Award Number: W81XWH-18-1-0700

TITLE: HIOC derivatives for the treatment of trauma-induced vision loss

PRINCIPAL INVESTIGATOR: P. Michael Iuvone, Ph.D.

CONTRACTING ORGANIZATION: Emory University
Atlanta, GA 30322

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Fort Detrick, Maryland 21702-5012

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6. AUTHOR(S)
P. Michael Iuvone
Frank E. McDonald

E-Mail:

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Emory University
Atlanta, GA 30322

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14. ABSTRACT

Pressure waves due to explosions can damage the neurons of the eye and visual centers in the brain, leading to visual function loss. There are currently few treatments for such injuries that can be deployed rapidly in the field to mitigate such damage. We are developing small molecule activators of TrkB, the cognate receptor for brain-derived neurotrophic factor (BDNF), which cross the blood/retina and blood/brain barriers. In preliminary studies, we have shown that our lead compound, N-[2-(5-hydroxy-1H-indol-3-yl)ethyl]-2-oxopiperidine-3-carboxamide (HIOC), protects against blast-induced retinal degeneration and vision loss when injected within three hours of trauma. In the first year of this project, we have focused on the development HIOC derivatives that have the potential to be more potent and efficacious than the parent compound. Thus far, 16 derivatives have been synthesized and chemically characterized.

15. SUBJECT TERMS
Blast injury, trauma, vision loss, TBI, therapeutics, medicinal chemistry

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	21	19b. TELEPHONE NUMBER *(include area code)*

Table of Contents

Page

1. INTRODUCTION:

Retinal damage followed by vision loss caused by traumatic blast-related injury, sports injury, or other blunt force trauma to the eye is a serious public health issue, affecting military personnel and the general public. To mitigate the damage from these injuries, the subject of our research is to develop small molecule activators of tropomyosin-related kinase receptor type B (TrkB), the cognate receptor for brain-derived neurotrophic factor (BDNF). Our lead compound, *N*-[2-(5-hydroxy-1H-indol-3-yl)ethyl]-2-oxopiperidine-3-carboxamide (HIOC) protects against blast-induced retinal degeneration and vision loss. The purpose of the current funded research project is to prepare HIOC derivatives designed for better blood brain/retina barrier penetrance and greater potency than HIOC, to examine the efficacy and potency of these derivatives in preventing vision loss following ocular trauma, and to perform pharmacokinetic and toxicological analyses of the most promising of these derivatives. The scope of this research aims to develop new pharmaceutical treatments for trauma-induced vision loss, and to collect preclinical data on efficacy, potency, pharmacokinetics, and safety/toxicity, ultimately leading to an Investigational New Drug (IND) application with the FDA, in a treatment form that can be quickly administered following injury to the eye, on the battlefield or in a public emergency environment.

2. KEYWORDS:

trauma, neuroprotection, retina, optic nerve, TrkB, BDNF, brain, TBI, acylation, fluoroaromatic, medicinal chemistry, methylation, pyridine, serotonin, tryptamine

3. ACCOMPLISHMENTS:

What were the major goals of the project?

The major goals were to develop effective, battlefield-deliverable treatments for traumatic blast-related retinal and visual system damage. Specific aims included:
Chemical synthesis of new HIOC derivatives (50% complete);
Examine the efficacy and potency of HIOC derivatives in activating TrkB and preventing vision loss following ocular trauma; and
Pharmacokinetic and toxicological analyses of lead compounds

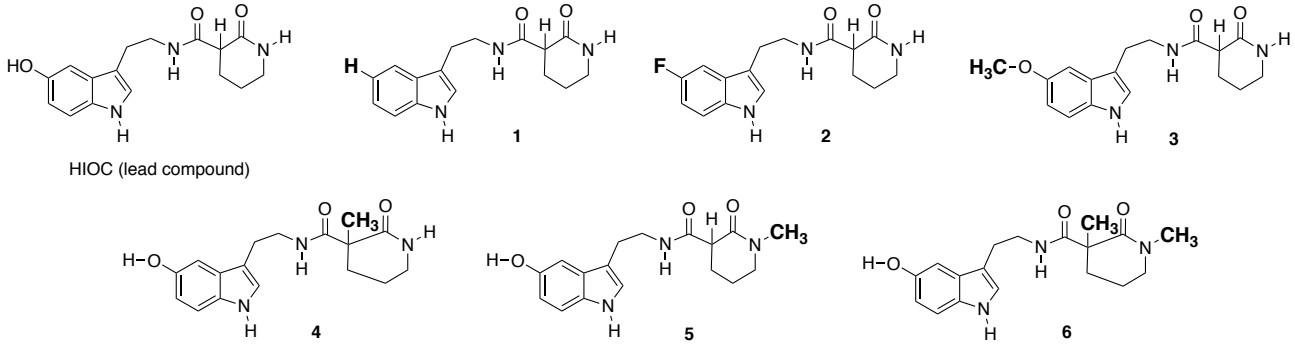
What was accomplished under these goals?

