Sound Science
A novel investigation using new treatment and MRI techniques to uncover the secrets of Meniere's syndrome

A prospectus of cooperation submitted to:
The American Hearing Research Foundation

Submitted by:
<Name redacted for privacy>
<Address redacted for privacy>
<Address redacted for privacy>

Dr. Jennifer <redacted>, Principal Investigator
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- **Project timeline**: 
- **Staffing**:
  - Dr. Jennifer <Redacted>, M.D., Principal Investigator  
  - Behrouz D. <Redacted>, Investigative Assistant  
  - Michael <Redacted>, Project Coordinator

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### Table 1: Summary of Budget
Executive Summary

Morbid Meniere's (MM) is a debilitating disease that affects the hearing and balance of over 600,000 Americans at any given time. The result of endolymphatic fluid buildup within the inner ear (endolymphatic hydrops), this particularly insidious and unpredictable illness leads to permanent hearing loss, debilitating vertigo, an inability to work and ultimately isolation. Although the cause of MM remains unknown, there is a large body of evidence showing the effectiveness of a medication called Betahistine in reducing its worst symptoms. Betahistine is an orally administered, histamine-like H1/H3 antagonist also known by the manufacturer's label "SERC".

Although the evidence suggests Betahistine's efficacy in symptom reduction, especially regarding the symptoms of vertigo, little is known about the mechanisms behind its success. Preliminary data imply that while Betahistine seems to reduce the symptoms of MM; it may or may not reduce the hydrops from which the symptoms actually arise. Since it's the hydrops that ultimately damages the hearing and balance systems, it is critical from a treatment perspective to understand the mechanisms behind Betahistine's success. Furthermore, if it can be shown that Betahistine does indeed reduce the hydrops of Meniere's affected ears, a more detailed investigation into the mechanisms of Betahistine will likely lead to a better understanding of the cause of the disease.

Although the aforementioned reasons alone seem to warrant an investigation of Betahistine the data also suggest that, in the process of reducing the symptoms of MM, Betahistine may also diminish the efficacy of other hydrops reducing treatments such as middle ear Dexamethasone perfusion. Should this be the case, it is imperative that Betahistine's affect on hydrops be determined. To accomplish this, a quantitative analysis must be undertaken in order to maximize the benefits of Betahistine for patients currently responding to Dexamethasone treatments. Unfortunately, to date, it has not been possible to directly observe the endolymphatic hydrops of MM victims and make these determinations.

However, a technique recently developed by Nakashima (et al.) allows this obstacle to be overcome by using FLAIR MRI with a middle ear perfusion of Gadolinium tracer. The tremendous historical safety profile of Gadolinium as a contrasting agent makes this new procedure ideal for use with active MM patients, and allows for quantitative and qualitative measurements of Betahistine's affect on hydrops. In addition, these direct observations will also allow our research team to scrutinize the absorption path of medications delivered through a middle ear perfusion (such as Dexamethasone) as well as determine how Betahistine might affect this path. The multiple tiers of information which will be gleaned as a result of this project will advance not only our understanding of endolymphatic hydrops resulting in Morbid Meniere's, but will offer insight into the efficacy of a number of treatments and, ultimately, allow for a significantly better management of the disease.

Our research team is based at the practice of Dr. Jennifer <Redacted>, one of the most recognized specialists in the treatment of Morbid Meniere's in the State of California. As
an adjunct clinical assistant professor with the Department of Otolaryngology at <Redacted>, a consultant in Otology-Neurotology and Skull-Base Surgery for <Redacted>, and a certified Otolaryngologist in the United States and Canada, she is the ideal choice for the role of principal investigator within our project. Her team, along with the radiological specialists at Silicon Valley MRI, will perform and evaluate the Betahistine treatments, the Gadolinium perfusions and the FLAIR MRI.

Our estimated cost for the complete project is $75,000 based on the expected enrollment of 5 paid volunteer patients. The cost breakdown is shown in the following table...

<table>
<thead>
<tr>
<th></th>
<th>Fee per single Gadolinium perfusion and complete associated series of MRI examinations</th>
<th>Total per patient</th>
<th>Total for project</th>
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Morbid Meniere's syndrome is a debilitating and terrifying illness, which devastates the lives of hundreds of thousands of Americans of all ages, genders and income levels. Since its discovery over 150 years ago, little progress has been made towards understanding of its underlying components due to the inability to directly observe this incapacitating illness in affected individuals. However, the miracles of modern technology have finally risen to the challenge of overcoming this hurdle. We now have a real opportunity - for perhaps the first time since its discovery - to obtain data that will not only immediately improve the lives of those affected, but potentially lead to a cure. We hope the American Hearing Research Foundation will join us in our commitment to the elimination of this terrible illness once and for all.

