OMB Number: 4040-0001
Expiration Date: 11/30/2025

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE	State Application Identifier

1. TYPE OF SUBMISSION*

❍ Pre-application ● Application ❍ Changed/Corrected Application

4.a. Federal Identifier

b. Agency Routing Number

c. Previous Grants.gov Tracking Number

2. DATE SUBMITTED | **Application Identifier**

5. APPLICANT INFORMATION **UEI*:** PNSWLGJ46247

Legal Name*: EYESONIX INC.
Department:
Division:
Street1*: 10380 Wilshire Blv #1404
Street2:
City*: Los Angeles
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 90024-4757

Person to be contacted on matters involving this application
Prefix: First Name*: Donald Middle Name: N. Last Name*: Schwartz Suffix:
Position/Title: President & Founder
Street1*: 10380 Wilshire Blvd #1404
Street2:
City*: Los Angeles
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 90024-4757
Phone Number*: 562-221-9733 Fax Number: Email: dschwartz@eyesonix.com

6. EMPLOYER IDENTIFICATION NUMBER *(EIN) or (TIN)** 92-2825975

7. TYPE OF APPLICANT* R: Small Business

Other (Specify):
Small Business Organization Type ❍ Women Owned ❍ Socially and Economically Disadvantaged

8. TYPE OF APPLICATION*

● New ❍ Resubmission
❍ Renewal ❍ Continuation ❍ Revision

If Revision, mark appropriate box(es).

❍ A. Increase Award ❍ B. Decrease Award ❍ C. Increase Duration
❍ D. Decrease Duration ❍ E. Other *(specify)* :

Is this application being submitted to other agencies?* ❍Yes ●No What other Agencies?

9. NAME OF FEDERAL AGENCY*
National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER
TITLE:

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
Enduring Non-Invasive Glaucoma Treatment with Low-Power Ultrasound

12. PROPOSED PROJECT
Start Date* Ending Date*
12/01/2024 11/30/2025

13. CONGRESSIONAL DISTRICTS OF APPLICANT
CA-036

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: First Name*: Donald Middle Name: N. Last Name*: Schwartz Suffix:
Position/Title: President & Founder
Organization Name*: EYESONIX INC.
Department:
Division:
Street1*: 10380 Wilshire Blv #1404
Street2:
City*: Los Angeles
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 90024-4757
Phone Number*: 562-221-9733 Fax Number: Email*: dschwartz@eyesonix.com

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested*	$304,369.00
b. Total Non-Federal Funds*	$0.00
c. Total Federal & Non-Federal Funds*	$304,369.00
d. Estimated Program Income*	$0.00

16.IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?*

a. YES ○ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:
DATE:

b. NO ● PROGRAM IS NOT COVERED BY E.O. 12372; OR
○ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

● I agree*

** The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.*

18. SFLLL or OTHER EXPLANATORY DOCUMENTATION File Name:

19. AUTHORIZED REPRESENTATIVE

Prefix: First Name*: Donald Middle Name: N. Last Name*: Schwartz Suffix:
Position/Title*: President & Founder
Organization Name*: EYESONIX INC.
Department:
Division:
Street1*: 10380 Wilshire Blv #1404
Street2:
City*: Los Angeles
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 90024-4757
Phone Number*: 562-221-9733 Fax Number: Email*: dschwartz@eyesonix.com

Signature of Authorized Representative*
Post Populate Submitter Signature

Date Signed*
04/01/2024

20. PRE-APPLICATION File Name:

21. COVER LETTER ATTACHMENT File Name:

424 R&R and PHS-398 Specific
Table Of Contents

OMB Number: 4040-0010
Expiration Date: 11/30/2025

Project/Performance Site Location(s)

Project/Performance Site Primary Location

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name:	EYESONIX INC.
UEI:	PNSWLGJ46247
Street1*:	103880 Wilshire Blvd #1404
Street2:	
City*:	Los Angeles
County:	
State*:	CA: California
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	90024-4757
Project/Performance Site Congressional District*:	CA-036

Additional Location(s) File Name:

Tracking Number:

Opportunity Number: . Received Date:

OMB Number: 4040-0010
Expiration Date: 11/30/2025

RESEARCH & RELATED Other Project Information

1. Are Human Subjects Involved?* ❍ **Yes** ● **No**

1.a. If YES to Human Subjects

Is the Project Exempt from Federal regulations? ❍ Yes ❍ No

If YES, check appropriate exemption number: _ 1 _ 2 _ 3 _ 4 _ 5 _ 6 _ 7 _ 8

If NO, is the IRB review Pending? ❍ **Yes** ❍ **No**

IRB Approval Date:

Human Subject Assurance Number

2. Are Vertebrate Animals Used?* ❍ **Yes** ● **No**

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ❍ Yes ❍ No

IACUC Approval Date:

Animal Welfare Assurance Number

3. Is proprietary/privileged information included in the application?* ● **Yes** ❍ **No**

4.a. Does this project have an actual or potential impact - positive or negative - on the environment?* ❍ **Yes** ● **No**

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ❍ Yes ❍ No

4.d. If yes, please explain:

5. Is the research performance site designated, or eligible to be designated, as a historic place?* ❍ **Yes** ● **No**

5.a. If yes, please explain:

6. Does this project involve activities outside the United States or partnership with international collaborators?* ❍ **Yes** ● **No**

6.a. If yes, identify countries:

6.b. Optional Explanation:

	Filename
7. Project Summary/Abstract*	Project_Summary_EyeSonix_2024.03.27.pdf
8. Project Narrative*	Project_Narrative__EyeSonix_2024.03.27.pdf
9. Bibliography & References Cited	Literature_Cited_EyeSonix_2024.03.27.pdf
10.Facilities & Other Resources	Facilities_EyeSonix_2023.03.31.pdf
11.Equipment	Equipment_EyeSonix_2023.03.27.pdf

PROJECT SUMMARY

Glaucoma is the leading cause of irreversible blindness worldwide, impacting approximately 3 million individuals in the United States and about 80 million globally. Current treatments primarily focus on reducing intraocular pressure (IOP), with pharmaceutical eye drops as the typical first-line treatment for early-stage glaucoma. However, poor patient compliance with these self-administered pharmaceutical regimens is a longstanding challenge that contributes to disease progression, necessitating more invasive and risk-prone treatments such as laser therapy and surgery. There is thus a need for effective, non-invasive treatments to reduce IOP without the compliance problems and frequent side effects of pharmaceuticals.

To address this unmet need, EyeSonix has developed Therapeutic Ultrasound for Glaucoma (TUG), a non-invasive, low-cost outpatient procedure with a portable device to reduce IOP and potentially halt or even reverse glaucoma progression. Based on observations of lowered IOP by ultrasonic procedures employed during cataract surgery, TUG uses low-intensity divergent ultrasound to reduce IOP by enhancing the outflow of aqueous humor through non-destructive mechanical vibration and mild hyperthermy that stimulate a transient inflammatory response and debris clearing from the trabecular meshwork. Preliminary results suggest that a single, well-tolerated 10-minute treatment not only yields a lasting $\geq$20% reduction in IOP in 80% of treatment-naïve patients for 1 year, but shows evidence of being neuroprotective, restoring lost retinal nerve fiber thickness and visual field in some patients. TUG thus shows promise as a non-invasive glaucoma treatment that will improve the health and quality of life of millions of glaucoma patients.

To support the further commercial development of TUG in this Phase I SBIR project, we propose two specific aims. In Aim 1, we will perform mechanistic studies using a bovine organ culture model to determine the effects of TUG protocol treatment on the expression levels of beneficial proteins that have been shown to be stimulated in eye tissues by ultrasound or elevated temperature in other contexts, including matrix metalloproteinase 3 (MMP-3) and tumor necrosis factor alpha (TNF-α). In Aim 2, we will advance the development of a β-prototype by incorporating real-time measurement of two parameters key to the safety and efficacy of the procedure: intraocular temperature and applied force. Successful completion of these Aims will advance understanding of the mechanism-of-action of TUG and improve its safety profile, improving patient outcomes and supporting the design of clinical trials in pursuit of FDA approval through the 510(k) pathway. With the potential to replace first-line pharmaceutical treatments and reduce reliance on more risk-prone or invasive treatments, TUG represents a transformative approach to glaucoma management, promising to improve the quality of life for millions affected by this debilitating condition.

PROJECT NARRATIVE

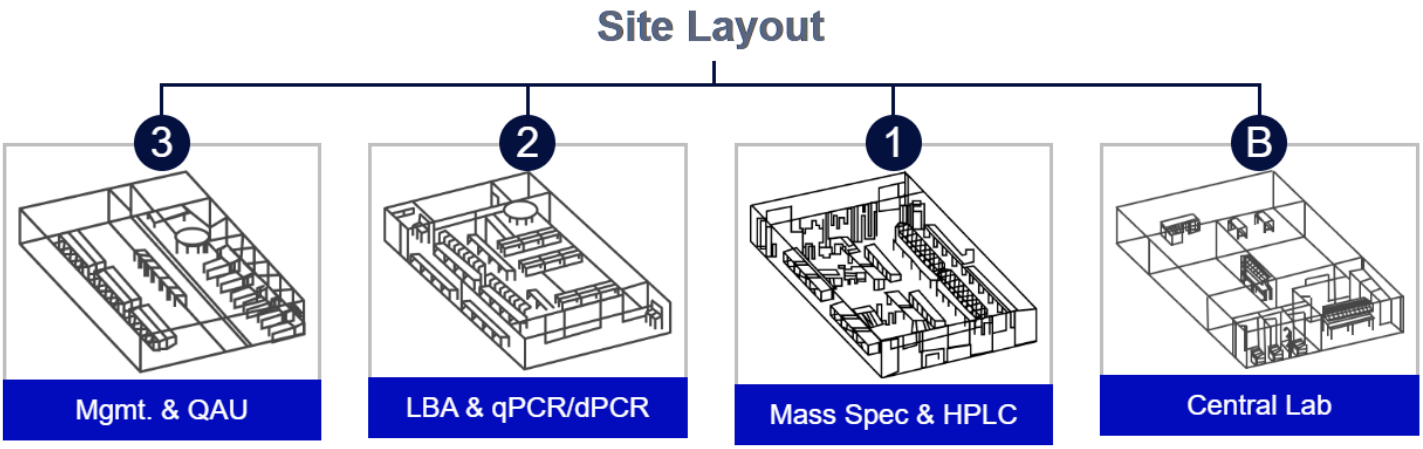
Current first-line treatments for glaucoma—the leading cause of irreversible blindness—suffer from poor patient compliance, leading to frequent progression of disease and necessitating more risk-prone, expensive, or invasive procedures such as laser treatment and surgery. EyeSonix has pioneered therapeutic ultrasound for glaucoma (TUG), a non-invasive outpatient treatment that achieves lasting reduction of intraocular pressure and even recovers previous visual field losses in some patients. This Phase I SBIR project will improve the safety profile and patient outcomes of TUG by (1) determining the biochemical mechanism of TUG protocol treatment in an animal organ culture model, and (2) integrating into the prototype device the capability to measure temperature and applied force, paving the way for successful clinical trials in support of FDA approval.

FACILITIES AND OTHER RESOURCES

Environment –Contribution to Success
The facilities and other resources available to PI Donald Schwartz and his team, both at the primary performance site and at that of the Contract Research Organization (CRO) NorthEast BioLab (NEBL), include everything needed to undertake and complete the proposed research project successfully.

The primary site of laboratory work, NEBL, has over 20 years of experience delivering 600+ studies and 400+ custom bioanalytical methods for the bioanalysis of therapeutics, metabolites, and biomarkers, as well as clinical trial kitting and biosample storage. Founded in Mar 2003 by Ex-Bayer scientists with extensive hands-on experience in therapeutic development and discovery, they have built a reputation as a service-based small business partnering with research groups from academic labs at Yale, Brown, Dana-Farber, Columbia, Duke, MD Anderson, Sarah Cannon, Sloan Kettering, Moffitt, UChicago, and UCSF, etc. to top 10 pharmaceutical and emerging biotech companies. They are a full-service, GLP and GCP compliant, FDA audited, DEA Schedule II-IV approved, Watson LIMS® enabled bioanalytical laboratory. Their independent Quality Assurance Unit (QAU) ensures that the entire management and laboratory staff is well trained and methodically performs lab activities in compliance with applicable regulations and guidance from FDA, OECD, and EMA.