1) Major activities: In year 1, Dr. Christopher L. Walker has synthesized 16 new analogs of HIOC in quantities > 70 mg, sufficient for initial biological assessment of TrkB activation. The compounds prepared to date represent two of the three series of analogs proposed, which will also increase lipophilicity, directed toward improving blood brain/retina barrier penetrance. In the course of the synthetic work, Dr. Walker has also collected extensive NMR characterization data on the compounds depicted below, to establish spectroscopic trends with specific changes in the HIOC structure.

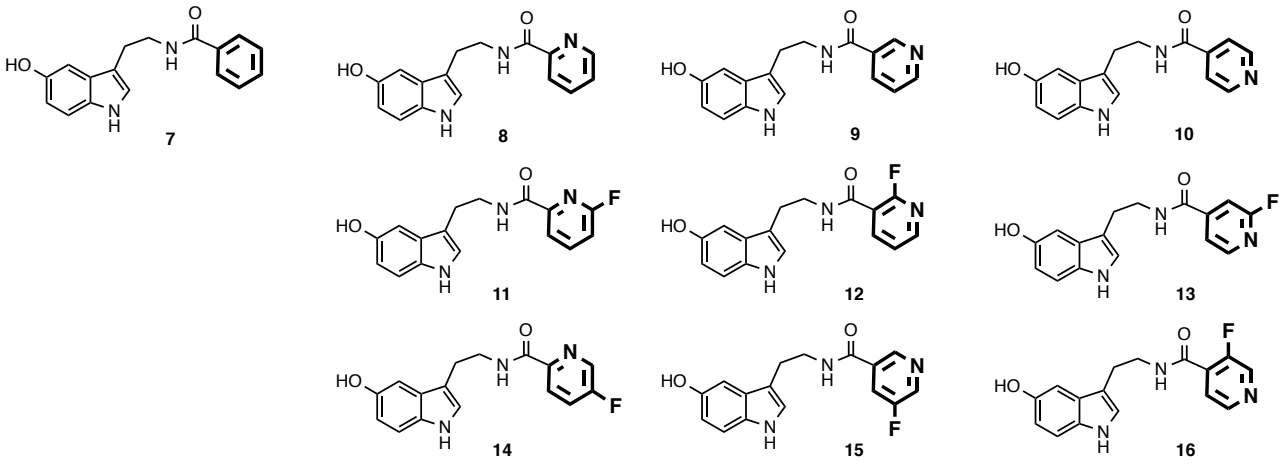
2) Specific objectives: Objectives include developing a structure-activity relationship scheme for TrkB activation and the associated protective effects, preventing vision loss following ocular trauma, by systematic modifications of HIOC affecting hydrogen bonding characteristics, while simultaneously increasing lipophilicity of these compounds.

3) Significant results and key outcomes: Dr. Walker synthesized and purified compounds **1** - **16** in scales ranging from 70 - 260 mg, which are sufficient quantities to initiate *in vivo* studies in mice. These were proposed as groups of three series, for which we have made significant progress in preparing analogs in Series A and in Series C.

Series A: systematically replaces hydrogen bond donor atoms, to test the hypothesis that some but not all of the hydrogen bond donor atoms of HIOC constitute the pharmacophore for TrkB activation. Each compound arises from chemoselective *N*-acylation of serotonin hydrochloride or the corresponding tryptamine derivative, with a lactam-carboxylic acid activated as a mixed anhydride by *N*,*N*-carbonyldiimidazole (CDI). Compounds **1** and **2** are single atom replacements of the phenolic hydroxyl group, and compound **3** blocks the hydrogen bond donor characteristics of this hydroxyl group (and is an analog of melatonin). Compound **4** blocks potential enolic character of the 1,3-dicarbonyl unit of HIOC, whereas compound **5** blocks the hydrogen bond donor characteristics of the lactam nitrogen. Compound **6** bearing two methyl groups arose from a byproduct generated in early attempts to prepare **4** and **5**, and represents an additional opportunity to test the pharmacophore hypothesis. As expected, the rate of acylation of the *alpha*-methyl precursors to **4** and **6** is diminished, but still proceeds to high conversion by extending the reaction time from 3 hours (for HIOC) to 12 - 15 hours.



Series C: replaces the chiral lactam ring with planar heteroaromatic and fluoroaromatic rings, to test the role of hydrogen bond acceptor characteristics on the pharmacophore for TrkB activation. Each compound arises from CDI-promoted *N*-acylation of serotonin hydrochloride with the commercially available pyridyl- or fluoropyridylcarboxylic acid. The heteroaromatic carboxylic acids required longer time for reaction compared with the lactam carboxylic acid precursor to HIOC, but we achieved sufficient conversion to produce at least 70 mg of each analog. The benzamide **7** is a control compound for the remaining pyridine and fluoropyridine derivatives **8** - **16**. In particular, compound **12** places an electronegative fluorine where the lactam carbonyl is located in HIOC, with the remaining compounds as systematic movements of nitrogen and fluorine around the aromatic ring.



