UCI Office of Research
Research Management System

Animal Use Protocol

Title

General Information

Project Overview

Provide a non-technical, lay-language summary of your project.
Uncheck this box to remove all text from the box below

We are developing a prosthetic device) that potentially could restore hearing to the deaf. The device consists of and thereby elicits a sensation of sound. This is an alternative to a conventional cochlear implant, which is positioned in a fluid-filled compartment, separated from the auditory nerve by a wall of bone. Our results from short-term non-survival studies in anesthetized animals indicate that, compared to a cochlear implant, These results suggest that would offer substantial improvements for hearing replacement for human patients.

In ongoing experiments, we plan to test the safety and efficacy of long-term implantation of of cats. Those tests are needed before the implant can begin to be translated to human trials. We also will conduct experiments with conventional cochlear implants to evaluate the effects of deafness and long-term stimulation on transmission of timing information, with the goal of improving hearing by present-day users of conventional cochlear implants.

Study Characteristics

Animal Biosafety Level
ABSL-1

Will animals be physically restrained for more than brief periods without the use of sedation or anesthesia?
Yes

Will paralytic agents be used in live animals under this protocol?
No

Will surgical procedures be performed under this protocol?
Yes

Type of surgical procedure(s) to be performed (check all that apply):
Major

Will animals recover from surgical procedures (survival surgery)?
Yes

Will multiple survival surgeries be performed on a single animal?
No

Project Continuation

Is this application a three-year de-novo renewal of a previously approved protocol?

Yes

Total # of animals used in the last 3 years

Did any adverse or unanticipated events with animal health, behavior or well-being occur during the last 3 year period of this study, that was not previously reported to the IACUC?

Progress Summary

Justification for Continuing the Project

Adverse events and unanticipated problems:

There have been no adverse effects on animal health, behavior, or well-being.

Justification for Continuing the Project

We feel that we are very close to obtaining successful chronic implantations of an and that those results will provide a pathway toward human trials. We also are adding two elements to the protocol. One involves animal tests of a conventional cochlear implant. Those studies are intended to address the poor sensitivity to temporal fine structure that is common among human implant users. The second is an addition of animal behavioral tests. These are intended to confirm or refute our previous physiological results suggesting that will improve perceptual sensitivity to temporal fine structure.

List the previously approved protocol number

Summarize the progress made on the project during the last 3-year period.

In previous published work, we have conducted non-survival experiments (acute) using from that is not suitable for chronic implantations. In the past 3 years, we have focused on evaluating devices that could be implanted chronically. Acute experiments with an off-the-shelf device from yielded results that were marginally acceptable. Tests of chronic implantation of that device were unsuccessful, however, in that we could not elicit responses from stimulation of the device in the days after the implantation. A more promising device is being custom made for us by In cute implantations of the device, results were mixed, but each provided directions for improvements.

Total Number of Animals Used in the last 3 years

10 animals, category D

Funding Source	Funding Status	Award/Proposal #	Billing Account #
	Awarded		
	Pending		
	Awarded		
	Pending		

Funding & Billing Information

Funding sources not captured in table above.
Additional Funding Information

Experimental devices ( ) are being provided free of charge from

Has the project undergone peer-review by an extramural sponsor/funding agency (e.g., NIH study section)?
Yes

Provide information regarding peer review below if necessary.

A protocol closely similar to the present one was reviewed by an NIH panel for the successful application for contract which ran through

PI Home Department

Species

Cat

Cat

Species Justification

Explain why the proposed species is the most appropriate model for this research.
Uncheck this box to remove all text from the box below

Proposed experiments will be conducted in cats. The experiments require chronic implantation of

The cat is a widely accepted species for studies involving the auditory nerve because the size and location of the auditory nerve permit reasonably easy access for physiological recording and stimulation. The cat's auditory nerve is comparable in diameter to that of the human. The cat's central auditory system has been well studied, which provides needed background data for the present study. A smaller animal (e.g., guinea pig or rat) would not be suitable because the auditory nerve is too small relative to the physical scale of the und relative to the human auditory nerve. Also, we have demonstrated that cats are capable of sophisticated auditory discriminations similar to those that are planned, whereas efforts to train guinea pigs in more than simple detection tasks have been unsuccessful. A non-human primate arguably might be a better model for human. The in a non-human primate, however, would have its own idiosyncrasies, unlike that in either cat or human, so a non-human primate would not provide any special surgical or anatomical insights. Functionally, it would be difficult to argue that the basic physiological principles of cat, monkey, and human, so monkeys would offer no benefit over cats.

