PI: **SHERA, CHRISTOPHER A**	Title: Understanding Otoacoustic Emissions	
Received: 06/30/2018	Opportunity: PA-18-484 Clinical Trial:Not Allowed	Council: 01/2019
Competition ID: FORMS-E	FOA Title: NIH Research Project Grant (Parent R01 Clinical Trial Not Allowed)	
2R01DC003687-22A1	Dual:	Accession Number: 4191818
IPF: 7636101	Organization: [redacted]	
Former Number:	Department: Otolaryngology	
IRG/SRG: AUD	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 22: [redacted]	Animals: Y Humans: Y Clinical Trial: N Current HS Code: 30 HESC: N	New Investigator: N Early Stage Investigator: N
Senior/Key Personnel:	*Organization:*	*Role Category:*
Christopher Shera	[redacted]	PD/PI
Carolina Abdala	[redacted]	Co-Investigator
John Oghalai	[redacted]	Co-Investigator

OMB Number: 4040-0001
Expiration Date: 10/31/2019

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
DC003687

b. Agency Routing Number

2. DATE SUBMITTED
2018-06-29

Application Identifier
7632282

c. Previous Grants.gov Tracking Number

5. APPLICANT INFORMATION

Organizational [redacted]

Legal Name*: [redacted]
Department:
Division:
Street1*: [redacted]
[redacted]
[redacted]
County:
State*: [redacted]
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: [redacted]

Person to be contacted on matters involving this application
Prefix: First Name*: Rosemarie Middle Name: Last Name*: Gonzales Suffix:
Position/Title: Contract and Grant Officer
Street1*: [redacted]
[redacted]
[redacted]
[redacted]
[redacted]
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: [redacted]
Phone Number* [redacted] Fax Number: Email: [redacted]

6. EMPLOYER IDENTIFICATION NUMBER *(EIN) or (TIN)** [redacted]

7. TYPE OF APPLICANT* O: Private Institution of Higher Education

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*
Understanding Otoacoustic Emissions

12. PROPOSED PROJECT
Start Date* 04/01/2019
Ending Date* 03/31/2024

13. CONGRESSIONAL DISTRICTS OF APPLICANT
[redacted]

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: Dr. First Name*: Christopher Middle Name: Last Name*: Shera Suffix:

Position/Title: Professor

Organization Name*: [redacted]

Department: Otolaryngology

Division: [redacted]

[redacted] Number: Email*: [redacted]

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested* [redacted]

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*: Rosemarie Middle Name: Last Name*: Gonzales Suffix:

Position/Title*: Contract and Grant Officer

Organization Name*: [redacted]

Department: Div of Contracts and Grants

Division: Vice President For Research

Street1*: [redacted]

Province:

Country*: USA: UNITED STATES

ZIP / Postal Code*: [redacted]

Phone [redacted] Fax Number: Email*: [redacted]

Signature of Authorized Representative*

Rosemarie Gonzales

Date Signed*

06/29/2018

20. PRE-APPLICATION File Name:

21. COVER LETTER ATTACHMENT File Name:Shera_Cover_Letter1012773856.pdf

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

OMB Number: 4040-0010
Expiration Date: 10/31/2019

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: [redacted]

[redacted]

Street2:

City*: [redacted]

[redacted]

Province:

Country*: USA: UNITED STATES

Zip / Postal Code*: [redacted]

Project/Performance Site Congressional District*: [redacted]

Additional Location(s) File Name:

Funding Opportunity Number: PA-18-484. Received Date: 2018-06-30T00:58:58.000-04:00

OMB Number: 4040-0001
Expiration Date: 10/31/2019

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 00005906

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 A3518-01

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*	Shera_Project_Abstract1012773832.pdf
8. Project Narrative*	Shera_Project_Narrative21012773833.pdf
9. Bibliography & References Cited	Shera_Literature_Cited1012773834.pdf
10.Facilities & Other Resources	Shera_Facilities1012773835.pdf
11.Equipment	Shera_Equipment1012773836.pdf

Funding Opportunity Number: PA-18-484. Received Date: 2018-06-30T00:58:58.000-04:00

Project Summary

Realizing the potential of otoacoustic emissions (OAEs) as noninvasive probes of cochlear function requires understanding the physical and physiological mechanisms that generate and shape these sounds. To address important unresolved issues of cochlear mechanics while improving our understanding of OAE generation, we propose three aims involving innovative theoretical modeling rigorously tested by experimental measurements. The first Aim studies the action of “suppressor” tones on OAE generation by testing the hypothesis that suppressors can both reduce the strength of existing OAE sources and create new sources of wave reflection within the cochlea. We determine whether suppressors can accurately map out the distribution of OAE generators in models where the distribution is known in advance and test whether eliminating sources created by the suppressor can improve the measurement of cochlear frequency selectivity using OAE suppression tuning curves. The second Aim studies the nature of the micromechanical irregularity believed necessary for the generation of reflection-source OAEs. We test whether efferent-induced changes in OAEs can be explained by the hypothesis that activation of medial olivocochlear (MOC) efferents alters the spatial pattern of irregularity. Using both measurements and models, we also explore the hypothesized but previously unrecognized role of irregularity on the generation of distortion-source OAEs and its modulation by contralateral acoustic stimulation. The third Aim explores the micromechanics of cochlear wave amplification and its consequences for OAE generation. Modeling work studies OAE generation in models incorporating forms of spatial feed-forward/backward amplification suggested by the oblique geometry of the outer hair cells. We also combine state-of-the-art measurements of organ of Corti vibration using optical coherence tomography (OCT) with theoretical inverse methods to study how the assumed coupling between the modes affects the generation and propagation of OAEs. Completion of these Aims will significantly enhance our understanding of OAE generation and its relationship to cochlear mechanics. The Aims are also directly relevant to improving the power of OAE-based diagnostics and other technological applications—such as hearing aids and preprocessors for speech-recognition devices—that benefit from knowledge of cochlear amplification, nonlinearity, and signal processing.

Project Narrative

Our experiments and models address the mechanisms by which healthy ears generate sound. Sounds from the ear, known as otoacoustic emissions (OAEs), are widely used for noninvasive tests of hearing function. By improving our understanding of how OAEs are produced within the cochlea, and how they can be used to probe aspects of cochlear function important for human communication, the proposed work will enhance the power of clinical hearing tests and help improve the design of auditory prosthetic devices.

Facilities and Other Resources

Laboratories: The [redacted] Department of Otolaryngology [redacted] School of Medicine provides a rich, multidisciplinary environment for auditory neuroscience that encourages and nurtures scientific discourse and collaboration. The growing Department includes faculty with interests in basic science, translational science, biomedical engineering, and clinical practice.

Dr. Shera and the members of the Auditory Physics Group have their primary research laboratory and office space in the Auditory Research Center (ARC) at the [redacted] School of Medicine. The laboratory features a vibration-isolated, electrically-shielded, and temperature-controlled sound booths fully equipped for research studies on human subjects. All experimental hardware is controlled using custom data-acquisition software written and maintained by the PI and members of the group. In addition, the group has access to three full-time sound-attenuating research booths located in the Hearing Research Lab (HRL) on the [redacted] campus, a short walk from the PI's office. Each site provides faxing, copying, computer support, a front desk staff, and a waiting area for study participants. These facilities also provide private space for obtaining informed consent and sharing personal health information.

The Auditory Research Center also houses other research laboratories where human studies are performed [redacted] Auditory researchers that require "wet lab" space are located in either the Zilkha Neurogenetics Institute or in the adjacent Broad Center for Regenerative Medicine [redacted] Finally, the [redacted] Family Center for Childhood Communication adjacent to the main University Park Campus serves as home for research involving pediatric cochlear and brainstem implants [redacted]

Altogether, there are >50 faculty, staff, and trainees involved in auditory research within the [redacted] Department of Otolaryngology, and we interact and work together as a matter of routine. This invigorating atmosphere provides ample opportunity for discussions, collaborations, and learning. The group is highly collaborative and diverse, allowing the skill sets of each investigator to be a resource for the other members. This is a practice promoted by the department and university and a philosophy shared by all.

Animals: The vivarium is located in the basement of the [redacted] Institute where [redacted] lab is located. The facility is AAALAC-approved with 24-hour care provided by the vivarium staff. [redacted] is the head veterinarian and director of the [redacted] Department of Animal Resources (DAR). DAR and the staff of the vivarium assist faculty, staff, and students in carrying out animal-based research and teaching activities [redacted] The vivarium also offers surgical and diagnostic laboratory services, assistance with ordering anesthetic drugs and supplies, assistance with rodent euthanasia, and animal orders and transfers and breeding. Training programs in Animal Care and Use are also offered to principal investigators, staff, and students, as well as education programs for Laboratory Animal Technicians. Animals will be transferred from the animal facility to [redacted] laboratory for recordings. The laboratory features two vibration-isolated, electrically-shielded, and Temperature-controlled sound booths and is equipped with a ventilation hood for the safe handling of animals during the course of the experiments. All experimental hardware is controlled using custom data-acquisition software written and maintained by [redacted] his team.

Computers and Data Acquisition Equipment: All research laboratories have multiple networked computers that are available for software development, data collection, analysis, and computational modeling of the mechanical data for the proposed research. Networked laser printers and scanners are available for lab and office use. Computer support is provided by USC Information Technology Services. All research personnel have dedicated workstations linked via ethernet and secure wireless to the USC network and to a shared drive for data storage and backup. The network provides access to email and library services, including MEDLINE, PubMed, and a vast collection of eJournals. USC provides university-wide licenses for MATLAB and JMP statistical analysis tools, as well as software

for word processing, data analysis, and making figures.

The experimental chambers at the ARC, where the human OAE experiments will take place, have RME Babyface Pro Audio Interfaces and a National Instruments PXI chassis housing an embedded dual-core computer controller and three NI PXI-4461 24-bit dual input-output boards for generating electrical signals to drive acoustic transducers and for recording analog responses. All experimental hardware is controlled using custom data-acquisition software written by the PI in LabVIEW and MATLAB. In addition to the data-acquisition equipment listed above, the sounds booths are equipped with miscellaneous acoustic drivers, transducer assemblies, filters, and OAE probes (i.e., Etymotic Research ER10X, ER10A, ER10B+, and ER10C probe systems).

Office: The Department of Otolaryngology maintains office and workspace for the PI and co-investigators (post-doctoral research fellows, graduate students) in the Auditory Research Center on the campus of the [redacted] School of Medicine. Conference facilities are available on-site for lab meetings, and desks and carrels are provided for visitors and consultants. An administrative assistant is available as needed to help with research endeavors.

Other resources: [redacted] offers state of the art facilities in all major areas. [redacted] fosters a collaborative spirit between schools and laboratories, facilitating interactions between laboratories and investigators. There are imaging (including light, TEM, and SEM setups), sequencing, bioinformatics, and biostatistics core labs in adjacent buildings that can be accessed on a fee basis. In addition, there are gene array and Next Gen sequencing facilities available. A machine shop is available on a fee-for-servce basis. Translational research involving human patients is a strength of [redacted] The otology clinics are set up to facilitate adult and pediatric research and many (if not most) hearing loss patients are enrolled in some type of research study.

Major Equipment

Auditory Physics Group (USC Auditory Research Center)

- Double-walled, RF shielded sound booth for human subject testing
- Soundcards (RME Babyface Pro and Lynx II)
- Transducers for delivering stimuli to participants, including insert earphones (Etymotic Research ER2 and ER3A)
- Portable oscilloscope (Tektronix)
- Otoacoustic emission probe microphone systems (Etymotic Research ER10A, ER10B+, ER7, ER10C, and ER10X)
- Desktop computers for data collection
- Two GSI16 Audiometers, two GSI TympStar Immittance meters, two Interacoustic middle-ear analyzers, and two otoscopes.
- Backsaver Zero-Gravity ergonomic chairs for adult OAE testing
- Bruel & Kjaer digital sound level meter #2250, ear simulator #4127, and ¼-inch microphone #4134 and amplifier for calibrating data-acquisition probes
- National Instruments PXI chassis housing an embedded dual-core computer controller and three NI PXI-4461 24-bit dual input-output boards
- Larsen-Davis microphone amplifier
- Pistonphone for microphone calibrations

Oghalai Lab (USC Zilkha Neurogenetics Institute)

200 kHz Swept-Source VOCTV Imaging Suite

- Double-walled, RF shielded sound booth
- Custom-built, fiber based swept-source OCT system
- Vibration isolation table
- Surgical instruments
- Temperature-regulated heating pad
- Custom-machined animal head holder with ear bars
- Zeiss dissecting microscope (Stemi-2000) with fiberoptic light source
- National Instruments PCIe-6251 DAQ in one computer and another PXIe chassi with NI boards, including a computer controller, an ADC, and an FPGA.
- Cochlear Monitoring Program (CMP) custom software developed in Python and C++ to present sound stimuli and record the responses
- Power amplifier (Servo 600, Samson Technologies Corp., Syosset, NY)
- Two high frequency speakers for generating sound stimuli for mouse auditory measurements
- Probe tip microphone, calibrating microphone, and conditioning amplifier (microphone types 8192 & 5939, NEXUS conditioning amplifier, Bruel and Kjar, Demark)
- Bioamplifier (DP-311, Warner) to record electric field potentials
- Oscilloscope (Tektronix)

50 kHz Swept-Source VOCTV Imaging Suite

- Double-walled, RF shielded sound booth
- Custom-built, fiber based swept-source OCT system
- Vibration isolation table
- Surgical instruments
- Temperature-regulated heating pad
- Custom-machined animal head holder with ear bars
- Zeiss dissecting microscope (Stemi-2000) with fiberoptic light source
- National Instruments PCIe-6251 DAQ in one computer and another PXIe chassi with NI boards, including a computer controller, an ADC, and an FPGA.

- Cochlear Monitoring Program (CMP) custom software developed in Python and C++ to present sound stimuli and record the responses
- Power amplifier (Servo 600, Samson Technologies Corp., Syosset, NY)
- Two high frequency speakers for generating sound stimuli for mouse auditory measurements
- Probe tip microphone, calibrating microphone, and conditioning amplifier (microphone types 8192 & 5939, NEXUS conditioning amplifier, Bruel and Kjar, Demark)
- Bioamplifier (DP-311, Warner) to record electric field potentials
- Oscilloscope (Tektronix)

Spectral-Domain OCT Imaging Suite

- Optical coherence tomography setup (spectral domain) – custom built hardware and software
- Moveable objective microscope and all optical components designed for *in vivo* imaging (MOM, Sutter)
- Optical components designed to carry the laser to the microscope, and target it in 3-D space using galvometer-driven mirrors
- National Instruments PXIe chassis with a computer controller, I/O boards, and a FPGA.
- Custom Python and C++ software to drive the imaging equipment and present sound stimuli
- *In vivo* dissecting microscope on a boom stand (Zeiss)
- Vibration isolation table
- Surgical instruments
- Temperature-regulated heating pad
- Custom-machined animal head holder with ear bars
- Power amplifier (Servo 600, Samson Technologies Corp., Syosset, NY)
- Two high frequency speakers for generating sound stimuli for mouse auditory measurements
- Bioamplifier (DP-311, Warner) to record electric field potentials
- Oscilloscope (Tektronix)
- Laser doppler interferometer with digital displacement decoder (VDD-660, Polytech PI)

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: Dr. First Name*: Christopher Middle Name Last Name*: Shera Suffix:

Position/Title*: Professor
Organization Name*: [redacted]
Department: Otolaryngology
Division: [redacted]
[redacted]
Street2:
City*: [redacted]
County:
State*: [redacted]
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: [redacted]

Phone Number*: [redacted] Fax Number:

E-Mail*: [redacted]

Credential, e [redacted]

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

Degree Type: Ph.D Degree Year: 1992

Attach Biographical Sketch*: File Name: Shera_NIH_Biosketch_2018051012773850.pdf

Attach Current & Pending Support: File Name:

Funding Opportunity Number: PA-18-484 . Received Date: 2018-06-30T00:58:58.000-04:00

PROFILE - Senior/Key Person

Prefix: Dr. First Name*: Carolina Middle Name Last Name*: Abdala Suffix:

Position/Title*: Professor of Research
Organization Name*: [redacted]
Department: Otolaryngology
Division: [redacted]

Phone Number*: + [redacted] Fax Number:

E-Mail* [redacted]

Credential, e.g., agency login:

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

Degree Type: Degree Year:

Attach Biographical Sketch*: File Name: Shera_Abdala_NIH_Biosketch1012773851.pdf

Attach Current & Pending Support: File Name:

PROFILE - Senior/Key Person

Prefix: First Name*: John Middle Name Last Name*: Oghalai Suffix:

Position/Title*:
Organization Name*: [redacted]
Street2:
City*: [redacted]
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: [redacted]

Phone Number*: [redacted] Fax Number:

E-Mail* [redacted]

Credential, e.g., agency login:

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

Degree Type: MD Degree Year: 1994

Attach Biographical Sketch*: File Name: Shera_Oghalai_NIH_Biosketch1012773855.pdf

Attach Current & Pending Support: File Name:

Tracking Number: GRANT12665698 Funding Opportunity Number: PA-18-484 . Received Date: 2018-06-30T00:58:58.000-04:00

OMB No. 0925-0001/0002 (Rev. 10/15 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH

NAME: Christopher A. Shera

eRA COMMONS USER NAME: [redacted]

POSITION TITLE: Professor of Otolaryngology and Physics & Astronomy, University of Southern California

EDUCATION/TRAINING:

Haverford College, Haverford PA	B.A.	05/1983	Physics
California Institute of Technology, Pasadena CA	Ph.D.	06/1992	Physics
Massachusetts Institute of Technology, Cambridge MA	Postdoctoral	11/1997	Neurophysiology

A. Personal Statement

As head of USC's Auditory Physics Group (apg.mechanicsofhearing.org) in the Caruso Department of Otolaryngology, I have broad expertise in auditory physiology and mechanics, cochlear modeling, and otoacoustic emissions (OAEs). Areas of special interest include cochlear nonlinearity (compression, suppression) and the biophysical mechanisms of cochlear amplification, wave propagation, and OAE generation. Work in my laboratory combines innovative measurements with the power of mathematical and computational modeling. Together, we work towards the goal of understanding cochlear function and signal processing while developing the power of OAEs as noninvasive probes of peripheral auditory function for applications in both the research laboratory and the clinic. Historically, a key aspect of our work involves collaborations with others in the field who have experimental or other facility beyond our reach. Past and present collaborators include Carolina Abdala, Nigel Cooper, John Guinan, Philip Joris, and Andrew Oxenham. With this application, I am excited to plant the seeds of a promising new collaboration with John Oghalai, who has just joined the hearing research faculty at USC and brings with him deep expertise in cochlear imaging and the measurement of organ of Corti vibrations using optical coherent tomography (OCT).

Shera CA. Laser amplification with a twist: Traveling-wave propagation and gain functions from throughout the cochlea. *J Acoust Soc Am* 122:2738–2758 (2007).

Kalluri R, Shera CA. Measuring stimulus-frequency otoacoustic emissions using swept tones. *J Acoust Soc Am* 134:356–368 (2013). PMC3732205

Verhulst S, Dau T, Shera CA. Nonlinear time-domain cochlear model for transient stimulation and human otoacoustic emission. *J Acoust Soc Am* 132:3842–3848 (2012). PMC3528681

Charaziak KK, Shera CA. Compensating for ear-canal acoustics when measuring otoacoustic emissions. *J Acoust Soc Am* 141:515–531 (2017). PMC5848844

B. Positions and Honors

Positions and Employment

1983–1994 Graduate Research Assistant, Los Alamos National Laboratory
1992–1994 Research Associate, Signition Inc.
1994–1997 Postdoctoral Research Fellow, Research Laboratory of Electronics, MIT
1994–2016 Research Associate, Department of Otolaryngology, Massachusetts Eye & Ear Infirmary
1997–1999 Instructor of Otology & Laryngology, Harvard Medical School
1999–2004 Assistant Professor of Otology & Laryngology, Harvard Medical School
1999–2005 HST Affiliated Faculty, Harvard–MIT Division of Health Sciences & Technology
2004–2005 Associate Professor of Otology & Laryngology, Harvard Medical School
2005–2013 Associate Professor of Otology & Laryngology and Health Sciences & Technology, HMS
2013–2016 Professor of Otology & Laryngology, Harvard Medical School
2016– Professor of Otolaryngology and Physics & Astronomy, University of Southern California

Other Experience and Professional Memberships

1985– Member, American Association for the Advancement of Science
1989– Member, Acoustical Society of America (Fellow 2001)

1989–	Member, Association for Research in Otolaryngology
2001–	Member, American Physical Society
2007–	Member, American Auditory Society
2007–	Member, History of Science Society
2005–2009	Member, NIH/NIDCD AUD Study Section
2008–2014	Member, ASA Technical Committee for Psychological and Physiological Acoustics
2010–	Ad-Hoc Reviewer, Multiple NIH/NIDCD Special Emphasis Panels, Board of Scientific Counselors, and CDRC Study Section
2011–	Curator (with Elizabeth Olson), Mechanics of Hearing Digital Library
2012–	Associate Editor, *Journal of the Acoustical Society of America*
2017–	Member, ASA Technical Committee for Psychological and Physiological Acoustics
2017–	Co-Chair (with Carolina Abdala), ARO Scientific Program Committee

Honors

1979	U.S. Presidential Scholar
1979	Geraldine R. Dodge Foundation Grant
1982	Phi Beta Kappa Society
1984–1987	National Science Foundation Graduate Fellow
1994–1997	NRSA Postdoctoral Fellowship, NIH/NIDCD
2001	Fellow, Acoustical Society of America
2007	Irving M. London Teaching Award, Harvard Medical School / MIT

C. Contributions to Science

I. Mechanism-Based OAE Taxonomy

To provide a foundation for understanding otoacoustic emissions (OAEs), we showed—contrary to the then-current consensus—that OAEs arise from at least two distinct mechanisms in the cochlea: linear reflection and nonlinear distortion [1]. Synthesizing diverse work in the field, we proposed an OAE taxonomy based on mechanisms of emission generation, rather than characteristics of the evoking stimulus. The recognition of multiple generation mechanisms allows one to make sense of previously anomalous or otherwise discrepant observations, such as different susceptibilities to ototoxic drugs and puzzling variation among species. The mechanism-based taxonomy now provides the standard framework for the interpretation of OAEs.

