AWARD NUMBER: W81XWH-18-2-0033

TITLE: Objective Assessment of Auditory Pathway Integrity and Functional Hearing Abilities

PRINCIPAL INVESTIGATOR: Kenneth W. Grant, PhD

CONTRACTING ORGANIZATION: The Geneva Foundation
Tacoma, WA 98402

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

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Objective Assessment of Auditory Pathway Integrity and Functional Hearing Abilities

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Walter Reed National Military
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8901 Wisconsin Ave
Bethesda, MD 20889-0001

8. PERFORMING ORGANIZATION REPORT

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U.S. Army Medical Research and Materiel Command
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13. SUPPLEMENTARY NOTES

14. ABSTRACT
In preparation for imminent hair cell regeneration clinical trials, it is essential to develop a systematic approach to assess the degree of functional hearing restoration as the regeneration of hair cells, the reintegration of these cells and their associated neural pathways within the auditory system, and the reorganization of the auditory cortex to newly restored sound inputs progresses over time. Therefore, the purpose of developing a functional assessment battery is to provide multiple opportunities to demonstrate success, from early physical reintegration of the cochlea through the thalamus-cortical pathway (such as tests of outer and inner hair cell, brainstem, and efferent system activity), to simple and more complex sound discrimination crucial for understanding speech in noisy environments. To demonstrate the utility of this functional assessment battery, listeners with a wide range of hearing loss from normal hearing to moderate-to-severe hearing loss will evaluated to establish expected values for different degrees of hearing damage. To validate the repeatability of the functional assessment battery, a subset of listeners with varying degrees of hearing loss will be tested on multiple occasions. Finally, the extent to which simple and complex pre-attentive discrimination abilities, as well as cochlear reintegration measures, can predict complex speech in noise performance will be evaluated.

15. SUBJECT TERMS

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

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

The U.S. involvement in Iraq and Afghanistan has resulted in unprecedented amounts of trauma to the auditory system. This damage may manifest itself in patients complaining of difficulty understanding speech in complex backgrounds while at the same time presenting with normal to near-normal audiometric thresholds. Standard clinical audiometric tests fail to properly diagnose the true extent of hearing damage, and current rehabilitation strategies may not restore hearing to a functioning status appropriate for military readiness. To address this problem, biotechnology companies are working on techniques to restore hearing through regeneration of cochlear hair cells. This research project seeks to develop and validate an objective battery of tests to track the various stages of reintegration and reorganization necessary to restore hearing to a functional state appropriate for active-duty service.

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

Hearing loss, hearing restoration, electroencephalography

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

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

Aim 1: Identify objective pre-attentive and unbiased measures that differentiate between normal hearing systems and those with auditory dysfunction and establish expected values of those measures for varying degrees of hearing loss. (Months 1-18)

- **Major Task 1.1:** Finalize all hires (completed 12/27/2018). Replace Dr. Kimberly Jenkins (completed 08/12/2019). Obtain IRB approval (completed 10/14/2018). Program and pilot all test measures. (90% complete)
- **Major Task 1.2:** Administer the proposed test battery to the three hearing groups to compare results that likely represent stages of incremental improvement during hearing restoration. (not yet initiated)

Aim 2: Assess differences between individual's objective test measures between sessions to determine reliability of the test measure. (10% complete via pilot testing)

- **Major Task 2.1:** Re-administer the proposed test battery to a subset of participants from the three hearing groups at multiple time periods to determine within-subject differences. (not yet initiated)

Aim 3: Evaluate the ability to predict functional measures of speech in noise performance from objective measures of the physical integrity of the auditory system. (ongoing)

- **Major Task 3:1** Determine the minimum number of tests necessary to provide adequate information about the comprehensive functionality of the entire auditory pathway for clinical feasibility. (ongoing)

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

Most of the computer programming and initial pilot testing has been completed. Based on the results of these pilot tests, it was discovered that the equipment used for obtaining middle ear reflexes is insufficient for our purposes. In order to elicit a reflex in moderate to severe hearing-impaired individuals, elicitor levels required (> 110 dB) cannot be achieved with the current clinical equipment and "no response" became the most frequent measure. To overcome this limitation, we have made arrangements to acquire (on loan) an ER10X system with a broadband probe for measuring the middle-ear-muscle reflex (MEMR). The ER10X will come from Dartmouth College and will be available for our use through a CRADA between the Geneva Foundation and Walter Reed. Dr. Kimberly Jenkins has decided to leave the project and has taken a full-time position in our audiology clinic. We have hired a replacement, Dr. Rebecca Lewis, who will be joining our team on August 12, 2019. At this early stage of development, no data are yet available. With Dr. Jenkins now in the Audiology Clinic, we feel that our access to potential research subjects will increase. We anticipate start of data collection in September, 2019.