4) Other Accomplishments: An undergraduate student, Mr. Taylor Dover, joined this project in spring semester 2019, and is working part-time with the co-PI, Prof. Frank McDonald, and with Dr. Walker. He has learned how to prepare HIOC on a scale of several hundred milligrams, as HIOC is a control substance for the pharmacological research activities of the PI's laboratory.

Dr. Dwipayan Bhattacharya, who joined the project in February, has prepared cultures of NIH/3T3 cells expressing TrkA, TrkB, and TrkC to be used to testing the HIOC derivatives. He has been establishing assay conditions to assess TrkB activation. An ACURO appendix was submitted for preparing rat cortical neurons for testing the derivatives, but it is still under review. We just received ACURO approval for testing the derivatives in vivo in mice.

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

Dr. Walker has gained substantial professional development in several areas relevant to this project in his first year on the project. Not only are the compounds significantly different from those that he has prepared in the past, he has also for the first time received substantial training in multidimensional NMR spectroscopic characterization, which is routine in the co-PIs laboratory but perhaps not yet as common at some other institutions. In addition, Dr. Walker audited a "Biology of the Eye" graduate-level course in spring semester 2019. He has also completed professional scientific ethics training, required of all postdoctoral associates employed at Emory University. Dr. Walker prepares a quarterly report one month in advance of each of the quarterly reports required for this grant, and has received detailed instruction on writing experimental preparations, and general advice on scientific writing. As the co-PI Prof. McDonald teaches a writing workshop for chemistry graduate students, he has also introduced some of the same writing techniques in one-on-one mentoring with Dr. Walker.

Dr. Walker mentors an undergraduate student, Mr. Taylor Dover, working part-time on this project in preparation for an honor's thesis that he will defend in spring 2021. In addition, as Dr. Walker is the most senior non-faculty member of the McDonald laboratory, he assists with training new graduate and undergraduate student researchers as they enter the McDonald laboratory. Dr.

Walker is a daily role model for less experienced personnel in the McDonald laboratory, and undoubtably for some of the other research groups in the department of chemistry as well.

Dr. Bhattacharya has developed several new laboratory skills needed for our project. He is currently taking the professional scientific ethics course, and will be mentoring an undergraduate student this semester.

How were the results disseminated to communities of interest?

Nothing to Report

What do you plan to do during the next reporting period to accomplish the goals?

1. Complete the synthesis of the remaining HIOC derivatives
2. Initiate testing of the derivatives in cultured cells and in vivo in mice.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

Nothing to report

What was the impact on other disciplines?

As one of the primary starting materials for these analogs, serotonin hydrochloride, is relatively expensive, we are exploring alternative approaches to the chemical synthesis of serotonin and other tryptamines. This work may also be relevant to the preparation of analogous substances such as melatonin.

What was the impact on technology transfer?

Nothing to Report

What was the impact on society beyond science and technology?

Nothing to Report

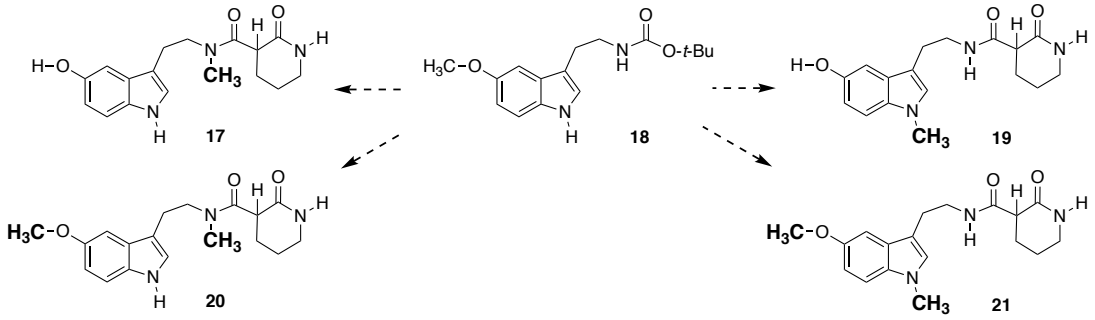
5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

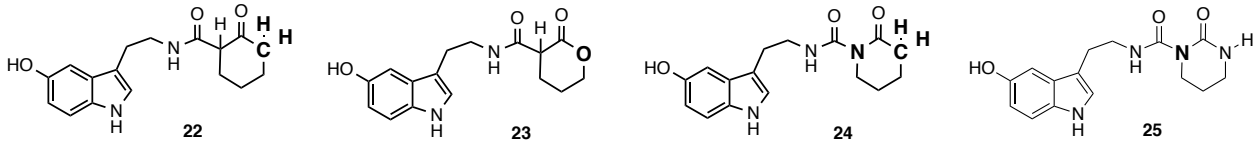
Nothing to Report

Actual or anticipated problems or delays and actions or plans to resolve them

Upon encountering difficulties in preparing precursors for two of the Series A compounds, we eventually concluded that the literature preparations were not reproducible. This created a substantial delay in completing this series, but we have recently revised the synthetic approach accordingly. To prepare the *N*-methyl indole analog **17**, we successfully prepared doubly protected serotonin derivative **18** at the very end of year 1. Work in progress will demonstrate selective *N*-methylation of the indole as required for the preparation of **17**, and we expect that reduction of the carbamate will enable the extension of our synthesis protocol to provide *N*-methyl analog **19**. Both of these syntheses will rely on chemoselective deprotection of the *O*-methyl ether, but also offer opportunities for two more analogs, **20** and **21**.