In subsequent studies [2,4] we tested the dual-mechanism model for OAE generation and explored its potential for extending the power and precision of OAE-based clinical diagnostics. For example, we verified a major prediction of the OAE taxonomy—namely, that so-called distortion-product otoacoustic emissions (DPOAEs), previously thought to arise by nonlinear distortion operating at two different cochlear locations, actually comprise a mixture of OAEs produced by the two different source mechanisms. Source component “unmixing” is now widely used to improve the power of DPOAE measurements.

In other evaluations of the framework [3], we tested key predictions of three competing models of spontaneous otoacoustic emission (SOAE) and demonstrated that mammalian SOAEs result from amplitude-stabilized, intracochlear standing waves caused by multiple internal reflection, rather than from the autonomous oscillation of hair-cell soma or their bundles. According to the analysis, spontaneous OAEs are emergent phenomena that result from the cochlea’s acting as a biological analog of a laser oscillator.

[1] Shera CA, Guinan JJ. Evoked otoacoustic emissions arise by two fundamentally different mechanisms: A taxonomy for mammalian otoacoustic emissions. *J Acoust Soc Am* 105:782–798 (1999).

[2] Kalluri R, Shera CA. Distortion-product source unmixing: A test of the two-mechanism model for DPOAE generation. *J Acoust Soc Am* 109:622–637 (2001).

[3] Shera CA. Mammalian spontaneous otoacoustic emissions are amplitude-stabilized cochlear standing waves. *J Acoust Soc Am* 114:244–262 (2003).

[4] Kalluri R, Shera CA. Near-equivalence of human click-evoked and stimulus-frequency otoacoustic emissions. *J Acoust Soc Am* 121:2097–2110 (2007).

II. Coherent Reflection Theory

We explained the physical mechanisms underlying the class of evoked otoacoustic emissions (OAEs) now known as reflection-source OAEs [5]. The theory indicates that these OAEs arise through a process that we dubbed “coherent reflection” and involving wave backscattering by densely distributed micromechanical irregularities along the organ of Corti (e.g., spatial variations in the forces produced by outer hair cells). In subsequent work [6], we extended the theory to account for the complicated geometry of fluid motion near the peak of the traveling wave. Contrary to published theoretical arguments, we showed that these so-called short-wave effects significantly enhance, rather than suppress, the production of OAEs. The modeling framework we introduced was subsequently extended by others to model distortion-source OAEs, and coherent-reflection theory has since become the standard understanding of how OAEs are generated within the cochlea.

Among numerous subsequent studies, we tested the coherent-reflection model in chinchilla [7] by showing that the characteristics of mechanical tuning revealed by auditory-nerve responses accurately predict the measured properties of reflection-source OAEs, at least in the basal half of the cochlea. (In the apex, things are more complicated and other emission components are present—see [18].)

In addition, we successfully extended the coherent-reflection model to show how analogous mechanisms can account for stimulus-frequency emissions in animals, such as lizards, that have tuned mechanical responses but lack basilar-membrane traveling waves [8]. Coherent reflection thus provides a common framework for understanding otoacoustic emissions in a wide range of mammalian and non-mammalian species.

[5] Zweig G, Shera CA. The origin of periodicity in the spectrum of evoked otoacoustic emissions. *J Acoust Soc Am* 98:2018–2047 (1995).

[6] Shera CA, Tubis A, Talmadge CL. Coherent reflection in a 2-dimensional cochlea: Short-wave versus long-wave scattering in the generation of reflection-source otoacoustic emissions. *J Acoust Soc Am* 118:287–313 (2005).

[7] Shera CA, Tubis A, Talmadge CL. Testing coherent reflection in chinchilla: Auditory-nerve responses predict stimulus-frequency otoacoustic emissions. *J Acoust Soc Am* 124:381–395 (2008). PMC2677332

[8] Bergevin C, Shera CA. Coherent reflection without traveling waves: On the origin of long-latency otoacoustic emissions in lizards. *J Acoust Soc Am* 127:2398–2409 (2010). PMC2865438

III. Cochlear Mechanics and Wave Propagation

My approach typically involves theoretical analysis of experimental data to constrain models of cochlear function. For example, in early work we analyzed measurements of the cochlear input impedance to identify a new symmetry in cochlear mechanics (now called “tapering symmetry”) that requires that the width of the basilar membrane and the cross-sectional areas of the scalae taper in opposite directions [9]. We showed that violation of this symmetry would result in a dramatic decline in middle-ear efficiency at low frequencies.

Subsequent work [10] established the mechanisms responsible for the puzzling phenomenon known as “BM frequency glides,” changes over time in the instantaneous frequency of the basilar-membrane (BM) or auditory-nerve response to acoustic clicks. Although previous models for glides suggested that they arose through the differential build-up and decay of multiple micromechanical resonances local to each radial cross section of the organ of Corti, we identified the glide as the global consequence of the dispersive character of wave propagation in the cochlea.

In other work [12], we combined theory and experiment to address a long-standing controversy in cochlear mechanics [11]: Whether otoacoustic emissions propagate within the cochlea as longitudinal sound waves in the fluid or via transverse surface waves involving the basilar membrane. Our results show convincingly that reverse propagation involves basilar-membrane traveling waves (see also [16]).

[9] Shera CA, Zweig G. A symmetry suppresses the cochlear catastrophe. *J Acoust Soc Am* 89:1276–1289 (1991).

[10] Shera CA. Frequency glides in impulse responses of the basilar membrane and auditory nerve: Their scaling behavior and origin in traveling-wave dispersion. *J Acoust Soc Am* 109:2023–2034 (2001).

[11] Shera CA, Tubis A, Talmadge CL. Do forward and backward-traveling waves occur within the cochlea? Countering the critique of Nobili et al. *J Assoc Res Otolaryngol* 5:349–359 (2004).

[12] Shera CA, Tubis A, Talmadge CL, de Boer E, Fahey PF, Guinan JJ. Allen–Fahey and related experiments support the predominance of cochlear slow-wave otoacoustic emissions. *J Acoust Soc Am* 121:1564–1575 (2007).

IV. Cochlear Nonlinearity and Amplification

Perhaps my primary professional interest is the understanding of traveling-wave amplification and its control by nonlinearity and other feedback mechanisms operating within the cochlea. Work in this area has been varied. For example, by analyzing the fine-time structure of measurements of basilar-membrane and auditory-nerve responses to acoustic clicks, I showed that the cochlear amplifier operates primarily by modifying the effective resistance of the cochlear partition, rather than its stiffness [13]. This result ruled out many, if not most, contemporaneous cochlear models, in which outer-hair-cell forces produced significant changes in the reactance and the resonant frequencies of the system. Approximate intensity-invariance of the resonant frequencies of the cochlear filters is now recognized as a general principle of cochlear function; the feature is incorporated not only in most models but also in preprocessors used in machine hearing applications, such as sound indexing, music information retrieval, and speech recognition.

In other work [14], we performed simultaneous auditory-nerve and otoacoustic measurements to replicate, extend, and explain a major confounding result in cochlear physiology: Why the so-called “Allen-Fahey experiment,” a clever paradigm designed to measure the power gain of the cochlear amplifier using DPOAEs, showed no evidence of cochlear amplification. Although this classic null result was widely attributed to the effects of two-tone suppression, we showed that suppression actually increases the apparent gain measured by the paradigm, heightening the contradiction. We then showed how the experimental findings can be understood as a consequence of phase cancellation among distributed DPOAE sources. Our analysis demonstrated that when generating DPOAEs the cochlea acts as a “distortion beamformer” in which the directionality of the distortion source, and thus the relative magnitudes of the reflection- and distortion-source components in the DPOAE, is tuned by the primary frequency ratio.

In another major study of cochlear amplification [15], I analyzed published auditory-nerve-fiber responses to noise using a novel inverse method to derive functional properties of the cochlear traveling wave (“propagation and gain functions”), including its wavelength and power gain. The results established the existence and form of traveling-wave amplification throughout the cochlea, including the first (and still only) demonstration of power amplification in the apical half. Analysis of the propagation and gain functions showed that the cochlear amplifier has properties resembling those of an active optical medium, enabling the mammalian cochlea to operate as a wideband, hydromechanical laser analyzer. When the round-trip power gain is sufficiently high, multiple internal reflection can give rise to self-sustaining intracochlear standing waves, and the inner ear spontaneously emits sound (see also [3]).

Most recently [16], we tested predictions of the internal reflection model by making simultaneous otoacoustic and basilar-membrane (BM) mechanical measurements. Our results showed that the rippling patterns often observed in BM frequency responses (and the waxing and waning seen in BM and auditory-nerve click responses) are strongly correlated with the acoustic interference pattern measured in ear-canal pressure, consistent with a common origin involving the generation and reflection of otoacoustic emissions.

[13] Shera CA. Intensity invariance of fine time structure in basilar-membrane impulse responses: Implications for cochlear mechanics. *J Acoust Soc Am* 110:332–348 (2001).

[14] Shera CA, Guinan JJ. Cochlear traveling-wave amplification, suppression, and beamforming probed using noninvasive calibration of intracochlear distortion sources. *J Acoust Soc Am* 121:1003–1016 (2007).

[15] Shera CA. Laser amplification with a twist: Traveling-wave propagation and gain functions from throughout the cochlea. *J Acoust Soc Am* 122:2738–2758 (2007).

[16] Shera CA, Cooper NP. Basilar-membrane interference patterns from multiple internal reflection of cochlear traveling waves. *J Acoust Soc Am* 133:2224–2239 (2013). PMC4109360

V. Cochlear Frequency Tuning and Tonotopy

Last but not least, a major focus of my work has been to develop both new measurement and analysis tools and new applications for otoacoustic emissions whose purpose is to tells us things we do not already know about the cochlea and, indeed, about hearing. Much of this work is fundamentally comparative. For example,

by combining otoacoustic and psychophysical measurements we showed [17] that human cochlear tuning is both two-to-three times sharper, and has a different dependence on frequency, than was commonly believed based on the widespread presumption that auditory-nerve recordings in small laboratory animals could be applied directly to humans. Our results raised important questions about the mechanical, biophysical, and evolutionary origins of these prominent species differences in cochlear tuning and indicated that many models of human hearing function needed revision.

As a test of the assumptions underlying our noninvasive methods for estimating cochlear tuning, we showed [18,19] that otoacoustic estimates of cochlear tuning in both chinchilla and macaque match direct measures obtained from the auditory nerve in these species. We identified a function—the “tuning ratio”—whose form is nearly invariant in cats, guinea pigs, chinchillas, macaques, and humans. In the process, we introduced the notion of the “apical-basal transition CF,” a location in the cochlea that divides the cochlea into regions of apical-like and basal-like behavior. Taking account of this transition, whose approximate location varies from species to species, is crucial for making interspecies comparisons of cochlear function. Although our results confirmed that human cochlear tuning is exceptionally sharp, we found the spatial spread of excitation along the human basilar membrane to be comparable to that in other common laboratory animals. Our results support the use of otoacoustic emissions as noninvasive probes of cochlear tuning.

In related work [20], we predicted that mammalian cochlear frequency-position maps, although usually assumed to be smooth and continuous, actually manifest a staircase-like structure comprising plateaus of nearly constant characteristic frequency separated by abrupt discontinuities. The height and width of the stair steps are determined by parameters of cochlear frequency tuning and vary with location in the cochlea. We showed that stepwise tonotopy is an emergent property arising from wave reflection and interference within the cochlea (see also [16]), the same mechanisms responsible for the microstructure of the hearing threshold. As seeds for future experiments, we proposed possible functional and/or developmental relationships between the microstructure of the cochlear map and the tiered tonotopy observed in the inferior colliculus.

[17] Shera CA, Guinan JJ, Oxenham AJ. Revised estimates of human cochlear tuning from otoacoustic and behavioral measurements. *Proc Natl Acad Sci (USA)* 99:3318–3323 (2002). PMC122516

[18] Shera CA, Guinan JJ, Oxenham AJ. Otoacoustic estimation of cochlear tuning: Validation in the chinchilla. *J Assoc Res Otolaryngol* 11:343–365 (2010). PMC2914235

[19] Joris PX, Bergevin C, Kalluri R, Mc Laughlin M, Michelet P, van der Heijden M, Shera CA. Frequency selectivity in Old-World monkeys corroborates sharp cochlear tuning in humans. *Proc Natl Acad Sci USA* 108:17516–17520 (2011). PMC3198376

[20] Shera CA. The spiral staircase: Tonotopic microstructure and cochlear tuning. *J Neurosci* 35:4683–4690 (2015). PMC4363394

Complete List of Published Work

In My Bibliography at NCBI: http://1.usa.gov/1JtJMZt
At the Auditory Physics Group website: http://apg.mechanicsofhearing.org/#Publications

D. Research Support

Ongoing

R01 DC003687 Shera (PI) 1/1/99–12/31/18
Understanding Otoacoustic Emissions
Combined experimental and theoretical studies of the mechanisms of otoacoustic emission generation and related aspects of cochlear and middle-ear mechanics.
Role: PI

Completed During the Last 3 Years

None

OMB No. 0925-0001/0002 (Rev. 08/12 Approved Through 8/31/2015)

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: Carolina Abdala

eRA COMMONS USER NAME (credential, e.g., agency login): [redacted]

POSITION TITLE: Professor of Otolaryngology, Keck School of Medicine, University of Southern California

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date MM/YYYY	FIELD OF STUDY
California State University, Fullerton	B.A.	05/1983	Communicative Disorders
University of California, Santa Barbara	M.A.	06/1986	Hearing Science
University of Washington, Seattle WA	Ph.D.	06/1993	Hearing Science

A. Personal Statement

For the last two decades, my laboratory has applied otoacoustic emissions (OAEs) to the study of human cochlear function. We have conducted data collection in challenging subject populations such as day-old newborns and those in their 8th decade of life; we have tested and developed innovative data collection systems using sweeping stimulus tones (which allow for unparalleled frequency resolution and rapid data collection); we have analyzed DPOAEs by separating the distortion-product OAE into its dual components with offline signal processing to study each component independently and to disentangle the origin of our results; we have generated the only published report on the stimulus-frequency OAEs (SFOAE) in newborns and we are currently studying SFOAEs to an aging population. The consistent theme in my labs' work is to push the boundaries of OAE research into challenging populations, innovative data-collection systems, informative analysis schemes, and, eventually, to novel diagnostic applications. One such OAE application relevant to the current application includes the presentation of contralateral acoustic stimulation (CAS) to activate the medial olivocochlear reflex (MOCR) while measuring OAE amplitude and phase. There are many confounds in the implementation of this paradigm (e.g., middle-ear muscle reflex, poor SNR, DPOAE component-mixing), but we have extensive experience developing careful techniques and analyses to address these issues. Over the last decades, we have recorded reliable MOC reflexes in newborns, school-aged children, young-adults and the elderly, using both reflection- and distortion-type OAEs. Our studies of the auditory efferent system have allowed us to disentangle many of the potential confounds and describe changes in the efferent reflex throughout the arc of the human lifespan.

1. Abdala, C., Luo, P., & Shera, C.A. **(2015)**. Optimizing swept-tone protocols for recording distortion product product otoacoustic emissions in adults and newborns. *J. Acoust. Soc. Am.* 138(6): 3785-3799.
2. Abdala, C., Dhar, S., Ahmadi, M., and Luo, P. **(2014).** "Aging of the medial olivocochlear reflex and associations with speech perception," J. Acoust. Soc. Am. 135, 754.
3. Abdala, C., Mishra, S., and Garinis, A. **(2013).** "Maturation of the medial olivocochlear reflex revisited," J. Acoust. Soc. Am. 133, 938-950.
4. Abdala, C., Ma, E., and Sininger, Y. (**1999**). "Maturation of medial efferent system function in humans," J. Acoust. Soc. Am. **105**, 2392-2402.

B. Positions/Service and Honors

Employment

1987–1993	Graduate Research Asst., University of Washington, Infant Speech Perception Laboratory (Patricia Kuhl) and Electrophysiology Laboratory (Richard Folsom)
1993–1995	Post-Doctoral Scientist, House Ear Institute, Los Angeles, CA
1995–1998	Scientist I, House Ear Institute, Los Angeles, CA
1998–2006	Lecturer, California State University, Northridge. Communicative Disorders
1999–2007	Scientist II, House Ear Institute, Los Angeles, CA
2007–2013	Scientist III, Division of Communication and Auditory Neuroscience House Research Institute, Los Angeles, CA Co-Director, Children's Auditory Research & Evaluation Center
2008–	Faculty, Neuroscience Graduate Program, University of Southern California
2013–	Professor of Otolaryngology, Keck School of Medicine, University of Southern California

Honors

1986	Dean's Prize: Commencement Speaker; UC Santa Barbara, College of Letters & Science
2009	Visiting Scholar Award, Virginia Merrill Bloedel Center for Hearing Research, University of Washington, Seattle, WA
2013	Fellow of the Acoustical Society of America

Professional Memberships and Service

Memberships:

American Association for the Advancement of Science, Association for Research in Otolaryngology, American Auditory Society, Acoustical Society of America, American Speech and Hearing Association

Service:

1995–	Manuscript Reviewer: J Acoust Soc Am, J Assoc Res Otolaryngol, Hear Res, J Neurosci, Neurosci Letters, Ear Hear
2000–2009	Ad hoc grant reviewer: National Institutes of Health, NIDCD R03, R21, R01
2004–2007	Grant reviewer: National Science Foundation, Cognitive Neuroscience
2009–2012	Regular Study Section Member: National Institutes of Health, CSR AUD, (4-year term)
2010–	Executive Committee: Hearing & Communication Neuroscience T32 Training Grant, University of Southern California, Otolaryngology Department + Neuroscience Graduate Program
2012–	Associate Editor: J Acoust Soc. Am, Physiological Acoustics Section
2012–2014	Study Section Chair: National Institute of Health, CSR AUD (2-year term)
2013–2017	Program Committee: Association for Research in Otolaryngology
2017–	Co-Chair of the Scientific Program for the Association for Research in Otolaryngology

C. Contributions to Science

I. The functional status of the human cochlea at birth: Human infants do not respond to auditory stimuli in an adult-like way. Behavioral and electrophysiological (Auditory Brainstem Response, ABR) findings provide evidence of immature responses at birth but the *origin* of this immaturity was not well understood just 20 years ago. Some of my earliest studies confirmed adult-newborn differences across frequency using the click-evoked ABR recorded in notched-noise. As a postdoctoral researcher [redacted] I focused on developing targeted methods to assess human cochlear function at birth, targeting the question of the *origin* of infant auditory immaturities. We also strove to understand the mechanisms driving these age-related changes. Otoacoustic emissions (OAEs) offered a noninvasive and preneural window into the human cochlea. Over a decade and a half of work, we assessed cochlear tuning in newborns using DPOAE ipsilateral suppression; contralateral suppression of DPOAEs to measure the medial efferent reflex, DPOAE input/output functions to gauge cochlear compression, and DPOAE fine structure to understand the dual-source nature of OAEs and how it manifests at birth. The conclusions of this work include: a) the basal half of the cochlea is adult-like in most ways, showing sharp tuning, robust nonlinearities, and adult-like tonotopy; and b) the apical half of the

human cochlea shows residual immaturities at birth which may be related to the physical properties of the basilar membrane and other gross cochlear structures. Residual immaturies in the apex are most concretely manifest in distortion OAE phase-gradient delays, which are prolonged by almost one millisecond in the newborn cochlea for frequencies below 1.5 kHz. This finding cannot be easily explained by conductive factors. Infant immaturities in the behavioral response to low-frequency sound may indeed include a cochlear component.

