BIOGRAPHICAL SKETCH

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NAME: Rex, Tonia S.

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

POSITION TITLE: 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

I am a Professor of Ophthalmology and Visual Sciences, and my research is focused on mechanisms and neuroprotective strategies in visual system neurotrauma and glaucoma. I have a broad background in neurobiology, with specific training and expertise in the visual system and gene therapy. My laboratory developed a highly reproducible mouse model of indirect traumatic optic neuropathy (ITON) that recapitulates the delayed secondary neurodegeneration and vision loss described in some ITON patients. Using this model we identified that oxidative stress and the inflammasome pathway play key roles in ITON-induced secondary neurodegeneration and vision loss. Specifically, we detect increased superoxide and decreased mitochondrial superoxide dismutase, suggesting a role of mitochondrial dysfunction. The current application builds logically on this prior work. In summary, I have the expertise, leadership, training, expertise and motivation necessary to successfully carry out my portion of the proposed research project.

Ongoing and recently completed projects that I would like to highlight include:

NIH NEI U24EY029893
Role: PI 2018-2024
Retinal ganglion cell replacement in clinically relevant models of optic neuropathy

NIH NEI R01 EY022349
Role: PI 2018-2022
Erythropoietin-mediated antioxidant pathways in glaucoma

DARPA
Role: Collaborator 2021-2022
Identification of (sub)cellular first responders to TBI associated injuries via high-speed non-linear optical imaging.

DoD CDMRP W81XWH-15-1-0096

Role: PI 2015-2018
Neuroprotective strategies for the treatment of blast-induced optic neuropathy

Citations:

1. 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.
2. Bernardo-Colón A, Vest V, Cooper M, Calkins DJ, **Rex TS**. (2019) Progression and pathology of blast-induced indirect traumatic optic neuropathy. *Front Neurosci.* 13:719.
3. Naguib S, Backstrom JR, Gil M, Calkins DJ, **Rex TS**. (2021) Retinal oxidative stress activates the NRF2/ARE pathway: An early endogenous protective response to ocular hypertension. *Redox Biol.* 42:101883.

B. Recent Positions and Honors

Positions and Employment

2021-Present	Marlene and Spencer Hays Directorship in Translational Vision Research
2021-Present	Associate Vice Chair for Translational Research, Vanderbilt Eye Institute
2020-Present	Professor of Ophthalmology & Visual Sciences, Vanderbilt Eye Institute, Vanderbilt University Medical Center
2019-2021	Associate Director for Research, Vanderbilt Eye Institute
2015-2020	Associate Professor of Ophthalmology & Visual Sciences, Vanderbilt Eye Institute, Vanderbilt University Medical Center
2012-2015	Assistant Professor of Ophthalmology & Visual Sciences, Vanderbilt Eye Institute, Vanderbilt University
2007-2012	Assistant Professor of Ophthalmology, Hamilton Eye Institute, University of Tennessee Health Science Center

Selected Other Experiences and Professional Memberships

2021-present	NIH PED2 study section standing review
3/2019, 3/2021	Chair, NIH NEI K08/K23 Study Section
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
2016-2018	Member of ASGCT Neurologic & Ophthalmic Gene & Cell Therapy Committee
2014-present	VA CDA Study Section, ad hoc reviewer
2003-present	Member of American Society for Gene and Cell Therapy
1997-present	Member of Association for Research in Vision and Ophthalmology

Selected Honors

2022	ARVO Gold Fellow
2013	NEI Audacious Goals Winner
2011	Research Prevent Blindness Career Development Award
2011	Glaucoma Research Foundation Shaffer Prize
2006	XIIth International Symposium on Retinal Degeneration Travel Award
2006	Hope for Vision Young Investigator Award
1997	Association for Research in Vision and Ophthalmology Travel Award

C. Contributions to Science

1. **Role of redox in retina and optic nerve 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. In addition, the photoreceptors are one of the most highly metabolic cells in the body resulting in production of reactive oxygen species from the mitochondria. Long-term exposure to light is thought to contribute to the pathogenesis of age-related macular degeneration. 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. Influence of Findings: This study underscored the role of hydrogen peroxide in photoreceptor cell death from bright light exposure. My Role: I performed the experiments, assisted with the analyses, generated figures and assisted with editing of the manuscripts.

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.
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.
D. Naguib S, Backstrom JR, Gil M, Calkins DJ, **Rex TS**. (2021) Retinal oxidative stress activates the NRF2/ARE pathway: An early endogenous protective response to ocular hypertension. *Redox Biol.* 42:101883.

2. **Gene therapy.** Background: Retinal degenerations cause permanent blindness and, 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). 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. I am now applying gene therapy to the understanding and treatment of complex conditions. My Role: I designed studies, performed the experiments, assisted with the analyses, and participated in writing the manuscripts.
A. 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.
B. **Rex TS**, Peet JA, Surace EM, Calvert PD, Nikonov SS, Lyubarsky AL, Bendo E, Hughes T, Pugh EN Jr., Bennett J. (2005) The distribution, concentration, and toxicity of enhanced green fluorescent protein in retinal cells after genomic or somatic (virus-mediated) gene transfer. *Mol Vis.* 11:1236-1245.
C. 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
D. Backstrom JR, Sheng J, Wang MC, Bernardo-Colon A, **Rex TS.** (2020) Optimization of S. aureus dCas9 and CRISPRi elements for a single adeno-associated virus that targets an endogenous gene. *Mol Ther Meth Clin Dev.* 19:139-148

3. **Mechanisms and treatments for blindness due to blast-induced 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) Ocular blast injury exacerbated by disruption of the blood ocular barrier. *J. Neuroinflam.* 11:192

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

D. Naguib S, Bernardo-Colon A, Cencer C, Gandra N, **Rex TS.** (2020) Galantamine protects against synaptic, axonal, and vision deficits in experimental neurotrauma. *Neurobiol. Dis*. 134:104695

4. **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. 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

C. 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

D. DeJulius CR, Bernardo-Colon A, Naguib SN, Backstrom JR, Kavanaugh T, Gupta MK, Duvall CL, **Rex TS**. (2020) Sustained delivery of erythropoietin-R76E via PPS microparticles is more protective than delivery via PLGA particles in a mouse model of indirect traumatic optic neuropathy. *J Control Rel.* 10: 329:762-773.

5. **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.

The full list of published work is available at the following URL:
https://www.ncbi.nlm.nih.gov/myncbi/tonia.rex.1/bibliography/public/