AWARD NUMBER: W81XWH-15-1-0074

TITLE: Torsion-Induced Traumatic Optic Neuropathy (TITON): Animal Model for Diagnostics, Drug Delivery, and Therapeutics for Injuries to the Central Nervous System

PRINCIPAL INVESTIGATOR: Matthew Reilly, Ph.D.

CONTRACTING ORGANIZATION: Biomedical Engineering, The Ohio State University

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PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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5b. GRANT NUMBER
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6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Biomedical Engineering
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Columbus, OH 43210

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

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12. DISTRIBUTION / AVAILABILITY STATEMENT

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13. SUPPLEMENTARY NOTES

14. ABSTRACT
Deployment-related injuries to the central nervous system (CNS) have increased in frequency since World War II. The increasingly frequent use of improvised explosive devices over the past decade has dramatically increased the rate of these injuries. Unfortunately, rapid diagnosis of these injuries during the window of opportunity for significant CNS regeneration remains problematic. Further, no treatments have yet been developed to the point of clinical applicability which successfully regenerate CNS tissues. We have therefore developed and will use a unique and novel animal model of traumatic optic neuropathy (TON) which allows ready access to the central nervous system for studies on CNS regeneration.

15. SUBJECT TERMS
Nerve injury modeling; traumatic optic neuropathy; diagnosis; neural regeneration

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	15	19b. TELEPHONE NUMBER *(include area code)*

TABLE OF CONTENTS

1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

Traumatic optic neuropathy (TON) is a blinding injury to the optic nerve. While it is known to occur in a significant number of military and civilian injuries each year, no early diagnostic criteria or treatments are currently available. This critical gap is due, at least in part, to the lack of a suitable animal model. We have therefore developed a non-surgical model of TON, as well as several methods which may allow early diagnosis. Phase I of this study will establish those diagnostic criteria, while Phase II will use them to quantify changes in optic nerve structure and function following one of several candidate treatments.

2. KEYWORDS: *Provide a brief list of keywords (limit to 20 words).*

Nerve injury modeling; traumatic optic neuropathy; diagnosis; neural regeneration

3. **ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

What were the major goals of the project?
List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

	Target Date	Completion
Major Task 1: Develop injury diagnostics		
Milestone 1: ACURO approval	June 2019	100%
Milestone 2: Co-author manuscript on diagnostic methods for TON	June 2020	40%
Major Task 2: Develop vehicles for delivery of neuroprotective agents		
Milestone #3: Co-author manuscript on hydrogel "cast" for drug delivery and mechanical assistance for neuroprotection	Sept 2020	75%
Major Task 3: Characterization of optic nerve rescue by proposed treatments in vivo		
Milestone #4: Co-author manuscript on changes in optic track following treatment	Mar 2021	0%

What was accomplished under these goals?
For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

Major Task 1: Develop injury diagnostics
We have received both IACUC and ACURO approval for all animal experiments needed throughout the course of the proposed study. ACURO approval was received in late February 2020, nearly nine months after anticipated, resulting in significant delay to the start of experiments. Once approval was granted, animals were ordered and received in early March 2020 immediately prior to shutdown of our laboratories resulting from the COVID-19 pandemic.

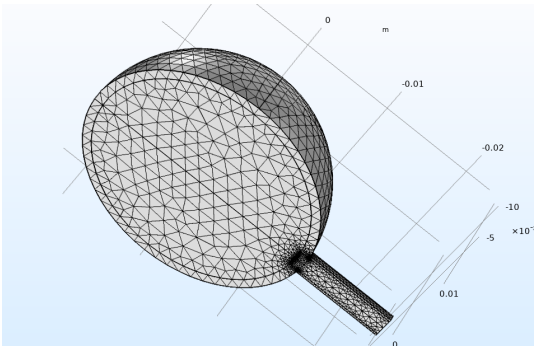


Figure 1: Finite element mesh of the eye and optic nerve. The model is halved on the optic axis to allow visualization of the ocular interior and optic nerve detail.

A computational mechanical model was developed to give insights into the mechanical mechanism driving traumatic optic neuropathy (TON) in the torsion-induced TON model (Fig.1). When this model is refined and validated with histological data, it may be easily extended to determine other likely insults which may induce similar damage to the optic nerve.