* Fee includes intratympanic injection of Gadolinium, and clinical review of FLAIR MRI results. Betahistine treatments and fees will be a part of the patient's normal treatment program and, thus, not associated with the expenses of the project.

** Fee includes the complete series of FLAIR MRI done at 2, 6, 12, 24 and 168 hours as well as review by the specialized radiological team of Silicon Valley MRI.
Statement of Need
The hearing loss and vertigo associated with Morbid Meniere's syndrome (MM) can be devastating to the lives of those affected. Profound hearing loss is debilitating regardless of cause, however when combined with the spontaneous, unpredictable vertigo attacks associated with MM a normal life can become literally impossible.

The cause of both the hearing loss and the vertigo in MM is a condition known as endolymphatic hydrops, which is defined as an uncontrolled buildup of the inner ear fluid endolymph. Due to the mechanical pressure hydrops places on the structures of the inner ear, this fluid buildup results in a fluctuating hearing loss which begins in the low frequencies. Simply put, with increased endolymphatic pressure the sound transducing membranes of the inner ear cannot vibrate properly, just like an over-tightened drumhead. The hearing fluctuations occur as the fluid pressure waxes and wanes in repeated, but completely irregular, tides causing the audible range to change from one moment to the next. Although this pressure, in and of itself, causes damage to the inner ear - the real problems arise when the drumhead finally tears. It is believed that this tearing is what causes not only the horrific whirling vertigo so characteristic of the disease, but is also what permanently destroys the hearing due to the mixing of endolymph with incompatible fluids from the other side of the ruptured membrane.

The medication Betahistine has been a miracle for many who suffer from this illness. Although the mechanisms behind this drug's efficacy remain a mystery, clinical trials throughout Europe and the Americas have shown it to significantly reduce the frequency and severity of Meniere's vertigo attacks. There are many theories as to how Betahistine works; however all of them fall into two basic camps. The first possibility is that Betahistine simply reduces the sensitivity of the ear's balance organs to vertigo by repressing the chemical receptors within them. This would reduce the symptoms of the disease without changing the root cause or the course of the illness. The other option is that Betahistine actually reduces the hydrops from which the symptoms arise. This would be the ideal situation, as it is the fluid pressure that ultimately results in damage to the ear.

Unfortunately, having had no reliable method of determining the level of hydrops within Meniere's patients, this debate remains unresolved. Under other circumstances this would only be unfortunate, as there are many illnesses which can only be "symptom suppressed" as they continue to run their destructive courses. However, there has been some evidence that Betahistine may, as a side effect, reduce the efficacy of other treatments such as the injection of dexamethasone steroid into the middle ear (known as intratympanic perfusion). This loss of efficacy might result from Betahistine's propensity to dilate the blood vessels of the inner ear, allowing the steroid to be systematically absorbed.

* Preceding Dr. Nakashima's technique, the only possible - albeit unreliable - measurement of the level of endolymphatic hydrops in Meniere's patients was to monitor the low frequency hearing. Due to the mechanical nature of the transitory low tone hearing loss, an inference can be made that when the low frequency hearing returns, the hydrops is reduced. However it is difficult to distinguish the transitory low tone hearing loss from the already permanent low tone hearing loss.
metabolized more quickly, or it may be the result of competition between the two drugs. Regardless, this possibility would be devastating for those patients who do respond to Dex treatments, as the steroid perfusion *does* appear to actually reduce the damaging hydrops - albeit temporarily.

Happily, there is a solution. Thanks to the pioneering work of Dr. Nakashima at Nagoya University, Japan[^3], there is a novel technique by which the actual endolymphatic hydrops of patients can be directly observed. After an intratympanic perfusion of the benign tracer Gadolinium, Dr. Nakashima was able to use 3D Fluid-Attenuated Inversion Recovery (FLAIR) MRI to follow both the absorption path of the Gadolinium through the middle ear, as well as directly see the extent of endolymphatic hydrops. To our, and Dr. Nakashima's, knowledge this is the first time hydrops has ever been directly observed in human patients. Since there is no natural animal model of endolymphatic hydrops, this alone was a great discovery.

However, this new method also creates the exciting, and rare, opportunity of a "no lose" scenario within Meniere's research. We propose using Dr. Nakashima's technique to document the level of hydrops within Meniere's patients before and after the onset of Betahistine treatment. With these new tools our team will be able to determine if the drug actually reduces the level of fluid buildup within the inner ear, or is simply masking the symptoms. The exciting part of a project like this is that the data obtained will be of tremendous value for both the researcher and the clinician regardless of what Betahistine's effect on hydrops turns out to be.

As an additional bonus, we will also be able to supplement Dr. Nakashima's data regarding the normal absorption path of medications delivered through an intratympanic injection, as well as determine if Betahistine affects this delivery route. This data alone will be of great importance since the treatment of many inner ear disorders depend on this type of drug administration, but little is known about its absorption characteristics. This ambiguity makes dosage determinations a difficult "educated guess" at best.