Laboratory
NEBL (35 Worth Ave. Hamden, CT) has a ~19,000 sq. ft. laboratory facility spanning four floors in New Haven, CT (USA). This facility is equipped for cytokine and chemokine bioanalysis utilizing ELISA, MesoScale Discovery Electrochemiluminescence, Luminex, Western Blot, Flow Cytometry, High-resolution Microscopes, commercially available biology kits, and qPCR/dPCR platforms. The broad immunoassay capabilities at NEBL are particularly relevant for Aim 1 of this proposal. The facility is also equipped with a heavy-duty backup generator, alarms and monitoring, and cloud-based backup systems.



Biohazards Handling and Disposal
Bovine tissue dissection and recovery will be performed within a Class II Biological Safety Cabinet, to protect against exposure due to aerosolization. Handlers will wear appropriate personal protective equipment, including lab coat, gloves, and safety glasses. All consumables (plastic tubes, serological pipettes, pipette tips) and debris are discarded as biohazard waste, autoclaved, and sent for incineration.

Intellectual Property
EyeSonix has secured multiple patents and filed numerous provisional and/or full patent applications related to the TUG technology (device, disposables, therapeutic use cases), including the issued US Patents 9125722, 8043253, and 7909781.

Computer
Data analysis, product design, and software development activities will be carried out on desktop computers currently in the company's possession.

Office
The EyeSonix team currently also has access to space sufficient for general office use and prototype development activities. Together with the laboratory facilities of NEBL, this space will be sufficient to complete the objectives of this Phase I proposal. To support future expansion, the EyeSonix team is actively seeking to rent additional office and laboratory space from JLABS, a Johnson & Johnson subsidiary that provides small businesses with access to capital-efficient lab space, equipment, and resources, and has a location within commute distance of the team.

Clinical
N/A

Animal
N/A

EQUIPMENT

All necessary equipment to carry out this project is in possession of EyeSonix or its CRO partner NorthEast BioLab (NEBL).

NEBL will serve as the fee-for-service GLP laboratory for the biochemical work in the proposed study, and possesses the following instrumentation relevant to this project:

- Meso Scale Discovery™ immunoassay plate readers
- Luminex™ immunoassay plate readers
- Bio-Rad Bio-Plex™ immunoassay systems
- SpectraMax™ and VICTOR Nivo™ immunoassay plate readers
- BioTek™ plate washers
- Watson™ laboratory information management system
- Dot-Compliance™ electronic quality management system
- Standard laboratory equipment, including pH meters, balances, centrifuges, turbovaps, biosafety cabinets, 4 °C, -20 °C, and -80°C storage

All NEBL equipment is validated and calibrated, and regularly audited and maintained by external vendors.

In addition, EyeSonix possesses its own specialized equipment related to the use and development of the Therapeutic Ultrasound for Glaucoma (TUG) device, including multiple working α-prototype TUG devices comprising a probe and generator unit, as well as standard electronics equipment including oscilloscopes, multimeters, soldering equipment, and power supplies.

Finally, as its team grows EyeSonix will pursue rental of additional laboratory space in JLABS, which provides access to a broad set of additional laboratory infrastructure and capital equipment.

OMB Number: 4040-0001
Expiration Date: 11/30/2025

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: First Name*: Donald Middle Name N. Last Name*: Schwartz Suffix:

Position/Title*: President & Founder
Organization Name*: EYESONIX INC.
Department:
Division:
Street1*: 10380 Wilshire Blv #1404
Street2:
City*: Los Angeles
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 90024-4757

Phone Number*: 562-221-9733 Fax Number:

E-Mail*: dschwartz@eyesonix.com

Credential, e.g., agency login: DONNSCHWAR

Project Role*: PD/PI Other Project Role Category:

Degree Type: MD, MPA, OD, BS Degree Year: 1977, 1968, 1967, 1964

Attach Biographical Sketch*: File Name: 1_Bio_Don_2024.03.27.pdf

Attach Current & Pending Support: File Name:

PROFILE - Senior/Key Person

Prefix: First Name*: Eric Middle Name Last Name*: Schultz Suffix:

Position/Title*: Chief Executive Officer
Organization Name*: EYESONIX INC.
Department:
Division:
Street1*: 10380 Wilshire Blvd #1404
Street2:
City*: Los Angeles
County:
State*: CA: California
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 90024-4757

Phone Number*: 650-521-4130 Fax Number:

E-Mail*: eric@eyesonix.com

Credential, e.g., agency login: ESCHULTZ

Project Role*: Co-Investigator Other Project Role Category:

Degree Type: MS, BS Degree Year: 2002, 1993

Attach Biographical Sketch*: File Name: 2_Bio_Eric_EyeSonix_2024.03.28.pdf

Attach Current & Pending Support: File Name:

OMB No. 0925-0001 and 0925-0002 (Rev. 10/2021 Approved Through 01/31/2026)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Donald N. Schwartz

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

POSITION TITLE: President and Founder

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
University of California, Los Angeles, CA	BS	05/1964	Psychology
University of California, Berkeley, CA	OD, M.Opt	05/1967	Optometry
University of Southern California, Los Angeles, CA	MPA	05/1968	Health Care Services
Universidad Autonoma de Guadalajara, Jalisco, Mexico	MD	05/1977	Medicine
Veterans Hospital, Long Beach, CA	Internship and Residency	05/1981	Internal Medicine
Hollywood Presbyterian Medical Center, Los Angeles, CA			Ophthalmology

A. Personal Statement

With over four decades of experience in both optometry and ophthalmology, I have significantly contributed to advancing the fields through clinical practice, education, and research. Notably, my work in developing a patented method of treating glaucoma using ultrasound technology showcases my commitment to innovation and patient care. This work includes significant hands-on experience with the therapeutic device in the context of both clinical and animal studies, leading to a deep understanding of its capabilities and necessary areas of improvement to ensure its successful transition into clinical use. In addition, my work and role as an educator has been instrumental in training the next generation of optometrists and ophthalmologists. In my role as the Founder and President of EyeSonix, I endeavor to bring a new medical device and method for the treatment of all stages of glaucoma using ultrasound. My diverse skill set, combined with my deep understanding of both administrative and clinical aspects of healthcare and leadership skills, makes me the ideal individual to act as Principal Investigator on this project.

Relevant patent:

DN Schwartz. Ultrasonic treatment of glaucoma. US 7909781B2, 2011. Assigned to EyeSonix in 2024.

B. Positions, Scientific Appointments, and Honors

Positions & Scientific Appointments

2022 – 2023 Physician, Seibel Vision and Surgery, Los Angeles, CA
2006 – Present Founder & President, EyeSonix, Los Angeles, CA
2005 – 2008 Director, American Board of Ophthalmology
2002 – 2008 Chairman of the Board, Eye Care Network, Los Angeles CA
1997 - 2000 Trustee American Academy of Ophthalmology, Doyestown, PA
1992 – 1992 President, California Academy of Ophthalmology, San Francisco, CA

1982 – Present	Adjunct Clinical Professor, University of Southern California, Keck School of Medicine
1988 – 2015	Associate Clinical Professor, Ophthalmology, University of California Irvine, Irvine, CA
1982 – 2021	Private Practice, Ophthalmology, Long Beach, CA

Honors

2002	“Distinguished Alumnus of the Year”, USC Doheny Eye Institute
2002	“American Academy of Ophthalmology Secretariat Award of Member Services”
2002 – Present	“Best Doctors in the United States", Western Edition
1996 – 1997	“Best Doctors in the United States", Western Edition
1995	"Jules Stein Living Tribute Award", Retinitis Pigmentosa International
1994	"1994 Clinical Teacher of the Year", USC Doheny Eye Institute
1994	Honor Award, American Academy of Ophthalmology
1993	Honor Award, California Association of Ophthalmology
1993	"Teacher of the Year (Specialist) 'Golden Apple Award'" - Memorial Long Beach

C. Contributions to Science

1. **Development and Clinical Application of Ultrasound in Treating Glaucoma.** I have led pioneering efforts in applying therapeutic ultrasound technology for glaucoma treatment, contributing to the development and clinical evaluation of a novel, non-invasive method for lowering intraocular pressure. This work culminated in the publication of key findings in the Journal of Therapeutic Ultrasound, demonstrating the potential of ultrasound-based treatments for lowering .

    1. **D. Schwartz.** Chapter 7 “The Effect of Ultrasound on Aqueous Dynamics” in Minimally Invasive Glaucoma Surgery by Francis, Sarkisian and Tan. Thieme, 2017
    2. **D. Schwartz,** J Samples, O Korosteleva. Therapeutic ultrasound for glaucoma: clinical use of a low-frequency low-power ultrasound device for lowering intraocular pressure. Journal of Therapeutic Ultrasound. 2014: 2 (15).
    3. **D. Schwartz**. Chapter 12 “Therapeutic Ultrasound for Glaucoma” in Surgical Innovations in Glaucoma. By JR Samples and IIK Ahmed. Springer, 2014.

2. **Advancements in Ophthalmic Education.** I have made significant contributions to the education and training of optometry and ophthalmology students and residents, particularly in the areas of optics, refraction, and cataract surgery. My long-standing involvement in courses offered to USC and UCI residents reflects my commitment to advancing ophthalmic education.

3. **Clinical Research in Ophthalmology.** I have participated as a clinical investigator in several studies, where I have contributed to the understanding of intraocular lens performance, age-related biologic markers versus chronological markers, and the safety and efficacy of new ophthalmic devices and treatments.

    1. K.E. Keller, S.K. Bhattacharya, T. Borrás […], **D. Schwartz** et al. Consensus recommendations for trabecular meshwork cell isolation, characterization and culture. Exp Eye Res 171, 164–173 (2018). 10.1016/j.exer.2018.03.001
    2. Section Editor. Optics and Refraction. Textbook of Ophthalmology. Kenneth Wright Williams & Wilkins. 1997

OMB No. 0925-0001 and 0925-0002 (Rev. 10/2021 Approved Through 01/31/2026)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Eric Schultz

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

POSITION TITLE: Chief Executive Officer

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
University of Pennsylvania, Philadelphia, PA	BS	05/1993	Applied Science
Stanford University, San Francisco, CA	MS	05/2002	Product Design

A. Personal Statement

With over 20 years of experience in medical device R&D, product design, and engineering, I am a passionate innovator and leader in the field of implantable and non-invasive ocular devices. My mission is to create life-changing solutions for patients with glaucoma and other eye conditions, using cutting-edge technology and design principles. As the CEO, CTO, and Co-founder of EyeSonix, I lead a multidisciplinary team of engineers, technicians, and clinicians, who share my vision of improving ocular health and quality of life for millions of people worldwide. I have overseen the development of many medical devices including those using ultrasound, several of which have made it through FDA approval and commercialization. In addition, I have 36 patents granted and pending, the majority of which apply to devices and methods for helping patients with ocular diseases and/or ultrasound-based devices. This experience makes me well-equipped to oversee the engineering development of the Therapeutic Ultrasound for Glaucoma (TUG) device prototype as described in this proposal, as well as its further development towards commercialization for clinical use.

Relevant Patents

Shunting systems having flow control assemblies with adjustable lumens of interlaced composition and associated systems, methods, and devices. Eric Schultz, Nicholas Lyford. WO2023091307. Published May 25, 2023

Adjustable shunts with shape memory actuators and associated systems and methods. Eric Schultz. WO2024026397. Published Feb 1, 2024

Ultrasound device for vulvovaginal rejuvenation. Stephanie Kaplan, Eric Schultz, Robert Blante, Bryan Flaherty. WO2022212728. Published Oct 6, 2022

Ultrasound device with attachable components. Ryan Taylor Krone, Holly Elizabeth Rockweiler, Lauren Paige Jones, Eric Schultz, Bryan Flaherty. US20220249876A1. Published Aug 11, 2022

B. Positions, Scientific Appointments, and Honors

2022 – Present CEO, CTO, Co-founder. EyeSonix, Los Angeles, CA
2020 – 2022 Director, R&D. Myra Vision, Campbell, CA
2019 – 2020 Director, Engineering. Madorra Inc, San Mateo, CA
2017 – 2019 Staff R&D Engineer. Earlens Corporation, Menlo Park, CA

2014 – 2017	Principal Product Designer. Mynosys Cellular Devices, Fremont, CA
2014 – 2014	Director, Engineering. Speck Design, Palo Alto, CA
2011 – 2014	Director, Product Development. AccuVein Inc, Menlo Park, CA
2008 – 2010	Director, Product Development. Axis Surgical Technologies, Mountain View, CA
2006 – 2008	Sr. R&D Engineer. Transcend Medical, Menlo Park, CA
2004 – 2006	Sr. Mechanical Engineer. Design 2 Matter, Mountain View, CA

C. Contributions to Science

1. **Therapeutic ultrasound device.** This research explores the use of high-frequency ultrasound to improve vaginal health. This technology has the potential to offer a new approach to managing post-menopausal vaginal dryness, affecting millions of women worldwide.