1. Abdala, C. & Folsom, R. (1995). The development of frequency resolution in human adults and infants as revealed by the ABR recorded with notched-noise masking. *J. Acoust. Soc. Am.,* 98:921-930.
2. Abdala, C. (1998). A developmental study of DPOAE ($2f_1$-f_2) suppression in humans. *Hear. Res.*121:125-138.
3. Abdala, C. (2003) A longitudinal Study of DPOAE ipsilateral suppression and input/output characteristics in human neonates. *J. Acoust. Soc. Am.* 114:3239-3250.
4. Abdala, C., Dhar, S. & Mishra, S. (2011). The breaking of cochlear scaling symmetry in human newborns and adults. *J. Acoust. Soc. Am.* May; 129: 3104-3114.

II. Disentangling outer/middle ear from cochlear immaturity. Although OAEs provide a preneural window into the human cochlea (and thus allowed me to separate peripheral from neural contributions to immaturity), OAEs are affected by the development of more peripheral segments of the auditory system: the outer and middle ear, which develop most notably over the first six months of life. Therefore, as a crucial step in defining the maturational status of human *cochlear* function, we had to account for and model the impact of developing ear-canal and middle-ear acoustics on OAEs. Much of this work was done with colleague, [redacted]. Among other techniques, we used DPOAE I/O functions to model the impact of an inefficient middle ear on forward transmission of the evoking stimulus, and the impact of reduced ear-canal area on reverse transmission of the OAE in infants. We were able to estimate effects and correct for them in our efforts to target cochlear mechanics in newborns. In implementing these corrections, my lab essentially defined the outer and middle ear transfer functions in newborns and how they influence OAE measurements. We found that the immature middle ear attenuates the stimulus driving the cochlea by ~15 dB (re: adult levels), and the reduced area of the newborn ear canal effectively boosts OAE levels in neonates by 13-17 dB. These findings allowed us to disentangle cochlear from conductive immaturities and attribute many of the age effects on level-dependent features of the OAE to ear-canal and middle-ear factors, not cochlear immaturity. These experiments modeled and defined the impact of a growing neonatal ear canal and middle ear on OAE-based metrics of cochlear mechanics and provided the field with a model for how conductive immaturities impact otoacoustic emissions and the measurement of hearing. Our careful consideration of newborn ear-canal and middle-ear acoustics allowed us to interpret OAE results in neonates as cochlear or conductive in nature.

1. Abdala, C., Keefe, D. & Oba, S. (2007). A longitudinal study of DPOAE suppression tuning and acoustic admittance in human infants from birth through six months of age. *J. Acoust. Soc. Am.* 121:3617-3627
2. Keefe E. & Abdala, C. (2007). Theory of forward and reverse middle-ear transmission applied to otoacoustic emissions in infant and adult ears. *J. Acoust. Soc. Am.* 121:978-993.
3. Abdala, C. & Keefe, D. (2006). Effects of middle-ear immaturity on DPOAE suppression tuning in infant ears. *J. Acoust. Soc. Am.* 120:3832-3842.
4. Keefe, D.H. & Abdala, C. (2011). Distortion product otoacoustic emission suppression tuning in human infants using absorbed sound power. *J. Acoust. Soc. Am.* 129:EL108-113.

III. Translational impact. Much of the work my lab has conducted over the last two decades to understand human cochlear mechanics during maturation has also contributed to the refinement of OAEs in their application to hearing diagnosis and screening. For example, we have characterized the normative DP-gram (spectrum) from prematurity through six months of age; we have described infant DPOAE fine structure, which impacts the effect of test frequency selection during hearing assessment; we have described optimal parameters for DPOAE measurement in newborns; we have implemented state-of-the-art OAE swept-tone methodology in newborns (versus discrete tone presentation); and we are the first lab to publish stimulus-frequency OAEs measured in newborns. These studies were translational in nature, guiding the application of OAEs to newborn hearing diagnosis and screening.

1. Abdala, C. & Dhar, S. (2010). Differences in distortion product otoacoustic emission phase recorded from human neonates using two popular probes. *J. Acoust. Soc. Am*. 128:EL49-55.
2. Abdala, C. & Dhar, S. (2010). DPOAE phase and component analysis in human newborns. *J. Acoust. Soc. Am*. 127:316-325
3. Abdala C., Oba, S. & Ramanathan, R. (2008). Changes in the DP-gram during the preterm and early postnatal period. *Ear Hear.* 29:512-523.
4. Abdala, C. (1996). DPOAE ($2f_1 - f_2$) amplitude as a function of f_2/f_1 frequency ratio and primary tone level separation in human adults and neonates. *J. Acoust. Soc. Am.* 100:3726-3740.

IV. The dual-source DPOAE in newborns and adults. In 1999, Shera and Guinan formalized and tested an updated taxonomy for OAEs, showing that reverse-traveling waves were initiated in the cochlea by two different mechanisms: nonlinear distortion and linear reflection. The DPOAE is a mixed emission, including both distortion and reflection energy, hence the term "dual-source DPOAE". Any measurement of DPOAEs should take its dual-source nature into consideration, because each of the two components is differently affected by natural and experimental manipulations. In fact, they may also be differently sensitive to pathology (as we hypothesize in this grant project). The work from my laboratory helped confirm the independent effect of various factors (e.g., medial efferent activation, maturation, aging, stimulus level) on each OAE component and lent support to the dual-source model of OAE generation. We have conducted this work by applying swept-tone OAE methodology, non-FFT based analysis algorithms (least-squares fitting), and component separation techniques (inverse FFT) to estimate DPOAE reflection- and distortion-component amplitude and phase throughout the human lifespan. In defining how DPOAE components are impacted independently, we have accounted for spurious and confounding variables in the measurement and interpretation of OAEs and how they elucidate developmental trends in cochlear maturation. Our work has corrected an overly simplistic view of OAE measurement and confirmed that one must consider the complexity of cochlear generation mechanisms when applying OAEs for experimentation or clinical evaluation.

1. Abdala, C., and Kalluri, R. (2017). "Towards a joint reflection-distortion otoacoustic emission profile: Results in normal and impaired ears," J. Acoust. Soc. Am. 142, 812.
2. Abdala, C. Guérit, F., Luo, P. & Shera C.A. (2014). Distortion-product otoacoustic emission reflection-component delays and cochlear tuning: Estimates from across the human lifespan. *J. Acoust. Soc. Am*. 135:1950-1958.
3. Abdala, C., Dhar, S. & Kalluri, R (2011). Level dependence of distortion product otoacoustic emission phase is attributed to component mixing. *J. Acoust. Soc. Am.* 129:3123-3133.
4. Abdala, C. & Dhar, S. (2010). DPOAE phase and component analysis in human newborns. *J. Acoust. Soc. Am*. 127:316-325.

V. A continuum of maturation and aging. My lab has embraced the notion that "maturity" is a moving target, which makes it difficult to define a homeostatic adult-like response with respect to cochlear function. For this reason, our most recent work defines changes in human cochlear function and the mechanisms driving these changes during a continuum of maturation and aging. We now study lifespan changes in cochlear function to better understand this arc of cochlear change throughout life. This model has allowed us to pinpoint mechanisms driving these changes and track the shifts throughout decades of life without *a priori* notions about when maturity is achieved or what the proper referent should be. We have begun to describe shifting features of the aging cochlea by considering both reflection and distortion OAEs separately. We have found that reflection OAEs are relatively preserved in the aging cochlea (compared to distortion OAEs), possibly due to increased mechanical irregularities in aging tissue (OHC loss, tissue degradation, etc.). We are in the process of modeling and further defining these aging-related shifts by studying both distortion OAEs and stimulus-frequency OAEs during senescence.

1. Abdala, C., Luo, P. & Shera, C. (2017). Characterizing spontaneous otoacoustic emissions across the human lifespan. J. Acoust Soc, 141, 1874.
2. Ortmann, A. & Abdala, C. (2016). Changes in the Compressive Nonlinearity of the Cochlea During Early Aging: Estimates From Distortion OAE Input/Output Functions. *Ear Hear.* 37, 306-314.

3. Abdala, C. Guérit, F., Luo, P. & Shera C.A. (2014). Distortion-product otoacoustic emission reflection-component delays and cochlear tuning: Estimates from across the human lifespan. *J. Acoust. Soc. Am*. 135:1950-1958.
4. Abdala, C. & Dhar, S. (2012). Maturation and aging of the human cochlea: A view through the DPOAE looking glass. *J. Assoc. Res. Otolaryngol.*13:403-421.

Complete list of published work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/carolina.abdala.1/bibliography/40697758/public/?sort=date&direction=ascending.

D. Other Support

Ongoing Research Support

R01 DC003552 Abdala (PI) 1998–2020
NIH/NIDCD
Human Cochlear Function: A Continuum of Maturation and Aging.
This project studies the timeline of changes in the human peripheral auditory system from the perinatal period through senescence and the mechanisms driving these changes using reflection- and distortion-source otoacoustic emissions. Role: Principal Investigator

Completed Research Support

R01 DC003552-10 S1 Abdala (PI) 2009–2012
NIH/NIDCD
Administrative Supplement
Peripheral Auditory System Function in Humans: A Continuum of Maturation and Aging.

R01 DC003552-10 S1 Abdala (PI) 2009–2012
NIH/NIDCD
Equipment Supplement
Peripheral Auditory System Function in Humans: A Continuum of Maturation and Aging.

OMB No. 0925-0001/0002 (Rev. 08/12 Approved Through 8/31/2015)

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: John S. Oghalai

eRA COMMONS USER NAME (credential, e.g., agency login): [redacted]

POSITION TITLE: Tiber Alpert Professor and Department Chair

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 Wisconsin, Madison, WI	B.S.	05/1990	Electrical Engineering
University of Wisconsin, Madison, WI	M.D.	05/1994	Medicine
Baylor College of Medicine, Houston, TX	Internship	06/1995	General Surgery
Baylor College of Medicine, Houston, TX	Residency	06/2001	Otolaryngology
Baylor College of Medicine, Houston, TX	Post-doc (2 yrs)	06/1998	Neuroscience Research
UCSF, San Francisco, CA	Fellowship	06/2003	Neurotology

A. Personal Statement

I am a clinician-scientist and I work both in the lab and care for patients with otological disorders. My clinical practice is Neurotology, and I specialize in caring for patients with hearing and vestibular disorders. My research program is dedicated towards understanding mechanisms within the cochlea that underlie progressive sensorineural hearing loss and to translating these techniques to improve human hearing. It includes basic, translational, and clinical arms. I have a rich experience with using advanced optical techniques and electrophysiological measures to assess auditory function from the cellular to systems level. I also am experienced in running translational and clinical research studies involving human subjects with inner ear disorders.

Positions and Honors

Positions and Employment:

2001-2003 **Clinical Instructor and Fellow in Neurotology/Skull Base Surgery**, Dept. of Otolaryngology - Head and Neck Surgery, University of California - San Francisco, San Francisco, CA.

2003-2009 **Assistant Professor (Tenure Track)**, Bobby R. Alford Department of Otolaryngology – Head and Neck Surgery, Baylor College of Medicine, Houston, TX.

2004-2010 **Clinic Chief, The Hearing Center at Texas Children's Hospital**, Houston, TX.

2005-2015 **Adjunct faculty member**, Department of Bioengineering, Rice University, Houston, TX.

2008-2010 **Secondary faculty appointment,** Department of Neuroscience, Baylor College of Medicine, Houston, TX

2009-2010 **Associate Professor (Tenured)**, Bobby R. Alford Department of Otolaryngology – Head and Neck Surgery, Baylor College of Medicine, Houston, TX.

2010-2015. **Associate Professor, University Line with Tenure**, Department of Otolaryngology – Head and Neck Surgery, Stanford University, Stanford, CA

2010-2017 **Director, Stanford Children's Hearing Center**, Stanford, CA

2015-2017 **Professor, University Line with Tenure**, Department of Otolaryngology – Head and Neck Surgery, Stanford University, Stanford, CA

2017-pres **Leon J. Tiber and David S. Alpert Professor and Chair,** Tina and Rick Caruso Department of Otolaryngology – Head and Neck Surgery, University of Southern California, Los Angeles, CA

2017-pres **Program faculty, Hearing and Communication Neuroscience Training Program**, USC

Other Experience and Professional Memberships:

- Alpha Omega Alpha (1994-pres)
- The American Academy of Otolaryngology - Head and Neck Surgery (1995-pres.)
  - Co-chair of the Research Forum for the Annual Academy Meeting (2005-2010)
  - Research Steering (CORE) Committee (2007-2012)
- The Association for Research in Otolaryngology (1995-pres.)
  - Member of the committee on patient advocacy group relations (2000-2002)
  - JARO Publications Committee (2004-2007; 2012-2015)
  - Animal Research Committee (2007-2010)
- Otology and Neurotology, editorial board member (2005-pres.)
- IEEE Journal of Translational Engineering in Health and Medicine, Associate Editor (2012-pres.)
- Deafness Research Foundation Grant Reviewer (2010-11)
- Chair, Research Committee – American Neurotology Society (2014-2017)
- Executive Secretary, Research Committee – American Otological Society (2016-pres)
- Laryngoscope, Associate Editor- Otology/Neurotology Section (2015-pres)
- NIH/NIDCD Study Sections (CDRC full-time member: 7/2014-6/2018; CDRC 2/2014; AUD: 9/2009; Special emphasis panels: 2/2006, 11/2006, 5/2010, 7/2010, 3/2011, 9/2011, 3/2012, 10/2012, 11/2012, 7/2014, 3/2014)

Honors and Awards:

- Stanford School of Medicine Faculty Fellow (2012)
- The Dawn and Brook Lenfest Grant in Auditory Science (2004)
- Neurotology Trainee Award from the American Neurotology Society (2002)
- Voted Administrative Chief Resident by the other residents (2000-2001)
- Resident Teaching Award (for peer and medical student teaching) (2000)
- Texas Association of Otolaryngology - Head and Neck Surgery Resident Paper Award (1998 & 1999)
- The J. Charles Dickson Award for Basic Science Research (1997, 1998, and 1999)
- ARO Midwinter Meeting Resident Travel Awards (1997, 1998, 1999, & 2001)
- The Evan and Marion Helfaer Scholarship (1993)
- The Youmans Award in Medical Physiology (1992)

B. Contribution to Science

1. We have sought to understand normal cochlear physiology by studying the non-linear biomechanical processes that underlie the high auditory sensitivity and sharp frequency selectivity of mammalian hearing. Our team has developed a non-invasive optical technique to measure vibrations within the cochlea. We have found that the tectorial membrane sustains traveling waves and demonstrates sharper frequency tuning than the basilar membrane. In addition, we discovered that low frequency hearing is not sharply tuned by cochlear amplification like it is for high frequency hearing.
   a) Lee HY, Raphael PD, Park J, Ellerbee AK, Applegate BE, **Oghalai JS** (2015) Noninvasive in vivo imaging reveals differences between tectorial membrane and basilar membrane traveling waves in the mouse cochlea. Proc Natl Acad Sci 112: 3128–3133.
   b) Lee HY, Raphael PD, Xia A, Kim J, Grillet N, Applegate BE, Bowden A, **Oghalai JS.** (2016) Two-dimensional cochlear micromechanics measured in vivo demonstrate radial tuning within the mouse organ of Corti. J Neurosci. 36:8160–8173.
   c) Xia A, Liu X, Raphael PD, Applegate BE, **Oghalai JS** (2016) Mechanical hair cell properties do not amplify the traveling wave within the chicken basilar papilla. Nat Commun. 7:13133.
   d) Recio-Spinoso A, **Oghalai JS** (2017) Mechanical tuning and amplification within the apex of the guinea pig cochlea. J Physiol. Apr 6; PMID: 28382742.

2. We have also sought to study mechanisms of hearing loss, with the ultimate goal of better treating our patients. We study the basis of cochlear pathology following noise and blast trauma. In particular, we examine how hair cells and auditory dendrites/neurons are lost. Furthermore, we study transgenic mice

with targeted mutations in cellular biomechanics. This allows us to probe the roles of the different structures within the organ of Corti. As one example of the fruits of this research, we have discovered that blast-induced cochlear synaptopathy can be minimized by treating post-traumatic endolymphatic hydrops.

a) Xia A, Gao SS, Yuan T, Osborn A, Bress A, Pfister M, Maricich SM, Pereira FA, **Oghalai JS** (2010) Deficient forward transduction and enhanced reverse transduction in the alpha tectorin C1509G human hearing loss mutation. Dis Model Mech 3: 209–223.
b) Song Y, Xia A, Lee HY, Wang R, Ricci AJ, **Oghalai JS** (2015) Activity-dependent regulation of prestin expression in mouse outer hair cells. J Neurophysiol: jn.00869.2014.
c) Kim J, Xia A, Grillet N, Applegate BE, **Oghalai JS** (2018) Osmotic stabilization prevents cochlear synaptopathy after blast trauma. Proc Natl Acad Sci U S A: in press
d) Dewey JB, Xia A, Mueller U, Belyantseva IA, Applegate BE, **Oghalai JS**. Mammalian auditory hair cell bundle stiffness affects frequency tuning by increasing coupling along the length of the cochlea. Cell Rep 2018; in press.

3. I also direct research to improve cochlear implant outcomes, which has more direct and immediate clinical relevance. One representative project is to develop an evidence base for when children with both deafness and developmental delays should undergo cochlear implantation. Another project is to develop the translational technology for non-invasively measuring speech perception within the auditory cortex of cochlear implant users. The ultimate goals of these efforts are to improve human health using carefully-designed, hypothesis-driven, NIH-funded clinical and translational research studies.
   a) Sevy ABG, Bortfeld H, Huppert TJ, Beauchamp MS, Tonini RE, **Oghalai JS** (2010) Neuroimaging with near-infrared spectroscopy demonstrates speech-evoked activity in the auditory cortex of deaf children following cochlear implantation. Hear Res 270: 39–47.
   b) **Oghalai JS**, Caudle SE, Bentley B, Abaya H, Lin J, Baker D, Emery C, Bortfeld H, Winzelberg J (2012) Cognitive outcomes and familial stress after cochlear implantation in deaf children with and without developmental delays. Otol Neurotol 33: 947–956.
   c) Pollonini L, Olds C, Abaya H, Bortfeld H, Beauchamp MS, **Oghalai JS** (2014) Auditory cortex activation to natural speech and simulated cochlear implant speech measured with functional near-infrared spectroscopy. Hear Res 309: 84–93.
   d) Olds C, Pollonini L, Abaya H, Larky J, Loy M, Bortfeld H, Beauchamp MS, **Oghalai JS** (2015) Cortical Activation Patterns Correlate With Speech Understanding After Cochlear Implantation. Ear Hear. DOI:10.1097/AUD.0000000000000258.

Complete List of Published Work in MyBibliography (120 current publications in PubMed):

https://www.ncbi.nlm.nih.gov/sites/myncbi/1R725cOelFEAq/bibliography/40679618/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support:

R01 DC013774-01A1 (PI: Oghalai) **4/10/2015-3/31/20**
NIH-NIDCD
Optical coherence tomography for 3D measures of cochlear mechanics in vivo
Mammals hear when the highly-organized organ of Corti vibrates in response to sound pressure waves and stimulates hair cells. Herein, we propose to develop the technology to image these vibrations non-invasively in 3D. We will then determine the impact of outer hair cell passive stiffness and active force generation on the vibratory patterns using transgenic mouse strains.

R01 DC014450-01 (PI: Oghalai) **5/1/2015-4/30/20**
NIH-NIDCD
Cochlear mechanics in the mouse
Mammals hear when the highly-organized organ of Corti vibrates in response to sound pressure waves and stimulates hair cells. Herein, we propose image these vibrations non-invasively and understand how these structures work together to create high auditory sensitivity and sharp frequency tuning. This question remains unsolved and is clinically important because while hearing aids can compensate for the loss of sensitivity, we have no treatments for the loss of frequency tuning.

R13 DC015965 (PI: Oghalai) **4/01/17-3/31/22**
NIH-NIDCD
Conference on implantable auditory prostheses
This supports the bi-annual auditory prosthesis conference that Bob Shannon has run for many years. Bob Shannon, PhD is listed as the co-PI, but it is really his grant and he runs the conference. I am only listed as the PI because Bob is retired and does not have PI status at USC any longer.

Completed Research Support:

MR130316 (PI: Cheng; role: co-investigator) **9/30/2014-9/29/2017**
Department of Defense
Regenerating the blast and noise damaged cochlea
This project applies Wnt signaling or reprogramming factors to regenerate the blast or noise damaged cochlea. I collaborate by developing and performing noise- and blast-exposure procedures, as well as with the assessment of cochlear function after the exposure.

