative clinical diagnostic tools for visual and auditory dysfunction due to traumatic brain injury.

R01 EY022349
Role: PI 2018-2022
Erythropoietin-mediated antioxidant pathways in glaucoma
The major goals of this project are to: 1) determine the role of the Nrf2 pathway and the antioxidant response element in EPO-R76E mediated protection of the retinal ganglion cells; and 2) quantify safety and neuroprotection in both a mouse and a non-human primate model of glaucoma using EPO-R76E loaded microparticles.

U24 EY029893
Role: PI 2018-2023
Retinal ganglion cell replacement in clinically relevant models of optic neuropathy
The goals of this project are to: 1) Establish a tree shrew model of glaucoma; 2) Establish a tree shrew model of blast-induced traumatic optic neuropathy; and 3) Optimize retinal ganglion cell transplantation in both models.