   Relevant patent:

   S Kaplan, **E Schultz**, R Blante, Bryan Flaherty. *Ultrasound device for vulvovaginal rejuvenation.* WO2022212728. Published Oct 6, 2022

2. **Minimally invasive diagnostic visualization for spinal surgery.** In collaboration with colleagues, I contributed to the development of minimally invasive surgical techniques for the spine. This research focuses on novel diagnostic visualization tools that aid surgeons during spinal fusion procedures. This technology has the potential to revolutionize minimally invasive spine surgery by providing improved visualization within a smaller surgical field.

   Relevant patent:

   EE Schultz, JS Cybulski, X Ouyang. *Hand-held minimally dimensioned diagnostic device having integrated distal end visualization.* EP2451338, Active.

3. **Ocular implants for glaucoma treatment.** I helped advance the field of ocular implants for glaucoma treatment through US Patent 11291585, titled "Shunting Systems with Rotation-Based Flow Control Assemblies, and Associated Systems and Methods." This invention pertains to a novel implant design that regulates aqueous humor outflow, a critical factor in reducing eye pressure. This technology has the potential to revolutionize the way we manage glaucoma by offering a more precise and potentially long-term treatment option.

   Relevant patent:

   E Schultz, R Chang, T Saul, R Lilly, M Drews, C Argento, K Sapozhnikov. *Shunting systems with rotation-based flow control assemblies, and associated systems and methods.* US 11291585: Active

4. **Sensing *via* brain-computer interfaces.** I contributed to the development of brain-computer interface (BCI) technology through US Patent 7263393, titled "Biofeedback Ring Sensors." This invention explores the use of finger sensors to control video games through brain signals. While the application targets video game control, the underlying BCI technology has the potential for broader applications in rehabilitation and neurological research.

   Relevant patent:

   K Smith, C Bell, J Delaney, T Gilbreath, E Alipour, T Nutt, **EE Schultz**. *Biofeedback Ring Sensors.* US7263393. Active

OMB Number: 4040-0001
Expiration Date: 11/30/2025

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 1

UEI*: PNSWLGJ46247

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: EYESONIX INC.

Start Date*: 12-01-2024 **End Date*:** 11-30-2025 **Budget Period: 1**

A. Senior/Key Person

	Prefix	First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base Salary ($)	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits ($)*	Funds Requested ($)*
1 .		Donald	N.	Schwartz		PD/PI	150,000.00	1.20			15,000.00	3,750.00	18,750.00
2 .		Eric		Schultz		Co-Investigator	200,000.00	0.60			10,000.00	2,500.00	12,500.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name:

Total Senior/Key Person **31,250.00**

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Scientist	6.96			58,000.00	14,500.00	72,500.00
1	**Total Number Other Personnel**					**Total Other Personnel**	**72,500.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**103,750.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 1

UEI*: PNSWLGJ46247
Budget Type*: ● Project ❍ Subaward/Consortium
Organization: EYESONIX INC.

Start Date*: 12-01-2024 **End Date*:** 11-30-2025 **Budget Period: 1**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item	**Funds Requested ($)***
1 . Laser Vibrometer	55,000.00
Total funds requested for all equipment listed in the attached file	
Total Equipment	**55,000.00**

Additional Equipment: File Name:

D. Travel	**Funds Requested ($)***
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	500.00
2. Foreign Travel Costs	
Total Travel Cost	**500.00**

E. Participant/Trainee Support Costs	**Funds Requested ($)***
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees **Total Participant Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 1

UEI*: PNSWLGJ46247
Budget Type*: ● Project ❍ Subaward/Consortium
Organization: EYESONIX INC.

Start Date*: 12-01-2024 **End Date*:** 11-30-2025 **Budget Period: 1**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	6,750.00
2. Publication Costs	500.00
3. Consultant Services	13,000.00
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	24,000.00
7. Alterations and Renovations	
8. Data Management and Sharing Costs	0.00
9. NorthEast BioLab	15,398.00
Total Other Direct Costs	**59,648.00**

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	**218,898.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . MTDC	40.00	163,898.00	65,559.00
		Total Indirect Costs	**65,559.00**

Cognizant Federal Agency
(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	**284,457.00**

J. Fee	Funds Requested ($)*
	19,912.00

K. Total Costs and Fee	Funds Requested ($)*
	304,369.00

L. Budget Justification*	File Name: Budget_Justification_ +Quote_EyeSonix_2024.03.27.pdf

RESEARCH & RELATED Budget {F-K} (Funds Requested)

BUDGET JUSTIFICATION

Upon careful review of the budget required to complete the Aims as outlined, and review of the eligible waiver topics, we respectfully request the following budget outlined that is in excess of the hard cap. The proposed work falls under the 2023 SBA-approved NEI Topic E for awards over statutory budget limitations (Glaucoma and Optic Neuropathies: New therapeutic agents, instruments, and procedures for the diagnosis and treatment of glaucoma). Because we are developing a new therapeutic ultrasound device for the treatment of glaucoma—specifically the lowering of intraocular pressure and, in some cases, reversal of retinal nerve damage—we request a hard-cap budget waiver for this proposal.

PERSONNEL (Y1: $103,750)

Senior/Key Personnel

Donald N. Schwartz, MD, PI (Y1: 1.2 months), Founder and President of EyeSonix, Inc., will contribute 10% effort to this project. As project PI, he will oversee and manage all aspects of the proposed aims. Additionally, Dr. Schwartz will directly execute the biochemical studies of Aim 1 directed at determining the mechanism-of-action of therapeutic ultrasound for glaucoma (TUG). Dr. Schwartz has over four decades of experience in both optometry and clinical ophthalmology, and has conducted or contributed to several clinical research studies, including preliminary clinical studies showing TUG's potential for lowering intraocular pressure and providing neuroprotection in glaucoma patients. The total salary requested for Dr. Schwartz is $18,750.

Eric Schultz, MS, Co-I (Y1: 0.6 months), Co-Founder, CTO, and CEO of EyeSonix, Inc., will contribute 5% effort to this project. As project Co-I, he will primarily oversee the prototype development activities for the TUG device outlined in Aim 2. He has over 20 years of experience in medical device R&D, product design, and engineering, and has pioneered the development of several implantable and non-invasive medical devices. He has 36 patents granted or pending, the majority of which apply to devices and methods for helping patients with ocular diseases and/or ultrasound-based devices. The total salary requested for Mr. Schultz is $12,500.

Other Personnel

Scientist/Engineer (Y1: 6.96 months), a new hire, will contribute primarily to the prototype development activities of Aim 2 under the supervision of Mr. Schultz. With experience in electrical engineering and/or medical device development, this scientist/engineer will specifically execute activities related to integration and testing of thermal and force sensing into the TUG probe, as well as additional prototype improvements such as an internal timer, battery pack, and form-fitting handle. The total salary requested for this new hire is $72,500.

The fringe benefits for Employees are 25.0% of the funds requested.

RESEARCH AND RELATED BUDGET

Equipment (Y1: $55,000): VibroGo VGO-200 Portable Laser Vibrometer (see attached Quote for initial estimate, minus shipping and insurance added). This instrument, which provides non-contact vibration measurements of surfaces, is critical for prototype development activities (Aim 2) because it will provide feedback on how the ultrasound-generating characteristics of the TUG device probe are impacted by modifications for temperature or force sensing, which will have a direct impact on the viability of solutions chosen as it will affect the clinical performance of the device.

Travel (Y1: $500): We request funds to cover the cost of occasional travel to CRO sites for research-related or troubleshooting activities.

Participant/Trainee Support Costs: N/A

Materials and Supplies (Y1: $6,750): We request funds to cover the following materials and supplies for carrying out the proposed aims, particularly for prototype development activities in Aim 2:

- Outsourced prototype materials and parts for test fixtures ($5000)

- Lab equipment for testing; i.e. fixtures and other lab hardware ($1000)
- Basic machine shop tooling and associated items ($500)
- 3D printer material and associated costs ($250)

Publication Costs (Y1 $500): We request funds to partially cover publication of results in a peer-reviewed journal and/or presentation at a national or regional conference.

Automatic Data Processing and Computer Services: No funds requested

Consultant Services (Y1: $13,000)

Bryan Flaherty, PhD ($2,500). Dr. Flaherty is a trained bioengineer and industry expert. He will will provide consulting on the development of medical devices that can deliver non-invasive therapy. He has extensive experience in the available tools and methods for therapeutic energy devices and his expertise will be utilized to advance TUG. Dr. Flaherty's consulting rate $250/hour. See quote in letter of support.

Stephanie Kaplan ($10,500) is a medical device development and ultrasound therapy expert with decades of experience in the field. She will be working with EyeSonix as an operations and product development consultant. Stephanie's consultant rate $350/hour and she will be providing up to 30 hours of her time to this project. See quote in letter of support.

Equipment or Facility Rental/User Fees (Y1: $24,000)**:** We request funds to rent space at a JLABS incubator site and expand upon our current space as new staff are hired to contribute to this project and the commercial development of TUG. A quote for a rental agreement is being pursued and will be provided during JIT.

Data Management and Sharing: No funds requested

Technical Assistance: No funds requested

Contract Research Organization: (Y1: $15,398): We request funds to cover the bioanalytical studies of Aim 1 by the contract research organization NorthEast BioLab (NEBL), which has extensive capabilities in ELISA and multiplexed immunoassays such as the Bio-Plex, Luminex, and MesoScale Discovery platforms. A quote is being pursued and will be provided at JIT. The anticipated cost is based on prior experience with similar biochemical analyses of animal tissues that do not involve *in vivo* live animal studies. A formal quote is being pursued and will be provided at JIT. EyeSonix will incur any quoted costs in excess of the requested amount through use of private investment funds. See letter of support.

INDIRECT COSTS
A rate of 40% of total direct costs is requested. This amount is appropriate to cover the company's current projected indirect costs. It is consistent with NIH's policy for SBIR proposals when the company does not already have a previously negotiated indirect cost rate.

FEE
A fee of 7% of total costs (direct and indirect) is requested per the SBIR/STTR Application Guide, which states: "A reasonable fee, not to exceed 7% of total costs (direct and indirect) for each Phase (I and II) of the project, is available to small business concerns receiving awards under the SBIR/STTR program."

This fee will support EyeSonix Inc.'s growth by facilitating resource expansion and personnel development, aligning with the industry's typical profit margin for research and development work in the industry.

Quotation

Polytec

Quotation Number: **U5007017/1**
Quotation Date: **Mar 26, 2024**
Salesperson: Rob Warmbold
Salesman Phone: +1 949-943-3035
+1 561-207-1238

Polytec, Inc. • 16400 Bake Parkway • Irvine, CA 92618 • USA

EyeSonix
Attn: Accounts Payable
.2650 Elm Ave.
USA
Long Beach, California 90806
USA

Here is the quotation as promised.

Item#	Description	Quantity	Quantity Price USD
1	VibroGo VGO-200 Portable Laser Vibrometer	1	
	Option / **Description**		
	VGO-SONIC — VGO-SONIC	1	
	• VGO-DispOut — Displacement Output	1	$
	• A-CBL-0001 — Ethernet Cable RJ 45/M12 5 m D-coded	1	
	• VIB-A-T02 — Standard Tripod	1	$
	• VGO-BW-100kHz — Frequency Bandwidth 100 kHz	1	
	• VGO-VEL-2.0m/s — Maximum Velocity 2.0 m/s	1	
		SUBTOTAL:	$37,700
2	VibSoft-VL Data Acquisition Software	1	
	Option / **Description**		
	VibSoft-VL — VibSoft-VL for VibroLink Ethernet Data Interface	1	
	SW-VIBSOFT-VL - SW-VibSoft-VL License for VibSoft-VL	1	
	CH-VL — Ethernet	1	
	VIB-S-SM-B — Basic Software Maintenance VIB	1	
	VIB-S-BW100K — Bandwidth 100 kHz	1	
	VIB-S-SigPro — Signal Processor	1	
	VIB-S-VBEng — Scripting and open data interface	1	
		SUBTOTAL:	$5,400

TOTAL:		**$43,100**
Tax	**%**	**$3,879**
Total		

Terms of Delivery: FCA (Incoterms 2020) Waldbronn, Germany
Expiration Date: May 24, 2024
Payment Terms: 30 days net

Quotation

Quotation Number:	Quotation Date:
U5007017/1	**Mar 26, 2024**

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Order and payment terms are subject to credit approval by Polytec. All purchase orders are subject to Polytec´s standard terms and conditions. Items listed are covered by Polytec's limited hardware warranty. For complete details including the limited warranty and to see how PolyCare™ can extend this to 7 years.