R21 HD08231901A1 (Bhutani; Role: co-investigator) **12/1/2015-11/30/2017**
NIH/NICHD
Bilirubin Binding Capacity to Assess Bilirubin Load in Preterm Infants.
This project evaluates two new innovative nanotechniques to quantify bilirubin load for the first time in the context of a clinical decision algorithm to identify those most at risk for any bilirubin-related neurotoxicity

T32 DC015209 (PI: Oghalai) **7/1/2016-7/31/2017**
NIH-NIDCD – Grant was transferred to another PI when I moved from Stanford to USC.
Clinician-Scientist Training Program in Otolaryngology
This program aims to train otolaryngology residents and post-residency graduates to become physician scientists. It is designed to provide intense research experiences, a structured didactic program, and close mentorship and guidance in how to integrate clinical and research activities. Trainees will be ingrained with the philosophy that research is intrinsic to an academic surgeon's career and that they should build their career by sustaining excellence in both research and clinical care. If our training program is successful, our graduates will become independent NIDCD-funded investigators in faculty positions in academic departments. The ultimate long-term goal, of course, is for them to improve human health by advancing our field via scientific discovery that is translated to clinical care.

P30 DC010363 (PI: Heller; role: co-investigator) **9/18/09-7/31/17**
NIH/NIDCD
Stanford OHNS Core Center

The Core Center at Stanford Otolaryngology - Head & Neck Surgery aims to support the research endeavors of a central group of 11 Principal Investigators working on topics related to auditory and vestibular neurobiology. It is meant to generate a central hub of knowledge, technology, and collaboration for R01- funded basic researchers as well as clinicians, thereby spawning new ideas and translational advances. I am the Director of the Physiology Core.

R01 DC007910-05A1 (PI: Steele; role: co-investigator) 10/1/05-6/30/17
NIH/NIDCD
Three-dimensional and multi-scale organ of Corti biomechanics
This proposal attempts to test the feed-forward feedback model of cochlear amplification by incorporating in vivo morphological data that assesses the tonotopic structural interaction of Dieter cells with outer hair cells as well as by incorporating realistic receptor potential parameters for outer hair cells.

R01 DC010075 (PI: Oghalai) 9/18/09-8/31/16 (included a 2 yr no-cost extension)
NIH-NIDCD
Outcomes in Children with Developmental Delays and Deafness: A Randomized Trial
We hypothesize that development and quality of life will improve more in deaf children with developmental delays when treated with a cochlear implant compared to those treated with hearing aids. We will perform a clinical trial to answer the question of which intervention provides more benefit to this population of children using validated, norm-referenced tests. This study will provide essential evidence to support clinical decision-making in this population.

W81XWH-11-2-0004 (PI: Oghalai) 12/1/10-11/30/15 (includes a 2 yr no-cost extension)
Department of Defense
Diagnosis & Treatment of Blast-Induced Hearing Loss
Blast-induced hearing loss is a common injury sustained by military personnel and produces a long-term disability that requires chronic management. We will develop improved techniques for imaging of the ear and correlate the findings with a detailed assessment of the tissue, cellular, and genetic changes that occur within the ear using a novel mouse model of blast injury.

R56 DC010164 (PI: Oghalai) 8/1/10-7/31/12
NIH-NIDCD
Translation of near-infrared spectroscopy for use in clinical neuro-imaging of deaf children after cochlear implantation
The goal of this proposal is to develop near-infrared spectroscopy neuroimaging into a valid and reliable clinical tool to aid the care of children who hear through a cochlear implant. This technique is expected to enhance the ability of a cochlear implant team to program a child’s device.

K08 DC006671 (PI: Oghalai) 4/1/2004-3/31/2010 (includes a 1 yr no-cost extension)
NIH-NIDCD
Modulation of Cochlear Tuning
We study the relationship between the passive and active tuning properties of the cochlear partition and to develop techniques that can be used to change the cochlear frequency map.

R03 DC 05131 (PI: Oghalai) 8/1/2001-5/31/2004
NIH-NIDCD
Modulation of Cochlear Mechanics
The objective of these studies is to understand how drugs modulate the cochlear amplifier, specifically those that affect outer hair cell biomechanics.

OMB Number: 4040-0001
Expiration Date: 10/31/2019

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

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ○ Subaward/Consortium

Enter name of Organization: [redacted]

Start Date*: 04-01-2019 **End Date*:** 03-31-2020 **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 . Dr.	Christopher		Shera		PD/PI	0.00	7.8			[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]		[redacted]		[redacted]			[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]		[redacted]		[redacted]			[redacted]	[redacted]	[redacted]

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

Additional Senior Key Persons: File Name:

Total Senior/Key Person [redacted]

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
3	Post Doctoral Associates	30			[redacted]	[redacted]	[redacted]
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Engineer	1.2			[redacted]	[redacted]	[redacted]
4	**Total Number Other Personnel**					**Total Other Personnel**	[redacted]
					[redacted]		[redacted]

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

Funding Opportunity Number: PA-18-484 . Received Date: 2018-06-30T00:58:58.000-04:00

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

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: [redacted]

Start Date*: 04-01-2019 **End Date*:** 03-31-2020 **Budget Period: 1**

C. Equipment Description

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

Equipment Item	Funds Requested ($)*
1 . two Dell Precision T7910 high-performance scientific workstation	[redacted]
Total funds requested for all equipment listed in the attached file	
Total Equipment	[redacted]

Additional Equipment: File Name:

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

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)

Tracking Number: GRANT12665698 Funding Opportunity Number: PA-18-484 . Received Date: 2018-06-30T00:58:58.000-04:00

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

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: [redacted]

Start Date*: 04-01-2019 **End Date*:** 03-31-2020 **Budget Period: 1**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	[redacted]
[redacted]	[redacted]
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . Subject Fees	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	[redacted]

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . On Campus Research	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, [redacted]

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	[redacted]

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*
	[redacted]

L. Budget Justification*	File Name: Shera_Budget_Justification_final_v21012774141.pdf (Only attach one file.)

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

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 2

ORGANIZATIONAL DUNS* [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: [redacted]

Start Date*: 04-01-2020 **End Date*:** 03-31-2021 **Budget Period: 2**

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 . Dr.	Christopher		Shera		PD/PI	0.00	7.8			[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]		[redacted]		[redacted]			[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]		[redacted]		[redacted]			[redacted]	[redacted]	[redacted]

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

Additional Senior Key Persons: File Name:

Total Senior/Key Person [redacted]

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
3	Post Doctoral Associates	30			[redacted]	[redacted]	[redacted]
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Engineer	1.2			[redacted]	[redacted]	[redacted]
[redacted]	[redacted]				[redacted]		[redacted]
					[redacted]		[redacted]

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

Funding Opportunity Number: PA-18-484 . Received Date: 2018-06-30T00:58:58.000-04:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 2

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: [redacted]

Start Date*: 04-01-2020 **End Date*:** 03-31-2021 **Budget Period: 2**

C. Equipment Description

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

Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	

Additional Equipment: File Name:

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

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)

Tracking Number: GRANT12665698 Funding Opportunity Number: PA-18-484 . Received Date: 2018-06-30T00:58:58.000-04:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 2

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: [redacted]

Start Date*: 04-01-2020 **End Date*:** 03-31-2021 **Budget Period: 2**

F. Other Direct Costs	Funds Requested ($)*
1. Materials and Supplies	[redacted]
[redacted]	[redacted]
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8 . Subject Fees	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	[redacted]

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . On Campus Research	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, [redacted]

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	[redacted]

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*
	[redacted]

L. Budget Justification*	File Name: Shera_Budget_Justification_final_v21012774141.pdf (Only attach one file.)

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

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 3

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: [redacted]

Start Date*: 04-01-2021 **End Date*:** 03-31-2022 **Budget Period: 3**

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 . Dr.	Christopher		Shera		PD/PI	0.00	7.8			[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]		[redacted]		[redacted]			[redacted]	[redacted]	[redacted]

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

Additional Senior Key Persons: File Name: **Total Senior/Key Person** [redacted]

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
3	Post Doctoral Associates	30			[redacted]	[redacted]	[redacted]
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Engineer	1.2			[redacted]	[redacted]	[redacted]
[redacted]	[redacted]				[redacted]	[redacted]	[redacted]
					[redacted]		[redacted]

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

Funding Opportunity Number: PA-18-484 . Received Date: 2018-06-30T00:58:58.000-04:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 3

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: [redacted]

Start Date*: 04-01-2021 **End Date*:** 03-31-2022 **Budget Period: 3**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	

Additional Equipment: File Name:

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

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)

Tracking Number: GRANT12665698 Funding Opportunity Number: PA-18-484 . Received Date: 2018-06-30T00:58:58.000-04:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 3

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: [redacted]

Start Date*: 04-01-2021 **End Date*:** 03-31-2022 **Budget Period: 3**

F. Other Direct Costs		Funds Requested ($)*
1. Materials and Supplies		[redacted]
[redacted]		[redacted]
3. Consultant Services		
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs		
6. Equipment or Facility Rental/User Fees		
7. Alterations and Renovations		
8 . Subject Fees		[redacted]
	[redacted]	[redacted]

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	[redacted]

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . On Campus Research	[redacted]	[redacted]	[redacted]
		Total Indirect Costs	[redacted]

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, [redacted]

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	[redacted]

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*
	[redacted]

L. Budget Justification*	File Name: Shera_Budget_Justification_final_v21012774141.pdf (Only attach one file.)

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

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 4

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: [redacted]

Start Date*: 04-01-2022 **End Date*:** 03-31-2023 **Budget Period: 4**

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 .	Dr.	Christopher		Shera		PD/PI	0.00	7.8			[redacted]	[redacted]	[redacted]
2 .	Dr.	Carolina		Abdala		Co-Investigator		0.6			[redacted]	[redacted]	[redacted]

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

Additional Senior Key Persons: File Name: **Total Senior/Key Person** [redacted]

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
3	Post Doctoral Associates	30			[redacted]	[redacted]	[redacted]
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Engineer	1.2			[redacted]	[redacted]	[redacted]
[redacted]	[redacted]				[redacted]	[redacted]	[redacted]
					[redacted]		[redacted]

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

Funding Opportunity Number: PA-18-484 . Received Date: 2018-06-30T00:58:58.000-04:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 4

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: [redacted]

Start Date*: 04-01-2022 **End Date*:** 03-31-2023 **Budget Period: 4**

C. Equipment Description

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

Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	

Additional Equipment: File Name:

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

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)

Tracking Number: GRANT12665698 Funding Opportunity Number: PA-18-484 . Received Date: 2018-06-30T00:58:58.000-04:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 4

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: [redacted]

Start Date*: 04-01-2022 **End Date*:** 03-31-2023 **Budget Period: 4**

F. Other Direct Costs		Funds Requested ($)*
1. Materials and Supplies		[redacted]
[redacted]		[redacted]
3. Consultant Services		
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs		
6. Equipment or Facility Rental/User Fees		
7. Alterations and Renovations		
8 . Subject Fees		[redacted]
	[redacted]	[redacted]

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	[redacted]

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . On Campus Research	[redacted]	[redacted]	[redacted]
		Total Indirect Costs	[redacted]

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, [redacted]

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	[redacted]

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*
	[redacted]

L. Budget Justification*	File Name: Shera_Budget_Justification_final_v21012774141.pdf (Only attach one file.)

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

OMB Number: 4040-0001
Expiration Date: 10/31/2019

RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 5

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Enter name of Organization: [redacted]

Start Date*: 04-01-2023 **End Date*:** 03-31-2024 **Budget Period: 5**

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 . Dr.	Christopher		Shera		PD/PI	0.00	7.8			[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]		[redacted]		[redacted]			[redacted]	[redacted]	[redacted]

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

Additional Senior Key Persons: File Name: **Total Senior/Key Person** [redacted]

B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary ($)*	Fringe Benefits*	Funds Requested ($)*
3	Post Doctoral Associates	30			[redacted]	[redacted]	[redacted]
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Engineer	1.2			[redacted]	[redacted]	[redacted]
4	**Total Number Other Personnel**					**Total Other Personnel**	[redacted]
					[redacted]		[redacted]

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

Funding Opportunity Number: PA-18-484 . Received Date: 2018-06-30T00:58:58.000-04:00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 5

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: [redacted]

Start Date*: 04-01-2023 **End Date*:** 03-31-2024 **Budget Period: 5**

C. Equipment Description	
List items and dollar amount for each item exceeding $5,000	
Equipment Item	**Funds Requested ($)***
Total funds requested for all equipment listed in the attached file	
Total Equipment	
Additional Equipment: File Name:	

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

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)

Tracking Number: GRANT12665698 Funding Opportunity Number: PA-18-484 . Received Date: 2018-06-30T00:58:58.000-04:00

RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 5

ORGANIZATIONAL DUNS*: [redacted]

Budget Type*: ● Project ❍ Subaward/Consortium

Organization: [redacted]

Start Date*: 04-01-2023 **End Date*:** 03-31-2024 **Budget Period: 5**

F. Other Direct Costs		Funds Requested ($)*
1. Materials and Supplies		[redacted]
[redacted]		[redacted]
3. Consultant Services		
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs		
6. Equipment or Facility Rental/User Fees		
7. Alterations and Renovations		
8 . Subject Fees		[redacted]
	[redacted]	[redacted]

G. Direct Costs	Funds Requested ($)*
Total Direct Costs (A thru F)	[redacted]

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	Funds Requested ($)*
1 . On Campus Research	[redacted]	[redacted]	[redacted]
		Total Indirect Costs	[redacted]

Cognizant Federal Agency (Agency Name, POC Name, and POC Phone Number) DHHS, [redacted]

I. Total Direct and Indirect Costs	Funds Requested ($)*
Total Direct and Indirect Institutional Costs (G + H)	[redacted]

J. Fee	Funds Requested ($)*

K. Total Costs and Fee	Funds Requested ($)*
	[redacted]

L. Budget Justification*	File Name: Shera_Budget_Justification_final_v21012774141.pdf (Only attach one file.)

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

Budget Justification

Personnel

Christopher Shera, Ph.D. (Principal Investigator, 65% effort, 7.8 calendar months) The PI has responsibility for all aspects of this project, including theoretical and experimental design, software development, computational and mathematical modeling, data collection and analysis, and preparation of manuscripts. He will also be actively supervising and participating in the experimental and theoretical work of the postdoctoral fellows and any trainees who are recruited and supported by other means. This R01 is the PI's principal daily focus.

Carolina Abdala, Ph.D. (Co-Investigator, 5% effort, 0.6 calender month) Dr. Abdala is an expert in the measurement of MOC efferent effects in humans using OAEs. She will provide advice and assistance with the experimental design, data collection, and analysis for the OAE studies of Aim 2.

John Oghalai, M.D. (Co-Investigator, 5% effort, 0.6 calendar month in years 1 and 2) Dr. Oghalai is an expert in the use of optical coherence tomography (OCT) to measure the sound-induced motions of the organ of Corti in intact cochleae. He will provide advice and assistance with the experimental design, data collection, and analysis for the experimental studies of Aim 3b.

Karolina Charaziak, Ph.D. (Postdoctoral Fellow, 100% effort, 12 calendar months) Dr. Charaziak will be involved in all aspects of the work of Aim 1, including experimental design, data collection, theoretical and computational modeling, analysis, and writing and in the vibration measurements of Aim 3b including experimental design, data collection, and analysis. Dr. Charaziak is currently applying for a K99 award to pursue a different project jointly mentored by Drs. Shera and Oghalai. Should that grant be awarded, we will recruit another postdoctoral fellow to complete the work described here, under the supervision of the PI. We do not anticipate any problems filling this position.

Anders Christensen, Ph.D. (Postdoctoral Fellow, 75% effort, 9 calendar months) Dr. Christensen will be involved in the experimental work of Aim 2, including experimental design, data collection, analysis, and writing. When he finishes, sometime within the five-year grant period, we will recruit another research fellow or graduate student to complete the work described here, under the supervision of the PI. We do not anticipate any problems filling this trainee position.

Alessandro Altoè, Ph.D. (Postdoctoral Fellow, 75% effort, 9 calendar months) Dr. Altoè will be involved in the theoretical and computational studies of Aim 3b, including model design and implementation, simulations, analysis, and writing. When he finishes, sometime within the five-year grant period, we will recruit another research fellow or graduate student to complete the work described here, under the supervision of the PI. We do not anticipate any problems filling this trainee position.

Ping Luo, M.S.E.E. (Research Engineer, 10% effort, 1.2 calendar months) Mr. Luo will provide engineering and software support for the experiments of Aims 1, 2, and 3. Mr. Luo has over 15 years' experience working in acoustics and electronics laboratories, where he was implemented and refined OAE measurement software, designed and calibrated acoustical and electronic hardware for data-collection systems, adapted data-analysis algorithms for studies on otoacoustic emissions and cochlear mechanics, and made precision acoustic measurements.

we propose a 3% merit -based salary increase annually.

Equipment (year 1 only)

Scientific workstations for high-performance computing: Funds are requested to purchase two Dell Precision T7910 high-performance scientific workstations (dual 10-core processors, 128 GB memory, 1 TB SSD, and 21" flat-panel monitor at [redacted]/workstation with discount) for the mathematical and computational modeling studies of Aims 1, 2, and 3. The scientific workstations currently used by the PI and postdoctoral fellows are more than five years old and need significantly improved processing speeds and additional memory to run the cochlear model simulations.

Materials and Supplies (incremented by [redacted] per year)

Eartips and miscellaneous supplies: Funds [redacted] are requested for disposable eartips for coupling probe assemblies to the subject's ear and other miscellaneous supplies used in the experiments (e.g., batteries, gloves,

surgical tape, laboratory notebooks and stationery supplies, printer supplies, acoustical tubing, electrical connectors and adapters, data storage media and services).

Technical books: Funds [redacted] are requested to purchase technical books necessary for the proposed research.

Animals and surgical supplies: Funds [redacted] yr in years 1 and 2) are requested for the purchase and housing of mice and for necessary surgical supplies.

Travel

Funds are requested for one trip per year for the PI and Postdoctoral Fellows to a scientific meeting (such as the ARO Midwinter Meeting) to present results from the projects funded by this R01 [redacted]

Other Expenses

Publication costs: Funds [redacted] /yr) are requested to cover the cost of publishing papers in the *Journal of the Acoustical Society of America* (approx [redacted] per article) and other relevant journals, the costs of publishing color figures [redacted] per figure in *JASA*), and printing of posters for meetings such as the ARO Midwinter Meeting. The annual figure is based on the expected publication rate of three papers and two posters per year.

Miscellaneous software licenses: Funds [redacted] yr) are requested to cover the yearly cost of software usage licenses, maintenance, and upgrades for scientific computing and remote file-sharing software used by the PI and his trainees (Adobe Creative Suite [redacted], Mathematica [redacted] Dropbox [redacted] Logmein Pro [redacted]

Subject fees and expenses: Funds [redacted] are requested for subject participation incentives [redacted] and reimbursed public transportation or parking expenses

Equipment maintenance and repair: Funds [redacted] are requested to cover miscellaneous manufacturing, maintenance, repair, and/or replacement costs for transducers, amplifiers, filters, electronics, and other small equipment used in the experiments.

RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals ($)
Section A, Senior/Key Person	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
1. Domestic	[redacted]
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	[redacted]
1. Materials and Supplies	[redacted]
[redacted]	[redacted]
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Other 1	[redacted]
[redacted]	[redacted]
10. Other 3	
Section G, Direct Costs (A thru F)	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]

PHS 398 Cover Page Supplement

OMB Number: 0925-0001

Expiration Date: 03/31/2020

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)

Tracking Number: GRANT12665698

Funding Opportunity Number: PA-18-484 . Received Date: 2018-06-30T00:58:58.000-04:00

PHS 398 Cover Page Supplement

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. 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

5. 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:

Tracking Number: GRANT12665698 Funding Opportunity Number: PA-18-484 . Received Date: 2018-06-30T00:58:58.000-04:00

PHS 398 Research Plan

OMB Number: 0925-0001
Expiration Date: 03/31/2020

Introduction	
1. Introduction to Application (for Resubmission and Revision applications)	Shera_Introduction1012773854.pdf
Research Plan Section	
2. Specific Aims	Shera_Specific_Aims1012773838.pdf
3. Research Strategy*	Shera_Research_Strategy1012773840.pdf
4. Progress Report Publication List	Shera_Progress_Report_Publication_List1012773843.pdf
Other Research Plan Section	
5. Vertebrate Animals	Shera_Vertebrate_Animals1012773841.pdf
6. Select Agent Research	Shera_Select_Agents1012773842.pdf
7. Multiple PD/PI Leadership Plan	
8. Consortium/Contractual Arrangements	
9. Letters of Support	Shera_Oghalai_Letter_of_Collaboration1012773853.pdf
10. Resource Sharing Plan(s)	Shera_Resource_Sharing1012773844.pdf
11. Authentication of Key Biological and/or Chemical Resources	Shera_Authentication_Plan1012773857.pdf
Appendix	
12. Appendix	

Tracking Number: GRANT12665698
Funding Opportunity Number: PA-18-484. Received Date: 2018-06-30T00:58:58.000-04:00

INTRODUCTION

We thank the reviewers for highlighting the strengths of the application and for their constructive criticism. Responses to the noted weaknesses of the proposal are summarized below.