Our initial attempts to prepare Series B compounds revealed that some of the carboxylic acid precursors are quite prone to decarboxylation. We have some preliminary results suggesting that we can conduct the required *N*-acylation as long as we do not isolate or store the carboxylic acid. We have temporarily deferred further work on Series B so that we can concentrate completing Series A compounds, however we anticipate focusing our efforts toward Series B compounds early in year 2 of the grant. Specific target compounds include **22** - **25**, which modify the hydrogen bond donor and acceptor characteristics of the 1,3-dicarbonyl sector, as described in the grant application.



We experienced difficulty in demonstrating TrkB phosphorylation in the NIH/3T3 cells. This may be due to poor specificity of the antibodies used or the culture conditions. We are testing additional antibodies and other approaches to investigate TrkB activation.

HIOC derivative testing in cortical neurons and in mice was delayed by ACURO protocol review time.

Changes that had a significant impact on expenditures

Since April 2019, Dr. Chris Walker's salary and benefits have been supported by the NIH Vision Training Grant. As the synthesis portion of the project is on schedule, we currently seek a second postdoctoral associate to work primarily within the Iuvone laboratory, to accelerate the pharmacological aspects of this research.

Dr. Bhattacharya was unable to start working on the project until February 2019 due to the need to complete a postdoctoral fellowship and relocate to Atlanta.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

Nothing to Report

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:

Publications, conference papers, and presentations

Journal publications. Nothing to Report

Books or other non-periodical, one-time publications. Nothing to Report

Other publications, conference papers, and presentations.

Poster based on our preliminary data was presented at the Winter Conference on Brain Research: "Protection from TBI-induced vision less by N-acetylserotonin derivative HIOC through a BDNF/TrkB receptor mechanism." Abstract is in the Appendix.

Website(s) or other Internet site(s) Nothing to Report

Technologies or techniques Nothing to Report

Inventions, patent applications, and/or licenses
On April 29, 2019, Emory University submitted a provisional U.S. patent application

"*N*-Acetylserotonin Derivatives as TrkB Activators and Uses Thereof." serial number 62/839,964

Other Products Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Paul Michael Iuvone
Project Role:	Principal Investigator
Researcher Identifier:	miuvone
Nearest person-month worked:	4
Contribution to project:	Organization, coordination of team activities, regulatory protocols (IACUC/ACURO), and planning next steps
Name:	Frank E. McDonald
Project Role:	Co-PI
Researcher Identifier:	FRANK_MCDONALD
Nearest person-month worked:	3
Contribution to project:	Prof. McDonald has supervised all of the synthetic work, including reviewing primary data and characterization of new compounds.
Name:	Christopher L. Walker
Project Role:	Postdoctoral Associate
Researcher Identifier:	CWALKE
Nearest person-month worked:	12
Contribution to project:	Dr. Walker has conducted all of the synthetic work described in this report.
Name:	Taylor Dover
Project Role:	Undergraduate student researcher
Researcher Identifier:	
Nearest person-month worked:	2
Contribution to project:	Mr. Dover has learned the techniques required for the synthesis of HIOC, to date producing a 200 mg batch.
Name:	Dwipayan Bhattacharya
Project Role:	Postdoctoral Associate
Researcher Identifier:	DBHAT24
Nearest person-month worked:	7
Contribution to project:	Dr. Bhattacharya has been establishing assay conditions to determine the effect of HIOC and HIOC derivatives in TrkB, TrkA, and TrkC activation in vitro.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Other than the current award, we have had the following changes in active support:

Iuvone – new support

R01 EY028578-01A1 (Gawne) 7/1/18-6/30/23 0.6 calendar months
Univ. Alabama / NIH/NEI $19,106 (sub only)
Effects of wavelength on achieving and maintain emmetropia
The grant focuses on the effects of long wavelength light in the development and maintenance of emmetropia.
Role: Collaborator

1 I01 RX002806-01A1 (Boatright) 10/1/18 - 9/30/22 1.8 calendar months
Atlanta VAMC/VARR&D $268,554
A TrkB Activator for Treatment of Glaucoma
The goal of this project is to assess whether a BDNF TrkB receptor agonist protects visual function and retinal structure in animal models of glaucoma.
Role: Co-investigator