One of the current limitations of this model (and the model of hydrogel contraction which follows) is the availability of mechanical properties for the various tissues comprising the optic nerve. We have therefore established experimental protocols to measure these properties in both tension and shear. Quasi-static, uniaxial tension was applied to intact porcine optic nerves using an ElectroForce system (TA Instruments; New Castle, DE) to a maximum stretch ratio Λ of 120% while the required force was measured and used to compute the Cauchy (true) stress σ. A two-parameter Mooney-Rivlin hyperelastic constitutive model was then fitted to the data from each nerve sample (Fig. 2). A shear rheometer (Kinexus ultra+; Malvern Panalytical; Malvern, UK) was used to characterize the shear behavior of the optic nerve (Fig. 3). Samples were taken from proximal, basal, and middle regions of the nerve from paired fresh porcine and bovine eyes. A rotational shear strain was applied with a titanium upper plate at 5%/s to a maximum of 300-400% strain. While additional experiments are needed, preliminary results suggest that these protocols may be adapted to measure the properties of isolated dura, allowing the first estimation of the axonal bundle properties.

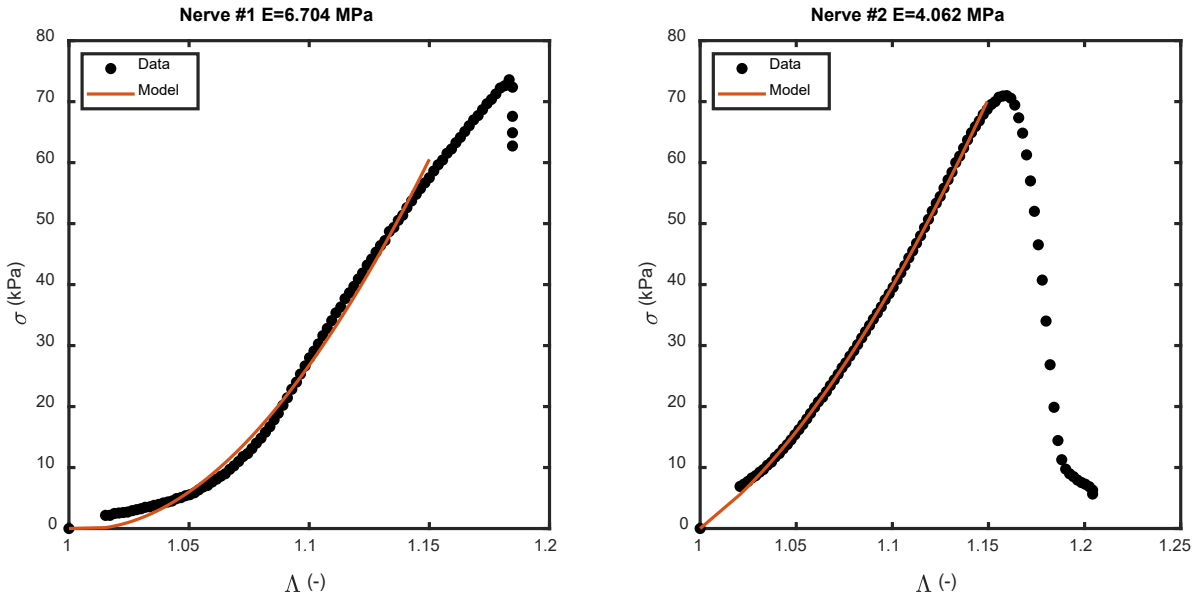


Figure 2: Stress-stretch data (circles) from two fresh, intact porcine optic nerves under quasi-static tension to failure fitted with a two-parameter Mooney-Rivlin model (red line).