The clinic of Dr. Jennifer <Redacted> (Inc.) is excited to be a part of this research. Although there are a handful of dedicated and motivated researchers working towards a cure for the devastation of Morbid Meniere's, the numbers are still small. The number of professionals investigating the fluid dynamics of endolymph is even less and, to our knowledge, we are the first clinic with the opportunity to directly research Betahistine's effect on hydrops. We hope the good people of the American Hearing Research Foundation are as pleased about this project as we are, and will join us in this exciting endeavor.
Project Description

Objectives
We at <Redacted for privacy> Inc. are excited to be undertaking this project as we expect it to deliver a large amount of valuable data on multiple subjects with a minimal amount of effort when compared to many medical research proposals. This project is designed to...

- Examine the methods of efficacy associated with Betahistine treatment of Meniere's syndrome, specifically that of its ability to reduce endolymphatic hydrops.
- Provide valuable information regarding the general pathology of Meniere's syndrome by observing the general physical characteristics of endolymphatic hydrops and its effect on the membranes of the inner ear.
- Examine details regarding the absorption and subsequent metabolism of medications delivered through an intratympanic middle ear perfusion, which is a common drug delivery system for those suffering from inner ear disorders.
- Examine Betahistine's effect, positive or negative, on intratympanic middle ear perfusion by observing the pre-Betahistine and post-Betahistine absorption and consequent metabolism of perfused Gadolinium.

Methods
Approximately 100,000 new diagnosis of Meniere's syndrome are made each year. Much has been learned since it was first observed by Prosper Meniere in 1848, however little concrete evidence into its cause has been uncovered due to the inaccessibility of the inner ear, and the invasiveness of any procedures which directly observe the disease mechanisms. While the root cause of the syndrome remains a mystery, most researchers agree that the symptoms themselves arise from a buildup of endolymphatic fluid pressure within the inner ear (endolymphatic hydrops). One of the characteristic symptoms of Meniere's is the fluctuating low frequency hearing loss, which is attributed to the mechanical interference of the excess fluid pressure with the hearing membranes of the inner ear. As a result, the hearing of individuals is often used to assess the level of hydrops actively occurring, although it has been an unreliable indicator at best.

Betahistine for the treatment of Meniere's syndrome has been available in Europe since the mid 1960's, and has recently been allowed into the U.S. for investigative use. In that time, the methods behind its efficacy have remained predominantly unknown for many of the same reasons as those of the disease itself. Studies have shown that Betahistine has a positive effect towards the control of Meniere's associated vertigo, however studies regarding its effect on hearing continue to be mixed - leaving us blind as to how Betahistine may, or may not, affect the level of damaging hydrops.
Our research is designed to overcome these obstacles and provide the medical community with needed clues into the mechanisms behind Betahistine's efficacy. In addition to this primary goal, our methods will also provide critical insight into related subjects such as the absorption path of intratympanically delivered medications as well as provide for a direct observation of hydrops. For all the benefits it will provide, our project is surprisingly simple.

Individuals will be selected from a volunteer pool of Meniere's patients already opting to begin Betahistine treatment. As the research prospectus will be presented to patients by their attending physicians at the time of the decision to start Betahistine therapy, advertising costs will be minimized or completely eliminated. Before beginning oral Betahistine, volunteers will undergo a middle ear perfusion of Gadolinium tracer; a contrasting agent which is frequently used to highlight specific anatomical features during magnetic resonance imaging (MRI).

Once perfused, a specific form of MRI known as 3D Fluid-Attenuated Inversion Recovery (FLAIR) MRI will be done at intervals of 2, 6, 12, and 24 hours after perfusion to watch the travel of Gadolinium as it absorbs into, and eventually exits from, the inner ear. A follow-up MRI will also be done at one week to determine if the Gadolinium has been completely metabolized out of the inner ear spaces. Since the Gadolinium enters the perilymphatic fluid of the inner ear (which surrounds the endolymphatic fluid space), but does not enter the endolymphatic fluid itself - a boundary is clearly delineated allowing for the direct observation of the endolymphatic fluid volume. In other words it allows us to visually determine the level of hydrops, as well as the effect of hydrops on the distention of inner ear membranes.\(^3\)

This, in and of itself, is of great clinical significance since there are no truly reliable animal models of endolymphatic hydrops and, as such, the effect of hydrops in humans has previously only been observed post-mortem. Following the path of the Gadolinium through the ear is of equal value, as intratympanic perfusion is a common method of drug delivery for patients with inner ear disorders however little is known about its absorption and exit rates making dosing a best-guess task. The most valuable phase, however, comes with the second series of MRI.