Iuvone – completed

R01 EY04864-34 (Iuvone) 7/1/83-8/31/19 0.6 calendar months
NIH/NEI
Neuromodulators and circadian clocks: roles in retinal function and dysfunction
The grant focused on the role of dopamine and clock genes in the regulation of circadian retinal physiology.
Role: PI

R01 EY025307-02 (Nickla) 1/1/16-12/31/18 0.6 calendar months
New England College of Optometry/NIH/NEI
Vision, eye growth rhythms, and retinal signals in refractive development
Circadian clocks play key roles in emmetropization. The goal of this proposal was to provide unique information about refractive development that may lead to novel approaches to the treatment of progressive myopia in children.
Role: co-investigator

McDonald – new support

NIH R21GM127971 04/01/18 - 03/31/20 1.0 summer months
Title: "Overcoming Steric Challenges in Glycosylations"

National Institutes of Health $400,616
The major goal of this project is to establish highly diastereoselective syntheses of glycoside linkages, arising from acyclic polyoxygenated terminal alkynes and sterically hindered cyclic secondary alcohols of protected carbohydrates.
Role: Principal Investigator

McDonald – completed

NSF-CHE-1531620 08/01/15 - 07/31/18 0 calendar months
Title: "MRI: Acquisition of a 600 MHz NMR Spectrometer for Chemistry"
National Science Foundation
The goal of this grant was to acquire a new nuclear magnetic resonance spectrometer, installed in 2016.
Role: Principal Investigator

NSF-CHE-1626172 09/01/16 - 08/31/19 0 calendar months
Title: "MRI: Acquisition of a High Intensity Microfocus X-ray Diffractometer"
National Science Foundation $322,461
The goal of this grant was to acquire a new X-ray diffractometer for chemical structure determination, installed in 2017.
Role: Principal Investigator

PERS-8310100017 07/01/17 - 06/30/18 0.25 summer months
Title: "Overcoming Steric Challenges in Glycosylations"
Emory College of Arts and Sciences $10,000
The major goal of this seed grant was to obtain preliminary results on a novel strategy for glycoside synthesis.
Role: Principal Investigator

Updated Support Pages are attached.

What other organizations were involved as partners?

Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

Nothing to Report

QUAD CHARTS: Updated Quad Chart is attached.

9. APPENDICES:

1. Other Support of P. Michael Iuvone

2. Other Support of Frank E. McDonald

3. Abstract of "Protection from TBI-induced vision less by N-acetylserotonin derivative HIOC through a BDNF/TrkB receptor mechanism."

TU22. Protection From TBI-Induced Vision Loss by the N-Acetylserotonin Derivative HIOC Through a BDNF/TrkB Receptor Mechanism

*P. Michael Iuvone**

N-Acetylserotonin activates BDNF/TrkB receptors but it's biological half-life following systemic injection is too short to be therapeutically useful. In this study we determined if HIOC, a structural analog of N-acetylserotonin with a longer half-life, prevents loss of visual function when administered after exposure to blast injury to the eye or head, examined HIOC's effect on optic nerve axon preservation, and investigated the role of BDNF/TrkB receptors in its neuroprotective effect. Mice were exposed to a single ~48psi blast directed at the eye or a 70 psi blast to the head. They were injected with vehicle or HIOC (40mg/kg, ip) 30 min before, or 0.25hr, 1hr, 3hr, or 24hr after exposure to blast. Injections continued daily for 6 days. Contrast sensitivity and visual acuity were measured 1 week, 1 month, and 4 months after exposure to blast by optokinetic tracking. Optic nerve axon counts were made 4 months after blast exposure in mice treated initially 15 min after blast. To test the role of BDNF/TrkB receptors, mice were treated with ANA-12, a selective TrkB antagonist, 2.5 hrs before each HIOC or vehicle injection. Results: In vehicle-treated mice, blast significantly reduced contrast sensitivity ($p<0.001$), but not visual acuity compared to naïve controls that were not exposed to blast. At 1 and 4 months after blast, both contrast sensitivity ($p<0.001$) and visual acuity ($p<0.001$) were reduced compared to naïve controls. In mice initially treated with HIOC 30 min before or 0.25hr, 1hr, or 3hr after blast, contrast sensitivity and visual acuity were significantly better than vehicle-treated mice ($p<0.001$), and not significantly different than naïve controls. If the initial treatment with HIOC was delayed by 24hr after blast, the protective effect on visual function was not observed. Four months after exposure to blast, axon numbers in the optic nerve were significantly reduced in vehicle-treated mice ($p<0.001$), but in HIOC treated mice. Pretreatment with ANA-12 completely blocked the protective effect of HIOC against blast-induced vision loss. Conclusion: HIOC preserves vision in mice exposed to blast if the initial treatment is within a critical period (<3hr). Treatment with HIOC for 1 week preserves visual function for at least 4 months. The effect of HIOC is mediated by activation of BDNF/TrkB receptors.

OTHER SUPPORT

IUVONE, P.M.