These items are controlled by the U.S. Government and authorized for export only to the country of ultimate destination for use by the ultimate consignee or end-user(s), either in their original form or after being incorporated into other items, without first obtaining approval from the U.S. government or as otherwise authorized by U.S. law and regulations.

Delivery for a purchase is 12 to 14 weeks from the receipt of order. Cost of shipping and insurance are the customer´s responsibility. All of our systems are available for leasing, rental or testing services. Timing for delivery on demo systems, rentals, & testing service orders will be agreed at the time of order as they are available on a first come first served basis. If faster delivery is required, please discuss with your Polytec representative.

Submit purchase orders to orders@polytec.com with the payments made to: Polytec, Inc., 16400 Bake Parkway, Irvine, CA 92618. Phone: (949) 943-3033 Fax: (949) 679-0463

Thank you once again for your interest. Please don´t hesitate to call if there is anything we can help with.

Best regards,

Polytec Inc.

Rob Warmbold
Territory Manager
(561) 207-1238

RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals ($)	
Section A, Senior/Key Person		31,250.00
Section B, Other Personnel		72,500.00
Total Number Other Personnel	1	
Total Salary, Wages and Fringe Benefits (A+B)		103,750.00
Section C, Equipment		55,000.00
Section D, Travel		500.00
1. Domestic	500.00	
2. Foreign		
Section E, Participant/Trainee Support Costs		
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other		
6. Number of Participants/Trainees		
Section F, Other Direct Costs		59,648.00
1. Materials and Supplies	6,750.00	
2. Publication Costs	500.00	
3. Consultant Services	13,000.00	
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs		
6. Equipment or Facility Rental/User Fees	24,000.00	
7. Alterations and Renovations		
8. Other 1	0.00	
9. Other 2	15,398.00	
10. Other 3		
11. Other 4		
12. Other 5		
13. Other 6		
14. Other 7		
15. Other 8		
16. Other 9		
17. Other 10		
Section G, Direct Costs (A thru F)		218,898.00
Section H, Indirect Costs		65,559.00

Section I, Total Direct and Indirect Costs (G + H)	284,457.00
Section J, Fee	19,912.00
Section K, Total Costs and Fee (I + J)	304,369.00

OMB Number: 4040-0001
Expiration date: 11/30/2025

SBIR/STTR Information

Agency to which you are applying (select only one)*

❍ DOE ● HHS ❍ USDA ❍ Other:

SBC Control ID:* 002585565

Program Type (select only one)*

● SBIR ❍ STTR

❍ Both (See agency-specific instructions to determine whether a particular agency allows a single submission for both SBIR and STTR)

Application Type (select only one)*

● Phase I ❍ Phase II ❍ Fast-Track ❍ Direct Phase II ❍ Phase IIA ❍ Phase IIB ❍ Phase IIC

❍ Commercialization Readiness Program (See agency-specific instructions to determine application type participation.)

Phase I Letter of Intent Number:

* Agency Topic/Subtopic:

Questions 1-8 must be completed by all SBIR and STTR Applicants:

1a. Do you certify that at the time of award your organization will meet the eligibility criteria for a small business as defined in the funding opportunity announcement?* ● Yes ❍ No

1b. Anticipated Number of personnel to be employed at your organization at the time of award.* 10

1c. Is your small business majority owned by venture capital operating companies, hedge funds, or private equity firms?* ❍ Yes ● No

1d. Is your small business a Faculty or Student-Owned entity?* ❍ Yes ● No

2. Does this application include subcontracts with Federal laboratories or any other Federal Government agencies?* ❍ Yes ● No

If yes, insert the names of the Federal laboratories/agencies:*

3. Are you located in a HUBZone? To find out if your business is in a HUBZone, use the mapping utility provided by the Small Business Administration at its web site: http://www.sba.gov * ❍ Yes ● No

4. Will all research and development on the project be performed in its entirety in the United States?* ● Yes ❍ No

If no, provide an explanation in an attached file. Explanation:*

5. Has the applicant and/or Program Director/Principal Investigator submitted proposals for essentially equivalent work under other Federal program solicitations or received other Federal awards for essentially equivalent work?* ❍ Yes ● No

If yes, insert the names of the other Federal agencies:*

6. Disclosure Permission Statement: If this application does not result in an award, is the Government permitted to disclose the title of your proposed project, and the name, address, telephone number and email address of the official signing for the applicant organization to state-level economic development organizations that may be interested in contacting you for further information (e.g., possible collaborations, investment)?* ● Yes ❍ No

7. Does the application include a request of SBIR or STTR funds for Technical and Business Assistance (TABA)? If yes, please follow the agency specific instructions to provide the budget request and justification. (Please answer no if you plan to use the agency TABA vendor, which does not require you to include a request for TABA funds in your application.)* ❍ Yes ● No

8. Commercialization Plan: The following applications require a Commercialization Plan: Phase I (DOE only), Phase II (all agencies), Phase I/II Fast-Track (all agencies). Include a Commercialization Plan in accordance with the agency announcement and/or agency-specific instructions.*

Attach File:*

OMB Number: 4040-0001
Expiration date: 11/30/2025

SBIR/STTR Information

SBIR-Specific Questions:

Questions 9 and 10 apply only to SBIR applications. If you are submitting ONLY an STTR application, leave questions 9 and 10 blank and proceed to question 11.

9. Have you received SBIR Phase II awards from the Federal Government? If yes, provide a company commercialization history in accordance with agency-specific instructions using this attachment.* ❍ Yes ● No

Attach File:*

10. Will the Project Director/Principal Investigator have his/her primary employment with the small business at the time of award?* ● Yes ❍ No

STTR-Specific Questions:

Questions 11 - 13 apply only to STTR applications. If you are submitting ONLY an SBIR application, leave questions 11 - 13 blank.

11. Please indicate whether the answer to BOTH of the following questions is TRUE:* ❍ Yes ❍ No

(1) Does the Project Director/Principal Investigator have a formal appointment or commitment either with the small business directly (as an employee or a contractor) OR as an employee of the Research Institution, which in turn has made a commitment to the small business through the STTR application process; AND

(2) Will the Project Director/Principal Investigator devote at least 10% effort to the proposed project?

12. In the joint research and development proposed in this project, does the small business perform at least 40% of the work and the research institution named in the application perform at least 30% of the work?* ❍ Yes ❍ No

13. Provide UEI of non-profit research partner for STTR.*

OMB Number: 0925-0001

Expiration Date: 01/31/2026

PHS 398 Cover Page Supplement

1. Vertebrate Animals Section

Are vertebrate animals euthanized? ○ Yes ● No

If "Yes" to euthanasia

Is the method consistent with American Veterinary Medical Association (AVMA) guidelines?

○ Yes ○ No

If "No" to AVMA guidelines, describe method and provide scientific justification

2. *Program Income Section

*Is program income anticipated during the periods for which the grant support is requested?

○ Yes ● No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

*Budget Period	*Anticipated Amount ($)	*Source(s)

3. Human Embryonic Stem Cells Section

*Does the proposed project involve human embryonic stem cells? ❍ Yes ● No

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://grants.nih.gov/stem_cells/registry/current.htm. Or, if a specific stem cell line cannot be referenced at this time, check the box indicating that one from the registry will be used:

Specific stem cell line cannot be referenced at this time. One from the registry will be used.

Cell Line(s) (Example: 0004):

4. Human Fetal Tissue Section

*Does the proposed project involve human fetal tissue obtained from elective abortions? ❍ Yes ● No

If "yes" then provide the HFT Compliance Assurance

If "yes" then provide the HFT Sample IRB Consent Form

5. Inventions and Patents Section (Renewal applications)

*Inventions and Patents: ❍ Yes ❍ No

If the answer is "Yes" then please answer the following:

*Previously Reported: ❍ Yes ❍ No

6. Change of Investigator/Change of Institution Section

❑ Change of Project Director/Principal Investigator

Name of former Project Director/Principal Investigator

Prefix:

*First Name:

Middle Name:

*Last Name:

Suffix:

❑ Change of Grantee Institution

*Name of former institution:

OMB Number: 0925-0001
Expiration Date: 01/31/2026

PHS 398 Research Plan

Introduction	
1. Introduction to Application (for Resubmission and Revision applications)	
Research Plan Section	
2. Specific Aims	Specific_Aims_EyeSonix_2024.03.27.pdf
3. Research Strategy*	Research_Strategy_EyeSonix_2024.03.27.pdf
4. Progress Report Publication List	
Other Research Plan Section	
5. Vertebrate Animals	Vertebrate_Animals_EyeSonix_2024.03.27.pdf
6. Select Agent Research	
7. Multiple PD/PI Leadership Plan	
8. Consortium/Contractual Arrangements	
9. Letters of Support	LOS_merged_2024.03.27.pdf
10. Resource Sharing Plan(s)	Resource_Sharing_Plan_EyeSonix_2024.03.27.pdf
11. Other Plan(s)	DMSP_EyeSonix_2024.03.27.pdf
12. Authentication of Key Biological and/or Chemical Resources	Authentication_Plan_EyeSonix_2024.03.27.pdf
Appendix	
13. Appendix	

SPECIFIC AIMS

Glaucoma is the leading cause of irreversible blindness, affecting approximately 3 million people in the United States and 76-80 million worldwide[1–4]. While treatments targeting reduction of intraocular pressure (IOP) are available, they have significant drawbacks. First-line therapies include prescription eyedrops, which suffer from poor patient compliance, high cost, frequent side effects, and possible interactions with other medications[2,5]. Due to these limitations, first-line treatments often fail to halt glaucoma progression. Second-line therapies include laser-based (e.g., laser trabeculoplasty[6]) and other surgical procedures[7–9] to lower IOP, but these are invasive, harbor potential for serious side effects and, in the case of laser treatment, require expensive specialized equipment. **EyeSonix has developed therapeutic ultrasound for glaucoma (TUG), a non-invasive outpatient procedure with a portable device that provides a more effective and economical treatment that will improve the health and quality of life of millions of glaucoma patients.**

Beginning in the 1980s, *high-intensity* focused ultrasound (HIFU) was successfully used to treat refractory glaucoma[10–12]. HIFU successfully reduced IOP by damaging the ciliary epithelium and reducing aqueous humor production[13,14]; however, this ultimately *decreased* visual acuity in 9-43% of patients, contributing to the procedure's gradual abandonment.[15] In contrast, **TUG uses gentler *low-intensity* divergent ultrasound to reduce IOP by improving *outflow* of aqueous humor.** Preliminary data suggest that a single, well-tolerated, 10-minute TUG treatment with a portable device yields a lasting ≥20% reduction in IOP in 80% of treatment-naïve patients for 1 year. Unlike other solutions, **there is early evidence that TUG not only reduces IOP and can halt progression of glaucoma, but is neuroprotective, increasing the thickness of the retinal nerve fiber layer and neuroretinal rim, and even partially reverses visual field loss in some patients**. TUG thus has the potential to supplement and even replace first-line pharmaceutical treatments of glaucoma, circumventing compliance issues, reducing reliance on invasive surgical treatments, and potentially reversing glaucoma vision loss.

The proposed mechanism of action is twofold. First, TUG reduces IOP through mild localized hyperthermia and pressure waves that trigger a transient inflammation within the trabecular meshwork, leading to secretion of beneficial cytokines (e.g., TNF-α) as well as matrix metalloproteinases (e.g., MMP-3), improving outflow *via* debris clearance and tissue remodeling. Second, TUG promotes restoration of retinal nerve tissue *via* mechanotransduction that triggers a transient inflammation in the retina, increasing production of proinflammatory cytokines and promoting repair of nerve tissue. To maximize the safety and clinical efficacy of TUG, a better understanding of the mechanism of action is required, as well as integrated monitoring and feedback on critical procedural parameters such as temperature, applied force, and timing. **In this project, we therefore propose the following Aims directed at identifying the mechanism of action of TUG and incorporating critical safety and quality features into a new β-prototype device.**

Aim 1. Determine the biochemical effects of TUG treatment in a bovine organ culture model.