Animal Characteristics

List the specific strains that will be used.
Uncheck this box to remove all text from the box below

Domestic short-hair (DSH) cats

Do any of the strains listed above have special health conditions or phenotypic abnormalities?
Uncheck this box to remove all text from the box below

no

Additional Information about Species/Strains

Rationale & Alternatives

Search Results

Date of Search	Time period from	Time period to	Database	# of Results	Keywords
Apr-27-2017	Jan-01-2014	Apr-27-2017	PubMed	744	
Apr-27-2017	Jan-01-2014	Apr-27-2017	Web of Science	1230	

Database Searches

Discussion of Search Results
Uncheck this box to remove all text from the box below

The literature search failed to show any instances of *in vitro* studies that could provide the sorts of safety data needed for the present study.

There have been several studies that use multi-site recording arrays to increase the rate of data acquisition from each animal and, thereby, reduce the number of animals needed. For instance, a 32-site recording probe can increase the rate of data acquisition by a factor of 32 compared to a typical single-site tungsten electrode. Of the various systems reported, we are convinced that single-shank thin-film systems like those that we plan to use provide the greatest efficiency and reliability.

There is essentially no scientific overlap between the proposed work and previous studies aside from the overlap with pilot studies There are only a few labs working on novel auditory prosthetics, and close communication between those groups prevents duplication of efforts. The LR served as the For those reasons, is well aware of the present state of auditory prosthesis research.

Other Sources Used to Consider Alternatives

Replacement

Discuss efforts to partially or fully replace live animals with in vitro models, (i.e. cell culture), computer simulation, or use of a less-sentient species (e.g. insects).
Uncheck this box to remove all text from the box below

This is a very empirical project, testing the body's reaction to an implanted prosthetic device, and simply is not feasible for modeling.

Reduction

Describe the steps you have taken to reduce the number of animals to the minimum required to obtain scientifically valid data.
Answer

As much as possible, we will address multiple experimental aims in each animal, thereby reducing the number of animals that will be needed. For instance, in the CI-SB animals we will monitor effects of long term deafness and electrical stimulation of one ear on scalp-recorded potentials, psychophysics, and (in a terminal experiment) single neuron activity. In the terminal experiment, we also will obtain control data from the contralateral unstimulated ear.

Refinement

Explain how the experimental design and procedures have been refined to improve efficiency and minimize pain and distress.
Uncheck this box to remove all text from the box below:

The experimental design has been refined by procedures to permit multiple recordings of scalp evoked activity over the course of weeks to months and, in terminal experiments, by the use of multiple-site recording arrays that permit simultaneous recordings at multiple brain sites.

Study Segments

Experimental Design	Species
Cochlear Implants	Cat
	Cat

Cochlear Implants

Species

Cat

Experimental Design Summary

Does this study segment tab describe the establishment and maintenance of a breeding colony?

Describe the rationale behind the experiment or the hypothesis being tested in this study segment.
Uncheck this box to remove all text from the box below

1. Cochlear implants. We have preliminary evidence that transmission of temporal information from a conventional cochlear implant (CI) to the brain is degraded by a period of deafness without electrical stimulation. This is of considerable significance to human cochlear implant users. We plan to evaluate effects of a 4-month period of deafness on temporal

sensitivity measured physiologically and psychophysically (i.e., by a quantitative measure of perception), and to test how loss of temporal acuity due to a period of deafness might be restored by daily electrical stimulation with a CI. These experiments also will provide a baseline for comparison with novel stimulation.

1. A. Acute cochlear implantation with neural recording from inferior colliculus. In a non-survival experiment under Nembutal anesthesia, each animal will be implanted with a CI and will be studied with neural recording from the ICC in a single 10-to-18-hr experiment. The purpose is to work out details of CI implantation and to learn characteristics of spread of activation of the auditory pathway after acute deafening. We also will work out surgical details for chronic implantation and positioning of the transcutaneous connector.

1.B. Chronic CI implantation with chronic electrical stimulation. The purpose of this experiment is to work out technical and surgical details of chronic implantation and stimulation, with a survival period of 4 months. Then, the terminal experiment will reveal the spread of activation in these animals that have never had an extended period of deafness without electrical stimulation.

1.C. Chronic CI implantation with responses tracked over 4 months of deafness. The purpose of this experiment is to test the hypothesis that transmission of temporal information is severely degraded after periods of deafness in the absence of electrical stimulation. This will serve as a baseline for studies of restoration of temporal acuity by daily CI electrical stimulation (in 1.D.).