Uncertain significance of the fluid waveguide model. Aim 3 explores the micromechanics of cochlear wave amplification and its consequences for OAE generation. Unfortunately, reviewers were unconvinced that the previous focus of Aim 3a—van der Heijden's fluid-waveguide model and its controversial claim that passive "mode-swapping" provides a viable basis for cochlear frequency selectivity[1]—was worthy of further pursuit. We have therefore refocused the modeling work of this sub-Aim on a topic more clearly related to the main thread of the application and its emphasis on addressing fundamental issues of cochlear mechanics relevant to OAE generation. The revised Aim 3a explores the implications for OAE generation of the oblique, *Y*-shaped geometry formed by the outer hair cells and phalangeal processes of the Deiter's cells. This striking anatomical feature of organ-of-Corti cytoarchitecture has been hypothesized to provide a key micromechanical component of the cochlear amplifier.[2] Models that incorporate this concept predict that cochlear wave propagation is necessarily anisotropic (i.e., different for waves traveling in the two directions), a prediction with significant consequences for our understanding of OAE generation.

Limited spatial resolution of OCT measurements. Although OCT measurements of the motions of the different parts of the organ of Corti are revolutionizing our understanding of cochlear mechanics, the ability to unambiguously resolve cellular or subcellular structures remains limited. Thus, when we use the term "reticular lamina" (RL) we mean that the measurements are from the center of the upper portion of the outer-hair-cell region, as determined visually by the experimenter. Typically, we can discern the tectorial membrane and the tunnel of Corti, so a measurement point is selected that is under the tectorial membrane and adjacent to the tunnel. Additionally, we use 2-D cross-sectional images with vibratory magnitudes and phases plotted in pseudocolor for every point in the image to further guide the selection of the measurement location. Depending on stimulus frequency and amplitude (and also on measurement angle), differences in response magnitude and/or phase between regions can help to discriminate the structures. In practice, therefore, the resolution of OCT vibrometry is much better than suggested by the anatomical scans. Nevertheless, the finite spatial resolution of current vibration measurements is an important reason that we employ somewhat more abstracted phenomenological models involving coupled modes of motion rather than finite-element models designed to represent the microanatomy of the organ of Corti in realistic detail.

Histology to visualize and quantify the irregularity. Unfortunately, modeling studies suggest that the micromechanical irregularities believed responsible for scattering traveling waves—and, as we hypothesize here, for introducing spatial variations in the operating point or other characteristics of the hair-bundle nonlinearity—are likely to be small and not necessarily discernible in the anatomy. This is especially true of the dynamical irregularity we hypothesize to be transiently induced by activation of MOC efferents. The introduction of controlled, artificial irregularities—for example, though the careful placement of heavy beads on the basilar membrane[3] or via the targeted inactivation of specific outer hair cells[4]—may help circumvent this problem, and we are exploring the feasibility of these more invasive experiments for future projects.

Subject numbers not determined by power analysis. The questions we pose here are not fundamentally statistical in character. Rather than looking for confirmation of hypothesized differences between groups, we seek robust relationships within individuals that reveal mechanisms or previously unrecognized patterns. Because our process of data collection and analysis is an iterative one, involving considerable back-and-forth with theoretical modeling, the most informative analysis metrics or procedures cannot be fully known in advance, and traditional power analysis is therefore not possible. Instead, our human and murine subject numbers are estimates based on 25 years of experience with the number of good data sets needed to achieve robust conclusions.

Sex as a biological variable. Although small sex differences in OAE amplitudes have been reported in humans—no doubt due in part to systematic differences in ear-canal and cochlear dimensions and/or cumulative noise exposure—we have no reason to expect significant sex differences in the basic mechanisms of cochlear function or OAE generation explored here. Nevertheless, we will analyze all our data for possible sex effects.

SPECIFIC AIMS

Otoacoustic emissions (OAEs) constitute a powerful noninvasive window on the mechanics of the cochlea. OAEs provide both valuable assays of cochlear function and unique tools for exploring fundamental issues about how the cochlea works, especially in humans. Correct understanding and application of the information OAEs carry back to the ear canal requires a solid interpretive framework that describes inner-ear mechanics in general and emission generation in particular. To pursue the complementary goals of improving the diagnostic utility of OAE measurements while exploring basic, unresolved issues of cochlear mechanics, we propose three Aims that leverage the power of combining empirical and theoretical studies:

Aim 1. Test the dual effect of suppressor tones on the distribution of OAE sources. Otoacoustic measurements often employ additional stimulus tones for the purpose of reducing or eliminating contributions from OAE sources located in particular regions of the cochlea (e.g., when assessing cochlear frequency selectivity by measuring OAE suppression tuning curves). However, our preliminary modeling studies suggest that "suppressor" tones have a dual effect: They can both reduce the strength of existing OAE sources and induce new sources that would not otherwise be present. Using measurements and models of stimulus-frequency and click-evoked OAEs, we test the hypothesis that suppressors can create new sources of wave reflection within the cochlea. Preliminary modeling work predicts that the dominant effect of the suppressor tone depends systematically on stimulus parameters. **Aim 1a** tests these predictions experimentally in human ears while **Aim 1b** explores their physical basis using OAE models. **Aim 1c** determines whether the results can be applied to improve the measurement of OAE suppression tuning curves. Unraveling the effects of suppressor tones has important implications for understanding and exploiting the frequency-specificity of OAE measurements.

Aim 2. Probe the nature of micromechanical irregularity and its role in OAE generation. Although models indicate that spatially irregular variations in cochlear micromechanics play an essential role in the wave scattering responsible for reflection-source OAEs, the nature of this irregularity has yet to be understood. Micromechanical irregularity has conventionally been regarded as static and structural (e.g., arising from random, cell-to-cell variations in outer-hair-cell geometry). However, our preliminary results suggest that the irregularity involved in OAE generation can also have an important dynamical component whose action can alter the standard interpretation of OAE measurements. The modeling work of **Aim 2a** tests the hypothesis that *reducing* the gain of the cochlear amplifier by activating the medial-olivocochlear (MOC) efferents can actually *increase* reflection-source OAEs by changing the spatial pattern of micromechanical irregularities. Motivated by our preliminary data, the experiments of **Aim 2b** test the intriguing idea that micromechanical irregularity can shape the properties of distortion- as well as reflection-source OAEs. Combining nonlinear cochlear models and OAE measurements in humans, we test the hypothesis that irregularity, in addition to scattering traveling waves, can modulate the generation of nonlinear distortion, and that this modulation is enhanced by contralat-eral acoustic stimulation. Understanding micromechanical irregularity and its modification by MOC activation is crucial for interpreting, and perhaps improving, OAE-based tests of efferent function.

Aim 3. Explore the micromechanics of cochlear wave amplification and its consequences for OAEs. Complex modes of motion in the organ of Corti—their existence long inferred from auditory-nerve recordings, from in-vitro studies of excised cochleae, and from computational models—have now been observed in direct measurements from the intact cochlea. The full import of these modes, and of the intricate cytoarchitecture that subserves them, remains unclear, but they may require significant revision to our understanding of cochlear amplification and OAEs. **Aim 3a** studies OAE generation in models incorporating forms of spatial feed-forward/backward amplification suggested by the oblique geometry of the outer hair cells. Although such models can match measured mechanical responses, published arguments suggest that they cannot produce realistic reflection-source OAEs. We will test these arguments and determine how the existence and properties of OAEs constrain the micromechanics of cochlear wave amplification. **Aim 3b** combines multi-mode cochlear models and measurements of organ of Corti vibration to explore how assumptions about the modes of motion, their coupling with one another, and their interactions with the cochlear fluids affect (i) the form of the impedances determined by solving the cochlear "inverse problem" and (ii) the locus of OAE generation and the latency of reverse propagation to the ear canal. Model results will be calibrated against otoacoustic and mechanical measurements made using optical coherence tomography (OCT).

RESEARCH STRATEGY

A. BACKGROUND AND SIGNIFICANCE

Overall impact. Notwithstanding the wealth of information now available about the cellular, molecular, and genetic mechanisms of hearing, much remains unknown about the basic functional operation of the cochlea, including the mechanisms of OAE generation. For example, imaging techniques such as optical coherence tomography and vibrometry have recently revealed unexpected internal motions within the organ of Corti and along the tectorial membrane.[5–8] Although the intricate structural architecture of the organ of Corti has always harbored the potential for supporting multiple vibrational modes, parallel pathways of energy propagation, and non-local mechanisms of wave amplification, the implications of this newly revealed mechanical complexity remain unclear and controversial.[1,9,10]

Our long-term research strategy combines innovative theoretical and experimental studies to develop and apply quantitative models that address these and other fundamental issues. Historically, our approach has yielded novel insights into cochlear mechanics (e.g., the recent prediction that the cochlear frequency-position map has a staircase-like structure correlated with the critical band[11]), key concepts and theories about the generation and propagation of otoacoustic emissions (e.g., reflection, distortion, beamforming[12–16]), new ways of using OAEs to learn about hearing (e.g., estimating the bandwidths of human cochlear tuning using OAE delays[17–20]), and powerful measurement and analysis paradigms (e.g., calibration of intracochlear distortion sources,[16] swept stimulus-frequency OAEs,[21] emitted pressure level[22]). Thus, in addition to enhancing the clinical and scientific value of OAEs as noninvasive probes of hearing function, our approach has demonstrated that OAEs have much to teach us about basic issues of cochlear mechanics.

Continuing this productive strategy while building upon substantial recent progress (see **Progress Report**), the research program pursued here explores essential but unresolved issues in cochlear mechanics and otoacoustic emissions. These include the nonlinear action of suppressor tones and the circumstances under which they reveal the sources producing otoacoustic emissions; the nature of the micromechanical irregularity believed to underlie the generation of click-evoked and stimulus-frequency OAEs; the implications of organ of Corti cytoarchitecture for cochlear amplification and OAE generation; and the functional significance of the multiple coupled modes of motion revealed by recent mechanical measurements. By studying the physical and physiological mechanisms responsible for generating and shaping OAEs, the proposed work promises to provide significant insight into the mechanisms underlying both otoacoustic emissions and the normal operation of the cochlea. Work of this sort addresses a nascent paradigm shift in cochlear mechanics while laying the essential foundation for developing new, more powerful probes of hearing.

Aim 1. Two-tone suppression and OAEs

The interpretation of OAE measurements often relies on a key but largely untested assumption derived from studies of two-tone suppression in auditory-nerve and basilar-membrane responses: Namely, that so-called "suppressor" tones act to eliminate contributions from OAE sources located in particular regions of the cochlea. For example, the standard suppression method of measuring SFOAEs assumes that presentation of a second tone at a nearby frequency reduces the amplitude of the emission evoked by the probe.[23,24] Our previous work has validated this assumption—for near-probe suppressors in the basal half of the cochlea—by comparing the SFOAEs derived using suppression with those obtained using methods that do not involve additional tones.[25] However, the suppression assumption is often applied beyond its known region of validity. For example, by fixing the probe and varying the frequency of the second tone over a wide range (**Fig. 1**), multiple studies have applied the suppression assumption to map out the distribution of SFOAE generators within the cochlea.[26–28] The results suggest that a significant fraction of the total SFOAE originates in the basal, tail-region of the traveling wave, contrary to the predictions of most OAE models.[29] These studies, if valid, have significant implications for models of OAE generation and thus for the interpretation of OAE measurements.

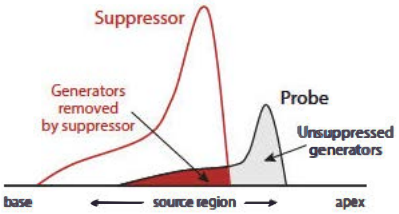

Figure 1. Suppressor tones are often assumed to remove probe-frequency SFOAE generators at locations where the wave envelope overlaps with the probe.

Our preliminary modeling results, however, call the basis of these mapping studies into question.[30] In brief, we hypothesize that the effects of suppressor tones on OAEs are more complicated than their effects on

either basilar-membrane motion or auditory-nerve responses. More specifically, our theoretical work, recently collaborated by others,[31] indicates that the suppressor tone can act not only to reduce the strength of existing OAE sources but also to *induce* new (i.e., artifactual) sources that would not otherwise be present.[30] The model predicts that the strength, latency, and net contribution of these induced sources depends on the frequency of the suppressor tone relative to the probe—although the induced sources contribute little when the suppressor is close to the probe, they can come to dominate the OAE when the suppressor is moved further away.

By testing the validity of the suppression assumption for reflection-source OAEs, our results have significant potential to revise the interpretation of studies that employ suppressor tones to probe (or to manipulate) the locus of OAE generation. For example, the finding that "suppressors do not always suppress" would have major implications for understanding SFOAE suppression tuning curves (STCs) and for their interpretation as objective estimates of cochlear frequency selectivity.[32–39] Indeed, measured SFOAE STCs often have apparently anomalous features (e.g., multiple lobes that vary somewhat idiosyncratically from ear to ear) whose origin is not yet well understood. Similar anomalies appear in the STCs of other OAE types, including both distortion-product[40,41] and spontaneous emissions.[42] These anomalous features have lead to the conclusion that OAE suppression tuning curves, although useful at the group level, provide unreliable estimates of cochlear frequency selectivity in individual ears.[36,43] Our preliminary results suggest a promising new methodology for reducing the confounding effects of suppressor tones and improving the reliability of SFOAE STCs.

Aim 2. Micromechanical irregularity and OAE generation

Because the organ of Corti is a biological structure, its mechanical properties presumably vary somewhat irregularly with position. When introduced into cochlear models, small micromechanical irregularities have a remarkable effect—by disturbing the otherwise smooth forward flow of stimulus energy, they cause the model to emit sound (or its computational equivalent). As they propagate, traveling waves launched along the duct encounter the irregularities and are partially reflected back toward the stapes, producing reflection-source OAEs.[12,44] (By "irregular" we do not mean necessarily "random" or "discontinuous;" we use the term to describe any variation that occurs on spatial scales that are short compared to the wavelength of the traveling wave at its peak.) Although it may be natural to suppose that the irregularity most relevant for generating OAEs occurs in parameters that influence the forces produced by hair cells (e.g., the geometry or mechanical characteristics of the hair bundle), the dominant biological source of irregularity remains unknown.

Whatever its principal locus, the micromechanical irregularity involved in OAE generation has invariably been regarded as (i) static and structural—because OAE spectra in healthy ears remain stable over months and even years[45]—and (ii) unimportant for the production of distortion-source OAEs—because the phase-vs-frequency functions of distortion-source OAEs indicate that their sources are wave- rather than place-fixed.[14] Recent results from our lab and others, however, challenge both of these principles. For example, our preliminary modeling work suggests that the ostensibly static pattern of micromechanical irregularities characteristic of a given ear may be reversibly altered by activation of medial olivocochlear (MOC) efferents. Otoacoustic measurements from both human subjects[46] and guinea pigs[47] show that activation of the MOC system, which generally reduces the gain of the cochlear amplifier, can both inhibit and *enhance* the magnitude of reflection-source OAEs (e.g., either SFOAEs or the reflection component of DPOAEs). Importantly, enhancement can occur over wide frequency regions and is not limited to intervals where out-of-phase components combine to produce spectral notches. (Near notches, decreases in the level of either component can reduce the amount of destructive interference, producing the spurious impression that OAE levels have actually increased.) Our preliminary results (Fig. 2) suggest that this seemingly impossible combination—*reduced* cochlear gain accompanied by *increased* reflection-source OAEs—can be explained by coherent reflection theory[13] combined with the patchy innervation patterns of individual MOC efferent fibers revealed by anatomical studies.[48,49] We will test the hypothesis that by locally reducing the gain of innervated OHCs, efferent activation

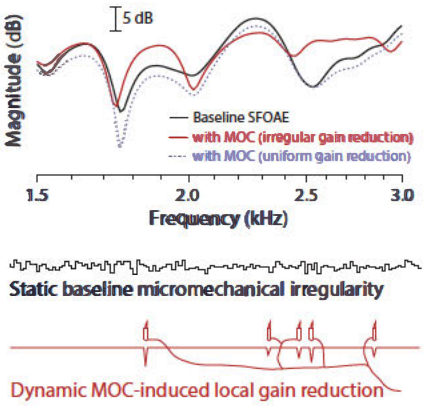

Figure 2. Although a spatially uniform decrease in cochlear gain reduces SFOAE levels from baseline (dotted line re black), a more irregular gain decrease due to patchy efferent innervation (bottom) can both reduce and enhance SFOAEs (red re black).

modifies the spatial pattern of micromechanical irregularities and thereby changes the effective strength of OAE reflection sources. Similar ideas—with permanent local irregularity due to aging substituting for the reversible changes induced by efferent activation—may account for the unexpected findings that elderly subjects often show relatively preserved reflection-source OAEs and surprisingly robust generation of SOAEs.[50,51]

Preliminary results also question the common presumption that micromechanical irregularity plays no role in the generation of distortion-source OAEs. The principal nonlinearity in the cochlea is thought to reflect the shape and operating point of the OHC transducer function (i.e., the sigmoidal relation between bundle displacement and receptor potential). If the transducer function, and hence the effective strength of the cubic nonlinearity, were to vary somewhat irregularly along the cochlea, then the magnitude of the distortion-source (or "generator component") of the $2f_1 - f_2$ DPOAE would vary with frequency. Because DPOAEs are mixtures of both short-latency distortion- and long-latency reflection-source OAEs,[14,15] rapid or irregular variations in the distortion component can be difficult to distinguish from interference arising from component mixing (i.e., from DPOAE fine structure). Our preliminary studies suggest, however, that the two can be disentangled using time-frequency analysis. As a simple, illustrative example, suppose the short-latency distortion component $D(f)$ has a sinusoidal amplitude modulation across frequency, $D(f) = D_0 + d\cos(2\pi f/\Delta f)$, where $d \ll D_0$ and Δf is the modulation period. Then, because $\cos(2\pi f/\Delta f) = \frac{1}{2}\left(e^{-i2\pi f/\Delta f} + e^{+i2\pi f/\Delta f}\right)$, time-frequency analysis of $D(f)$ will reveal three components: A principal component of magnitude D_0 at zero delay, a component of magnitude $d/2$ with positive delay ($\tau = 1/\Delta f$), and a component (also of magnitude $d/2$) with apparently *negative* delay ($-\tau$). Our previous theoretical work indicates that energy in the time-frequency plot can be interpreted in terms of the spatial distribution of the irregularities.[52] Our analysis thus predicts that spectral modulation of the DPOAE distortion component—arising from spatial irregularity in the strength of cochlear nonlinearity—manifests itself as DPOAE time-frequency components with negative delay. This signature negative delay—a convenient consequence of the analysis and not, of course, a true, physical delay—allows modulation of the distortion-source component to be identified and studied. Interestingly, our preliminary analysis of human DPOAEs has identified subjects with negative-delay components, as predicted. Furthermore, the data suggest that the magnitude and spectral pattern of negative-delay DPOAE components can be enhanced by contralateral acoustic stimulation (**Fig. 3**), suggesting that activation of MOC efferents modulates the form and/or operating point of OHC transducer functions. The proposed experiments and modeling work will pursue these intriguing preliminary findings and test the hypothesis that reflection- and distortion-source OAEs are sensitive to different micromechanical sources of irregularity.

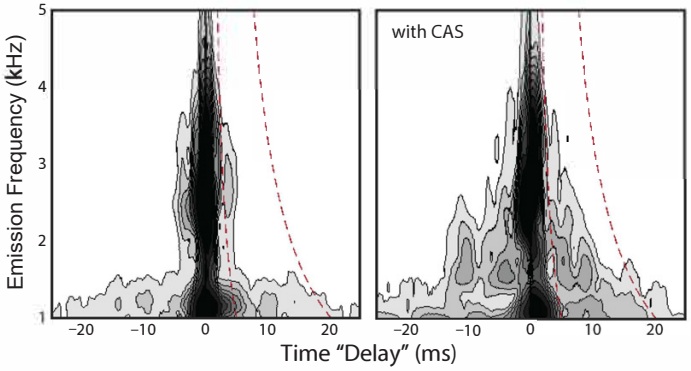

Figure 3. Time-frequency analysis of human swept-tone DPOAEs measured in the same subject both with (right) and without (left) activation of MOC efferents induced by contralateral acoustic stimulation (CAS) with wideband noise (60 dB SPL). Grayscales are identical in the two panels. Dashed lines delimit the time-frequency band expected for DPOAE reflection-source components. In this subject, CAS greatly enhances DPOAE components with nonzero "delays," both positive and negative. Stimulus parameters: $\{L_1, L_2\} = \{65, 55\}$ dB SPL, $f_2/f_1 = 1.22$.