The CRADA between Geneva and Walter Reed was established in January 2019. IRB approval was obtained in October 14, 2018. HRPO approval was obtained on January 24th, 2019.

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

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

Nothing to Report

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

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

Nothing to Report

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

During the next reporting period all test battery measures will be programmed and finalized. New equipment for measuring MEMR will be in place and calibrated. The recruitment and enrollment of participants will begin. Continuing review will be submitted to WR and HRPO.

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

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

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

Nothing to Report

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

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

Nothing to Report

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

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

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

Nothing to Report

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

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

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

Nothing to Report

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

Nothing to Report

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

Pilot testing to determine the most robust EEG measures continues to go slow due to the need for additional programming. Dr. Presacco left the project for personal reasons just shy of completing all programming. Dr. Bressler will complete programming in August, 2019. Additionally, the purchase of a wideband instrument for the acoustic reflex test is needed. We have secured an Etymotic ER10X wideband immittance probe which will be loaned to us from Dartmouth College.

Dr. Jenkins has begun a new position as a clinical audiologist in the Walter Reed National Military Medical Center Audiology Department. Dr. Lewis, our new Research Audiologist joined the team on August 12th and will be in charge of scheduling and running the study. Dr. Myers continues to handle all regulatory matters and will help with subject recruitment, data analysis and preparation of manuscripts.

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

Personnel turnover and delays in acquiring equipment have contributed to slower expenditures than originally predicted.

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

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

Significant changes in use or care of human subjects

Nothing to Report

Significant changes in use or care of vertebrate animals

Nothing to Report

Significant changes in use of biohazards and/or select agents

Nothing to Report

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

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

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

Nothing to Report

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

Nothing to Report

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

Nothing to Report

-

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

Nothing to Report

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

Nothing to Report

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

Nothing to Report

- **Other Products**

  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

  - *data or databases;*
  - *physical collections;*
  - *audio or video products;*
  - *software;*
  - *models;*
  - *educational aids or curricula;*
  - *instruments or equipment;*
  - *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
  - *clinical interventions;*
  - *new business creation; and*
  - *other.*

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

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

Example:

Name:	*Mary Smith*
Project Role:	*Graduate Student*
Researcher Identifier (e.g. ORCID ID):	*1234567*
Nearest person month worked:	*5*
Contribution to Project:	*Ms. Smith has performed work in the area of combined error-control and constrained coding.*
Funding Support:	*The Ford Foundation (Complete only if the funding support is provided from other than this award.)*

Name:	Kenneth Grant
Project Role:	Principle Investigator
Researcher Identifier	N/A
Nearest person month worked:	3
Contribution to Project:	Dr. Grant has drafted and submitted the necessary regulatory paperwork and has assisted in developing the proposed test battery.
Name:	Kimberly Jenkins
Project Role:	Associate Investigator
Researcher Identifier	N/A
Nearest person month worked:	Intermittent
Contribution to Project:	Dr. Jenkins has worked with the EEG consultant to develop the proposed test battery, assisted with drafting necessary regulatory paperwork to begin the protocol and has conducted pilot testing of the battery measures.
Name:	Jennifer Myers
Project Role:	Project Manager
Researcher Identifier	N/A
Nearest person month worked:	6
Contribution to Project:	Dr. Myers has worked with Dr. Grant to draft and maintain necessary regulatory paperwork.
Name:	Alessandro Presacco
Project Role:	Consultant
Research Identifier:	N/A
Nearest person month worked:	Intermittent
Contribution to the Project:	Programming for EEG measures and analyses of EEG data
Name:	Sandeep Phatak
Project Role:	Consultant
Research Identifier:	N/A
Nearest person month worked:	Intermittent
Contribution to the Project:	Programming for EEG stimuli and analyses of EEG data
Name:	Scott Bressler
Project Role:	Consultant
Research Identifier:	N/A
Nearest person month worked:	Intermittent
Contribution to the Project:	Programming for EEG stimuli and analyses of EEG data

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

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

Dr. Jenkins has begun a new position as a clinical audiologist in the Walter Reed National Military Medical Center Audiology Department. Dr. Lewis, our new Research Audiologist, joined the team on August 12th and will be in charge of scheduling and running the study.

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

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

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

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

Walter Reed National Military Medical Center (WRNMMC)

Organization Name:	The Center for Neuroscience and Regenerative Medicine (CNRM)
Location of Organization:	Rockville, MD
Partner's contribution to the project:	In-Kind Support. Under this collaboration, the project uses CNRM Core Resources for recruitment purposes

Dartmouth College

Organization Name:	Dartmouth
Location of Organization:	Hanover, NH
Partner's contribution to the project:	In-Kind Support. Loaner agreement established to borrow equipment.