Once the initial pre-Betahistine set of observations have been made, the patient begins the planned Betahistine treatment. Those patients who continue the treatment for 3 months (the normal length of time to determine treatment benefit) will then undergo a second round of Gadolinium perfusion with complete series of MRI. Once completed, the initial MRI sequences will be compared with the post-treatment series and evaluated for changes to the severity of hydrops (see section "Research Protocol").

The exciting part of this project is that valuable data will be obtained regardless of the patient’s responsiveness to Betahistine therapy. Even if a patient were unable to complete the full Betahistine treatment, or the second series of MRI, the data obtained from the initial series still maintains its full value.
**Project timeline**

The project has been specifically designed to leave flexibility within the timeline to allow for the selection of ideal candidates. Our goal is to complete a "before and after" series on 5 participants within the first year after project inception, with the option of completing another 5 candidates during the second year as funding permits. Each patient will be involved with the research portion of the project for a total of four months, including pre-enrollment counseling, and based on the current patient load of Dr. <Redacted> it is expected we will be able to enroll one to two patients per calendar quarter.

**Staffing**

<Redacted> for privacy> Associates and Services, Inc. (<Redacted>) has over 35 years experience with hearing and balance health. Founded by Dr. Jennifer <Redacted>, M.D., <Redacted> is a recognized leader in difficult to treat oto-neurological disorders, including Meniere's syndrome, and has helped hundreds of children and adults preserve their hearing and quality of life. Dr. <Redacted>’s team provides both medical management and surgical intervention for the therapeutic benefit of patients, and has a long research history with skull-base surgical and reconstructive techniques.

**Dr. Jennifer <Redacted>, M.D., Principal Investigator**

Principal Investigator and founder of EARS, Dr. Jennifer <Redacted>, M.D. is dedicated to the diagnosis and treatment of oto-neurological disorders involving hearing loss, balance and the facial nerve. As a highly skilled surgeon for acoustic neuroma, cochlear implantation, stapedotomy and vestibular surgeries she has performed hundreds of delicate micro-surgical procedures to preserve the hearing and balance of her patients.

Dr. <Redacted> has been practicing Otology-Neurotology in San Jose since 1998 and has owned her private practice since 2000. Dr. <Redacted> is a board certified Otolaryngologist in the U.S. and Canada, as well as being a fellow of the Royal College of Physicians and Surgeons of Canada. Dr. <Redacted> is also a Clinical Associate Professor in the Department of Otolaryngology at <Redacted> University, and a surgical consultant in Otology-Neurotology and Skull-Base Surgery at <Redacted> Santa Clara and <Redacted> Fremont Centers.

As a reflection of her commitment to both community and her profession, Dr. <Redacted> is a member of many professional associations and committees including the American Academy of Otolaryngology; the Canadian Society of Otolaryngology, Head and Neck Surgery; and the American Neurotology Society. She was an investigating surgeon in the FDA clinical trial of the <Redacted>™ middle ear implant and her current research interests lie in tissue adhesives and bone cements in otologic surgery, as well as the physiology of Meniere's syndrome and endolymphatic hydrops.

**Behrouz D. <Redacted>, Investigative Assistant**

M.S., PA-c, MMAc

Dr. <Redacted>’s clinical research and physician's assistant, Behrouz <Redacted>, holds a B.S. in Biological Sciences from UC <Redacted>; an M.S. in Medical Sciences from the <Redacted> School of Medicine's Physician Associate Program; and is National
Commission on Certification of Physician Assistants (NCCPA) certified. Mr. <Redacted>'s expertise lies in the comprehensive evaluation and treatment of balance disorders, vertigo, hearing loss, tinnitus, and other otologic and neuro-otologic conditions. His background in internal medicine, gastroenterology and hepatology, which includes extensive experience in public health as well as clinical and biomedical research, make him an ideal clinical and research associate for Dr. <Redacted>'s investigative team.

**Michael <Redacted>, Project Coordinator**

Mr. <Redacted> is an undergraduate student with the University of <Redacted>, and with <Redacted>, Connecticut and is pursuing a degree in Molecular Biotechnology with the intent of completing his Ph.D. in Molecular Biology and Biotechnology. His desire is to research inner ear pathologies including Meniere's syndrome and Sudden Sensorineural Hearing Loss, and will be functioning in the role of project coordinator as an intern under the direct tutelage of Dr. <Redacted> and Mr. <Redacted>. We are excited to have him on our team and look forward to the contributions he will make within the field of clinical inner ear research.

**Michael <Redacted>**

PA-c

Mr. <Redacted> has a background in clinical laboratory science and is a graduate of the Health Laboratory Science programs at the <Redacted> University School of Medicine and Health Sciences as well as a graduate of the <Redacted> Academy of Health Sciences and the <Redacted> University School of Medicine Primary Care Associate Program.