To better understand the mechanism of action, we will determine the biochemical effects induced by TUG using tissue dissection and biochemical analysis of 3-5 bovine eyes following *ex vivo* treatment with ultrasound according to existing TUG protocols, as well as comparison to an equal number of untreated control eyes. Changes in expression levels of MMP-3, TNF-α, mTOR, BDNF, NGF and GNDF following TUG protocol treatment will be assessed, compensating for statistical effects of multiple comparisons. Analyses will focus on tissues from the anterior chamber, ciliary body, trabecular meshwork, and retina.

Milestone 1. Demonstrate a ≥50% increase in expression level of one or more of the following biomarkers: MMP-3, TNF-α, mTOR, BDNF, NGF and GNDF.

Aim 2. Build β-prototype TUG device incorporating safety and quality control features.

Following regulatory advice and user feedback, we will improve the safety profile of our existing α-prototype by incorporating integrated monitoring of temperature (to ensure mild and controlled hyperthermia), applied force (to maintain ultrasound intensity within target range), a timer for monitoring and controlling procedural parameters, and a smaller form-fitting handpiece to enhance user control.

Milestone 2A. Integrated reporting of intraocular temperature with accuracy and precision of ± 1 °C.

Milestone 2B. Integrated reporting of applied force with accuracy and precision of ± 1 gf (gram-force).

Milestone 2C. Production of a working β-prototype incorporating all the above safety and quality features.

Expected Outcomes. We anticipate successful completion of these Aims to positively influence clinical outcomes, the likelihood of FDA approval, and the adoption of TUG. Following the successful completion of this study, we will seek Phase II SBIR funding to aid in performing a clinical trial in pursuit of FDA approval by the 510(k) pathway.

SIGNIFICANCE

Problem: First-line pharmaceutical treatments for glaucoma are costly and suffer from low patient compliance, leading to frequent disease progression. Glaucoma is a group of optic neuropathies characterized by progressive degeneration of retinal ganglion cells, resulting in cupping of the optic disc and loss of vision[16]. It is the leading cause of irreversible blindness, affecting approximately 3 million people in the United States and 76-80 million worldwide as of 2020[1–4]. Since glaucoma disproportionately affects the elderly, its prevalence is expected to increase as the mean age of the population rises in the coming years. By far the most common type is open-angle glaucoma, accounting for more than 80% of cases in the United States[17]. The biological basis of glaucoma is poorly understood[18], but key clinical correlates of glaucoma risk include elevated intraocular pressure (IOP), CDR asymmetry, and disc hemorrhage[19].

The only proven method to treat glaucoma is the reduction of IOP[20], which has been shown by several multicenter trials to prevent or slow progression of the disease[21–23]. The first-line approach for reducing IOP is the use of pharmaceuticals (typically formulated as prescription eye drops) such as prostaglandin analogs, beta blockers, α_2-adrenergic agonists, or carbonic anhydrase inhibitors[7]. These medications generally reduce IOP by lowering production of aqueous humor or increasing its uveoscleral and/or trabecular outflow. However, patient compliance with these self-administered pharmaceutical treatments is widely recognized as a significant and persistent challenge[24–26], with one recent study estimating a mean adherence level (in terms of prescriptions filled) of only 66.5%[5]. This poor compliance may be due in part to frequently observed adverse effects (local or systemic)[27] as well as inconvenience and forgetfulness[26]. These pharmaceutical treatments are also a major expense for patients and payers[27]. Poor compliance with topical treatment regimens is a likely factor in the progression of glaucoma and consequent loss of vision.[28]

Second-line glaucoma therapies are invasive, have adverse effects, and often require costly equipment. Failure of first-line treatments may necessitate more invasive interventions to reduce IOP. These include laser treatments such as selective laser trabeculoplasty (SLT)[6] as well as surgical procedures[7–9]. As with pharmaceuticals, these second-line therapies are directed at either reducing aqueous humor production (cyclocryocoagulation, laser cyclophotocoagulation) or improving its outflow (SLT, trabeculectomy, deep sclerotomy)[7]. While laser treatments are typically safe, they produce transient adverse effects (redness, discomfort) in up to 65.7% of cases, as well as complications such as transient pressure spikes, excessive pressure reduction (hypotony), corneal abrasion, inflammation, and pupillary deformity[7,29]. While more cost-effective overall than some pharmaceutical options, laser therapy requires expensive and specialized equipment that may not be available to clinics in developing countries and other underserved areas. Surgical treatments are still more invasive (e.g., involving implantation of a stent in the canal of Schlemm or ripping the trabecular meshwork); for example, a series of multicenter randomized controlled trials showed that nearly 35% of trabeculectomy operations had one or more complications, including bleb encapsulation, corneal edema, hypotony, and bleb-related endophthalmitis. In recent years, minimally invasive glaucoma surgery (MIGS) has provided a safer alternative to other surgical options; however, it is also not free of complications and is generally less effective at reducing IOP[30]. There is thus a need for less invasive treatments that do not rely on patient compliance with pharmaceutical regimens.

Rigor of prior research: Ultrasonic treatment of glaucoma shows promise, but previous high-intensity approaches have limitations. Beginning in the 1980s, a treatment for glaucoma known as high-intensity focused ultrasound (HIFU) became available, and was used for the treatment of refractory glaucoma[10–12]. HIFU reduces IOP primarily by damaging the ciliary epithelium (i.e., cyclodestruction) and reducing aqueous humor production[13,14]. However, this procedure has gradually been abandoned beginning in the 1990s for two main reasons. First, the increased availability of laser therapies provided another less-invasive alternative to glaucoma surgery. Second, since HIFU achieves IOP reduction through focused damage of eye tissues that produce aqueous humor, it carries the risk of persistent and excessive pressure reduction (hypotony) and other complications that can actually reduce visual acuity[31]. Ultimately it was found that HIFU produces complications that compromise vision

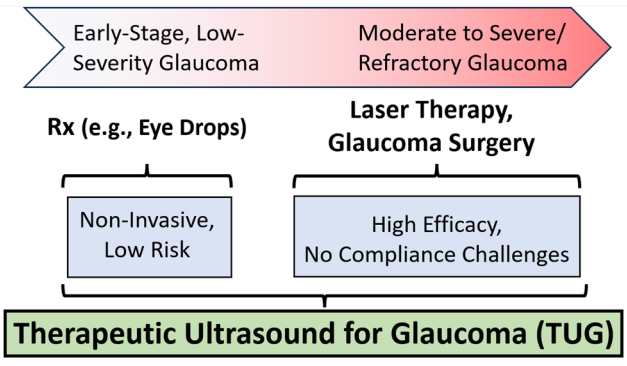

Figure 1. EyeSonix Inc.'s Therapeutic Ultrasound for Glaucoma (TUG) provides effective treatment with a well-tolerated, non-invasive procedure that avoids the compliance issues of pharmaceutical therapies, making it suitable for glaucoma of all stages and levels of severity.

in perhaps 9-43% of patients, making it less attractive than laser therapies such as SLT.[15]

In contrast to these earlier ultrasound approaches, TUG (**Fig. 1**) uses gentler low-frequency, low-power dispersive ultrasound to reduce IOP while greatly reducing the potential for harm, combining the low invasiveness of pharmaceutical treatments while avoiding their compliance issues. The TUG approach was inspired in part by the observation that pharmacoemulsification—a low-intensity ultrasound procedure employed in cataract surgery—reduces IOP in patients with coexisting glaucoma[32,33], often reducing the need for glaucoma medication[34]. In contrast to the cyclodestructive mechanism of HIFU, it was found that low-intensity ultrasound treatment induces a potentially IOP-lowering stress response in trabecular meshwork cells, providing a possible mechanism of action for these observations[35]. Based on these observations, the EyeSonix team has collected preliminary data supporting the efficacy and safety of the therapeutic use of a low-intensity ultrasound device designed expressly for glaucoma treatment (i.e., TUG), as well as a possible mechanism of action for the TUG procedure (see **APPROACH, Preliminary results**). Developing a better understanding of the mechanism of action of TUG (**Aim 1**), as well as improving the safety profile and consistency of the device (**Aim 2**) prior to FDA clinical trials, are the main goals of this proposal.

Impact on healthcare system. There are approximately 4.2 million people worldwide who are blind due to glaucoma. If we assume a market penetration of 20% and complete halting of glaucoma progression by TUG, at any given time approximately 840,000 patients could be spared preventable blindness by TUG treatment. Globally, the annual direct cost of glaucoma treatment ranges from $623 per year (for early-stage glaucoma) to $2511 per year (for end-stage disease); since the majority of patients have early-stage glaucoma, we assume an average cost of $1000 per patient per year. By 2040 an estimated 80 million patients worldwide will have glaucoma; assuming only 50% (40 million) of these know they have glaucoma, total direct costs of treatment worldwide will be approximately $40B. If 20% of these are treated with TUG with a savings of $400 per patient, this would be a savings of $3.2B to healthcare systems worldwide.

INNOVATION

Relative to existing approaches, TUG possesses several competitive differentiators (**Table 1**) that position this technology to create a strong impact in glaucoma therapy.

TUG uniquely combines high efficacy and low potential for adverse effects. Our preliminary data suggest that TUG achieves persistent reduction of IOP for at least 12 months in a single, well-tolerated outpatient procedure lasting approximately 10 min, and potentially halts or even reverses glaucoma progression (see **APPROACH, Preliminary results**). Thus, unlike pharmaceutical treatments, TUG does not require any long-term compliance of patients with a regimen of self-administered medication. Furthermore, unlike HIFU, laser treatments, and surgery, TUG does not achieve its result through targeted destruction of tissue, but instead by more diffuse effects such as mildly elevated temperature and a locally stimulated stress response (see **APPROACH, Preliminary results**).

As a low-cost, portable solution, TUG has great potential to reach underserved communities. Pharmaceutical, laser, and surgical treatments often cost over 2.5% the median annual household income in both developing and developed countries, limiting access to these treatments in underserved communities[36]. While SLT treatment per-case can cost less than a 3-year course of certain pharmaceutical treatments, it requires specialized equipment and training that are not accessible to all clinics[36]. In contrast, TUG employs a small, low-cost, hand-held device with much greater potential for adoption in medically underserved areas. This will be further enhanced in the β-prototype we develop here (see **Aim 2**) with features such as battery power for greater portability and feedback regarding temperature and device positioning for enhanced usability.

Strength of the EyeSonix Team. The EyeSonix, Inc. team comprises the combination of experience in device engineering, commercialization, clinical ophthalmology, and medical research needed to successfully complete this project and bring TUG to market. **Donald Schwartz, OD, MD** is President and Founder of EyeSonix, and will serve as PI for this project. He has more than three decades of experience in ophthalmology encompassing all standard treatment modalities for glaucoma, and will supervise all aspects of this project, with especial focus on the animal model studies of Aim 1. **Eric Schultz, MS** is CEO, CTO, and Co-Founder of EyeSonix, and will serve as Chief of Engineering in this project. With many years of leadership experience in biomedical startup companies, including those commercializing other ultrasound-based devices, he will supervise the development and testing of the β-prototype as outlined in Aim 2. Medical Advisors include **Jagdeep Kakadia, MD, PhD,** and **Ramesh Shah, MD**, who have hands-on experience with early studies of TUG treatment in India; **Vincent Patella, OD**, who is a world expert in visual field analysis and developed the algorithm for the present-day static perimetry used worldwide; and **John Samples, MD**, who has published hundreds of peer-reviewed articles and books on glaucoma. This combination of scientific, medical, and entrepreneurial experience equips the EyeSonix team to bring TUG successfully to the clinic and market. **Alan Robin, MD** is immediate past executive VP of the American Glaucoma Society and Associate Professor at the Wilmer Eye Institute. **Dale Heuer, MD** past chair of Ophthalmology at the Medical College of Wisconsin.

Intellectual property. EyeSonix has secured multiple patents and filed numerous provisional and/or full patent applications related to the TUG technology (device, disposables, therapeutic use cases), including the issued US Patents 9125722, 8043253, and 7909781.