8. SPECIAL REPORTING REQUIREMENTS

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

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

9. APPENDICES:

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

Objective Assessment of Auditory Pathway Integrity and Functional Hearing Abilities

LogNo: RH170022
W81XWH-18-2-0033

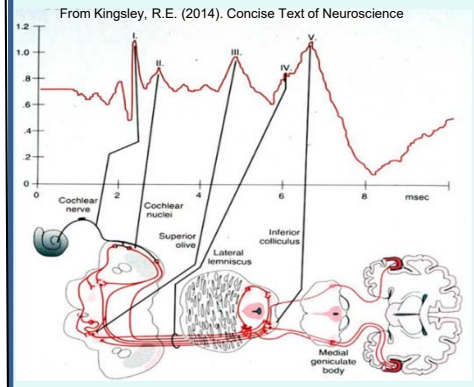
PI: Kenneth W. Grant **Org:** Walter Reed National Military Medical Center **Award Amount:** $737,994

Study/Product Aim(s)

This proposal aims to improve techniques for validating future hearing restoration techniques, with focus on hair cell and other cochlear supporting cell regeneration.
Aim 1: Identify objective measures that differentiate between normal hearing systems and those with auditory dysfunction, and establish expected values of those measures for varying degrees of hearing loss.
Aim 2: Assess differences between individual's objective test measures between sessions to determine reliability of each test measure.
Aim 3: Evaluate the ability to predict functional measures of speech in noise performance from objective measures of the physical integrity of the auditory system following hair cell restoration.

Approach

A battery of objective and pre-attentive auditory and electrophysiological measures will be developed that allows one to track the success of regeneration techniques throughout the auditory system pathways over time (early physical reintegration of the cochlea through the thalamus-cortical pathway, simple and more complex sound discrimination crucial for understanding speech in noisy environments). To demonstrate the utility of this functional assessment battery, listeners with a wide range of hearing loss from normal hearing to moderate-to-severe hearing loss will be evaluated to establish expected values for different degrees of hearing damage.



Top: Normal brainstem auditory evoked responses showing first 10 ms, corresponding to peaks I through V obtained from brainstem nuclei. Bottom: Anatomical cartoon shows approximate origin of each of the peaks indicated.

Hearing loss is the second most prevalent disability among Veterans according to the Annual Veterans Benefits Report FY16. Recent studies at US military training sites demonstrate significant impact of hearing loss on military operational effectiveness, including sharp decreases in mission success, a greater chance of getting killed by enemy fire, and an increase in fratricide. Clearly, the impact of hearing loss extends far beyond quality of life issues and has a direct effect on military readiness.

Research to protect and restore functional hearing has become a top priority within the Defense Health Agency J9, Research and Development Directorate. Among the most promising new strategies is the use of gene therapy and/or small molecules to regenerate cochlear hair cells. With human clinical trials expected to begin in the next 18 months effective, time-efficient and objective validation measures of new therapeutic remediation are of the utmost importance.

Preliminary data indicate differences in behavioral and electrophysiologic tests between listeners with clinically normal-hearing thresholds and bilateral minimal hearing loss (all categorized within the H1 hearing profile).

Timeline and Total Costs	FY18	FY19	FY20	FY21
Set up contractual agreements with Geneva Foundation and finalize all hires. Obtain IRB approval. Program and pilot all test measures.				
Finalize all IRB requirements. Aim 1: Cross-sectional study investigating differentiation of test battery between hearing groups.				
Aim 2: Within-subjects assessment assessing differences between individual results between sessions to determine test reliability.				
Data analysis and poster/podium presentations at local, national, and international conferences.				
Aim 3: Evaluate ability of objective measures to predict functional measures of speech in noise performance. Manuscript submission and dissemination of data.				
Estimated Total Budget: $737,994	$255K	$243K	$252K	

Goals/Milestones

FY18 Goals

☒ Identify project manager – will start in January 2019
☒ Program and test 80% of EEG measures. Remainder to be completed by month 6

FY19 Goals

☒ Write and submit eIRB protocols.
☒ Complete all pilot testing
☐ Begin recruitment and data collection for aims 1 and 3.

FY20 Goals

☐ Continue recruitment and data collection for aims 1 and 3.
☐ Begin recruitment data collection for aim 2.
☐ Begin data analysis.
☐ Poster/podium presentations of findings (to date).

CY21 Goal

☐ Finish all data collection and analysis.
☐ Manuscript submission and dissemination of overall findings.

Budget Expenditure to Date
Projected Expenditure: $323,544
Actual Expenditure: $77,546.02