Active

1R01 EY027711-03 (MPI: Iuvone/Lang) 4/01/17 –3/31/21 1.3 calendar months
NIH $394,024
Regulation of eye development by an Opsin5-dopamine pathway
This multi-PI proposal seeks to examine the role in vascular development of the eye of a newly discovered intrinsically photosensitive retinal ganglion cell (ip5RGC) that utilizes neuropsin (OPN5) as its visual pigment. We will test the hypothesis that OPN5 regulates hyaloid regression and retinal vascularization during development by affecting circadian clocks and dopamine.
Role: corresponding PI
Specific aims:
Aim 1. To determine whether ip5RGCs form physical connections with dopaminergic amacrine cells.
Aim 2. To assess whether OPN5 regulates dopamine acutely or via the retinal circadian clock.
Aim 3. To determine the mechanism by which DA regulates vascular development in the eye.
Name and Address of the funding agency's Grants Officer:
Thomas Greenwell, Ph.D.
Program Director, Retinal Neuroscience
National Eye Institute
5635 Fisher Ln, Suite 1300
Bethesda, MD 20892-2510
greenwellt@mail.nih.gov

P30 EY06360-32 (Iuvone) 4/1/97 - 8/31/21 0.6 calendar months
NIH/NEI $393,737
P30 Core Grant for Vision Research
This grant provides core facilities for NEI funded investigators at Emory University and collaborating metro Atlanta institutions of the Atlanta Vision Research Community. The award provides services for 20 laboratories.
Role: PI
Specific aims:
The goal of the Atlanta Vision Research Community (AVRC) core grant is to provide support and scientific expertise for individual, collaborative, and pilot research in the areas of Structural Biology and Imaging (SBI), Functional Genomics and Proteomics (FGP), and Biostatistics and Informatics (BSI) as they relate to basic and translational eye research. The Specific Aims of the AVRC are to enhance the capabilities of NEI-funded investigators and the institutions for conducting vision research by:
1. Providing research services and resources to improve quality and productivity of NEI-supported R-series research projects;
2. Fostering vision research and collaboration among vision researchers in the Atlanta metro area including the Department of Ophthalmology and other clinical and basic science groups at Emory University, Georgia State University, Georgia Institute of Technology, Morehouse School of Medicine, and the Atlanta Veterans Administration Medical Center by providing a stable base of support for essential core facilities relevant to vision research;
3. Providing Core support for pilot collaborations for new vision research grant proposals;
4. Facilitating the vision research of new faculty;
5. Aiding recruitment of new vision research faculty with high quality Cores;

6. Providing Core scientific resource support for pre- and postdoctoral fellows supported through our NEI Training Grant (T32EY007092-29), K-, and F-series awards;
7. Encouraging non-vision scientists to study vision by offering Core support.
Name and Address of the funding agency's Grants Officer:
Ellen S. Liberman, Ph.D.
Program Director, Center Core Grant and Construction Grant Programs
National Eye Institute
5635 Fisher Ln, Suite 1300
Bethesda, MD 20892-9300
esl@nei.nih.gov

R01 EY016435-11 (Pardue) 1/1/05-04/30/23 1.2 calendar months
Georgia Inst of Technology/NIH/NEI $21,533 (sub only)
Retinal mechanisms of refractive development
This project exploits mouse models with retinal pathway defects to investigate the retinal mechanisms controlling refractive development and eye growth.
Role: co-investigator
Specific aims:
Aim 1: Determine whether ambient illumination levels alter susceptibility to myopia.
Aim 2: Determine whether basal levels of dopamine turnover and dopamine receptors are altered under each ambient illumination.
Aim 3: Determine whether melanopsin or Cx36 mediates refractive development in each ambient illumination.
Name and Address of the funding agency's Grants Officer:
Jerome R. Wujek, Ph.D.
Program Director, Myopia and Refractive Error
National Eye Institute
5635 Fisher Ln, Suite 1300
Bethesda, MD 20892-2510

1R01 EY026291-01A1 (Tosini) 8/1/16 – 7/31/21 0.75 calendar months
Morehouse Sch. Med./NIH/NEI $50,000 (sub only)
Circadian regulation of RPE functions
This proposal seeks to characterize the circadian clock in RPE and its entrainment by dopamine signaling, and to determine the relative roles of retinal and RPE circadian clocks in the daily rhythm of photoreceptor disc shedding and phagocytosis.
Role: co-investigator / consortium PI
Specific aims:
Aim 1. To determine the type of D2-like receptors that mediates the entrainment of the circadian rhythm in the RPE.
Aim 2. To determine the mechanisms by which DA phase-shifts the circadian clock in the RPE.
Aim 3. To determine the role of DA signaling in the regulation of the daily rhythm of disk shedding.
Aim 4. To determine the roles of RPE, photoreceptor, and inner retinal clocks in circadian disk shedding and phagocytosis.
Name and Address of the funding agency's Grants Officer:
Lisa Neuhold, Ph.D.
Program Director, Myopia and Refractive Error
National Eye Institute
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lneuhold@mail.nih.gov

R01 EY028578-01A1 (Gawne) 7/1/18-6/30/23 0.6 calendar months
Univ. Alabama / NIH/NEI $19,106 (sub only)
Effects of wavelength on achieving and maintain emmetropia
The grant focuses on the effects of long wavelength light in the development and maintenance of emmetropia.
Specific aims:

1. To determine the optimal parameters for the red light to generate the maximum STOP signal with minimal exposure and learn if red-light STOP signals show non-linear summation.
2. To determine if the red light "treatment" can produce consistent STOP signaling over a long period of time in the maintenance phase of emmetropization.
3. To use both analysis of retinal dopamine, and of gene expression in the retina and post-retinal signaling cascade, to determine if red-light STOP signals act via the same pathways as other STOP stimuli.