**Sarika <Redacted>**

M.S., CCC-A

Ms. <Redacted> holds a B.S. in Speech and Hearing Sciences, from <Redacted>, India; an M.S. in Audiology from <Redacted> University and is pursuing her doctorate in Audiology from the <Redacted> College of Optometry.

**Christine R. <Redacted>**

M.S., CCC-A

Ms. <Redacted> has an M.S. in Speech/Language Pathology from <Redacted> State University; a B.S. from the College of <Redacted> in Albany, NY; and is certified in Speech/Language Pathology and Audiology from the American Speech-Language-Hearing Association.

**Erica M. <Redacted>**

M.S.

Ms. <Redacted> has a Masters degree in Audiology from <Redacted> State University and has completed graduate work in Speech Pathology at <Redacted> State University, East Bay. She also holds a B.S. in Speech Pathology & Audiology, with a Psychology Minor, from <Redacted> State University, <Redacted>. 
Karina <Redacted>
Ms. <Redacted>’s credentials include a Diploma in Medical Assisting from <Redacted> College and she specializes in audiometric analysis of adults and children.

Cynthia J. <Redacted>
OTR
Ms. <Redacted> is a graduate of <Redacted> State University's Occupational Therapy program (with honors) and has extensive experience in hospital, outpatient, nursing home and home health settings. Cynthia has been working in the specialty area of vestibular and balance therapy for the past nine years.

Johnathon <Redacted>, Office/Human Resource Manager.

Jacqui <Redacted>, Billing Manager.

Allyson <Redacted>, Front Office Manager and Community Liaison.

Krista <Redacted>, Front Office Receptionist.

Kathy <Redacted>, Front Office Receptionist.

Evaluation
Although the evaluation of research data is described in the "Research Protocol" section, we wanted to briefly describe the procedures we will be using to evaluate the success of the program itself. Throughout the venture we will maintain comprehensive notes about what we encounter as the project progresses. We will also request patients fill out questionnaires after each series of examinations. At the conclusion of the project, an evaluation document will be prepared with the following sub-categories...

1. Enrollment success.
   1.1. Were we successful in recruiting volunteers for the project?
   1.2. Was the project description adequate for participant understanding based on participant responses?
   1.3. Was the enrollment method timely for project completion?
   1.4. What factors lead to the inclusion/exclusion of specific individuals?

2. Patient comfort level during Gadolinium administration and MRI (based on patient comments and questionnaire).
   2.1. What was the patient response to the Gadolinium administration?
   2.2. What was the patient response during MRI examination?
   2.3. What was the patient response to the number of, and timeframe for, MRI examination?

3. Effective/ineffective procedural techniques.
   3.1. What problems did we encounter regarding the administrative handling of the project?
   3.2. What successes did we have with the administrative handling of the project?

4. Evaluate patient completion rates.
4.1. What were the dropout rates between pre and post Betahistine treatment?
4.2. What were the reasons given for patient dropout?

5. Data comparison.
   5.1. Were there difficulties with the methods of scientific measurement used?
   5.2. What difficulties were encountered regarding the pre and post Betahistine measurements?

   6.1. Did we complete within budgetary constraints?
   6.2. What unexpected expenses were encountered?
   6.3. Were there any overages/under-runs for the project?

7. Lessons learned.
Budget

The advantage of this project is that we will be using the services of existing medical practices, with existing facilities and staff. This allows us to tally all of our expenses by the individual patient load. As is common in this type of medical research, Dr. <Redacted> and the specialists at <Redacted> MRI have agreed to include the Gadolinium treatments, imaging, results review and follow-up care as a "per patient" fee, making the estimation of costs very simple.

As the inclusion criteria for this project is very specific, and is based on new and existing Meniere's patients volunteering to include this research as a part of their ongoing medical treatment, this per patient schedule allows us the flexibility to include ideal candidates as circumstances, protocol and medical suitability allow without incurring additional overhead expenses due to unproductive times between patient tests. Additionally, as Dr. <Redacted> and her peers will be presenting the option of joining this research project directly to patients who are beginning Betahistine treatment, there will be no advertising costs.

Our goal is to enroll and evaluate a minimum of 5 patients at a total cost of $75,000, however as additional testing would only be advantageous to the project, we will be seeking supplementary funding with the hopes of enrolling an additional 5 participants. To complement the support we hope to get from the Georgia Birtman Grant, we will also be pursing funding from the National Organization for Rare Disorders, Inc. (NORD), the National Institute for Deafness and Other Communications Disorders (NIDCD) and the National Organization for Hearing Research Foundation (NOHR).
## Table 1: Summary of Budget

<table>
<thead>
<tr>
<th>Participant</th>
<th>Cost per single Gadolinium perfusion with associated series of MRI examinations and evaluations.</th>
<th>Total cost per patient (one pre, and one post Betahistine treatment.)</th>
<th>Total for project (5 patients)</th>
<th>Notes</th>
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</thead>
<tbody>
<tr>
<td>The clinical team of Dr. Jennifer &lt;Redacted&gt;</td>
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**Notes**

A Patient reimbursement for participation at $500 per injection and single series of FLAIR MRI.