Aim 3. Micromechanics of cochlear wave amplification and OAEs

Aim 3a. OAE generation in models with spatial feed-forward/feed-backward (FF/FB) amplification.

The oblique geometry of the organ of Corti seems likely to play an essential role in mammalian cochlear amplification. Some models incorporating this geometry suggest that the cochlear amplifier operates through mechanisms involving the spatial feed-forward and/or feed-backward (FF/FB) of OHC somatic forces. In these models, OHCs sense stereociliary displacement at one location but produce forces and motion at another, their somatic forces being transmitted along the organ of Corti via the Y-shaped cytoarchitecture of the OHCs and phalangeal processes of the Deiter's cells (see **Fig. 4**).[2,53–58] Because of traveling-wave propagation, the longitudinal separation between the locations of OHC sensing and forcing introduces phase shifts that can yield a form of negative damping, amplifying traveling waves as they propagate.

Although FF/FB amplification appears attractive for anatomical and engineering reasons,[59] and models incorporating these principles appear capable of reproducing BM mechanical measurements,[2,56,58] the viability

of the mechanism as an explanation for *in vivo* cochlear amplification remains unclear. Heuristic arguments[60,61] suggest that FF/FB amplification suffers from the very virtue that makes it so attractive and stable from an engineering perspective: the amplification it provides depends on the direction of wave propagation. The oblique geometry introduces a directionality to the amplifier—whereas forward-traveling waves are boosted, reverse-traveling waves are squelched. Unlike other forms of negative damping (e.g., time-delayed stiffness), spatial FF/FB amplification may therefore be effectively "one-way." This anisotropy would not be a problem—indeed, it might be an advantage for cochlear signal processing near threshold, where it would alleviate complications due to standing waves—were it not for the existence of otoacoustic emissions, which indicate that amplified energy escapes from the cochlea via mechanisms involving reverse traveling waves. (Although the possible role of "fast waves" must be borne in mind, the accumulated evidence against a dominant role for compressional waves in the reverse propagation of OAEs is compelling.[3,62–68]). Thus, current models of FF/FB amplification might be significantly constrained by the existence and properties of OAEs.

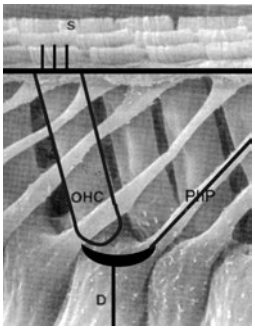

Figure 4. *Y*-shaped geometry of the organ of Corti may underlie somatic amplification by OHCs.[58]

Since the arguments against FF/FB amplification remain heuristic, testing their validity becomes crucial for understanding the contributions and possible limitations of FF/FB mechanisms to cochlear amplification.[69] Resolving the question is just as important, however, for understanding OAEs and their applications to research and the clinic. If the mammalian cochlea does, in fact, implement spatial FF/FB amplification, then current interpretations of OAEs in terms of cochlear mechanics—interpretations derived largely from studies of OAE generation in classical, point-impedance models—may require modification.

Aim 3b. Organ of Corti vibrational modes and OAE generation

Until recently, the common view of cochlear micromechanics regarded the organ of Corti as providing a lever-like proportional coupling of basilar-membrane (BM) motion to the reticular lamina (RL), whose shearing motion relative to the overlying tectorial membrane then deflect the stereocilia of the inner hair cells.[70] By pushing and pulling on the BM, the outer hair cells (OHCs) appear to amplify the traveling wave but do not, in this view, significantly modify the dominant pattern of simple, almost rigid-body motion. We now know from direct mechanical measurements in the intact cochlea that this view is incomplete, perhaps even fundamentally misleading—the motion of the organ of Corti revealed by imaging techniques such as optical coherence tomography (OCT) appears far more complex than previously supposed.[6–8] For example, rather than moving together in simple proportion, the basilar membrane and reticular lamina evidently vibrate with strikingly different amplitudes and phases. Furthermore, the frequency tuning of the compressive nonlinearity measured at these two locations within the organ of Corti (BM and RL) appears qualitatively different: Whereas compressive responses measured on the BM (and in the auditory nerve) are largely confined to the tip region of the traveling wave, the motion of the reticular lamina remains nonlinear at frequencies far into the tail region below CF. Although the potential relevance for cochlear function of multiple modes of vibration ("degrees of freedom") in the organ of Corti has long been recognized—whether from notches in rate-level functions and other telling responses of the auditory-nerve,[71–74] from the complex motions evoked by electrical stimulation in excised cochleae,[75,76] or from representations of cochlear micromechanics in computational models[58,77–79]—none of these seminal studies envisioned the details now emerging.

Whereas the complexities of cochlear motion are finally coming into view, the functional and theoretical implications of these modes for the basic mechanical operation of the cochlea and for the generation of OAEs remain unclear. Current theoretical understanding of OAE generation derives almost entirely from models in which the motion of the organ of Corti couples to the cochlear fluids—and through the fluids outward to the middle ear and ear canal—via the basilar membrane. The recent discovery that reticular-lamina motion can be larger than that of the BM, and has a different dependence on stimulus level, raises important questions about the micromechanical basis of OAE generation. For example, do the properties and tuning of OAEs correlate better with the motion of the RL than they do with the BM?[10] And, are the reflections responsible for otoacoustic emissions a consequence of coupling between modes?[80]

Seeking simple insights into the functional significance of the multiple coupled modes of motion revealed by

recent measurements, we propose a combination of theoretical models and mechanical measurements of BM and RL motion to address these interrelated questions. We will measure BM and RL motion (in collaboration with Dr. John Oghalai and his laboratory here at USC) and use the data to derive multi-mode cochlear models, with representations of both BM and RL motion, using the inverse method. (In the context of cochlear mechanics, the term "inverse method" refers to theoretical analysis procedures that combine experimental data and model assumptions about coupling to derive the empirical form of the complex wavenumber or effective mechanical impedances within the cochlear partition.) We will vary the model assumptions about fluid coupling to the organ of Corti—for example, whether the fluid couples primarily to the motion of the BM or the RL—and determine the impact on the OAEs predicted by the model. Comparison with OAEs measured in the same preparations will determine whether, and if so, how, current theories of OAE generation need revision.

B. INNOVATION

In the years since their discovery, OAEs have found widespread but diagnostically limited use in audiology clinics and research labs, where they serve primarily to detect (but not to describe) OHC-related hearing loss with roughly half-octave frequency resolution. Research has demonstrated, however, that OAEs have the potential for providing far more detailed and frequency-specific information about normal hearing and its dysfunction. Beginning with the development of the coherent-reflection model[12,81] and the mechanism-based classification scheme for OAEs,[14,82] our goal has been to discover and apply knowledge of OAE generation to develop the power of OAEs as noninvasive probes of hearing.

In the current application, this pioneering research program comes together with our continuing attention to the biophysics of cochlear wave propagation, nonlinearity, and amplification.[16,83–86] These threads unite here to address fundamental issues about otoacoustic emissions and their origins in cochlear mechanics. **Aim 1** combines empirical and theoretical studies to address the central but still unresolved question of whether "suppressors" always suppress. Understanding the answer to this question—so simple to ask but surprisingly difficult to answer—is crucial for proper interpretation of OAE-based measurements of cochlear frequency selectivity and other applications that attempt to localize OAE generation within the cochlea by using additional stimuli to interfere with their production. Technical innovations made during the current grant period[21,22] facilitate the efficient measurement of SFOAEs over a wide frequency range. When combined with the synergy of concurrent modeling studies, these innovations allow us to address these long-standing issues using a powerful new experimental paradigm. **Aim 2** is motivated by exciting new preliminary results that promise to provide a long-sought experimental handle on the nature of the "micromechanical irregularity" hypothesized to underlie the generation of reflection-source OAEs. Our findings suggest that irregularity has dynamical as well as static components and can be reversibly modulated via stimulation of MOC efferents. Furthermore, our discovery of distortion-source OAE components with "negative delay"—made possible by technical innovations in OAE measurement methodology and analysis—supports the novel hypothesis that micromechanical irregularities affect the OHC transducer nonlinearity and may therefore play a more substantial role in cochlear mechanics and OAE generation than previously recognized. **Aim 3** probes the theoretical implications of the intricate micromechanical anatomy and complex internal motions now becoming evident in the in-vivo response of the organ of Corti. Models that simplify the complexities of cochlear micromechanics underlie much of what we think we know about cochlear mechanics, including the existence of traveling-wave power amplification and the physics of OAE generation. But are these models, despite their historical and conceptual successes, too simple to capture the essential operations of the cochlea? To address these questions, we combine innovative theoretical analysis and state-of-the-art techniques for measuring cochlear motions in vivo. The goal is explore whether basic insights gleaned from models derived using the inverse method need modification in light of recent mechanical data. These data raise intriguing (but not necessarily correct) alternatives to our classical conceptions of cochlear function (e.g., boosting the response by swapping energy between vibrational modes or generating OAEs by fluid coupling to the reticular lamina rather than the BM).

C. APPROACH

Aim 1. Two-tone suppression and OAEs

Rationale. Preliminary modeling studies predict that "suppressor" tones can act not only to reduce the strength

of existing SFOAE sources but also to induce new sources that would not otherwise be present.[30,31] Testing these predictions experimentally requires a paradigm that can distinguish whether changes observed when presenting the suppressor tone result from the creation of new sources or from the removal of old ones. Because individual sources can contribute to the total SFOAE with different phases (e.g., constructively or destructively), this task is not as easy as it might appear. A simple example illustrates the problem: If presenting an additional tone increases a measured SFOAE value from $2 \rightarrow 3$, one cannot legitimately conclude that the suppressor acts by creating a new source of value 1, although that is the apparent effect. If the original SFOAE (of value 2) is formed by adding two components with different magnitudes and opposite phases [e.g., $2 = 3 + (-1)$], then the same net change ($2 \rightarrow 3$) occurs if the additional tone acts as a suppressor and selectively *eliminates* the component with negative phase. (The tone might suppress only one of the two components because the components arise at different spatial locations.)

Figure 5 shows preliminary data illustrating the effect of a suppressor tone on the generation of human SFOAEs. Time-frequency analysis[87] of high-resolution swept-tone SFOAEs reveals what can be difficult to appreciate from a conventional, discrete-tone emission spectrum: In addition to reducing the overall emission level (most of which occurs at a latency of 10–12 stimulus periods in the figure), the suppressor appears to induce additional short-latency components not present in the absence of the suppressor. In this example, the suppressor *appears* to create new short-latency components (e.g., those with delays ~2 periods and centered on the region marked with an ×). We can determine whether the appearance of such short-latency components reflects an induction of new sources or a release from cancellation due to partial elimination of the old by measuring how the latency of the components at the probe frequency varies with the frequency of the suppressor: As the suppressor frequency increases relative to the probe, we expect that the latency of new (i.e., induced) components will *decrease* whereas the latency of pre-existing but now unmasked components will *increase*. To see this, note that if the suppressor *induces* new sources near the peak of its excitation pattern, then high-frequency suppressors—those that peak in the basal, tail region of the probe response where the probe phase varies slowly—will induce components with shorter latencies than will suppressors placed closer to the peak of the probe response, where the probe phase varies more rapidly. This qualitative pattern (i.e., higher frequency suppressors produce shorter latencies) is *reversed* if the suppressor *removes* existing sources that are otherwise in cancellation with sources at other locations. In this case, the measured delay of the short-latency component is determined not by phase slopes at the location of peak suppression but by phase slopes at the location of the sources that remain unsuppressed. For example, if high-frequency suppressors remove sources in the tail region of the probe response, where the phase gradients are shallow, then the surviving sources—the ones contributing to the measured emission—are located closer to the peak and have longer latencies.

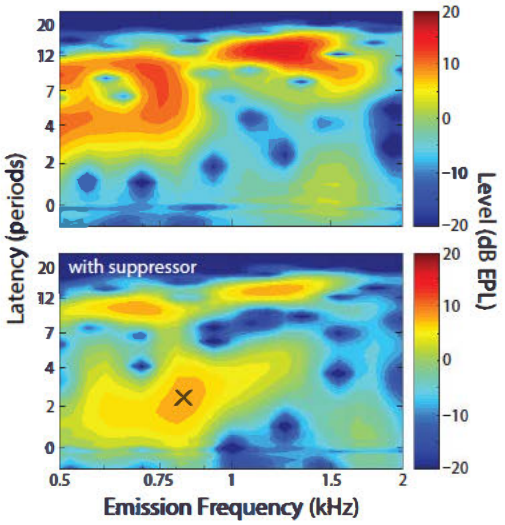

Figure 5. Time-frequency plots of human SFOAEs measured both in the presence (bottom) and absence of (top) an additional suppressor tone placed ~0.22 octave above the probe frequency. The suppressor both reduces overall emission levels and appears to create new sources at short latencies (×). SFOAE latency is given in periods of the probe frequency; SFOAE level in dB EPL.[22] Note the nonlinear latency axis along the ordinate. Probe and suppressor levels were 40 and 59 dB FPL, respectively.

Independent of the mechanisms by which they arise, the appearance of short-latency components due to presentation of the suppressor complicates the interpretation of SFOAE STCs as measures of cochlear frequency selectivity. Based on our preliminary data we conjecture that short-latency components induced by the suppressor are responsible for the multiple lobes and other anomalous features of these tuning curves. To test this hypothesis, we will compare SFOAE STCs measured using conventional suppression criteria, which are based on the magnitude of the total SFOAE, with the results of a new paradigm in which the short-latency components are first eliminated by time-frequency filtering.

Methods. Although DPOAE studies employing high-frequency "suppressor" or "interference" tones also suggest the involvement of basal generators,[41] we focus on SFOAEs because they are the simplest emission type to interpret theoretically. The interpretation of DPOAE studies is more complicated because of the possibility of

exciting multiple avenues of DP generation (e.g., via so-called "catalyst" or "harmonic" mechanisms[88]) due to the larger number of stimulus and combination tones simultaneously present in the cochlea.

The experimental methods of **Aim 1a** will be similar to those used for the preliminary results; all are extensions of those developed and used routinely in our lab. The basic methodology generalizes our "f_1-primary mimicker" paradigm[15] to swept tones.[21] Using this paradigm, we will measure SFOAEs in normal-hearing young adults using the interleaved suppression method[14] at probe frequencies from 0.5–8 kHz. Past success with measurements of this kind suggests that data from ∼20 subjects will suffice. To map out the level dependence, we will use probe levels spanning the range 20–40 dB FPL in 5 dB steps. The near-probe suppressor (f_s) used to extract SFOAEs at the probe frequency will be fixed at $L_s = 60$ dB FPL and a frequency 5% above the probe ($f_s/f_p = 1.05$). The additional "suppressor" tone whose effects we are studying (here called an "interference tone" (IT) to distinguish it from the near-probe suppressor) will be varied in frequency from 1 to 2.5 times f_s in tenth-octave steps. The effects of IT level will be determined using levels spanning the range 50–65 dB FPL. To improve SNRs at low frequencies, where subject and microphone noise are greatest, we will use log or accelerated sweeps.[89] Results obtained with SFOAEs will be compared with emissions evoked using clicks to test the hypothesis that suppressors have similar effects on all reflection-source OAEs, independent of the evoking stimulus.[90] Time-frequency analysis using continuous wavelet transforms (CWTs)[87] will be used to identify and separate short- and long-latency components of the emission. Unlike filtering performed using filter banks, CWT-based algorithms allow perfect reconstruction and reduce filtering artifacts.

To compliment and inform these experimental studies, **Aim 1b** will pursue the same issues using our time-domain model of an active, nonlinear cochlea.[91] We will test the validity of the suppression assumption computationally by simulating the experiment and using the method to map out the locations of SFOAE sources in models where the distribution of generators (e.g., roughness pattern) is known in advance. By using the model to probe the mechanisms by which suppressors modify OAEs, we aim to account for intriguing features of the data [e.g., the apparent variation with probe frequency in the magnitude of suppressor-related short-latency components (see Fig. 5)]. The methods used for the modeling work will extend those used for the preliminary results by employing our time-domain nonlinear model[91] rather than relying on the so-called "quasilinear" approximation, an approximation whose assumptions are not always satisfied and which can therefore yield misleading results.[92]

In broad outline, the SFOAE STCs of **Aim 1c** will be measured using the iso-response procedures of Charaziak et al.[36] but with two principal modifications: (i) We will construct STCs based on SFOAE residuals both before and after removing short-latency components using time-frequency filtering implemented using continuous wavelet transforms;[87] and (ii) We will measure SFOAEs using swept rather than discrete tones,[21] focusing on probe frequencies (f_p) where short-latency components have been identified in each subject (see **Fig. 5**). Together, these modifications allow us to compare STCs based on the total emission residual with those based on residuals from which short-latency components created or revealed by the suppressor have been removed. Octave-wide sweeps centered on the frequency of interest will be employed to expedite the data collection. Rather than varying the suppressor level adaptively, we will construct iso-response STCs offline from sweeps measured at suppressor levels spanning the range 20–80 dB SL in 5 dB steps. STCs at higher resolution can be obtained by interpolation. Since multiple lobes and other anomalous features are more prevalent at lower residual levels, and at suppressor frequencies greater than the probe, we will use iso-response criteria of -6 and 0 dB EPL and vary the suppressor from $0.9f_p$ to $2.1f_p$ with a resolution of 15 points/octave.

Expected results, potential problems, alternative strategies. Both our preliminary data for Aim 1a (see **Fig. 5**) and the anomalies evident in SFOAE STCs suggest that the magnitude of short-latency components created and/or unmasked by the suppressor (interference) tone will be largest at low probe frequencies (<2 kHz) and for interference tones placed about one-quarter octave or more above the probe frequency. By contrast, we expect the interference tone to suppress long-latency components of the SFOAE under all conditions. Near-probe interference tones should result in near total suppression of the SFOAE, consistent with previous results.[25] Based on preliminary modeling work, which indicates that high-frequency interference tones induce new SFOAE sources, we expect the group delays of the short-latency SFOAE components to decrease as the frequency of the interference tone increases. When necessary to improve the time-frequency resolution of the analysis, we will use

shorter, slower sweeps with finer probe and suppressor frequency resolution at frequencies where significant short-latency components appear.

We expect the modeling studies to reveal that suppressor tones can act not only as suppressors (i.e., as magnitude reducers) but also in at least two attendant but unintended ways. First, suppressors may act via cochlear nonlinearities to induce additional SFOAE sources (e.g., wave-fixed mechanical perturbations that scatter the probe traveling wave). Second, suppressors may modify responses to the probe by shifting their phases (rather than, or in addition to, reducing their amplitudes). Both hypothesized effects should be largest for moderate to high-level suppressor levels, and both can severely compromise the ability to reconstruct the distribution of SFOAE sources via vector subtraction. Although we expect the general pattern of our results to depend on qualitative features of the model—such as the phase coherence or cancellation that arises from the spatial variation of traveling-wave amplitude and phase—rather than on specific details of cochlear nonlinearities or amplification, we need to verify that our results are not somehow idiosyncratic to our particular model. We will establish the generality and potential limitations of our conclusions both by verifying our results using other models (e.g., that of Liu and Neely[93,94]) and by adopting alternate forms of the nonlinearity. To facilitate the interpretation of our numerical results, as well as to identify possible discrepancies, we will compare our results with semi-analytic expressions and/or results obtained using the quasilinear method whenever possible.

We expect our new protocol for measuring SFOAE STCs, in which suppression criteria are applied after filtering out short-latency emission components, to eliminate the anomalous features of STCs measured using conventional procedures in the same subjects. The experiments proposed here focus initially on the high-frequency flank of the STC, where confounding anomalies are most evident. However, if the new protocol seems likely to improve the reliability of STCs in individual subjects, we will extend the range of suppressor frequencies to capture the entire tip of the STC and test the method by comparing the results both to psychophysical tuning curves[36,95] and with tuning estimates obtained from SFOAE phase-gradient delays in the same subjects.[17,18]

Aim 2. Micromechanical irregularity and OAE sources

Aim 2a. MOC-efferent activity and reflection-source OAEs

Rationale. Recent studies of the effects of MOC efferent stimulation on OAEs[46,47] challenge our understanding not only of MOC efferent effects in the cochlea but also of the mechanisms of OAE generation and, more generally, the assumed relationship between OAE level changes and cochlear gain. Although activation of MOC efferents invariably appears to decrease the gain of the cochlear amplifier,[96–98] the magnitudes of corresponding reflection-source OAEs can be either reduced or enhanced over wide frequency intervals. To determine whether coherent-reflection theory can explain these seemingly contradictory results—decreased cochlear gain accompanied by increased OAE levels—we will construct and evaluate a computational model of efferent action in the cochlea in which activation of MOC efferent fibers has two principal effects: It both reduces the gain of the cochlear amplifier in the vicinity of OHCs contacted by active fibers and, by doing so in a patchy or nonuniform fashion consistent with the anatomy, modifies the spatial pattern of micromechanical irregularities by altering the spatial profile of gain along the cochlea.