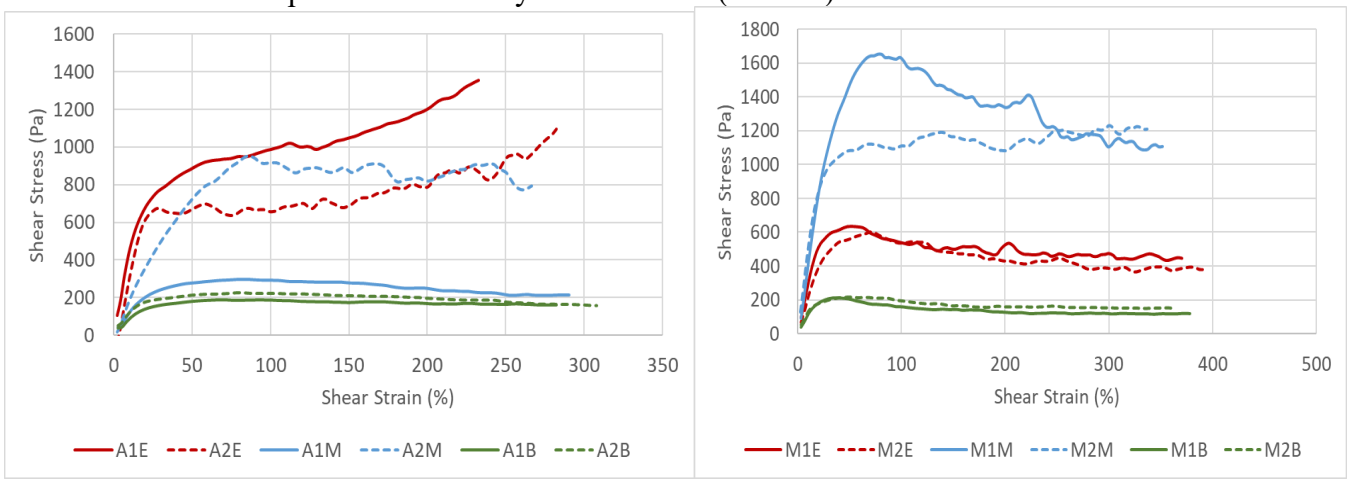


Figure 3: Shear rheometry data from porcine (left) and bovine (right) optic nerves. Red lines are from sections closest to the eye (E); blue lines are from the central (M) portion; green lines are from sections closest to the brain (B). Dashed and solid lines represent samples from paired eyes.

Major Task 2: Develop vehicles for delivery of neuroprotective agents

A computational model of the hydrogel contractile casting of the optic nerve was developed to estimate the range of gel mechanical properties required to achieve mechanical assistance of axonal regeneration (Fig. 4). This model was used to estimate the material properties necessary for candidate hydrogel cast formulations.

We thoroughly investigated alginate-based hydrogels that form in situ using calcium carbonate particle-initiated crosslinking rather than the traditional calcium chloride solution. This gives more tunable control over gelation kinetics. Gel pH was measured for various combinations of reagents (Fig. 5), and rheological and swelling studies were initiated to characterize gelation time, modulus, and ability to swell or contract (Fig. 4).

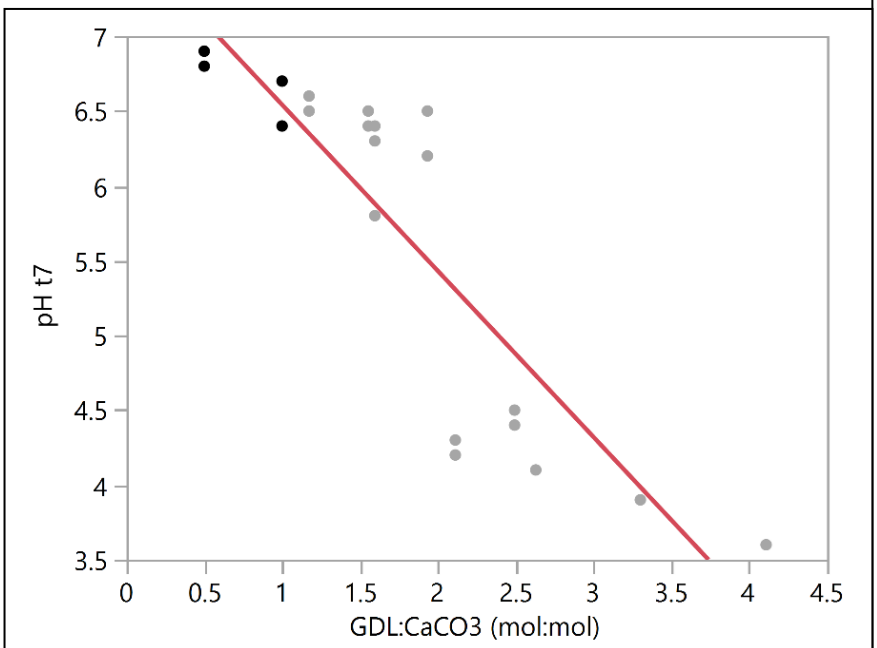


Figure 5: pH as a function of GDL:CaCO3 molar ratio.