1.D. Psychophysical measures of temporal acuity over a period of deafness and stimulation. Purposes of these experiments are to track any changes in temporal acuity measured with scalp recordings and psychophysics over a period of deafness with electrical stimulation. This will test the hypothesis that electrical stimulation preserves the temporal acuity that is lost during a period of deafness (as in Set 1.c). This segment also will also evaluate the use of the scalp-recorded Acoustic Change Complex (ACC) as a surrogate for psychophysical testing and will provide baseline results for comparison with perceptual studies in segment 2.C.

Does this study segment describe the establishment and maintenance of a breeding colony?
No

If multiple procedures will be performed under this experiment, describe the sequence and timing of all procedures for this experiment.
Uncheck this box to remove all text from the box below:

1.A. Procedures: Acute CI implantation; Neural recording from inferior colliculus (non-survival); 2 cats

1.B. Procedures: Systemic deafening; Chronic CI implantation; Chronic stimulation (4 months) with scalp recording at 2-wk intervals; Neural recording from inferior colliculus (as a non-survival terminal experiment). 2 cats

1.C. Procedures: Systemic deafening; 4 months of no stimulation; Chronic CI implantation; 4 months of scalp recording at 2-week intervals; Neural recording from inferior colliculus (as a non-survival terminal experiment). 4 cats

1.D. Procedures: Psychophysical training with normal hearing (about 3 months until asymptotic performance); Systemic deafening; 4 months of no stimulation; Chronic CI implantation; 4 months chronic stimulation with daily psychophysical training and testing with electrical stimulation and scalp recording at 2-week intervals; Neural recording from inferior colliculus (as a non-survival terminal experiment). 4 cats

-Depending on auditory brainstem responses after cochlear implantation, an in vivo CT scan may be performed to confirm implant placement. Cats will be anesthetized with ketamine/acepromazine and maintained as per other anesthesias on this protocol.

Animal Monitoring

Species	Monitoring Parameters	Monitoring Frequency	Responsible Person
Cat	signs of discomfort	daily	
Cat	signs of discomfort	daily	ULAR vivarium staff

Animal Monitoring Details

What, if any, clinical signs or symptoms are expected in response to the procedures/manipulations in this study?
Uncheck this box to remove all text from the box below

There is a possibility of transitory head tilt or postural change as a result of the deafening or cochlear/auditory nerve implantation.

Management Plan for Animal Monitoring

Documentation of Animal Monitoring

Endpoints

Experimental Endpoints

Humane Endpoints

What are the experimental endpoints for this study segment?
Uncheck this box to remove all text from the box below

1.A. Completion of 12-18 hr non-survival experiment.

1.B. End of 4 months of chronic deafness and stimulation followed by a terminal 12-18 hr non-survival experiment.

1.C. End of 8 months of chronic deafness (4 with no electrical stimulation; CI implantation; 4 more months, with brief electrical stimulation at 2-wk intervals) followed by a terminal 12-18 hr non-survival experiment.

1.D. End of ~3 months of training, 4 months of deafness, CI implantation, 4 months chronic electrical stimulation with psychophysical testing, Ending with terminal 12-18 non-survival experiment.

What clinical signs or other criteria will be used to determine that an animal must be removed from the study ahead of schedule (Humane Endpoint)?
Weight loss greater than 20% compared to pre-study weight or age-matched controls.
Inability to eat or drink.
Provide additional details about any checked items, or any other endpoint criteria:

Animals will be euthanized in the case of any intractable post-surgical infection or other adverse reaction.

Euthanasia

Will all research animals be euthanized at the conclusion of this experiment/study segment?
Yes

Indicate the euthanasia methods that will be used on the animals from these experiments - Check all that apply
You MUST...