APPROACH

Preliminary results. ***A single well-tolerated 10-minute TUG treatment reduces intraocular pressure for 12 months.*** In a randomized trial of n=26 participants (clinical trial #ISRCTN50904302), the potential of the α-prototype TUG device to reduce IOP in glaucoma patients was tested, using the contralateral (opposite) eye as an untreated control[2]. Eligibility criteria included (1) patients with open-angle glaucoma and without medical or laser treatment for at least 6 months, or patients presently on pharmaceutical treatment for glaucoma. It was found that a single 10-minute TUG treatment—comprising twelve 45-second applications of ultrasound around the limbus of the eye (**Fig. 2**)—reduced IOP by more than 5 mmHg, or >20% (**Fig. 3**). At 12-month follow-up, there was a persistent reduction of >20% in IOP in 80% of treatment-naïve (non-medicated) patients. Furthermore, in a 17-patient medication washout group, it was found that a single TUG treatment is more effective at reducing IOP than the pharmaceutical regimens the patients had been following. Importantly, the procedure was well-tolerated. When IOP was measured approximately 2 h after the procedure, no pressure spikes (as sometimes observed after laser treatments) were detected in any patients. Consistent with the expected inflammatory response to treatment, a small minority of patients reported mild irritation (n=3), discomfort (n=4), or pain (n=1) at 1-day follow-up, but these symptoms were gone one week after treatment[2]. This study thus provides an important proof-of-concept for the potential clinical utility of TUG for glaucoma treatment.

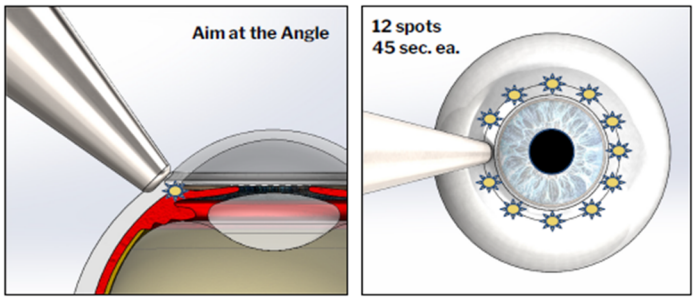

Figure 2. Standard TUG treatment protocol, in which low-power ultrasound is delivered to 12 spots around the limbus for 45 seconds each.

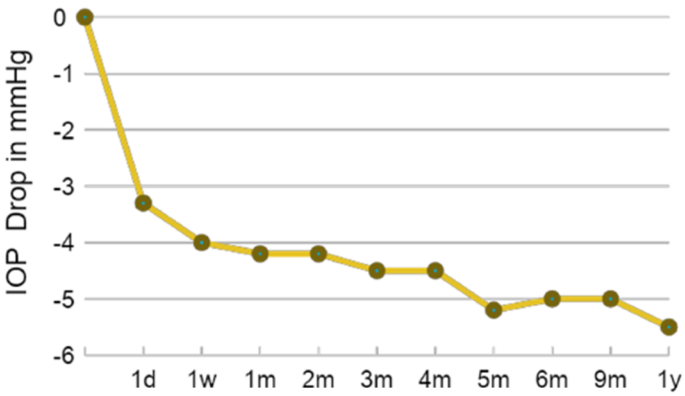

Figure 3. Randomized study of n=26 participants with glaucoma shows >5 mmHg (>20%) drop in IOP of the treated eye for 1 year following TUG treatment.

TUG treatment halts and/or reverses loss of retinal nerve fiber thickness and visual field in some patients. A retrospective review was performed of 29 diagnosed or suspected glaucoma patients who had been treated with TUG in one eye but not in the contralateral eye (unpublished, manuscript in preparation). In most cases only one TUG treatment in total was received. Comparison of the treated to the non-treated eye revealed a mean increase of 8% in the retinal nerve fiber layer (RNFL) after treatment, and a mean *decrease* of

Table 1. Competitive advantages of therapeutic ultrasound for glaucoma (TUG)

	TUG	Pharma	Laser Treatment	Surgery	MIGS	HIFU
Non-invasive treatment	✓	✓	✓	✗	✗	✓
Minimal adverse events	✓	✗	✓	✗	✗	✗
Patient compliance	✓	✗	✓	✓	✓	✓
Use for all glaucoma types	✓	✓	✗	✗	✗	✗
Minimal to no equipment	✓	✓	✗	✗	✗	✓
Potential for neuroprotection	✓	✗	✗	✗	✗	✗

7% in the non-treated eye (p<0.0038). Approximately 80% of treated eyes showed a lasting (>1 year) increase in RNFL thickness. This increase is evidence that TUG is, unlike other solutions, neuroprotective and may halt or even reverse progression of the neurological symptoms of glaucoma. Indeed, in at least six patients, the treated eye even showed an *increase* in visual field following treatment, including a striking recovery of a paracentral loss in one patient (**Fig. 4**); other patients showed increases in visual field index (VFI) from 61 to 74% or from 44 to 66% 12 months after treatment. While further studies are needed to assess the extent of visual field recovery, these preliminary results show that TUG has strong potential to halt the progression of glaucoma.

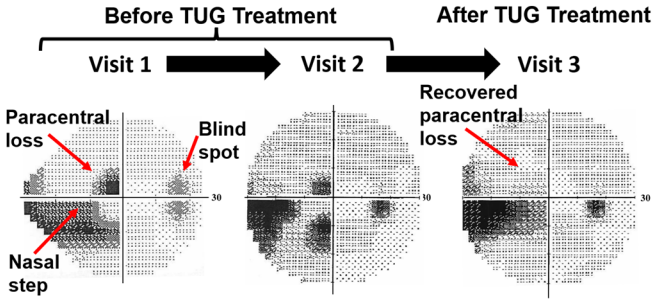

Figure 4. Example of recovery of paracentral visual field loss in a glaucoma patient after TUG treatment. Paracentral loss was evident in two separate visits 14 months apart, but absent following TUG treatment.

Preliminary animal organ study suggests elevation of TNF-α in response to treatment with TUG protocol. In another recent study, freshly harvested porcine eyes were subjected to the standard treatment with the α-prototype TUG device in order to investigate possible biochemical effects of the treatment (unpublished, manuscript in preparation). It was hypothesized that, just as selective laser trabeculoplasty (SLT) induces the release of cytokines within the trabecular meshwork of the eye, ultrasonic treatment would stimulate release of cytokines such as TNF-α to initiate a beneficial inflammatory response that would, in glaucoma patients, lead to clearing of debris and lowering of IOP. Control eyes were subjected to the same protocol (probe applied to eyes in the same manner and duration), but with the ultrasound disabled. After treatment of the porcine eyes with TUG, stationary organ culture was obtained at 24 hours; media was collected and frozen at -80 °C, and the concentration of the beneficial pro-inflammatory cytokine TNF-α was determined in media from both TUG-treated and non-treated control eyes. Results indicate elevated levels of TNF-α in TUG-treated eyes compared to the no-ultrasound control eyes (**Fig. 5**). In addition, immunohistochemistry imaged by confocal microscopy indicated elevated TNF-α in the trabecular meshwork of the TUG-treated eyes relative to control eyes. Although this was a limited study of just a single biomarker, it suggests a possible mechanism of action that will be more comprehensively investigated in **Aim 1** of this proposal by measuring several additional biomarkers in bovine eyes.

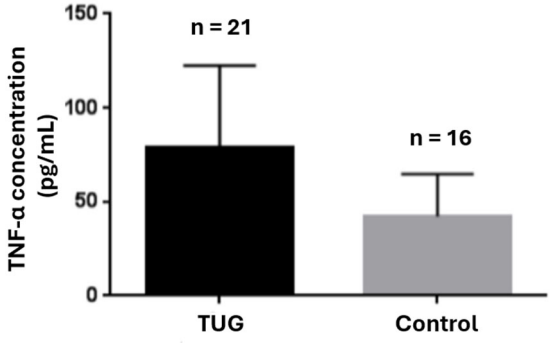

Figure 5. Preliminary ELISA study in porcine organ model indicates elevated expression of the beneficial cytokine TNF-α after treatment with TUG protocol. Unpaired t-test p=0.0052. Values reported are mean +/- 1 s.d.

Aim 1. Determine the biochemical effects of TUG treatment in a bovine organ culture model.

Table 2. Milestone for Aim 1		
Milestone		**Quantitative Metric**
1.	Measure changes in expression levels of MMP-3, TNF-α, mTOR, BDNF, NGF and GNDF after TUG protocol treatment	At least a 50% increase in expression level of one or more of these biomarkers following TUG treatment.

Rationale. A more comprehensive understanding of the mechanism of action of TUG will inform its further clinical development by offering insights into safety and efficacy, and thus increase the likelihood of FDA approval and successful deployment in the clinic. Knowledge of the biochemical impacts of TUG will enable more targeted design of the device as well as more informed optimization of performance as a function of procedural parameters such as the power and frequency of ultrasound used, duration of treatment, and frequency of treatment. It will also help us to anticipate any potential safety concerns or adverse effects that may arise from the device's use, such as potential for excessive inflammation in the days following treatment. Documentation of the TUG device's mechanism of action will be useful in submissions to the FDA for device approval, and will provide a foundation for further innovation and improvement of the therapy.

Study design. The objective of this Aim is a more comprehensive assessment of the biochemical effects of exposure of eye tissues to standard treatment with the TUG device. To this end, we will perform the standard TUG treatment on 3-5 bovine eyes with an equal number of non-treated control eyes. The eyes will be supplied fresh from the abattoir, cleaned, and then treated in the usual manner of TUG: application of low-intensity (2 W/cm^2) and low-frequency (40 kHz) ultrasound for 45 seconds at each clock hour around the limbus of the eye. They will then be stored in MACS® Tissue Storage Solution at room temperature for 24 hours. Each eye will be

dissected, and tissues obtained from the anterior chamber, the ciliary body, trabecular meshwork, and retina. The tissues will be flash-frozen and sent on dry ice to Northeast BioLab to conduct immunoassays of triggered proteins in the tissues: MMP-3, TNF-α, mTOR, BDNF, NGF and GNDF. These proteins were chosen because other studies have found them to be triggered by low-power ultrasound, and because they have been found to have other specific benefits for glaucoma, macular degeneration, or both.[37–50] Each sample will be assayed in triplicate in a blinded fashion, and results provided for further analysis.

Data analysis, statistical rigor, and bias. We will compare the expression level of each protein in tissues from TUG-treated eyes with those of control eyes, applying an unpaired t-test with a significance level of α=0.05 and using the Bonferroni correction for multiple comparisons[51]. To mitigate any potential for bias, we will numerically encode each supplied sample prior to shipping so as to not reveal to the analyzing laboratory whether it belonged to the treatment or control group. We will ensure that the TUG-treated and control groups are selected at random.

Expected outcomes. We expect TUG protocol treatment to result in elevated levels of TNF-α, MMP-3, and other biomarkers in the trabecular meshwork, and possibly other tissues of the eye. This would indicate that low-power, low-intensity ultrasound using the TUG protocol stimulates beneficial pro-inflammatory cytokines, matrix remodeling protein MMP-3, and neuroprotective biochemicals within the eye tissues, supporting this as the putative mechanism of action of the device in lowering IOP. The data acquired from this study will inform the design of future clinical trials as well as potential risks of adverse effects (e.g., due to excessive inflammation) that will be used in preparing a 510(k) Pre-Submission for the FDA in preparation for clinical trials.

Potential pitfalls and alternative approaches. (1) If increased expression is observed but is smaller than 50%, we will use initial results to conduct a new statistical power analysis to determine the sample size required to demonstrate the putative effect on each biomarker, and repeat the study on a new set of bovine eyes with the larger sample size. (2) A particular biomarker is not detected in either treated or controlled samples. Mitigation: We will re-attempt the analysis of specific biomarkers using more sensitive platforms such as Quanterix Simoa, employing a CRO to adapt existing sandwich pairs of antibodies to the chosen platform as necessary. (3) Problem: Bovine *ex vivo* protein synthesis not sufficiently robust to measure expression of all biomarkers. Mitigation: We will design and pursue corresponding studies in a porcine *ex vivo* system. In addition, we may design and pursue *in vivo* animal studies (e.g., by contracting with a CRO such as Powered Research, LLC), though this is beyond the scope of the funding available in an SBIR Phase I proposal.

Aim 2. Build β-prototype TUG device incorporating critical safety and quality control features.

Table 3. Milestone for Aim 2

Milestone		Quantitative Metric
2A.	Integrated monitoring of intraocular temperature	Accuracy and precision ± 1°C in the range of 43-44 °C.
2B.	Integrated monitoring of applied force	Accuracy and precision ± 1 gf (gram-force)
2C.	Completed β-prototype incorporating the above features	Functional prototype with temperature and pressure reporting

Rationale. The α-prototype TUG device (**Fig. 6**) was designed to produce ultrasound at the same low frequency of 40 kHz used in procedures for cataract surgery (i.e., pharmacoemulsion). However, the intensity was reduced to ~3 W/cm^2 with the intent to restrict the temperature within the focal area to 43-45 °C, which is below the temperatures that produce pain and necrosis[2,52,53]. This decision was informed by testing in a porcine eye that showed this intensity to raise the intraocular temperature to a stable 43-45 °C from a baseline of 36.5 °C[2]. To ensure consistency and maximize safety, the TUG device should have an integrated temperature measurement and reporting system to provide feedback during use. Furthermore, since the power of ultrasound delivered by the probe's piezoelectric components can be influenced by the force applied to the probe by the physician, it is important to provide feedback such that the delivered intensity remains close to the target of 3 W/cm^2. Finally, feedback from use of the α-prototype and the EyeSonix advisory board has suggested other improvements for enhanced usability and portability: (1) a timer for monitoring and controlling procedural parameters; (2) a smaller form-fitting handpiece to enhance user control and comfort; and (3) optional battery power for backup power and portability. The goal of this Aim is to produce a β-prototype incorporating the above features for enhanced safety and usability in preparation for FDA clinical trials.