B Fee includes intratympanic Gadolinium injection, pre and post injection patient care, clinical review of FLAIR MRI results, final comparisons of each individual's MRI series, and the final statistical analysis of the project in association with the project coordinator. Betahistine treatments and fees will be a part of the patient's normal treatment program and, thus, not associated with the expenses of the project.

C Fee includes the complete series of FLAIR MRI done at 2, 6, 12, 24 and 168 hours as well as the review of each MRI by the specialized radiological team of Silicon Valley MRI.

D Project coordination will be performed by Mike Rightmire in an unpaid internship as part of a degree in Molecular Biotechnology from UC Santa Cruz and Charter Oak State College. The principal investigator (Dr. Jennifer Maw) will be functioning in the supervisory role for this internship.
Conclusion
Meniere's syndrome is a debilitating inner ear disorder that affects the hearing and balance of over half a million Americans. Although progress has been made towards an understanding of the disease's mechanisms, it has been a slow and arduous task due to the inaccessibility of the inner ear and the inability to directly observe the pathology first hand. The medication Betahistine has demonstrated a significant efficacy towards the control of Meniere's symptoms, and has been a boon for those suffering from the illness, but little is known about the remedy's physiological functioning. An understanding of how Betahistine effects the ailment's underlying component of endolymphatic hydrops would not only allow for improved treatment of the malady, including better hearing preservation, but would offer clues into the etiology of the disease itself.

Thanks to a new technique involving FLAIR MRI with Gadolinium tracer, we now have a real opportunity to gain this insight as well as invaluable secondary data immediately useful to practitioner and researcher alike. With the support of the $75,000 Birtman grant from the American Hearing Research foundation, we at <Redacted for privacy> Associates and Rehabilitation Services feel we can make great contributions to assist in the eradication of this formidable illness once and for all. We are excited about this prospect, and equally excited at the opportunity to partner with the AHRF in this noble cause. We look forward to meeting with the AHRF's board and staff members to discuss a "sound future". 
Bibliography

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3. Tsutomu Nakashima, MD; Shinji Naganawa, MD; Makoto Sugira, MD; Masaaki Teranishi, MD; Michihiko Sone, MD; Hideo Hayashi, MD; Seiichi Nakata, MD; Naomi Katayama, PhD; Ieda Maria Ishida. Visualization of Endolymphatic Hydrops in Patients With Meniere’s Disease. Laryngoscope. 117(3):415-420, March 2007. [Laryngoscope]
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Appendix

Research Protocol

Intratympanic gadolinium injections pre and post betahistine in Meniere's patients

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Overview:

Betahistine has been used in Europe and the U.S. for the treatment of endolympathic hydrops resulting in Morbid Meniere's syndrome (MM) since the late 1960's. In that time a great deal of observed evidence has suggested Betahistine's efficacy in symptom reduction, however little is known about the mechanisms behind its success.

Preliminary data from patient interviews suggest that while Betahistine seems to reduce the symptoms of MM, it may do little to reduce the actual endolympathic hydrops from which the symptoms arise. Additionally, some data suggest that Betahistine may reduce the efficacy of other documented treatments for Meniere's - specifically that of intratympanic Dexamethasone perfusion.

A newly identified technique allows for the direct visualization of the magnitude of hydrops associated with MM by FLAIR MRI observation of Gadolinium after perfusion into the perilymph via intratympanic injection. Our proposal is to use this technique specifically with individuals suffering from diagnosed MM, before and after the introduction of Betahistine therapy, to determine if Betahistine reduces the hydrops associated with MM and/or interferes with the perfusion of Gadolinium within the perilymph after intratympanic injection.

Study Objectives:

Primary:
To determine if Betahistine reduces the amount of endolympathic hydrops associated with Meniere's syndrome.

Secondary:
To determine if Betahistine therapy interferes with the speed of Gadolinium perfusion through the perilymph of the inner ear after intratympanic injection.

Tertiary:
To determine if Betahistine therapy interferes with the quality (density and location) of Gadolinium perfusion through the perilymph of the inner ear after intratympanic injection.