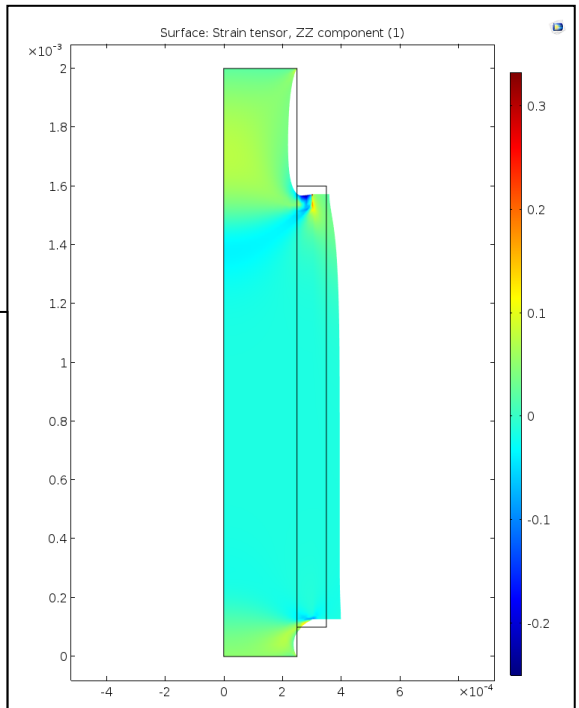


Figure 4: Axial strain distribution in the model optic nerve following hydrogel cast contraction. Of particular interest are the strains outside the casted area, which are slightly positive (indicating that the nerve would be under tension) and slightly negative within the casted region (indicating axial compression).

A statistically designed screening experiment was used to determine the relationships between hydrogel composition, gelation time, and complex shear modulus (Table 1, Fig. 6). Candidate formulations have been synthesized and mechanically characterized using dynamic shear rheometry. Release profiles of model molecules have been determined.

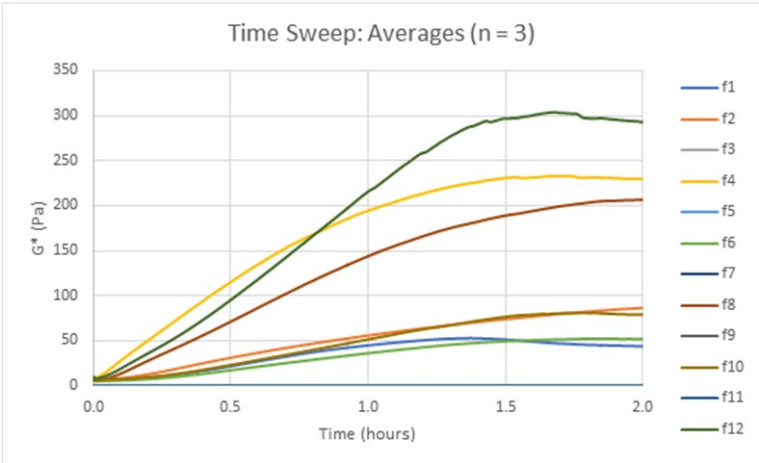


Figure 6: Measurement of gelation time and final complex shear modulus (G) for each hydrogel formulation.*

Based on the outcome of these screening experiments, additional formulations were evaluated to optimize the material. Alginate hydrogel formulations 10-21 have been characterized with regard to gelation time (Fig. 7) and complex shear modulus (Table 1). Formulations are grouped by low, medium and high GDL:CaCO3 ratios. As predicted, high GDL:CaCO3 ratios gelled rapidly while low to medium ratios gelled slowly (Note formulation 13 was not included in rheological testing). T-tests conducted on formulations found that all formulations except 11 and 14

were statistically different. Formulation 10 and 21 demonstrated the slowest and quickest gelation time, respectively. Injection feasibility is appropriate for all hydrogels, as formulation 21 solidified within 11 minutes.