Animal number calculation for experimental part Cochlear Implants

Cat		
	Max	Description
	12	total for Cochlear Implants
	12	**Cat**

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Procedure	Species
Aseptic Surgery Procedures (non-rodent mammal)	Cat
Neutering	Cat
Systemic deafening	Cat
Cochlear or auditory nerve implants	Cat
Inferior colliculus recording	Cat
Scalp recording of event-related potentials	Cat
Chronic electrical stimulation	Cat
Psychophysical training and testing	Cat
Euthanasia	Cat

Procedure Descriptions

Aseptic surgery will be conducted in the [redacted] All other procedures will be conducted in the P.I.'s laboratory in [redacted]

Aseptic Surgery Procedures: Surgical instruments are sterilized before each use. Autoclavable materials are sterilized by autoclaving. A glass bead sterilizer may be used to re-sterilize instrument tips.
Fur is removed from the surgical site. The surgical site is wiped with three alternating applications each of antiseptic (chlorhexidine or povidone-iodine) and 70% alcohol, working outwards from the center of the surgical field. Non-sterile areas of the animal are draped with sterile material, leaving only the surgical site exposed.
The surgeon wears a hair cover and surgical face mask. After washing and scrubbing hands and forearms with antiseptic soap, the surgeon dons sterile gown and sterile surgeon's gloves.
Aseptic technique is maintained throughout the surgical procedure by taking care to avoid touching non-sterile areas with sterile gloves or instruments.

Animals will receive one pre-op injection of meloxicam. Anesthesia will be induced with an initial dose of ketamine, i.m. Isoflurane in oxygen will be administered, initially with a mask and, after tracheal intubation, through an intratracheal tube connected to a re-breather circuit. Bupivicaine will be administered once, SQ, around wound margins. Buprenorphine will be administered immediately post-op, continuing at 12-hr intervals for 48 hrs.

Neutering: Animals will be neutered by ULAR veterinary staff, in most cases at the time of general anesthesia for systemic deafening. For neutering, the hair will be plucked over the scrotum. The skin

will be disinfected with alternative scrubs with Betadine and alcohol (3 each). Ophthalmic ointment will be instilled in the eyes to prevent corneal drying. A small incision will be made through the scrotum

over each testicle, the testicle will be removed, and the spermatocord and blood vessels ligated. The scrotal incision will be left open. All cats will receive meloaxicam at 0.2 mk/kg PO for 2 days post-neutering

and longer if needed.

Systemic deafening: Animals will be deafened by administration of kanamycin followed by ethacrynic acid as described by

. That procedure results in destruction of cochlear inner hair cells and total bilateral deafness

Anesthesia will be induced with an IM injection of ketamine (25 mg/kg) and acepromazine (0.15 mg/kg). A single injection of kanamycin (300 mg/kg dissolved in sterile saline) is administered subcutaneously.

After a delay of ~30 min (during which neutering will be performed), a solution of ethacrynic acid dissolved in saline (1 mg/ml) will be administered via i.v. infusion. The infusion is continued until no click-evoked auditory brainstem response (ABR; scalp recording procedures) are obtained at equipment maximum (~90 dB SPL). The needed amounts of ethacrynic acid vary widely among animals, but total injections

typical range from 15 to 28 mg/kg. ABR responses will be monitored for 4 h to ensure that hearing thresholds did not immediately recover. All animals will be given i.v. or subcutaneous fluids and maintained on a

heating blanket to support their normal body temperature during recovery from anesthesia.

Cochlear or auditory nerve implants: The cochlear stimulating arrays (CI's) are commercial devices

purchased from and are an animal version of the cochlear implant used clinically.

Each array consists of 8 platinum bands, 0.4 mm in diameter, spaced at 0.75 mm intervals on a silicone carrier. are custom experimental devices made for us by

Implantation of either device is done under general anesthesia, either Nembutal in the case of non-survival (acute) experiments

or isoflurane in the case of survival (chronic) experiments. Implantation of either type of device begins with exposure of the cochlear bulla. The bulla is opened with a carbide burr and the round window is visualized.

In cases in which the animal has not already been deafened systemically, the exposed cochlea will be deafened by withdrawal of perilymph with a cotton wick through the round window and infusion of 10% neomycin

sulfate in distilled water. For implantation of the cochlear device, a small cochleostomy is made with a 0.5-mm diameter diamond burr, approximately 1 mm ventral to the round window. The cochlear device is inserted through the cochleostomy, about 6 mm into the scala tympani. In conditions of chronic implantation,

the electrode wire will be further secured with silicone and acrylic.

In the case of acute implantations, wires connected to the cochlear

nerve device will be connected directly to a custom optically isolated current source. In the case of chronic implantations, electrical connections to the array will be brought under muscle and skin to a

skull–mounted connector. A stainless-steel cylinder will be placed around the skull connector to protect the connector. The floor of the cylinder and the base of the connector will be sealed with acrylic such that

the inside of the cylinder is outside of biological spaces. A screw-on cap will be placed over the cylinder.