Figure 6. The α-prototype TUG device comprising a control/driver module (left) and handheld probe (right).

Incorporation and testing of integrated monitoring of intraocular temperature. In previous animal studies of intraocular

temperature during TUG treatment, a K-type microthermocouple was positioned 0.5 mm below the surface of the eye at the limbus, and temperature monitored under ultrasound application using a digital thermometer[2]. Such a configuration would not be feasible in a non-invasive clinical procedure, and a thermocouple affixed to the tip of the probe would interfere with device performance. Instead, we will introduce a thermocouple on the body of the sonotrode approximately ~2 cm from the tip. To extrapolate to the intraocular temperature, we will perform calibration using the same microthermocouple setup described above while the TUG procedure is administered to a bovine eye in a water bath at 36.5 °C. The accuracy of the calibration will be assessed in three different bovine eyes held in water baths equilibrated to 37 to 47 °C, while simultaneously monitoring intraocular temperature with a microthermocouple. Each measurement will be performed three times to assess precision.

Incorporation and testing of integrated monitoring of applied force. Within the transducer handpiece is a stack of piezoelectric ceramic discs (sonotrode) that convert voltage to displacement and vice-versa. Therefore, a force applied to resist the displacement will change the voltage. Since the change in voltage correlates to the applied force, this voltage change will be measured (possible with current device circuit board) and calibrated to report on applied force. Calibration curves between voltage and force will be generated at varying applied force by mounting the probe onto a platform, aligning the probe with the direction of applied force, and using the mounting platform to bring the probe into contact with a secured bovine eye globe secured on a balance. The applied force (including at zero force/no contact) will be independently measured with the balance, and used to calibrate the force readout from transmuted voltage. The accuracy and precision will be tested by repeating the above procedure on at least 3 separate bovine eye globes with 3 replicates each, simultaneously monitoring applied force with a balance.

Additional features and finalization of prototype. A completed β-prototype will be constructed, incorporating into the generator a timer, rechargeable battery pack, and temperature and force monitors. A form-fitting handle for the probe will be developed in SolidWorks with most parts machined from Delrin. The challenge of this design is to minimize the form-factor while satisfying an IP67 rating. Performance in temperature and force monitoring will be re-verified according to the same methods described above, both under wall outlet and battery power.

Data analysis, statistical rigor, and bias. Precision and accuracy will be assessed by taking the mean and standard deviation of triplicate measurements of temperature and force. There is little potential for bias, but use of at least three separate eyes for each assessment will evaluate the generalizability of the temperature and force sensing modules.

Expected outcomes. Successful completion of this Aim will yield a working β-prototype TUG device with enhanced safety, usability, and portability features. These features will improve the consistency and safety of TUG treatment, and increase the chances of FDA approval and effective treatment of glaucoma. We will use the data generated here in a 510(k) Submission for the FDA.

Potential pitfalls and alternative approaches. (1) Because the thermocouple is ~2 cm from the tip of the sonotrode, the relationship between its temperature and that of the tip may depend in complex ways on factors such as the nonlinear generation of heat within the probe during the procedure as well as starting temperature, rendering simple calibrations inaccurate. In this event, fuzzy logic[54] and/or machine learning approaches will be trained to predict the temperature at the sonotrode tip based on inputs such as starting probe temperature and time after ultrasound initiation, and their performance rigorously tested for accuracy and reproducibility. (2) If we still do not meet our target metrics for temperature control, we will investigate other approaches for measurement such as low-cost infrared (FLIR) sensors[55]; these are not the preferred approach as they would add significant bulk and hamper usability, but are a viable backup strategy. (3) If target applied force metrics are not met, alternative strategies will be investigated, such as adding a mechanical force sensor behind the transducer stack.

Table 4 provides the proposed timeline for milestones of this Phase I project.

Table 4. Phase I Milestone Summary and Timeline		Month											
Milestone	**Description**	1	2	3	4	5	6	7	8	9	10	11	12
1.	Measure expression levels of key proteins after TUG protocol treatment												
2A.	Monitoring of intraocular temperature												
2B.	Monitoring of applied force												
2C.	Complete and test β-prototype												

Summary and future directions. TUG is positioned to provide an effective, safe, convenient, and portable first-line treatment for glaucoma, lowering IOP and potentially reversing previous loss of visual field. Following successful completion of these Aims, we will seek Phase II SBIR funding to perform a phase I clinical trial to evaluate safety and efficacy of the β-prototype device according to FDA guidance. The data collected on the mechanism-of-action in this study, as well as the safety features incorporated into the β-prototype, will be critical in guiding these future clinical studies and maximize the possibility of safe and effective deployment in the clinic.

PHS Human Subjects and Clinical Trials Information

OMB Number: 0925-0001

Expiration Date: 01/31/2026

Use of Human Specimens and/or Data

Does any of the proposed research in the application involve human specimens and/or data *	❍ Yes ● No
Provide an explanation for any use of human specimens and/or data not considered to be human subjects research.	
Are Human Subjects Involved	❍ Yes ● No
Is the Project Exempt from Federal regulations?	❍ Yes ❍ No
Exemption Number	❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8
Other Requested Information	

Delayed Onset Studies

Delayed Onset Study#	Study Title	Anticipated Clinical Trial?	Justification
The form does not have any delayed onset studies			

VERTEBRATE ANIMALS SECTION

The proposed study does not qualify as vertebrate animal research, as no live vertebrate animals will be used in this work. Instead, only tissues and organs from already deceased animals (cows) will be obtained from a licensed slaughterhouse that is in compliance with all local and federal regulations.

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Dale K. Heuer, MD
4581 W Montage Dr
Eagle, ID 83616-5206

March 19, 2024

Donald Schwartz, MD, President
EyeSonix Inc
10380 Wilshire Blvd #1404
Los Angeles, CA 90024

Dear Don:

This letter is to enthusiastically support EyeSonix' proposal that is being submitted to the NIH's SBIR program.

By way of introduction regarding my background, I completed a two-year clinical and research glaucoma fellowship at the Bascom Palmer Eye Institute, which is consistently ranked as the number one eye institute in the US. During my subsequent 34-year career in academic ophthalmology, I was clinical center investigator or co-investigator in several landmark multicenter glaucoma clinical trials, including the Fluorouracil Filtering Surgery Study, Collaborative Normal Tension Glaucoma Study, and the Collaborative Initial Glaucoma Treatment Study. As one of its three study vice chairs, I was also on the planning, executive, and endpoint committees of the Ocular Hypertension Treatment Study. Finally, I have held numerous American Glaucoma Society leadership positions (including serving as its 2019-2020 president) and was elected to the Glaucoma Research Society (an international society with limited membership).

Several studies, most notably the Laser in Glaucoma and ocular HyperTension (LiGHT) study have demonstrated the potential role for laser trabeculoplasty in the initial management of glaucoma and its potential advantages over topical ocular hypotensive medications. Treatment with EyeSonix' device reduces intraocular pressure by mechanisms similar to laser trabeculoplasty; however, it does not require the specialized equipment and sophisticated training that laser trabeculoplasty does. Therefore, EyeSonix' device has the prospects of broader, more cost-effective glaucoma treatment.

For over a decade, I have followed with interest EyeSonix' efforts to translate the founder's vision for this potentially game-changing treatment. The dedication and perseverance of his team speaks volumes with respect to the prospect for success with respect to bring this treatment to the market, which is poised for an alternative both to traditional topical medical treatment and to more the complicated treatment approach of laser trabeculoplasty.

I fully support EyeSonix and its team's endeavors to provide an improved/novel low power, non-invasive ultrasound for the treatment of open-angle glaucoma. I look forward to being kept apprised of your developments.

Sincerely,

Dale K. Heuer, MD
Emeritus Professor of Ophthalmology and Visual Sciences
Medical College of Wisconsin

Stephanie S. Kaplan
Palo Alto • California • 650 776 7311

3/15/2024

Donald Schwartz, MD
President and Founder, EyeSonix, Inc.
10380 Wilshire Blvd.
Los Angeles, CA 90024

Dear Don,

It's great to hear that EyeSonix is moving forward with the therapeutic ultrasound device. I am writing this letter of support for your NIH/SBIR application titled: "*Enduring Non-Invasive Glaucoma Treatment with Low-Power Ultrasound*". I look forward to working with you as an operations and product development consultant.

As you are aware, I have decades of experience in medical device development and ultrasound therapy. I look forward to our collaboration, and I am excited to see this device help the millions of people with glaucoma. As per our earlier terms, I will continue to receive $350/hour as a consultant and I will keep my hours to no more than 30 hours total. Having worked previously with your CEO, Eric Schultz, I am certain this venture will be successful. I look forward to collaborating with your team on this important endeavor.

Sincerely,

Stephanie Kaplan
Palo Alto, CA

From the Desk of
BRYAN FLAHERTY, PHD

3/15/2024

Donald Schwartz, MD
President
EyeSonix Inc
10380 Wilshire Blvd.
Los Angeles, CA 90024

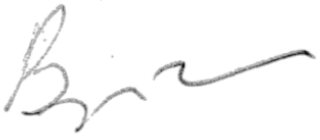
Dear Dr. Schwartz,

I am writing this letter to confirm my role as operations consultant in EyeSonix's SBIR application titled: "*Enduring Non-Invasive Glaucoma Treatment with Low-Power Ultrasound*", to be submitted to the NIH.

As a trained bioengineer and industry expert in the field of ultrasound, I have extensive knowledge of the available tools and methods for therapeutic energy devices. For many years, I have been involved in the development of medical devices that can deliver non-invasive therapy reliably and address the long-standing product development challenges to get them to market. I am excited at the prospect of the proposed ultrasound technology that will address the disease of glaucoma and more specifically the reduction of high intraocular pressure. This innovation will dramatically improve patient care performed worldwide and greatly improve the quality of scientific data obtained from clinical studies. As per our earlier terms, I will continue to receive $250/hour as a consultant with the understanding that I will work for 10 hours.

I fully support EyeSonix and your endeavors to provide an improved therapeutic ultrasound device. Best of luck in securing funding for this important work.

Sincerely,



Bryan Flaherty, PhD
Principal
Chanhassen, MN

35 Worth Avenue
Hamden, CT, 06518
(203) 361 3768
nebiolab.com

March 19, 2024

Subject: Capability Statement Regarding Performance of Bioanalytical Assays for the Studies Under, ["***Enduring Non-Invasive Glaucoma Treatment with Low-Power Ultrasound"***]

Donald Schwartz, MD
President
EyeSonix Inc
10380 Wilshire Blvd.
Los Angeles, CA 90024

Dear Dr. Schwartz,

The purpose of this letter is to elaborate on our support and capabilities for the collaborative multicenter project "***Enduring Non-Invasive Glaucoma Treatment with Low-Power Ultrasound"***, led by EyeSonix.

Specifically, this confirms the intent of NorthEast BioLab to provide services for the method development, validation, and regulated sample analysis.

NorthEast BioLab has worked with federal government agencies, such as the Department of Health and Human Services (HHS) and the Department of Defense (DOD) before, and is excited to support this study as an innovative and important program addressing the desperate unmet for a non-invasive, non-pharmaceutical treatment for Glaucoma.