Clinical Objective:

Primary Hypothesis:

\[ H_0 \text{ (Null Hypothesis)} = \text{Betahistine does not reduce the amount of endolympathic hydrops associated with Meniere's syndrome} = \hat{P}_{\text{Untreated}} \geq \hat{P}_{\text{Betahistine}} \]
**Secondary Hypothesis**

$H_0$ (Null Hypothesis) = Betahistine does not reduce the speed of Gadolinium perfusion within the perilymph of the inner ear after intratympanic injection = $\hat{P}_{\text{Untreated}} \leq \hat{P}_{\text{Betahistine}}$

**Tertiary Hypothesis**

$H_0$ (Null Hypothesis) = Betahistine does not reduce the completeness of Gadolinium perfusion within the perilymph of the inner ear after intratympanic injection = $\hat{P}_{\text{Untreated}} \leq \hat{P}_{\text{Betahistine}}$

**Protocol:**

**Overview**

A recent study done by Nakashima (et al.)\(^1\) used Gadolinium and 3D FLAIR MRI to visualize the speed with which Gadolinium is absorbed through the middle ear round window and infuses through the perilymph after intratympanic injection. Since Gadolinium fills the perilymphatic space (PS), but does not enter the endolymphatic space (ES), Dr. Nakashima was also able to clearly observe the boundaries between the perilymph and the endolymph of the inner ear.

By making comparisons between Meniere's and non-Meniere's participants, Dr. Nakashima was able to use the observed boundaries separating the ES from the PS, as well as the total volume of the PS, to clearly document the invasion of the ES into the PS due to endolymphatic hydrops. To his knowledge, this is the first direct visualization of endolymphatic hydrops.

We suggest using a similar method of Gadolinium perfusion, pre and post the start of Betahistine treatment, to determine what effect Betahistine may have on the fluid volume of endolymphatic hydrops and the ability of medications to infuse the perilymphatic space after intratympanic perfusion.

**Parameters of interest**

**Primary:**

The overall size of the perilymphatic space in endolymphatic hydropic patients measured before and after the start of Betahistine treatment.

**Secondary:**

The speed with which Gadolinium enters and completely infuses throughout the perilymph of the inner ear after intratympanic injection into, and absorption by, the middle ear.

**Tertiary:**

The density of the gadolinium in each perilymphatic area to which it infuses.
**Experimental method**

To best correlate the results of this study with the results of the Nakashima (et al.) study, the basic methods of that study will be replicated.

Patients with endolymphatic hydrops (EH) meeting the criteria set forth in the *Inclusion/Exclusion* section, who have not yet begun Betahistin treatment, will receive an intratympanic injection of Gadodiamide hydrate diluted eightfold with saline (v/v 1:7), with or without tympanic ventilation tube as per patient circumstances or preference, into a single EH affected ear.

The diluted Gadodiamide hydrate will be injected with the patient placed in the supine position with his/her head turned approximately 30° away from the sagittal line toward the untreated ear. The Gadolinium will be injected until a backflow of fluid into the external ear canal is observed under a microscope, or until the injecting physician is satisfied the middle ear has been filled with the maximum amount of solution it can safely sustain without exceeding 0.5 mL. The preferred minimum amount of diluted Gadolinium injected will be 0.4 mL. After the injection, the patient will remain in the supine position for 60 minutes with his/her head turned approximately 60° away from the sagittal line toward the healthy ear.

After 60 minutes post injection have elapsed, the patient will be prepared for 3D FLAIR MRI. A complete set of 3D FLAIR MRI images will be taken at 2, 6, 12, and 24 hours post injection. A final 3D FLAIR MRI set will be taken at one week (168 hours) post injection.

The scan parameters for the 3D-FLAIR sequences will be as follows: repetition time of 9,000 ms, effective echo time of 128 ms, inversion time of 2,500 ms, constant flip angle echo train with flip angle of 180 degrees for conventional turbo spin echo refocusing echo train, echo train length of 23, matrix size of 384 _ 384, 12 axial 2 mm thick slices to cover the labyrinth with a 16 cm square field of view, acceleration factor of two using the parallel imaging technique, generalized auto-calibrating partially parallel acquisitions. Voxel size was 0.4 mm _ 0.4 mm _ 2 mm. The number of excitations will be one, and the scan time will be 15 minutes.

Participants will then begin Betahistine treatment. Assuming no medical contraindications (such as adverse reaction or significant symptomatic increase) the participants will remain on the best Betahistine dosage as recommended by their physicians, but not less than 8mg TID, for a minimum of 3 months regardless of efficacy towards EH symptoms (assuming there is no negative symptomatic response). Patients will continue all additional medical treatments they were maintaining at the time of the pre-Betahistine MRI imaging, preferably without dosage change - however the post-Betahistine images should be postponed for at least one week following any intratympanic steroid or gentimyacin treatments, as well as being postponed for at least one week.
following any oral steroid dosing greater than that which was being maintained preceding the first set of images.

After three months of Betahistine treatment, the above procedures for Gadolinium injection and 3D FLAIR MRI will be repeated. The two sets of images for each patient will be compared as described in the section Method of measurement.