Inferior colliculus recording: We will record from the inferior colliculus (ICC; the principal structure of the auditory midbrain) as a measure of the spread of activation of the auditory pathway by electrical

cochlear

nerve stimulation. The ICC recordings are non-survival and will be done in acute experiment or as terminal experiment in animals that have already been studied chronically.

Experiments will be conducted under general anesthesia with Nembutal. A tracheal cannula will be inserted through a tracheostomy to insure an unobstructed airway. The animal's head will be placed temporarily in a

palato-orbital head holder. A midline incision will expose the dorsal surface of the skull. The wound margins will be infused with bupivicane, s.c. A steel skull fixture will be fixed to the skull, anterior to the coronal suture,

using stainless steel screws and dental acrylic. A steel bar attached to the skull fixture will be used to position the head during subsequent surgery.

The temporalis muscle on the right side will be reflected, and a 5 mm opening in the parietal bone will be made just dorsal to the parietal/temporal suture and just rostral to the tentorium. The dura will be incised and

reflected to expose the lateral and posterior occipital cortex. This cortex will be aspirated using a glass pipette and gentle suction to allow direct visualization of the tentorium and of the dorsal and lateral surface of

the inferior colliculus. A 32–channel acute recording probe (from) will be inserted into the center of the IC using a micromanipulator. The probe consists of a silicon shank, 15 microns thick and

50–100 microns wide, tapering to 15 microns wide at the tip. The probe is 5 mm long and will be inserted to a depth of ~3.5 mm. The silicon shank is bonded to a printed circuit board that will be mounted on a

custom–built headstage that will be held by the micromanipulator. The probe will be inserted into the inferior colliculus along a dorsolateral to ventromedial trajectory at a 45º angle off the parasagittal plane in the

coronal plane. The depth of the inferior-colliculus recording probe will be adjusted based on the responses of IC neurons to electrical stimulation through the cochlear or auditory nerve implant. Once the probe is at

the desired depth, it will be fixed in place

using the following procedure. The cortical deficit will be filled with 2% agarose dissolved in warm Ringer's solution. When the agar has solidified, the surrounding parietal and temporal bones and the proximal shank

of the recording probe will be covered with a thick layer of dental acrylic sealing the bony deficit and fixing the probe in place. Data collection consists of recording from the 32-channel inferior colliculus probe while

presenting parametrically varied electrical stimuli through various electrodes on the implant. Experiments typically last 10 to 18 hours.

Scalp recording of event-related potentials: Non-invasive scalp recordings will be used to monitor survival of chronically implanted electrodes and to monitor discrimination of various electrical stimuli by the auditory

pathway. We will record electrically-evoked potentials from the scalp with sub-dermal needle electrodes. Cats will be sedated with ketamine (25 mg/kg, i.m.) and acepromazine (0.1 mg/kg) to block the discomfort of

the electrode placement and to reduce movement artifact. Electrodes are placed at the vertex, both mastoids, and the middle of the back. Each animal will be studied multiple times at intervals of no less than

14 days. Depending on the time scale and the averaging procedure, we will record the auditory brainstem response (ABR), the auditory frequency following response (FFR), or the auditory change complex (ACC).

Chronic electrical stimulation: A subset of the animals that are implanted with cochlear devices will receive chronic electrical stimulation for the purpose of assessing how electrical stimulation might preserve or

enhance transmission of temporal activity in the deafened auditory system. Animals will be stimulated with electrical pulse trains for up to 8 hours per day, 7 days per week for up to 6 months. The

battery-powered stimulator will be worn in a mesh backpack and connected with a cable to the transcutaneous connector. Stimulus current levels will be adjusted according to dynamic ranges measured by ABR and ACC

and will be further adjusted if there is any sign of aversive response to stimulation. During stimulation, animals will be brought to the laboratory and housed in individual cages, with access to food, water, and

litter boxes. The laboratory will be attended by personnel throughout all stimulation periods, and animals will be monitored to guard against adverse responses to stimulation.

Psychophysical training and testing: Animals will be trained in a psychophysical (i.e., quantitative perceptual) task to measure discrimination of changing acoustical or electrical pulse trains, which will result in changes

in perceived pitch. The training and testing protocol is patterned after one [redacted] used successfully in a study of spatial hearing [redacted]

[redacted] On each trial, the cat will depress and hold a pedal, which will initiate a sequence of bursts of pulses at a standard pulse rate. After a variable time period, the pulse rate will change

to a faster rate (eliciting a higher pitch). The cat will be rewarded for releasing the pedal within 1800 ms of the change in rate. The reward will be a small portion of pureed canned cat food. Early releases or

misses will be punished with a 4-second time out period. As is standard practice in UCI ULAR, cats will receive food once per day. In this case, the food will consist of that received as rewards during the

psychophysical procedure. In addition, cats will be given free access to dry food for a limited period after each daily testing session. Cats will be lightly restrained during each testing session. The restraint consists

of a commercial restraint bag attached to the testing platform in a way that will permit free standing or sitting and movement of the head and limbs but which will prevent the animal from jumping off the platform

or turning more than about 180°.