The swelling and release profile of hydrogels were studied over a period of 14 days (Fig. 8). The mechanical

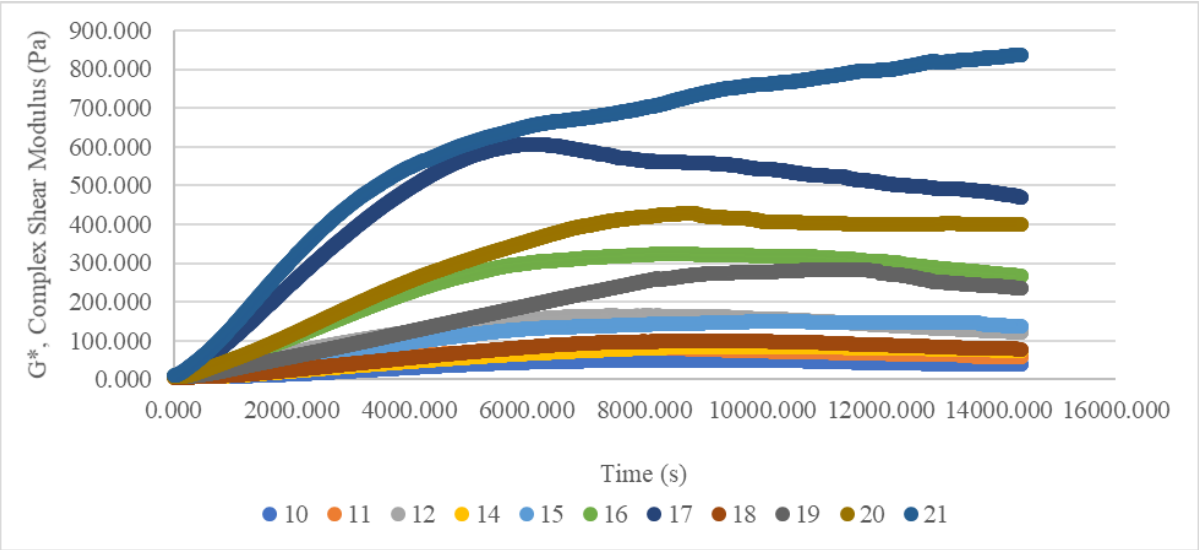


Figure 7: Complex shear modulus at 1 Hz as a function of time for formulations 10-21. Note that the final value was chosen as the representative value shown in Table 1 since the relevant stiffness of the gel is after gelation has completed and the gel has completely relaxed to equilibrium.

Table 1: Gelation Time and Shear Modulus for Optimization Formulations

Formulation	Gelation Time (s)	G* 1 Hz (Pa)
10	2803.333 ± 40.415	35.796 ± 15.624
11	2025.000 ± 120.208	60.172 ± 21.234
12	1223.333 ± 90.738	125.025 ± 48.098
14	2270.000 ± 26.258	60.252 ± 26.130
15	1516.667 ± 98.658	113.041 ± 53.077
16	1275.000 ± 247.487	246.670 ± 150.745
17	706.667 ± 59.231	558.659 ± 33.546
18	2190.000 ± 42.426	70.326 ± 33.546
19	1400.000 ± 72.111	187.389 ± 92.406
20	1055.00 ± 77.782	311.823 ± 134.006
21	660.000 ± 197.990	224.639 ± 111.196

integrity of hydrogels was compromised within 12-13 days. The higher the concentration of GDL and $CaCO_3$, the higher the degree of swelling. Among all hydrogels, initial burst release was observed, lasting until day 5. A slower, more sustained release followed with methylene blue release ranging from 60–90%. Low concentration hydrogels were found to increase the amount to MB release, possibly due to their larger pore size.

Together, these findings form the basis of a drafted manuscript we hope to submit in June 2020.

Major Task 3: Characterization of optic nerve rescue by proposed treatments in vivo

No progress to report.

What opportunities for training and professional development has the project provided?