Methods. Cochlear responses and OAEs will be simulated at low sound levels using an active 2D transmission-line model of the cochlea that incorporates both short- and long-wave behavior.[13] The reliability of the numerical simulations will be evaluated by comparing them to semi-analytic perturbative solutions obtained using the WKB approximation.[12,99] Model parameters will be scaled to create simulations of both the guinea-pig and human cochlea. As in the preliminary results (see **Fig. 2**), reflection-source OAEs will be produced by introducing micromechanical irregularities into the admittance of the organ of Corti. Activation of MOC efferents will be simulated by reducing the effective amplifier gain at cochlear locations corresponding to contacted OHCs. We will quantify the effects of variations in key variables, including: (i) the mean number of activated fibers; (ii) the mean number of OHCs contacted per fiber and their spatial distribution; (iii) the amplitude of the local gain reduction at each contacted OHC. We will simulate the effects of different MOC innervation profiles, including patterns that are spatially uniform, irregular or random, and quasi-realistic, the latter based on the statistics of measured anatomical distributions.[48,49] We will compare the simulated SFOAEs with the measurements of Berezina-Greene and Guinan[47] to determine whether the model can reproduce the major trends in the data, including the magnitudes and prevalence of SFOAE suppression and enhancement and the magnitude of cochlear

gain reduction, as assessed experimentally using compound-action-potential (CAP) threshold shifts.

Aim 2b. Micromechanical irregularity and distortion-source OAEs

Rationale. Preliminary data suggest that activation of MOC efferents in human subjects can significantly enhance DPOAE components with apparently "negative delay" (see time-frequency analysis in **Fig. 3**). We will use a combination of OAE measurements and computational modeling to explore the origin of these components. Using nonlinear cochlear models we will test the hypothesis that negative-delay DPOAE components can arise if activation of efferent fibers produces spatial variations in the form or strength of cochlear nonlinearity, thereby modulating the strength of OAE distortion sources irregularly with position. For example, the efferent-induced hyperpolarization and resulting elongation of OHC soma may alter the operating point of the hair bundle. We hypothesize that the putative efferent-induced mechanical irregularities also affect the generation of reflection-source OAEs. We will test this hypothesis experimentally by quantifying and comparing the effects of contralateral acoustic stimulation (CAS) on both DPOAEs and SFOAEs in the same human subjects.

Methods. We will measure distortion- and reflection-source OAEs in ∼20 normal-hearing young adults from 0.5–8 kHz using fast swept-tone paradigms now well developed in our lab.[21,100–102] DPOAEs and SFOAEs at standard primary levels and frequency ratios (i.e., $\{L_1, L_2\} = \{62, 62\}$ dB FPL, $f_2/f_1 = 1.22$ for DPOAEs and $\{L_p, L_s\} = \{37, 52\}$ dB FPL, $f_s/f_p = 1.05$ for SFOAEs) will be measured both with and without activation of MOC efferents using CAS. The spectral level of the contralateral elicitor—wideband noise, spectrally flattened to constant FPL—will be kept below the activation threshold for the middle-ear muscle reflex (MEMR), assayed using ipsilateral wideband reflectance.[103–105] Time-frequency analysis of the OAE spectra using continuous wavelet transforms[87] will be used to identify and separate short- and long-latency components of the total emission (at both positive and negative delays). The results will be used to estimate source distribution functions (i.e., the spatial pattern of irregularities contributing to the emission), using analysis methods previously described.[52] When measuring DPOAEs we need to distinguish long-latency components that arise via distortion sources from those arising as reflection-source OAEs. We will do this by selectively removing reflection-source OAEs from the total DPOAE in two independent ways and comparing the results for consistency: (i) By using a third stimulus tone ($L_3 = 52$ dB FPL) close to the distortion-product (DP) frequency ($2f_1 - f_2$) to suppress reflection-source OAEs arising near the peak of the DP traveling wave;[15,106,107] and (ii) By mathematically decomposing the results of the time-frequency (wavelet-transform) analysis into time-symmetric and time-asymmetric components.[108] Preliminary modeling results (see Background and Significance) predict that long-latency contributions to the distortion component should be nearly symmetric in time (i.e., contribute equally at positive and negative delays). Our comparisons will test these predictions.

The theoretical studies will use the cochlear models employed in Aim 2a, extended to include representations of cochlear nonlinearity as in Aim 1. As shown previously, the model reproduces the cochlear compression measured in basilar-membrane growth functions.[91] Efferent activation will be simulated as in Aim 2a and will be assumed to modify the effective operating point of the saturating nonlinearity. We hypothesize that this irregularity will produce correlated spatial modulations in the amplitudes and phases of both distortion and reflection components. As a check on the integrity of our results, time-domain solutions will be compared with solutions obtained both perturbatively (i.e., assuming the distortion components are small relative to the primary tones) and iteratively, using the quasi-linear method.[30,31,109]

Expected results, potential problems, alternative strategies. Consistent with the preliminary results, we expect that the strength of negative-delay components will vary with frequency and from subject to subject, and we will quantify correlations with other relevant metrics (audiometric and MEM thresholds, DPOAE and SFOAE levels, etc) as clues for understanding the variation across frequency and between subjects. Although the initial plan is to use standard stimulus parameters, measurements at a broader range of levels and frequency ratios will be made in a subset of subjects showing strong effects. We expect that source distribution functions inferred from the DPOAE and SFOAE measurements will be correlated, but shifted in frequency (since a place-fixed source at location x affects the distortion component when $\mathrm{CF}(x) \cong f_2$ and the reflection component when $\mathrm{CF}(x) \cong f_{\mathrm{SFOAE}}$, where CF is the local characteristic frequency). Artifactual components with apparently negative delay in the time-frequency representation can be created both by discontinuities at the low- and high-frequency ends of the measured emission spectrum and by subject and measurement noise. To avoid these

artifacts we will extend the measurements one-half octave below and above the frequency range of interest, employ spectral tapers to eliminate sharp discontinuities in the frequency domain, utilize stringent online artifact-rejection criteria, and analyze repeated measurements to guarantee that the relevant time-frequency features are robust and reproducible.

Aim 3. Micromechanics of cochlear wave amplification and OAE generation

Aim 3a. OAE generation in models with spatial feed-forward/feed-backward (FF/FB) amplification

Rationale. Our preliminary work provides the means to address the implications of spatial FF/FB amplification for OAE generation with rigorous modeling and analysis. The obvious strategy of comparing the OAEs (if any) produced by models utilizing FF/FB amplification with those produced by classical, point-impedance models fails if naively applied. The problem is that changing the underlying mechanics of the amplifier almost invariably modifies the basic macromechanical responses of the model (e.g., the magnitude and phase of BM velocity responses), and these secondary changes, although unintended, also modify the OAEs, confounding any clear interpretation of the results. (The problem is similar to that encountered in genetic experiments in which modifying or knocking out a gene, such as that for prestin, has unintended consequences that then frustrate definitive conclusions.[110]) Thus, to understand how OAE properties depend on the mechanisms of amplification, per se, one needs to control for changes in the traveling wave. Ideally, one wants to vary the unknown mechanics of the amplifier while leaving the known and measured macromechanical responses (e.g., BM velocity) unchanged. In preliminary studies, we have solved this problem and shown how to derive an FF/FB model with the same BM velocity pattern as a given classical model. The method employs an inverse method, and builds on our solution to a similar problem encountered when studying the effects of fluid dimensionality on the mechanisms of coherent reflection.[13]

Methods. Using our inverse method we will derive "response-matched" FF/FB models whose BM velocity responses are matched to those of the classical models we employed in earlier studies of coherent reflection.[13] The models will be supplemented with micromechanical irregularities ("roughness") to generate reverse traveling waves and reflection-source otoacoustic emissions.[12,81] We will determine how the amplitude and phase characteristics (e.g., phase-gradient delay) of the simulated OAEs depend on the normalized strength of the FF/FB forces and the spatial feed-forward/backward distance. By averaging the results across multiple in-silico "subjects" (i.e., different roughness patterns), we will determine statistical reliability and expected variance. We will compare the results with those obtained from classical models with the same BM responses and roughness patterns. Model responses will be solved using finite differences and methods previously described and validated.[13] We will employ both 1D and 2D models to investigate the dependence on long- and short-wave behavior and the transition between the two that occurs basal to the peak of the traveling wave.

Expected results, potential problems, alternative strategies. We expect to find that OAE properties (both amplitude and delay) depend systematically on the parameters of the FF/FB amplifier. Comparing the pattern of results to the known characteristics of OAEs will enable us to assess the contributions and possible limitations of the FF/FB mechanism and understand whether the principles of coherent reflection generalize to nonclassical forms of cochlear amplification. In its simplest form, our inverse method exploits the fact that the feed-forward/backward distances produced by the anatomical tilt are generally no more than a few hair cells in extent (e.g., 20–30 μm) and are therefore small compared to the wavelength of the traveling wave. To extend and check our results, we can relax this approximation. Should we encounter any problems, we will adopt an alternative method for solving the inverse problem in non-classical models developed by de Boer.[61] As always, we will attempt to compare our numerical results with analytic approximations whenever possible. Obtaining analytic results for FF/FB models will require care, since many familiar tools (e.g., the WKB approximation) implicitly assume isotropic wave propagation.

Aim 3b. Organ of Corti vibrational modes and OAE generation

Rationale. The unexpected vibrational modes now evident in organ-of-Corti micromechanics may have important implications for current understanding of OAE generation. In Aim 3b we (i) obtain mechanical data from intact cochleae; (ii) analyze it using inverse methods applied in dual-mode cochlear models that include representations of both BM and RL motion to derive effective impedances and wavenumbers; and (iii) use the

results to simulate the generation of reflection-source OAEs. We will determine how the results depend on the assumed coupling between BM and RL motion and the cochlear fluids and test the recent hypothesis that OAEs are better correlated to the motion of the RL.[10] (For comparison, standard cochlear models couple the fluid to the motion of the BM.) Model assumptions will be tested against independent measures of this coupling by comparing the simulated OAEs with emissions recorded concurrently with the mechanical measurements.

Methods. All measurements will be made in wild-type adult CBA mice using procedures well developed in the Oghalai lab,[7,21,111] whose experience suggests that high-quality data from ~20 mice will suffice for the inverse analysis and comparisons proposed here. In the OCT measurements, the apical turn of the cochlea (CF ~ 10 kHz) is imaged through the bone. High-reflectivity points corresponding to structures of interest are identified from depth scans (A-scans) targeting the RL and BM, which are identified in cross-sectional images (OCT B-scans) of the partition (**Fig. 6A**). Because vibratory data are derived from the phase of the interference signal, the motion resolution of the system is much better than its image resolution.[112,113] Vibrometry and OAE data will be collected simultaneously in response to three principal sets of stimuli: (i) swept tones at a variety of fixed intensities to measure BM and RL describing functions (20–80 dB SPL) and SFOAEs; (ii) pseudo-random noise at corresponding spectral levels to measure BM and RL transfer functions in response to linearizing stimuli appropriate for inverse analysis;[86,114–117] and (iii) pairs of tones (f_1,f_2) swept at fixed ratio (f_2/f_1) and level difference ($L_1 - L_2$) to monitor cochlear health using DPOAEs.[101] Our preliminary data demonstrate the ability of OCT vibrometry, usually applied to sinusoidal stimuli (e.g., tones or tone complexes), to measure BM and RL responses to wideband stimuli, such as clicks and noise (see **Fig. 6B,C**).

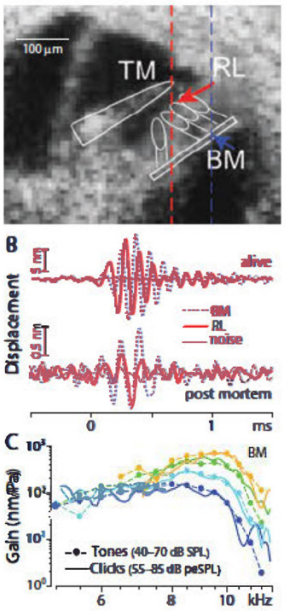

Figure 6. OCT image of the mouse cochlear partition obtained in the Oghalai lab. Dashed lines mark the optical axes for the RL (red) and BM (blue) locations. Panel B shows vibratory responses to wideband acoustic clicks recorded from the BM and RL. Panel C compares BM gain functions measured using clicks and tones at four stimulus levels.

The vibratory data will first be analyzed to test the analyticity constraints recently hypothesized to be universal features of mammalian cochlear responses.[118–120] The principal modeling studies will employ inverse methods adapted to the dual-mode modeling framework recently developed by Liu and Neely,[31,93,94,121] which provides convenient representations of both BM and RL motion and their coupling to cochlear macromechanics (e.g., fluid motion). In this model, the relative motions of the BM and RL define the transfer function H_{OHC}, which can be determined from the measurements. Simple modifications to the model equations allow fluid motion to couple to either the BM or RL.[93,121] BM motion is determined by H_{OHC} and an admittance Y_{BM}, whose empirical form can be determined using equations that depend on the assumed coupling. Reflection-source OAEs will be simulated by adding micromechanical irregularity to the impedances representing the BM and/or RL.

Expected results, potential problems, alternative strategies. Recent studies have shown that non-fluid coupling along the organ of Corti (e.g., via the tectorial membrane[5]) plays an important role in cochlear mechanics, and perhaps also in OAE generation. Although our long-term goal is to put everything together by studying and incorporating these additional modes of longitudinal coupling, our strategy here is to approach the problem systematically. We therefore begin by focusing on what we tentatively assume to be the dominant interaction: coupling between vibrational modes within a given radial cross-section. We expect direct mechanical coupling along the organ of Corti or tectorial membrane to be less important because the wavelength of the traveling wave is long compared to the distance between coupled elements and partition displacements and their longitudinal derivatives are small at low sound levels. More generally, the models we employ involve significant but strategic simplifications—necessarily so with respect to the living cochlea but also compared to models that provide more realistic representations of the anatomy and material properties.[58,78,79,122,123] These different modeling approaches are complementary and mutually informative; indeed, as borne out by the history of the field, both are necessary for understanding complex systems such as the cochlea.

Sex as a biological variable. We have no reason to expect significant sex differences in the basic mechanisms of cochlear function or OAE generation explored here. Nevertheless, for both the human and the mouse experiments we will strive for gender balance in the subject pool and analyze the data for possible correlations.

Progress Report

This report covers the period from 1 March 2013 to 1 June 2018. Progress on the prior Specific Aims produced 27 original publications (22 journal articles and 5 peer-reviewed conference papers) and three reviews/book chapters, for a total of 30 publications. An additional 14 published abstracts present work currently in preparation or submitted for publication. The last competitive renewal included three Aims with hypotheses targeting relationships between OAEs and the form and time course of the cochlear nonlinearities underlying compression and suppression (Aim 1), the mechanisms of cochlear wave amplification and reflection (Aim 2), and apical/basal differences in cochlear mechanics (Aim 3). Space constraints allow only a brief summary of major highlights. **Pub** numbers refer to the list **Publications Supported by This R01**.

Progress on the Aims includes significant advances in the methodology for measuring and extracting information from OAEs. These advances are both central to the experimental studies of Aims 1 and 3 and of broad benefit to the field. For example, we developed and characterized a new method for measuring SFOAEs using swept tones [**Pubs 1,22**]. The technique yields much higher frequency resolution and roughly an order of magnitude improvement in measurement efficiency compared to conventional, discrete-tone paradigms. The new method greatly enhances the utility of SFOAEs in laboratory and field studies; when implemented in commercial instruments, the method will enable clinical applications to exploit the advantages of SFOAE-based hearing assessment. In addition to developing the power of swept-tone SFOAEs, we determined optimal measurement and analysis protocols for recording swept-tone DPOAEs [**Pub 9**]. We also explained—and developed methods to circumvent—the previously confounding artifact that OAEs appear to depend on the rate and direction of the frequency sweep [**Pub 14**]. Finally, we developed and validated a method—emitted pressure level (EPL)—that resolves a long-standing difficulty: The reproducibility and diagnostic power of OAE measurements can be seriously compromised by the acoustics of the ear canal and transducer. The new procedure yields OAE measurements largely free of contamination by ear-canal acoustics, including biases introduced by variations in probe insertion depth [**Pubs 15,42**]. The use of emitted pressure provides a powerful way to reduce the variability of OAE measurements and thereby improve their ability to detect and differentiate cochlear changes.

Work on all three Aims produced important new findings. Studies of two-tone interactions and the round-window cochlear microphonic (CM) [**Pubs 17,23,40**] lead to a promising new diagnostic tool. Using a combination of models and measurements, we showed that the "residual CM" (rCM)—the difference between the CM measured with and without a suppressor tone—originate near the cochlear place tuned to the suppressor frequency. Thus, the rCM can serve as a sensitive indicator of OHC-dependent nonlinearity and cochlear gain, overcoming the poor place-specificity of conventional CM measurements. Our studies of OAEs and their relationship to the active mechanisms responsible for shaping the cochlea's mechanical response to sound focused on phenomena unexplained by most cochlear models. We showed that the complex temporal modulation apparent in the envelope of BM responses to acoustic clicks can be well explained by a process of iterated internal reflection within the cochlea [**Pub 10**]. The same mechanisms of wave reflection and interference underlie our unexpected prediction that the mammalian cochlear frequency-position map—usually regarded as smooth and continuous—actually manifests an emergent staircase-like structure comprising plateaus of nearly constant characteristic frequency (CF) separated by abrupt discontinuities [**Pub 7**]. Significantly, a similar stepwise tonotopy occurs along the main axis of the central nucleus of the inferior colliculus (CNIC). As in the CNIC, the step height of the cochlear map is approximately equal to the bandwidth of the auditory filter (critical band). To study the temporal dynamics of nonlinear suppression and compression in the cochlea, we have combined click-evoked OAEs (CEOAEs) with measurements and models of BM motion [**Pubs 19,26,35,36,43,46**]. Our results to date reveal an intriguing dichotomy whose implications we are still pursuing: Although cochlear responses to narrowband stimuli (beating tones) appear to require only instantaneous nonlinear damping, responses to broadband stimuli (clicks) suggest the existence of adaptive (history-dependent) cochlear nonlinearities such as automatic gain control. Finally, we characterized differences between the base and apex of the cochlea in human subjects using high-resolution maps of OAE phase extending 1–2 octaves lower in frequency than previous reports [**Pubs 24,44**]. The measurements corroborate the break in scaling near the midpoint of the human cochlea but also provide tantalizing evidence for the emergence of a second scaling region about two octaves closer to the apex.

Publications Supported By This R01

All papers are freely available online at the Auditory Physics Group website (apg.mechanicsofhearing.org).

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31. Alkhairy SA (2016) Development of cochlear models with high computational efficiency by using spatial and parametric transformations. MS Dissertation, Department of Electrical Engineering and Computer Science, Massachusetts Institute of Technology
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39. Berezina-Greene M, **Shera CA** (2016) Physiologically based simulation of MOC effects on SFOAEs. Assoc Res Otolaryngol Abs 39:PS866

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41. Bharadwaj H, Varghese L, Mehraei G, **Shera CA**, Shinn-Cunningham BG (2016) Evidence of auditory-nerve contribution to individual differences in suprathreshold brainstem temporal coding. Assoc Res Otolaryngol Abs 39:PS305
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43. Charaziak KK, Dong W, Altoè A, **Shera CA** (2018) Temporal interactions in basilar-membrane and otoacoustic-emission responses to pairs of clicks Assoc Res Otolaryngol Abs 41:PS465
44. Christensen AT, Abdala C, **Shera CA** (2018) Phase characteristics of low-frequency distortion emissions in humans. Assoc Res Otolaryngol Abs 41:PS760
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PHS Human Subjects and Clinical Trials Information

OMB Number: 0925-0001 and 0925-0002

Expiration Date: 03/31/2020

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	

Human Subject Studies

Study#	Study Title	Clinical Trial?
1	Understanding Otoacoustic Emissions	No

Section 1 - Basic Information (Study 1)

OMB Number: 0925-0001 and 0925-0002

Expiration Date: 03/31/2020

1.1. Study Title *

Understanding Otoacoustic Emissions

1.2. Is this study exempt from Federal Regulations * ❍ Yes ● No

1.3. Exemption Number ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8

1.4. Clinical Trial Questionnaire *

1.4.a. Does the study involve human participants?	● Yes	❍ No
1.4.b. Are the participants prospectively assigned to an intervention?	❍ Yes	● No
1.4.c. Is the study designed to evaluate the effect of the intervention on the participants?	❍ Yes	● No
1.4.d. Is the effect that will be evaluated a health-related biomedical or behavioral outcome?	❍ Yes	● No

1.5. Provide the ClinicalTrials.gov Identifier (e.g. NCT87654321) for this trial, if applicable

Section 2 - Study Population Characteristics (Study 1)

2.1. Conditions or Focus of Study

2.2. Eligibility Criteria

2.3. Age Limits	Min Age: 18 Years	Max Age: N/A (No limit)
2.4. Inclusion of Women, Minorities, and Children	Shera_Inclusion_of_Women__Minotities_and_Children1012773848.pdf	
2.5. Recruitment and Retention Plan	Shera_Recruitment_Retention1012773858.pdf	
2.6. Recruitment Status	Recruiting	
2.7. Study Timeline		
2.8. Enrollment of First Subject	04/01/2019	Anticipated

Inclusion of Women, Minorities, and Children

We will use adults age 18 and older. The reason for excluding children under 18 is that our experiments require that subjects sit quietly and nearly motionless while the acoustic measurements are being made; too much noise and/or movement by the subject invalidates the measurement. Even certain adults have a difficult time remaining sufficiently still and relaxed.