Psychophysical training will begin with normal-hearing cats, using acoustic stimulation. When the animals have reached asymptotic performance with acoustical stimuli, they will be deafened and implanted with a

cochlear electrode array, and training will commence using electrical stimulation.

Depending on auditory brainstem responses after cochlear implantation, an in vivo CT scan may be performed to confirm implant placement. Cats will be anesthetized with ketamine/acepromazine and maintained as per other anesthesias on this protocol. This will be performed in with [redacted] CT scanner in [redacted]

Euthanasia: Sedation with i.m. injection of ketamine followed by i.p. injection of a commercial barbiturate-based euthanasia agent (e.g., Fatal Plus, 150 mg/kg).

Cat

Species

Cat

Experimental Design Summary

Does this study segment tab describe the establishment and maintenance of a breeding colony?

Describe the rationale behind the experiment or the hypothesis being tested in this study segment.
Uncheck this box to remove all text from the box below

2.

2.A. Evaluation of a new chronically implantable electrode. In a non-survival experiment under Nembutal anesthesia, each animal will be implanted with an lectrode and will be studied with neural recording from the ICC in a single 10-18-hr experiment. The purpose is to work out details of mplantation with a new device from and to learn characteristics of spread of activation of the auditory pathway with that device after acute deafening. We also will work out surgical details for chronic implantation and positioning of the transcutaneous connector.

2.b. The purpose of this experiment is to develop the procedures for using the new Scalp potentials will be monitored at 2-week intervals to assess any changes in stimulation thresholds, operating ranges, or transmission of temporal information that might indicate a foreign-body reaction to lengthy intraneural implantation. This experiment is an assessment of safety and efficacy that will be essential in translation of timulation to human trials. The number of animals planned reflects the likely occurrence of experiments that fail to yield useful results due to technical challenges.

2.C. Perceptual responses to timulation. The purpose of this experiment is to confirm or refute predictions from our previous physiological results that timulation will provide enhance perceptual sensitivity and temporal acuity compared to conventional CI stimulation.

Does this study segment describe the establishment and maintenance of a breeding colony?
No

If multiple procedures will be performed under this experiment, describe the sequence and timing of all procedures for this experiment.
Uncheck this box to remove all text from the box below:

2.A. Procedures: Acute implantation; Neural recording from inferior colliculus (non-survival); 2 cats

2.B. Procedures: Systemic deafening mplantation; 6 months of scalp recording at 2-week intervals; Neural recording from inferior colliculus (as a non-survival terminal experiment). 8 cats

2.C. Procedures: Psychophysical training with normal hearing (about 3 months); Systemic deafening mplantation; 4 months psychophysical training and testing with electrical stimulation and scalp recording at 2-week intervals; Neural recording from inferior colliculus (as a non-survival terminal experiment). 6 cats

Animal Monitoring

Species	Monitoring Parameters	Monitoring Frequency	Responsible Person
Cat	signs of discomfort	daily	
Cat	signs of discomfort	daily	ULAR vivarium staff

Animal Monitoring Details

What, if any, clinical signs or symptoms are expected in response to the procedures/manipulations in this study?
Uncheck this box to remove all text from the box below

There is a possibility of transitory head tilt or postural change as a result of the deafening or cochlear/auditory nerve implantation.

Management Plan for Animal Monitoring

Documentation of Animal Monitoring

Endpoints

Experimental Endpoints

Humane Endpoints

What are the experimental endpoints for this study segment?
Uncheck this box to remove all text from the box below

2.A. Completion of 12-18 hr non-survival experiment.

2.B. End of 6 months of chronic deafness with brief electrical stimulation at 2-wk intervals followed by a terminal 12-18 hr non-survival experiment.

2.C. End of ~3 months of training, 4 months of deafness, CI implantation, 4 months chronic electrical stimulation with psychophysical testing, Ending with terminal 12-18 non-survival experiment.