Name and Address of the funding agency's Grants Officer:
Cheri Wiggs
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wiggssc@mail.nih.gov

1 I01 RX002806-01A1 (Boatright) 10/01/2018 - 09/30/2022 1.8 calendar months
Atlanta VAMC/VARR&D $268,554
A TrkB Activator for Treatment of Glaucoma
The goal of this project is to assess whether a BDNF TrkB receptor agonist protects visual function and retinal structure in animal models of glaucoma.
Role: Co-investigator
Specific Aims:

1. To assess the feasibility of using a TrkB activator as a treatment for glaucoma, we will test whether HIOC treatment protects RGCs and vision in a mouse model of induced ocular hypertension.
2. To gain additional translational insight, test whether HIOC treatment is protective in a naturally-occurring glaucoma mouse model, the DBA/2J mouse.

Name and Address of the funding agency's Grants Officer:
Lina Kubli, Ph.D.
Scientific Program Manager
Sensory Systems & Communication Disorders [RRD3]
Rehabilitation Research & Development Service (RR&D)
U.S. Department of Veterans Affairs
810 Vermont Avenue
NW Washington DC 20420
Lina.kubli@va.gov

Overlap
No scientific or budgetary overlap.

Completed

R01 EY04864-34 (Iuvone) 7/1/83-8/31/19 2.8 calendar months
NIH/NEI $250,000
Neuromodulators and circadian clocks: roles in retinal function and dysfunction
The grant focuses on the role of dopamine and clock genes in the regulation of circadian retinal physiology.
Role: PI
Specific aims:

1. To test the prediction that DA modulates circadian rhythms of contrast sensitivity via dopamine D4 receptor (D4R)-mediated regulation of cAMP signaling and circadian oscillators that drive rhythms with both CLOCK/BMAL1 and NPAS2/BMAL1 complexes.

2. To test the prediction that circadian rhythms of photopic ERG amplitudes are modulated by DA effects on photoreceptors via D4Rs, cAMP, and oscillators that use CLOCK but not NPAS2.

3. To test the prediction that DA protects photoreceptors against photo-oxidative stress via D4Rs on photoreceptors and via dopamine D5 receptors (D5Rs) and dopamine D2-like receptors on RPE cells by modulating a CLOCK-dependent circadian rhythm of susceptibility to light damage.

Name and Address of the funding agency's Grants Officer:
Thomas Greenwell, Ph.D.
Program Director, Retinal Neuroscience
National Eye Institute
5635 Fisher Ln, Suite 1300
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greenwellt@mail.nih.gov

R01 EY025307-02 (Nickla) 1/1/16-12/31/18 0.60 calendar months
New England College of Optometry/NIH/NEI $23,620 (sub only)
Vision, eye growth rhythms, and retinal signals in refractive development
Circadian clocks play key roles in emmetropization. This proposal will provide unique information about refractive development that may lead to novel approaches to the treatment of progressive myopia in children.
Role: co-investigator
Aim 1. Study the interaction of focus, defocus and visual exposure patterns on refractive development.
Aim 2. Assess the role of the luminance of ambient lighting on refractive development.
Name and Address of the funding agency's Grants Officer:
Cheri Wiggs, Ph.D.
Program Director, Myopia and Refractive Error
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OTHER SUPPORT

MCDONALD, FRANK E.

Active

W81WH1810700 09/15/18 - 09/14/20 1.0 summer months

Title: "HIOC derivatives for the treatment of trauma-induced vision loss"

Department of Defense - Vision Research Program $330,179 (co-PI McDonald portion of award)

The goals of this project are to develop new pharmaceutical treatments for trauma-induced vision loss and to collect preclinical data on efficacy, potency, pharmacokinetics, and safety / toxicity, ultimately leading to an Investigational New Drug (IND) application with the FDA.

Role: Co-Principal Investigator (with PI, P. Michael Iuvone; and co-PI Hans Grossniklaus)

Specific Aims:

1. Chemical synthesis of HIOC derivatives.
2. Examine the efficacy and potency of HIOC derivatives in activating TrkB and preventing vision loss following ocular trauma.
3. Pharmacokinetic and toxicological analyses of lead compounds.