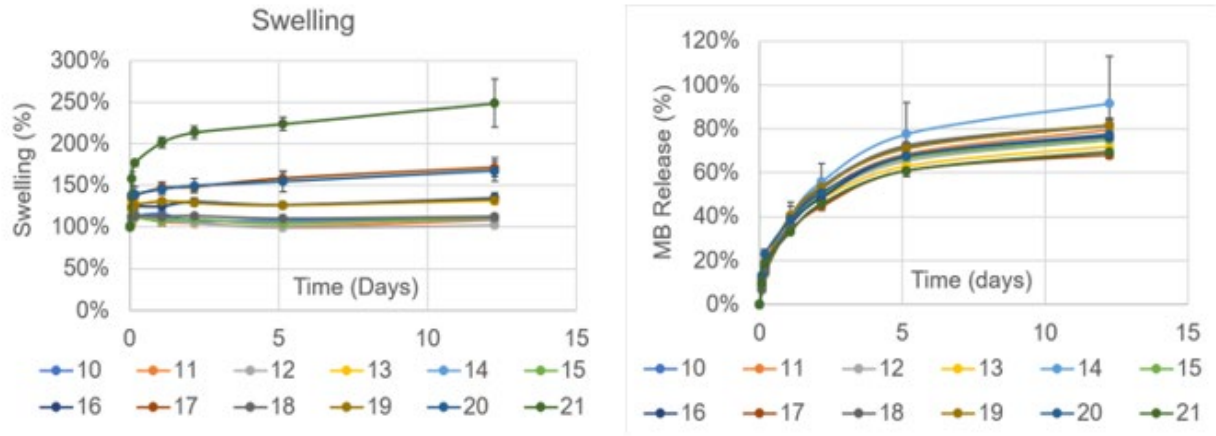


Figure 8: Volumetric change due to hygroscopic swelling (left) and release profile of methylene blue (right) in hydrogel formulations 10-21.

If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

While awaiting ACURO approval, our research assistant has received thorough training from Dr. Julie Racine learning the basics of visual electrophysiology, including rodent fERG, pERG, VEP, PhNR and have successfully performed each of those tests on mice provided by Dr. Colleen Cebulla. The tests were performed using the Celeris system which has greatly increased the speed and efficiency of collecting data.

An incoming PhD student in Dr. Reilly's laboratory will be trained online by our research assistant and Dr. Racine during the summer once the lab has re-opened. This will ensure long-term continuity of the project.

Lectures and Grand Rounds were provided in the School of Optometry and Department of Ophthalmology & Visual Science at Ohio State, as well as the School of Optometry at Indiana University.

Two related abstracts were presented at international meetings of the Society for Biomaterials and the Association for Research in Vision and Ophthalmology in April 2019.

How were the results disseminated to communities of interest?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Nothing to report.

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

We have received institutional approval to re-open our laboratories in mid-June 2020. At that time, we will begin animal experiments for Major Task 1 and continue experiments for Major Task 2.

Specifically, for Major Task 1, we will commence electrophysiological, magnetic resonance imaging (MRI)-based, matrix-assisted laser-desorption ionization imaging mass spectrometry (MALDI-IMS)-based and histopathological characterization of the optic nerve before and after injury. For Major Task 2, we plan to submit a manuscript summarizing the findings thus far. Having finalized the best formulation in terms of rheological and biocompatibility properties, the next step will be combining the alginate hydrogel with various collagen contents and testing their combination for the optimal percentage.

4. **IMPACT:** *Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Nothing to Report.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to Report.

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to Report.

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*

- *improving social, economic, civic, or environmental conditions.*

Nothing to Report.

5. **CHANGES/PROBLEMS:** *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

Changes in approach and reasons for change
Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Computational studies have been added to the study. This has allowed some important insights while awaiting ACURO approval and will continue now that laboratories have been closed indefinitely.

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Long delays in achieving ACURO approval have prevented progress on all animal experiments.

Sudden closure of all laboratories at Ohio State may cause unforeseen difficulties in completing the project according to the original budget and/or scope. The actual scope of these potential difficulties is unknown at this time.

Changes that had a significant impact on expenditures
Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

This was in part the result of ACURO's use of an erroneous e-mail address which appears to have been resolved. Contact was re-established in mid-December, requiring only minor comments from our group. While this issue has been resolved, nearly ten months passed before approval was finally granted. We made use of this time to improve training and protocols, as well as perform computational studies, but the personnel expenses incurred during this time were significant and not matched by experimental outputs as agreed in the Statement of Work.