**Method of measurement**

Results will be measured through visual comparison by panel members of all 3D FLAIR MRI slices taken for each patient. The comparisons will be made between the patient's pre and post betahistine treatment MRI.

Each panel member will annotate on a Varieties of Intuition Scale (VIS) the differences between each patient's set of MRI and record the differences comparing the following three areas of concern...

1. **The total area of the perilymphatic space in each anatomical space of the inner ear as visualized by the Gadolinium.** This comparison is to observe any possible difference in the intrusion of the endolymphatic space into the perilymphatic space to determine if Betahistine reduces the amount of hydrops.

2. **The specific anatomical areas of the inner ear perilymph into which Gadolinium infused.** This comparison is to determine if Betahistine prevents the Gadolinium from reaching specific anatomical areas of the perilymph.

3. **The density of Gadolinium found in the specific anatomical areas of the inner ear perilymph.** This comparison is to determine if Betahistine restricts or increases the concentration of Gadolinium in those areas to which it infuses.

**Method of statistical analysis**

1. Sample size dependent on volunteer base. Expected sample size of $T_X=5$.
2. Paired T Test
3. Data for any patient unable to complete at least one pre and post Betahistine MRI series will be evaluated for its value regarding general research into the physical characteristics of endolympathic hydrops and intratympanic perfusion, however the data will be excluded in its entirety from the study sample regarding the effects of Betahistine.

**Inclusion/Exclusion**

The target participant group for this study is individuals of either sex without restriction to age with diagnosed endolymphatic hydrops (EH) which has been
active for at least three months without remission preceding the start of the study who have not yet begun Betahistine treatment.

"Active" is defined as...
1. Individuals who have a significant low frequency hearing loss that does not recover to better than a 20 decibel loss in the 250-500 hertz range for the three months preceding the onset of the study.

2. Individuals who have had at least one vertigo episode typical to EH since the onset of symptoms (not restricted to three months preceding the study) or have a documented significant peripheral balance disorder assumed to be the result of the EH.

Safety subset

No known significant negative indications have been observed with the use of Gadolinium, including intratympanic Gadolinium injection, based on studies including the study conducted by Nakashima (et al.)

Patients will be closely monitored throughout the study and, in the event of any negative indications as the result of the Gadolinium or Betahistine treatments as perceived by the patient or patient's physician including any adverse increase in symptoms, the patient will be excluded from any further treatments or injections.

A failure of efficacy of the Betahistine treatments, without adverse increase in symptoms, will not be considered cause for removal from the program or cause for the discontinuation of Betahistine therapy unless it is so requested by the participant or considered in the best medical treatment of the patient by the attending physician.
Bibliography:

1. Tsutomu Nakashima, MD; Shinji Naganawa, MD; Makoto Sugiura, MD; Masaaki Teranishi, MD; Michihiko Sone, MD; Hideo Hayashi, MD; Seiichi Nakata, MD; Naomi Katayama, PhD; Ieda Maria Ishida: *Visualization of Endolymphatic Hydrops in Patients With Meniere’s Disease*. Laryngoscope. 117(3):415-420, March 2007. [Laryngoscope](http://example.com).
June 29th, 2007

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American Hearing Research Foundation
Attn: Timothy C. Hain, M.D., Vice President
8 South Michigan Avenue, Suite #814
Chicago, IL 60603-4539

Re: Application for the Birtman memorial grant

Dear Dr. Hain and the team of AHRF,

<Redacted for privacy> Associates and Rehabilitation Services is a <Redacted> based clinical and research practice founded by Dr. Jennifer <Redacted>, M.D., and is dedicated to the hearing and balance health of patients in and around the Silicon Valley area. We are excited to be undertaking a new research project to determine the effects of the drug Betahistine on endolymphatic hydrops. We believe this project will not only elucidate many unknowns about this effective treatment but will, in the process, provide the medical and research communities with a tremendous amount of valuable secondary data regarding the mechanisms of Meniere's disease and the pathways of intratympanically delivered drug systems.

We respectfully submit our proposal to the good people of the AHRF with regard to the $75,000 Birtman memorial grant. We believe that with these funds we can successfully bring this project to fruition and contribute a great deal of valuable information to the fight against hearing loss and crippling inner ear disorders. We know that the AHRF has a vested interest in diseases such as Meniere's, which is stealing the hearing of as many as 600,000 Americans, and are excited at the opportunity to create a partnership with your organization.

Please review our proposal at your leisure and contact us at any time with questions, or to schedule an occasion to meet. We hope our application meets your standards and vision, and await the opportunity to speak with you in person about this exciting prospectus. With your permission, we will follow-up this submission with a telephone contact to verify you have received everything required and to discuss the next step.

With many thanks for your time,

Dr. Jennifer <Redacted>, M.D.
Principal Investigator
<Redacted for privacy> Associates and Rehabilitation Services, Inc.
408.xxx.xxxx