Grants Officer:

Marc L. Mitchell, MBA

Science Officer

GDIT, in support of CDMRP, USAMRMC

Fort Dietrich, MD

marc.l.mitchell.ctr@mail.mil

OVERLAP: This grant

NIH R21GM127971 04/01/18 - 03/31/20 1.0 summer months

Title: "Overcoming Steric Challenges in Glycosylations"

National Institutes of Health $400,616

The major goal of this project is to establish highly diastereoselective syntheses of glycoside linkages, arising from acyclic polyoxygenated terminal alkynes and sterically hindered cyclic secondary alcohols of protected carbohydrates.

Role: Principal Investigator

Specific Aims:

1. Develop regio- and stereoselective intermolecular hydroalkoxyations of alkynes with carbohydrate alcohols, to form alkenyl alcohols in a single step.
2. Establish conditions for stereospecific intermolecular transalkenylations with carbohydrate alcohols, to form alkenyl ethers.
3. Identify parameters for stereoselective oxidative oxacyclizations of alkenyl ethers to close glycoside rings.

Grants Officer:

Robert G. Lees, Ph.D.

Program Director, Division of Pharmacology, Physiology and Biological Chemistry

National Institute of General Medical Sciences (NIGMS)

National Institutes of Health

45 Center Drive, 2AS.53H

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OVERLAP: No scientific or budgetary overlap

Completed

NSF-CHE-1531620 08/01/15 - 07/31/18 0 calendar months

Title: “MRI: Acquisition of a 600 MHz NMR Spectrometer for Chemistry”

National Science Foundation $629,930

The goal of this grant is to acquire a new nuclear magnetic resonance spectrometer, installed in 2016.

Role: Principal Investigator

Specific Aims:

1. Addressing challenging problems in structure characterization of polymers, natural products, inorganic clusters, and microscale measurements of yields.
2. Characterizing small molecule interactions with proteins.
3. Characterization of reactive intermediates in chemical and biomolecular processes.
4. Establishing connectivity and regioselectivity in synthetic products from new bond-forming processes.
5. Assigning stereochemistry in synthetic products from new bond-forming processes.
6. Variable temperature studies on unstable reactive intermediates, and measuring dynamics of nanoparticles and the corresponding release of therapeutic agents as a function of temperature.
7. Diversity-oriented synthesis methods, enabled by an automated sample changer.
8. Enhancing student training and education in NMR spectroscopic hardware and methods.
9. Promoting the participation of undergraduate students and underrepresented minorities in research programs.

Grants Officer:
Carlos A. Murillo, Ph.D.
Program Director, Integrative Chemistry Activities / Instrumentation
Division of Chemistry
National Science Foundation
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OVERLAP: No scientific or budgetary overlap

NSF-CHE-1626172 09/01/16 - 08/31/19 0 calendar months
Title: “MRI: Acquisition of a High Intensity Microfocus X-ray Diffractometer”
National Science Foundation $322,461
The goal of this grant is to acquire a new X-ray diffractometer for chemical structure determination, installed in 2017.
Role: Principal Investigator
Specific Aims:
1. Crystallographic analysis of microcrystalline (micrometer-dimension) research samples
2. Structural characterization of catalytic intermediates
3. Structural characterization of synthetic products and unexpected byproducts
4. Determination of absolute configuration of chiral non-racemic compounds
5. Determination of solid-state conformation and molecular orientation
6. Charge density studies in biologically active and coordination compounds
7. Introducing X-ray crystallography in the undergraduate curriculum
8. Formal graduate-level course work in X-ray crystallography, including hands-on training

Grants Officer:
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OVERLAP: No scientific or budgetary overlap

PERS-8310100017 07/01/17 - 06/30/18 0.25 summer months
Title: "Overcoming Steric Challenges in Glycosylations"
Emory College of Arts and Sciences $10,000
The major goal of this seed grant is to obtain preliminary results on a novel strategy for glycoside synthesis.
Role: Principal Investigator
Specific Aims:
1. Metal-catalyzed bimolecular coupling of alkyne-derived synthons to form vinylic ethers as latent glycoside bonds

2. Oxidative cyclizations of vinylic ethers to form sterically hindered glycoside bonds
Grants officer:
Ronald L. Calabrese, Ph.D.
Senior Associate Dean for Research
Emory College of Arts and Sciences
Atlanta, GA 30322
ronald.calabrese@emory.edu
OVERLAP: No scientific or budgetary overlap

NSF-CHE-1362249 07/01/14 - 06/30/17 0.35 summer months
Title: “Cascade Cyclization Synthesis of Fused Polycyclic Ethers”
National Science Foundation $390,000
The major goals of this project were to apply regio- and diastereoselective cyclization processes for the chemical synthesis of fused polycyclic ether natural products, represented by brevenal.
Role: Principal Investigator
Specific Aims:
1. Synthetic strategy for the ABC tricyclic core substructure of brevenal
2. Synthetic strategy for the CDE tricyclic cord substructure of brevenal
3. Applications of this strategy to the pentacyclic core structure of brevenal
4. Improving scientific communication skills
Grants officer:
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