Sudden closure of all laboratories at Ohio State may cause unforeseen difficulties in completing the project according to the original budget and/or scope. While experimental progress has halted indefinitely, we have added several computational approaches to make the best use of employee time. However, depending on how long our laboratories remain shuttered, continuing to pay employees may limit our ability to complete the agreed Statement of Work.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

No human subjects research will be performed to complete the Statement of Work.

Significant changes in use or care of vertebrate animals

Nothing to report.

Significant changes in use of biohazards and/or select agents

Nothing to report.

6. **PRODUCTS:** *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

  Nothing to Report.

  Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

  Nothing to Report.

  Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

  - Soltisz, A.M., Ruzga, M.N., Reilly, M.A., Swindle-Reilly, K.E., Spatial Variations in Optic Nerve Mechanical Properties, Association for Research in Vision and Ophthalmology, Annual Meeting, Vancouver, British Columbia, April 2019.
  - Soltisz, A.M., Thobe, S.M., Ruzga, M.N., Reilly, M.A., Swindle-Reilly, K.E., Evaluation of Semi-Interpenetrating Network for Treating Traumatic Optic Neuropathy, Society for Biomaterials, Annual Meeting, Seattle, Washington, April 2019.

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

  Nothing to Report.

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

  Nothing to Report.

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

  Nothing to Report.

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:
  - *data or databases;*
  - *physical collections;*
  - *audio or video products;*
  - *software;*
  - *models;*
  - *educational aids or curricula;*
  - *instruments or equipment;*
  - *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
  - *clinical interventions;*
  - *new business creation; and*
  - *other.*

  We have developed two novel computational mechanics models relevant to understanding the pathogenesis of traumatic optic neuropathy, as well as evaluation of mechanical aids to treatment. These finite element models allow thorough investigation of biomechanical mechanisms and, when supplemented with experimental data (as described above) may be useful for the study of additional diseases involving the optic nerve (e.g. glaucoma).
  - Computational chemo-mechanical finite element model of hydrogel nerve cast
  - Computational mechanical finite element model of ocular rotation

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?
Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

<u>Example:</u>

Name:	*Mary Smith*
Project Role:	*Graduate Student*

Researcher Identifier (e.g. ORCID ID): 1234567
Nearest person month worked: 5

Contribution to Project: Ms. Smith has performed work in the area of combined error-control and constrained coding.
Funding Support: The Ford Foundation (Complete only if the funding support is provided from other than this award.)

Name: Matthew Reilly
Project Role: PI
Researcher Identifier (e.g. ORCID ID): ORCID 0000-0001-8029-0084
Nearest person month worked: 3
Contribution to Project: Dr. Reilly has constructed mechanical models of ocular rotation and hydrogel casting.

Name: Katelyn Swindle-Reilly
Project Role: co-PI
Researcher Identifier (e.g. ORCID ID): 0000-0003-1739-0263
Nearest person month worked: 2
Contribution to Project: Dr. Swindle-Reilly has coordinated the hydrogel development, has attended meetings related to the research project, and has managed students performing experiments.

Name: Julie Racine
Project Role: co-PI
Researcher Identifier (e.g. ORCID ID): 0000-0003-4409-0936
Nearest person month worked: 1
Contribution to Project: Dr. Racine has developed visual electrophysiology protocols, trained graduate students and employees to implement them, and analyzed electrophysiological data.

Name: Andrew Soltisz
Project Role: graduate research assistant
Researcher Identifier (e.g. ORCID ID): 0000-0002-1493-3544
Nearest person month worked: 3
Contribution to Project: Mr. Soltisz conducted polymer synthesis and characterization related to the hydrogel cast development. He has also conducted optic nerve biomechanical testing.

Name: Courtney Maxwell
Project Role: Research Assistant
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 9
Contribution to Project: Ms. Maxwell has performed experiments with hydrogels, drug release, swelling, pH, rheological and biocompatibility testing. She has been investigating optic nerve testing.

Name: Danny Mackessy
Project Role: Research Assistant
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 9
Contribution to Project: Mr. Mackessy has learned to design and conduct electrophysiology experiments in collaboration with Dr. Racine.