What clinical signs or other criteria will be used to determine that an animal must be removed from the study ahead of schedule (Humane Endpoint)?
Weight loss greater than 20% compared to pre-study weight or age-matched controls.
Inability to eat or drink.
Provide additional details about any checked items, or any other endpoint criteria:

Animals will be euthanized in the case of any intractable post-surgical infection or other adverse reaction.

Euthanasia

Will all research animals be euthanized at the conclusion of this experiment/study segment?
Yes
Indicate the euthanasia methods that will be used on the animals from these experiments - Check all that apply You MUST...

Animal number calculation for experimental part **Implants**

Cat		
	Max	Description
	16	total implants
	16	**Cat**

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Procedure Descriptions

Cat

Total number of animals

Species	**Max**
Cat	28

USDA Pain Category	Species	Number of Animals	Number of Animals
USDA Category D	Cat	28	0

Animal Numbers Justification

Explain how the animal numbers were determined.

Will animals experience unrelieved pain/distress (category E procedures)?

Provide the scientific justification for the number of animals required for these studies.
Uncheck this box to remove all text from the box below

The acute experiments (Segments 1A and 2A) consist of electrical stimulation through a cochlear implant while recording from 32 sites along the tonotopic (i.e., frequency-representation) dimension of the inferior colliculus. The inferior colliculus recording serves as a monitor of activation of the ascending auditory pathway. Multiple experimental goals are addressed in each animal. That is, given a new electrode design, we will evaluate ease of implantation, threshold for activation of nerve fibers, specificity of activation, interaction among channels, transmission of timing information, and efficiency of stimulation with various waveforms. We anticipate that we will need to test cochlear implants in 2 cats and in 2 cats to adequately characterize those devices. Additionally, in 1.B., we have allowed for 2 animals in which to work out technical challenges of chronic cochlear implantation and stimulation.

In studies of effects of chronic deafness and cochlear implantation (1.C and 1.D) we have allowed enough animals to give an adequate estimate of the amount of inter-animal variation.

Segment 2 is technically more novel and challenging. For that reason, the numbers of animals in Segments 2.B. (8) and 2.C. (6) have been chosen to allow for the possibility of implant design modifications and some failures.

Will animals experience unrelieved pain/distress (category E procedures)?
No

Drugs & Agents

Anesthesia

Will animals receive anesthesia agents?
Yes

Species	Name of Drug/Agent	Dose Range *(list dose in mg/kg body weight)*	Route *(SQ, IP, IV etc.)*	Frequency *(how often given?)*	Duration of Treatment *(how long will treatment last?)*
cat	ketamine	25 mg/kg	IM	once	once
cat	isoflurane	0.5-2.0% in oxygen	IH	continuous during surgery	during surgery
cat	bupivicaine	0.2 ml/site	SQ	once, around wound margins	once
cat	nembutal	25 mg/kg	IV	~30-min intervals, as needed	during surgery
cat	acepromazine	0.1-0.15 mg/kg	IM	once, at 14-day intervals	throughout ~4 months of chronic data collection

How will the anesthesia be administered to the animals?

Will anesthetic gases be used in this project?
Yes

Method of Administration:
Answer:

vaporizer, 0.5-2% in oxygen

Agent Used:
Answer:

Isoflurane

Method Used to Capture Waste Gases:
Answer:

f/air canister

Analgesia

Will animals receive analgesics, sedatives, or other therapeutic agents (e.g. antibiotics, supplemental fluids, etc.)?
Yes

Species	Name of Drug/Agent	Dose Range *(list dose in mg/kg body weight)*	Route *(SQ, IP, IV etc.)*	Frequency *(how often given?)*	Duration of Treatment *(how long will treatment last?)*
cat	buprenorphine	0.005-0.01 mg/kg	SQ	12-hr intervals	48 hr post-op
cat	meloxicam	0.2 mg/kg	PO	once	pre op

Experimental & Other Agents

Will other agents be administered to animals?
Yes

Species	Name of Drug/Agent	Dose Range *(list dose in mg/kg body weight)*	Route *(SQ, IP, IV etc.)*	Frequency *(how often given?)*	Duration of Treatment *(how long will treatment last?)*
cat	glycopyrelate	0.02 mg/kg	IM	once	once, 30-min pre-op
cat	dexamethasone	1 mg/kg	IM	once	30 min pre-op
cat	ampicillin	10 mg/kg	IV	once	at beginning of surgery
cat	clavamox	62.5 mg/kg	PO	2/day	14 days post-op

Will Controlled Substances (as defined by the U.S. Drug Enforcement Administration) be used in the study?
Yes - list CSUA number:

Indicate which controlled substances will be used - Check all that apply:
CSUA #:

Will non-pharmaceutical grade (i.e. chemical grade) agents be used in live animals
No

Animal Locations & Husbandry

Food or Water Variations

Indicate the food or water variations that will be implemented in this protocol - Check all that apply:

Justification for the Food or Water Variations

Do the experiments or procedures require any special dietary requirements or restrictions, or additions to the normal drinking water?
No

Will food or fluid be restricted on this protocol?
Yes

Describe in detail the food or water restriction procedures.