Targeted/planned distribution of subjects: Our targeted mix with regard to gender, ethnic, and racial categories is based on the representation of these categories in the [redacted] area. Our Targeted Enrollment Table reflects the composition of the [redacted] area based on year 2010/2015 census statistics.

Rationale for gender and racial/ethnic targets: Women have larger otoacoustic emissions than men and are therefore preferred on technical grounds. Despite this preference for women, we will strive to achieve a representative mix of genders.

There is no known reason to expect differences in our results due to ethnic or racial categories. We will strive to achieve a representative mix with regard to ethnic and racial categories based on the representation of these categories [redacted]

Rationale for exclusions: We propose no exclusions.

Proposed outreach programs: We generally have no trouble obtaining a good sampling of minorities. If we fall short in achieving representative samples in an ethnic or gender category, we will seek help in recruiting from the [redacted] offices of minority affairs and recruit more subjects from the [redacted] staff and hospital visitors.

Inclusion Criteria: To provide useful data, our subjects must have normal hearing, good otoacoustic emissions, and be able to sit quietly for the duration of the measurements while following simple directions (e.g., responding with appropriate button presses when sounds are presented). Criteria such as good otoacoustic emissions can only be assessed after the subject has consented and initial screening measurements performed. Subjects in this category would be officially enrolled in the study but the otoacoustic data collected from them would be minimal and would not be used in subsequent analyses.

Most adults below the age of 40 or so fit our criteria. Thus, there is a very large population from which we can draw for these tests. Normal hearing adult subjects will be recruited from [redacted] student body and from nearby universities [redacted] Recruitment is done by personal contacts, email, and internet (e.g., via the lab website). Research staff will also invite participation through classroom visits.

When not all tests can be completed within the allotted time (typically 1–2 hours), or when additional tests seem warranted, we will ask subjects at the conclusion of a session whether they are available for additional measurement sessions. If we are unable to arrange additional sessions in person, we may contact a subject via email to ask if they are interested in volunteering for additional measurements.

Exclusion Criteria: We exclude non-adult subjects or subjects with hearing loss. Subjects with hearing loss usually have weak or unmeasurable OAEs. Subjects younger than 18 years of age often have difficulty sitting quietly during the session and are more difficult to measure. Although not technically excluded, subjects over ~40 often have otoacoustic emissions that are too weak and they are therefore less desirable for our study.

Withdrawal Criteria: Participants are free to withdraw from the study at any time. Most often, sufficient data are obtained in a single measurement session. When additional data are desired, subjects are invited to participate in additional sessions. Subjects who do not meet the criteria for providing useful data (e.g., good otoacoustic emissions, ability to sit still) are not invited back.

Inclusion Enrollment Reports

IER ID#	Enrollment Location Type	Enrollment Location
Study 1, IER 1	Domestic	University of Southern California

Inclusion Enrollment Report 1

Using an Existing Dataset or Resource* : ● Yes ❍ No

Enrollment Location Type* : ● Domestic ❍ Foreign

Enrollment Country(ies): USA: UNITED STATES

Enrollment Location(s): University of Southern California

Comments: As of 1 June 2018

Planned

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	0	0	0	0
White	0	0	0	0	0
More than One Race	0	0	0	0	0
Total	0	0	0	0	0

Cumulative (Actual)

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/ Alaska Native	0	0	0	0	0	0	0	0	0	0
Asian	8	8	0	0	0	0	0	0	0	16
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	0
Black or African American	5	0	0	0	0	0	0	0	0	5
White	13	8	2	4	1	0	0	0	0	28
More than One Race	3	0	0	0	0	0	0	0	0	3
Unknown or Not Reported	2	0	0	4	3	0	0	0	1	10
Total	31	16	2	8	4	0	0	0	1	62

Section 3 - Protection and Monitoring Plans (Study 1)

3.1. Protection of Human Subjects	Shera_Human_Subjects1012773846.pdf
3.2. Is this a multi-site study that will use the same protocol to conduct non-exempt human subjects research at more than one domestic site?	❍ Yes ● No ❍ N/A
If yes, describe the single IRB plan	
3.3. Data and Safety Monitoring Plan	Shera_Data_Safety_and_Monitoring1012773906.pdf
3.4. Will a Data and Safety Monitoring Board be appointed for this study?	❍ Yes ● No
3.5. Overall structure of the study team	

Protections for Human Subjects

Risks to Human Subjects

Human subjects involvement and characteristics: Human subjects will be involved in Aims 1 and 2. All human subjects research will be performed in the Auditory Research Center on the [redacted] medical campus and/or on the adjacent [redacted] campus; there are no collaborating sites. We will use adult subjects in good general health with normal hearing. The work involves no special classes of subjects.

We have no reason to expect differences in our results due to ethnic or racial categories, but women have larger otoacoustic emissions than men and are therefore preferred on technical grounds. Despite this preference, we will strive to achieve a representative mix of genders and ethnic backgrounds. Because of the general decline in hearing with age, and consequent difficulty in recording OAEs, we will prefer young adults in their 20's and 30's. However, since we wish to have a representative population, older subjects with measurable OAEs will also be included.

We expect to use about 75–100 subjects total over the five years of the proposed work. This number is based on past experience and a basic comparison unit of 20–25 subjects for each experiment. Additional subjects (10–20) will be used to develop, test, and revise experimental paradigms. Most subjects participate in multiple measurement sessions. The majority of our subjects are students whose availability varies from one semester to the next. Although some subjects participate over several semesters, many cannot and we need to continually recruit new subjects.

Our study involves only adult subjects with normal hearing thresholds (i.e., thresholds within 20 dB of normal and with no other known hearing pathology). Subjects with hearing thresholds outside of this range, or who do not have measurable OAEs, will be excluded. No other specific subpopulations will be excluded.

Sources of materials: We will not obtain physical specimens from any subject. Neither will we obtain any part of their medical record. Subjects will be asked to fill out a questionnaire regarding (i) any past or present hearing issues; (ii) their handedness; and (iii) their age, ethnicity, and other information per NIH guidelines.

Data collection involves measuring the subject's audiogram to determine hearing status and using insert earphones to record the subject's middle-ear reflectance and otoacoustic emissions (OAEs). The data are coded and subsequently identified only by subject number. The only connection between a subject's name, birth date, or other identifying information is via a secured written file. Access to this file is available only to the PI and to any co-investigator (e.g., graduate student, postdoctoral fellow) who is actively working on the project.

Potential risks: There are essentially no risks to the proposed measurements, all of which are very similar to standard clinical procedures. The proposed measurements involve listening to sounds presented by earphones held in the ear canal by foam or rubber plugs. The sounds presented will all be of low to moderate intensity, well within the guidelines of the Occupational Safety and Health Administration for acoustic stimuli. Subjects are reimbursed for their time, parking, and/or other transportation fares for their participation and incur no financial or legal risks.

Adequacy of Protection Against Risks

Recruitment and informed consent: Subjects will normally be recruited from personal contacts —principally employees of the [redacted] School of Medicine and students [redacted] Informed consent is obtained by the experimenter running the tests (i.e., by the PI, Research Associate, or Postdoctoral Fellows) when the subject comes to the laboratory. After prospective subjects read our informed consent form, we explain to them what the research is all about and what the measurements are like. We show them the sound booth and the chair that they will sit in, as well as the foam plug and inset earphone that will be put in their ear canal. We answer any questions they have. They then sign the informed consent form, the HIPPA form, the receipt of privacy notice, and they fill out our

questionnaire. No wavers of any elements of the informed consent will be sought.

Protection against risks: There are essentially no risks to our procedures and no special procedures are needed to prevent risk. The measurements employ only low to moderate sound intensities well within the range of sounds encountered in daily life and/or during clinical hearing tests. The equipment that drives the earphones has been electronically limited so that the highest possible output is 90–100 dB SPL. Subject identity will be coded by giving each subject a number and having all records from a subject stored and referred to only by the subject number. These measures should be adequate to insure essentially zero risk for hearing damage and to guarantee subject confidentiality. None of the proposed research involves vulnerable populations.

It is extremely unlikely that any harmful effects will result from this study. However, each subject will be given a copy of the consent form, which provides telephone numbers of the investigators and contact information for the local IRB. This information will allow subjects to report anything they feel has been a harmful effect of participating in the study. Should any substantial claim arise, the relevant [redacted] committees will be informed.

Potential Benefits of the Proposed Research to Human Subjects and Others

Potential benefits: Although we anticipate no particular benefit to individual subjects, we expect both scientific and clinical benefits to society that accrue from providing a better understanding of OAEs and cochlear function. In addition to helping develop improved clinical hearing tests for the future, our work should aid in understanding and interpreting current OAE tests. Improved understanding of normal cochlear function should also benefit the design of preprocessors for speech-recognition systems and hearing aids.

Risks in relation to benefits: The risks to subjects are minimal, and are certainly reasonable relative to the expected scientific and clinical value to society.

Data Safety and Monitoring

This study is not a clinical trial and therefore no formal data safety and monitoring plan is required. Although most of the issues addressed by such a plan are not pertinent to the application, a few are relevant to all studies involving human subjects.

Data collection and management: Obtaining informed consent and all data collection are conducted in the Auditory Physics Group's sound-attenuated booths at the Auditory Research Center and/or [redacted]Medical Center. The data collected are in the form of acoustic measurements from the ear canal of each subject. Data are coded with a combination of letters and numbers unrelated to the subject's name or other identifying information, such as the date the subject came in for testing. Once data are collected, they are no longer referred to or linked with any Private Health Information (PHI), such as the informed consent forms. Data are analyzed and managed using databases on password-protected computers and by written notation in lab notebooks. These notebooks and databases do not contain any patient identifiers, only the de-identified subject label.

Data storage: Data are stored on password-protected computers, in lab notebooks, and on paper hard copies. Electronic de-identified data are transferred securely (e.g., via secure wireless connections or via password-protected portable flash drives) to a separate password-protected computer for analysis. Lab notebooks and paper hard copy files of the data are stored in a locked filing cabinet in the office of the Principal Investigator or study personnel. The subject key linking a subject's PHI (informed consent) and the coded subject number is kept separate from the data in the locked files of the Principal Investigator (PI). Only the PI and study co-investigators have access to these files.

Data monitoring: The PI and study co-investigators monitor the study for any safety concerns related to participants. The investigators regularly review overall assessment of data collection, the number of subjects tested, the number of sessions resulting in successful data collection, any issues with data collection, any problems with the equipment or software, and any comments or concerns voiced by study participants. Weekly lab meetings are held between all those involved in the project. The PI and co-investigators are responsible for reporting any adverse events to the IRB.

Section 4 - Protocol Synopsis (Study 1)

4.1. Brief Summary

4.2. Study Design

4.2.a. Narrative Study Description

4.2.b. Primary Purpose

4.2.c. Interventions

Type	Name	Description

4.2.d. Study Phase

Is this an NIH-defined Phase III Clinical Trial? ❍ Yes ❍ No

4.2.e. Intervention Model

4.2.f. Masking ❍ Yes ❍ No

❑ Participant ❑ Care Provider ❑ Investigator ❑ Outcomes Assessor

4.2.g. Allocation

4.3. Outcome Measures

Type	Name	Time Frame	Brief Description

4.4. Statistical Design and Power

4.5. Subject Participation Duration

4.6. Will the study use an FDA-regulated intervention? ❍ Yes ❍ No

4.6.a. If yes, describe the availability of Investigational Product (IP) and Investigational New Drug (IND)/ Investigational Device Exemption (IDE) status

4.7. Dissemination Plan

Delayed Onset Studies

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

Vertebrate Animals

Proposed use of animals: We will use mice to perform acute experiments for the research proposed in Aim 3. Most mice to be studied will be adults, ranging in age from (P28) through three months of age. We anticipate the use of ~30 mice total for this research.

Justification: Animals are needed for these experiments because we seek basic knowledge that can only be obtained from a mammalian cochlea that is working normally and because we need to do invasive procedures (e.g., measuring the motions of the organ of Corti). Although we currently lack the basic knowledge necessary to construct comprehensive and realistic computer models of the auditory periphery, one of the long-term goals of our work is to make the measurements necessary to construct and test such a model. In addition, our work has a strong theoretical and modeling component that sharpens the experiments and helps reduce the number of animals required. There is ample evidence in the scientific literature demonstrating that mammalian cochleae cannot be maintained in good physiological condition using in vitro or ex vivo techniques. Cochlear amplification, which is characteristic of physiologically normal cochleae, has never been observed in vitro, for example. Since all of the main objectives in this proposal depend on the presence of cochlear amplification (i.e., of normal hearing), the only way to achieve the objectives is to perform experiments on living animals. In order to ensure that the answers obtained will be of direct relevance to human hearing, the animals have to be mammals. Because there is very little evidence that anesthesia has any direct effects on the cochlea, the experimental animals do not have to be either awake or behaving in order for us to study the processes of relevance to this project. This point is immensely fortuitous, as the only way to expose the cochlea for experimental studies without pain is to use surgical levels of anesthesia. All of the experiments to be performed in this project are to performed under deep surgical anesthesia, and none of them involve recovery from this anesthesia. We are using mice because their cochleae and hair cells use mechanisms that are similar to those found in humans. Thus, the results of this research will have general applicability to other mammalian species, including humans. In addition, mice offer the flexibility of using genetically identical as well as transgenic animals.

We expect that roughly 75–90% of our experiments will involve animals with good hearing and yield data suitable for use in publications. (Poor hearing results mostly from surgical difficulties, especially cochlear damage incurred during surgery.) Animals with poor hearing are used for developing experimental techniques and paradigms. High quality data from 20 mice should prove sufficient to test the hypotheses set out elsewhere. Our hypotheses are not statistical in nature (e.g., we are not looking for differences between groups of animals) and do not require data sets from many animals. Thus, the number of animals to be used is based not on statistical criteria but on our estimate of the number of good experiments needed to establish the reliability and reproducibility of our findings. In addition, we sometimes have unexpected loss of animals during anesthesia or when housed in the animal facility. We have supplemented our estimates to account for these issues.

Veterinary care: Animals are purchased and housed until the day of the experiment by the [redacted] Center for Comparative Medicine. A mouse facility is located in the basement of our research building. The animal services facilities are accredited by the American Association for Accreditation of Animal Laboratory Care (AAALAC). The facilities comply with Federal Law (89-544, 91-579) and meet NIH guidelines for the humane and appropriate care of laboratory animals.

Anesthesia and analgesia: All experiments are acute and the animal is kept fully anesthetized throughout the experiment. This regimen will include an IP injection of ketamine hydrochloride (80–100 mg/kg) and xylazine hydrochloride (5–10 mg/kg). No invasive procedures will be done until surgical anesthesia is reached. The depth of anesthesia will be assessed at 15 minute intervals with a paw pinch test. Supplemental doses of anesthetic will be administered at 1/4 the induction dose to maintain areflexia. The animal's body temperature will be maintained at 38–39°C using a rectal probe and an electric heating pad. Mice undergoing invasive surgical procedures will be euthanized following the procedure as described below.

Euthanasia: At the end of an experiment, animals are killed humanely, without recovery from anesthesia, by cervical dislocation after the mouse has been anesthetized by ketamine/zylazine as described above. This method is painless, easy to perform, and IACUC approved. It is consistent with the recommendations of the Panel on Euthanasia of the American Veterinary Medical Association.

Select Agents

Not applicable to this application.

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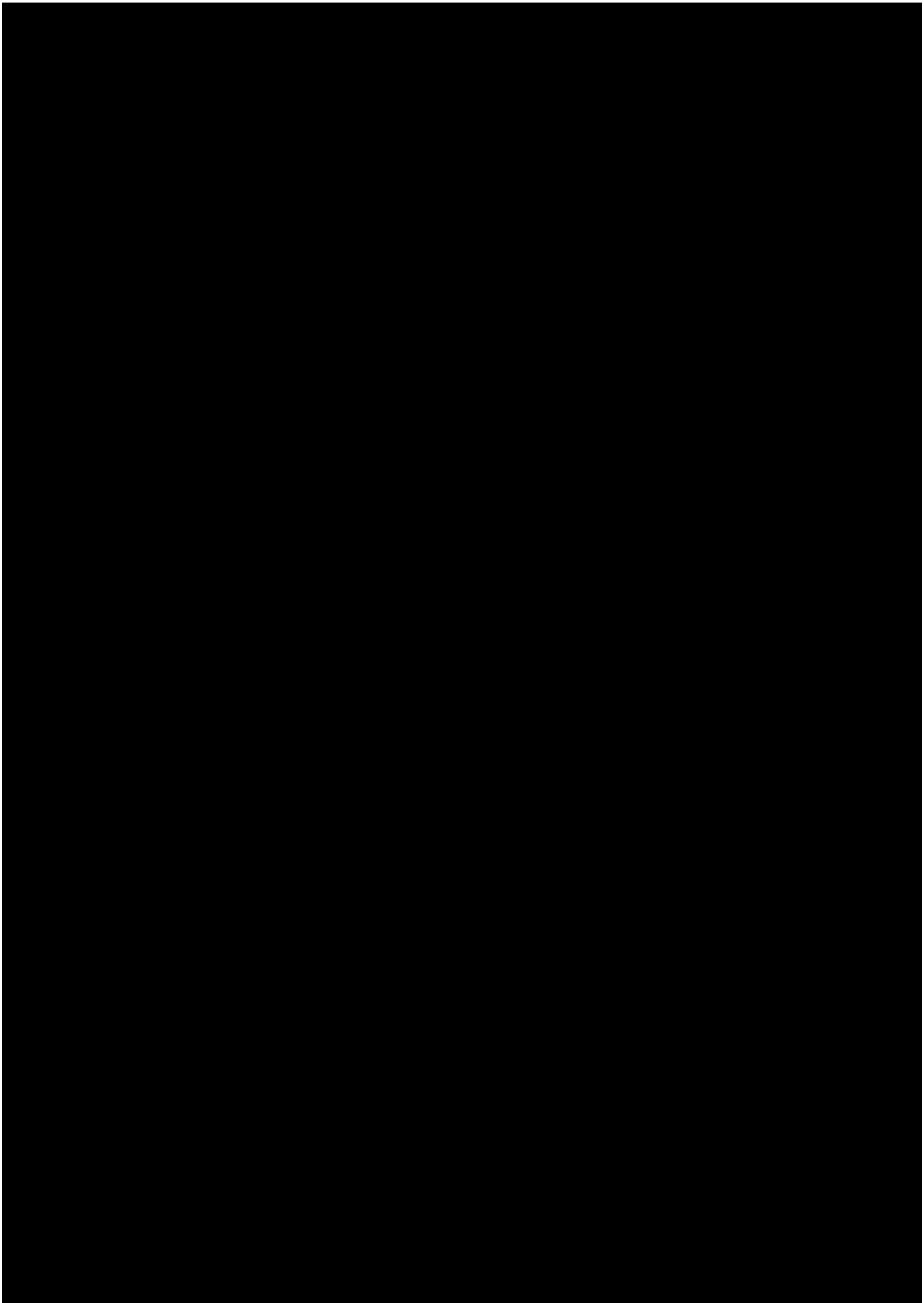

Resource Sharing

We will share the results of our work with the research community through peer-reviewed publications (approximately 3/yr) and presentations at international conferences, such as the meetings of the Association for Research in Otolaryngology, the Acoustical Society of America, and the Mechanics of Hearing Workshops (2/yr). Should journal space constraints preclude full descriptions of the experimental methods, the data analysis procedures, and/or the models and their parameters, we will make the necessary details and the corresponding computer software freely available on the lab website (apg.mechanicsofhearing.org) and/or via web-based software sharing and development platforms, such at GitHub. Data collected during the course of this project, de-identified to ensure the privacy of study participants, will also be made available (e.g., via the Auditory Physics Group Dataverse at the Harvard Dataverse Project).

Authentication of Key Biological and/or Chemical Resources

Mice: This study involves the use of wild-type CBA but neither transgenic nor mutant mice. Animal husbandry adheres to USC IACUC policy. Breeding takes place within the mouse facility by trained personnel, and records of each mating are kept so that mouse lines can be accurately maintained. Although not relevant here, transgenic lines are genotyped by qPCR according to standard procedures to assure integrity of the transgenic strain.