Introduction and Overview -

NorthEast BioLab is a bioanalytical lab Contract Research Organization located in a ~19,000 sqft facility in New Haven, CT (USA). We have 20+ years of experience delivering 600+ studies and 400+ custom bioanalytical methods for the bioanalysis of therapeutics, metabolites, and biomarkers, as well as clinical trial kitting and biosample storage. Our mission-driven team of ~30 employees (inc., ~10 Ph.D. Sr. Scientists) with independent Quality Assurance Unit and Sample Management teams has an excellent track record of advancing Non-GLP, GLP, and Clinical pharmacokinetic (PK/PD, TK, BABE, ADME), immunogenicity (ADA, NAb), PD biomarker, cell-based assay, and other custom bioanalysis assays. We offer Method Development and Validation using LC-MS/MS, ELISA, Meso Scale Discovery ECL, Luminex Multiplex, Flow Cytometry, qPCR/dPCR, and Western Blot, among other technologies. Our company has completed hundreds of preclinical and clinical studies where sponsors submitted our bioanalytical data to hundreds of new drugs (IND, NDA), generics (ANDA), and biologics (BLA) applications to US FDA and regulators abroad. Founded in Mar 2003 by Ex-Bayer scientists with remarkable hands-on experience in drug development and discovery, we have built our reputation as a service-based small business partnering with research groups from academic labs at Yale, Brown, Dana Farber, Columbia, Duke, MD Anderson, Sarah Cannon, Sloan Kettering, Moffitt, UChicago, and UCSF, etc. to top 10 pharmaceutical and emerging biotech companies. We are a full-service, GLP and GCP compliant, FDA audited, DEA Schedule II-IV approved, Watson LIMS® enabled bioanalytical laboratory.

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Facility & Equipment -

As evidenced by our current and ongoing engagement with your program, we can perform all needed bioanalytical services towards the development of your bioanalytical assay and are committed to providing these services under your contract award. We have eleven AB Sciex LC-MS/MS and two HPLC systems equipped with Analyst®, WinNonlin® and relevant software for data acquisition, processing, and reporting. Similarly, we offer large molecule cytokine and chemokine bioanalysis utilizing ELISA, MSD ECL, Luminex, Western Blot, Flow Cytometry, High-resolution Microscopes, commercially available biology kits, and qPCR/dPCR platforms. As needed, we would perform your assay development, qualification, and sample analysis on our instruments with appropriate software for data acquisition, processing, and reporting. All our equipment is calibrated and validated according to NorthEast BioLab Standard Operating Procedures (SOPs). Our independent Quality Assurance Unit (QAU) ensures that the entire management and laboratory staff is well trained and methodically performs lab activities in compliance with applicable regulations and guidance from FDA, OECD, and EMA. We have a comprehensive Quality Manual (QM) defining our Quality Management System (QMS) that is revised periodically. All our reagents get purchased from qualified vendors screened by QAU for passing our Vendor Approval System standards. We have dedicated logistics personnel who inspect your biological samples at receipt and document the end-to-end chain of custody. Our 25+ sample storage chambers (refrigerator, -20C, -70C, Nitrogen) are access-controlled (each unit key locked and dedicated personnel), have calibrated temperature probes, and are connected to continuous centralized monitoring and alarm notification system (EMS). The biological samples are segregated by protocol/study or method number, and we retain backup samples when possible. Routinely tested redundant gas generators automatically supply emergency backup power to our controlled storage chambers.

Biography of Key Personnel -

Our veteran and highly trained scientists are passionate about streamlining the development of your life-enhancing treatments. We seek satisfaction in fulfilling your therapeutic mission while upholding our high-quality service and quick turnaround reputation. Below, please find the bio of our key leaders who will be interacting with you:

Vipin Agarwal, PhD

Dr. Vipin Agarwal is President and CEO at NorthEast BioLab. He has extensive experience in the management of bioanalytical laboratories under GCP/GLP environment in the pharmaceutical industry. He has excellent knowledge of state-of-the-art instrumentation (HPLC, LC/MS/MS, automation in sample preparation) and a clear understanding of bioanalyses' role in the drug development process from discovery to market.

Dr. Agarwal is familiar with various aspects of the FDA's drug development requirements, including the submission of Investigational New Drugs (IND) and New Drug Applications (NDA). Before he founded NorthEast BioLab, Dr. Agarwal was Deputy Director, Bioanalytics at Bayer Pharmaceuticals. He has an MBA from Rensselaer Polytechnic Institute in Troy, NY, and a Ph.D. from the University of New Brunswick in Canada. Dr. Agarwal is an active member of the Journal of Liquid Chromatography & Related Technologies and the American Chemical Society.

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Ajay Bhargava, PhD

Dr. Ajay Bhargava is VP, Biology at NorthEast BioLab and has deep expertise in drug discovery and cancer biology. He is experienced in ELISA, molecular biology (RNA and DNA-based technologies), cell biology techniques, and high content screening; planning and optimizing appropriate assays to evaluate the mechanism of action and functionality of chemical entities (synthetic and natural products); and in vivo Xenograft models, PK/PD relationship and biomarkers for mechanism-of-action studies.

Dr. Bhargava has demonstrated leadership in moving projects from target identification to phase I clinical trials. At NorthEast BioLab, he has extensively developed and validated ELISA assays for pharmacokinetic analysis of biotherapeutics under GLP and FDA guidelines. He evaluated anti-cancer compounds in proliferation, mechanism of action (phosphoprotein western blot and cytoblots) assays, RGD binding assay, and tubulin polymerization assay.

Previously, Dr. Bhargava worked with Bayer Pharmaceuticals for 13 years as a Senior Research Investigator. He is a postdoc in Molecular Biology from Yale University and received his Ph.D. from the Indian Institute of Science, Bengaluru.

Ron Mays

Ron Mays is Laboratory Director at NorthEast BioLab. He has extensive laboratory experience and is considered a separation technology science expert. Mr. Mays comprehensively understands federal regulation guidelines, including GLP/GCP sample analysis, and has worked directly with the FDA during facility audits.

At NorthEast BioLab, he supervises all bioanalysis, sample management, and regulatory compliance activities. Mr. Mays performs internal auditing of clinical and method reports and reviews external audit findings, taking corrective action when necessary. He is responsible for developing and validating extraction methods of Bioanalytical compounds from biological matrices as per the FDA guidelines.

Before joining NorthEast BioLab, Mr. Mays was Sr. Associate Research Scientist at Bayer Pharmaceuticals. Previously, he spent six years at Ciba-Geigy as a Senior Analytical Technician. Mr. Mays received a bachelor's degree in chemistry from Charter Oak State College, New Britain, and an associate's degree in Chemistry from Hartford State Technical College.

Muraly Puttabyatappa BVsc, MVsc, PhD

Muraly Puttabyatappa is an Associate Director, Large Molecule Bioanalysis at NorthEast Biolab. He has 20+ years research experience in biomarker discovery using immune, qPCR and cell-based assays. His expertise spans assay development, optimization, and validation as per regulatory requirement to serve pharmacokinetic, pharmacodynamic, toxicokinetic and immunogenicity assessments.

Before joining NorthEast Biolab, Dr. Puttabyatappa was National Institute of Environmental Health Sciences (NIEHS) Research Fellow in Environmental Toxicology at University of Michigan. Dr. Puttabyatappa completed

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Post-Doctoral training at University of Michigan and University of Kentucky, Doctoral training at University of Maryland and Veterinary education from Kerala Agricultural University and University of Agricultural Sciences Bangalore, India.

Erin O'Brien, PhD

Erin O'Brien is a senior scientist at NorthEast BioAnalytical Laboratories. She specializes in pharmacokinetic analysis and chromatographic assays of therapeutics and biomarkers. She has extensive experience in developing and validating LC-MS/MS methods for regulated and non-regulated bioanalytical studies, as well as performing maintenance and troubleshooting of laboratory instrumentation. She also handles client communications and technical consultations, and writes method and study reports.

Erin obtained her Ph.D. in Chemistry from UC Berkeley, where she researched nanocrystal surface chemistry under the supervision of Prof. Paul Alivisatos. She developed and optimized statistical models of quantum dot surfaces, spear-headed a multi-laboratory collaboration using non-linear spectroscopy, and secured a grant for her project.

Erin has a strong background in computer skills, including Sciex Analyst, Watson LIMS, Certara Phoenix, MATLAB, Python, Java, Microsoft Office, Adobe Illustrator, Photoshop, Mnova, NanoAnalyze, and VESTA. She is proficient in data analysis and modeling, simple programming, and graphical presentation.

Conclusion -

At NorthEast BioLab, our vision to serve you stretches far beyond individual projects. My colleagues and I are pleased to provide partnership and local leadership to this study, which will provide an important opportunity to advance EyeSonix's goals. I offer my full support and look forward to collaborating with you and all the co-investigators on this collaborative project. NorthEast BioLab is fully capable of supporting this effort and looks forward to doing so on a fee-for-service basis. We are excited to continue working together on your pathbreaking drug research and development efforts.

Sincerely, your POC

Date: 2024.03.19 10:27:11 -04'00'

Vipin Agarwal, PhD, MBA
President & CEO | NorthEast BioLab
35 Worth Ave, Hamden, CT 06518
Direct: (203) 361-3768 | Cell: (203) 606-8840

Letter of Support for EyeSonix Grant Application

To: Donald Schwartz MD: **March 18, 2024**
10380 Wilshire Blvd. #1404
Los Angeles, CA 90024

I am writing to express my strong support for EyeSonix and its innovative work in the ultrasound technology field. As an investor with over 40 years of experience in accounting and financial analysis, I have been particularly impressed by the company's:

- **Strong Financial Management:** EyeSonix demonstrates a clear understanding of financial controls and cost management. From my review of the financial projections, I am confident in the company's ability to manage its resources effectively and achieve profitability.
- **Market Potential:** The global ultrasound market is experiencing significant growth, driven by advancements in technology and increasing demand in various healthcare sectors. EyeSonix is well-positioned to capitalize on this trend with its TUG glaucoma treatment.
- **Experienced Team:** The leadership team at EyeSonix possesses a deep understanding of the medical technology industry and a proven track record of success. Their expertise in research, development, and commercialization inspires confidence in the company's ability to execute its strategic vision.

In addition to the financial aspects, I am also drawn to the positive impact EyeSonix has on the healthcare field. Its potential to transform the treatment of glaucoma to a more patient friendly and cost savings method for treating this serious disease can truly be a game changer.

I am confident that EyeSonix is poised for significant growth and success. Based on my experience and analysis, I believe this is a company with a strong potential to generate significant returns for investors while making a positive contribution to the medical field.

Sincerely,

Marc Asheghian

Marc Asheghian CPA MST

RESOURCE SHARING PLAN

The proposed scope of work will not result in the production of (1) unique model organism research resources and/or (2) unique research tools as defined by the NIH in their guidance documents entitled “Model Organisms Sharing Policy” and “Research Tools Policy” available on the NIH website.

Consistent with Bayh-Dole Regulations EyeSonix Inc. is committed to the timely development of a commercial product with support from the NIH SBIR/STTR funding mechanism. Commercialization of the Therapeutic Ultrasound for Glaucoma (TUG) platform for treatment of glaucoma will lead to its broad dissemination and use by clinical ophthalmologists, thereby enhancing the value of NIH-sponsored research.

INTELLECTUAL PROPERTY RIGHTS

The investigators will assert copyright in scientific and technical articles based on data produced under the grant where necessary, but we will also make every effort to keep technologies developed as a result of this research project widely available and accessible to the research community. If additional patents are filed and the technology licensed, we will only seek exclusivity in cases where this approach is determined to be the best route for successful development of the technology for public use and benefit.

NIH Generated message:

The Other Plan(s) attachment included with the application is not evaluated during the peer review process but will be evaluated prior to a funding decision. Although part of the official submission, the attachment is maintained as a separate document in eRA Commons viewable by authorized users and is not part of this assembled application.

AUTHENTICATION OF KEY BIOLOGICAL AND/OR CHEMICAL RESOURCES

Overview:

The only key biological or chemical resources to be used in this project are antibodies, which will be solely used and authenticated by the Contract Research Organization (CRO) NorthEastBioLab (see Letter of Support).

1. Cell Lines

No cell lines will be used for this project.

2. Antibodies

Antibodies with reactivity against bovine MMP-3, TNF-α, mTOR, BDNF, NGF and GNDF will be used in this study. All immunoassays will be conducted by NorthEast BioLab (NEBL), a full-service, GLP and GCP compliant, FDA audited, DEA Schedule II-IV approved, Watson LIMS® enabled bioanalytical laboratory. All antibodies and assays used in this study will be authenticated by NEBL in accordance with GLP and FDA guidelines and established standard operating procedures (SOPs).

3. Specialty Chemicals

No specialty chemicals will be used for this project.

4. Purified Proteins

No purified proteins will be used for this project.

5. Vertebrate Animals

No vertebrate animals will be used for this project.

6. Plasmids

No plasmids will be used for this project.

7. Nucleic acids (e.g. siRNA, shRNA, gRNA, etc.)

No nucleic acids will be used for this project.