During periods of psychophysical testing (normally 5 days per week), animals will receive all their food in the laboratory . They will receive canned commercial cat food as behavioral reinforcement during psychophysical trials each day lasting as long as the animal is willing to work, typically 30-60 minutes. After the trials each day, the animal will be offered dry cat chow ad libitum for ~30 min prior to returning to the vivarium.

Animal Husbandry Variations

Indicate the animal husbandry variations that will occur - Check all that apply:

Justification for the Animal Husbandry Variations

Will there be deviations from standard environmental enrichment on this protocol?
No

Will wire-bottom caging be used?
No

Researcher-Maintained Animals

Will LAB STAFF provide basic routine husbandry and care for the animals?

Will animals be held in the lab (outside of the vivarium) for more than 12 hours?

An Emergency Plan is REQUIRED for the following scenarios:

Will animals be held outside of ULAR animal facilities (e.g. in the researcher's laboratory) for more than 12 hours?
No

Will the research team provide routine husbandry and care for animals housed in ULAR animal facilities?
No

Other Husbandry/Housing Variations

Describe any other variations or special considerations (not already captured in the sections above).

Will there be other husbandry deviations or special considerations regarding the animal use in this protocol?
No

Animal Locations

Indicate all locations where live animal procedures and/or housing will take place - Check all that apply:

Will any live animals (owned by UCI) be taken to offsite (non-UCI) locations for procedures?

Will any non-UCI site(s) and/or offsite locations be used for any procedures on UCI-owned animals?
No

List the lab areas (outside of the vivarium) where live animals are taken for any procedures or housing.
Uncheck this box to remove all text from the box below

Building	Room #	Location will be used for:		
		Non-surgical Procedures	Surgeries	Housing > 12 hrs
			Y	
		X		

Hazards & Safety

Chemical Hazards

Requirements for the Use of Potentially Hazardous Chemicals or Agents:

Biological Materials, Primary Cells or Cell Lines

Requirements for Use of Biological Materials:

Infectious Agents

Requirements for the Use of Infectious Agents:

Recombinant DNA

Preparation & Use of rDNA

Radioactive Hazards

Radiation Use Authorization (RUA) #:

Removal of Radioactive Waste & Monitoring of Radioactivity

Creation of New Transgenic Animals

Are you creating a NEW strain of transgenic animal by crossbreeding 2 different strains?

Animal Biosafety Levels

Indicate the animal biosafety levels - Check all that apply:

Other Hazards or Safety Considerations

Other Protocol Information

Provide any other information about this animal-use protocol (that is not captured in any other sections or tabs).

Personnel

Principal Investigator (PI)

Faculty Sponsor

Co-Investigator/Senior Researcher

Research Personnel

Other Research Personnel

Additional Personnel Information

Emergency Contact Information
Emergency Contact:

Add New User

Training Requirements

PI Qualifications

Description of PI Qualifications

Training Plan for Study Team Members

Describe the Principal Investigator's Qualifications to perform or oversee the research.
Uncheck this box to remove all text from the box below

is the director of the laboratory and is responsible for the design of the study and for oversight of all personnel. will actively participate in all surgery and data collection, and will oversee daily care and monitoring of the animals. has over /rs experience in experiments using cats.

Links to Other Protocols

Other Regulatory Review Requirements

Indicate if other regulatory reviews are required for this protocol - Check all that apply:

If additional details need to be discussed regarding any of the links above, describe them below.

Does this research involve the use of human adult or embryonic stem cells (including induced pluripotent stem cells) in live animals?
No

Is Institutional Biosafety Committee review/approval needed for any part of this research?
No

Is Institutional Review Board (IRB) review/approval needed for any part of this research?
No

PI Certification

PI Certification

I hereby acknowledge and assure the following:
By clicking this button, I certify that the above statements are understood and will be followed by all research team members.