Name: Wade Rich
Project Role: Research Assistant
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 8
Contribution to Project: Mr. Rich has been evaluating porcine optic nerve samples for cell separation techniques. He has also contributed to the development of biomechanical testing protocols for the optic nerve and

Name: Bharat Kumar
Project Role: Graduate Research Assistant
Researcher Identifier (e.g. ORCID ID): N/A
Nearest person month worked: 8
Contribution to Project: Mr. Kumar has been investigating the most appropriate staining protocols for accurate identification of protein biomarkers.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

The following new awards have been made to members of our team. Neither allows for investigator effort.

- Lion's Vision Gift - Barbara L. Crow Investigator-Concept Grant, A Multiscale Investigation of Ocular Tissue Properties and Biomechanical Response: 2019-2021, $15,000. Roles: Reilly: Co-PI; Swindle-Reilly: Co-PI
- Ohio State College of Veterinary Medicine, Pre-Clinical Model of Traumatic Optic Neuropathy (TON): 2019-2020, $7,500. Roles: Reilly: PI

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*

- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

Organization Name: Nationwide Children's Hospital
Location of Organization: Columbus, OH
Partner's contribution to the project Dr. Julie Racine, a visual electrophysiologist at Nationwide Children's Hospital, has been instrumental in training personnel for visual electrophysiology measurements and protocol development. She regularly comes to Ohio State for hands-on training and collaborative efforts.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to* ***https://ers.amedd.army.mil*** *for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.*

9. APPENDICES: *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.*

Torsional Indirect Traumatic Neuropathy (TITON): Animal Model for Diagnostics, Drug Delivery, and Therapeutics for Central Nervous System Injury

MR130235
W81XWH-15-1-0074-P00001

PI: Matthew A. Reilly **Org:** The Ohio State University

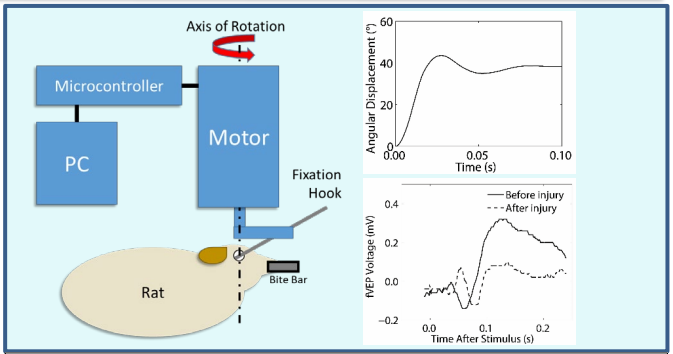
Award Amount: $902,737

Study Aims

- Diagnostics
  - Correlate TITON-induced changes using MRI, VEP, and ERG
  - Identify biomarkers with MALDI-IMS and scRNAseq
- Drug delivery vehicle
  - Develop and characterize drug reservoir hydrogel "cast"
- In vivo evaluation of candidate treatments
  - Treat with one or more therapeutic approach
  - Evaluate post-injury electrophysiology and histopathology

Approach

We have developed a new physiological model of indirect traumatic optic neuropathy (TON). This non-invasive technique achieves injury relevant to blast by rapidly rotating the eye to localize injury near the posterior insertion of the optic nerve. This model offers a simple platform for evaluating diagnostic and therapeutic modalities for TON. We will evaluate new local approaches to treatment including a novel hydrogel "cast" which also serves as a drug delivery reservoir.



Accomplishment: Formulation of the hydrogel "cast" for drug delivery to the optic nerve is nearly complete.

Timeline and Cost

Activities CY	Lead	2019	2020	2021
Develop injury diagnostics	Reilly			
Develop Tx delivery vehicles	Swindle-Reily			
Evaluate candidate Tx	Reilly			
Estimated Budget ($K)		**$382**	**$423**	**$99**

Updated: 29 April 2020

Goals/Milestones

CY19 Goals – Development of novel materials and methods

☑ Formulate hydrogel cast candidates

☐ Develop diagnostic criteria for TON

CY20 Goal – Treatment studies

☐ Determine metrics of TON in the in vitro RGC model

☐ Begin in vivo treatment studies in bilaterally injured rats

☐ Characterize treatment efficacy using MRI, DTI, BF

CY21 Goal – Treatment studies

☐ Complete in vivo treatment studies

Comments/Challenges/Issues/Concerns

Budget Expenditure to Date

Projected Expenditure: $437,000

Actual Expenditure: $391,888