


Translational Hearing Center

Resources for CTR Investigators

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Current strategies to rehabilitate sensory deficits


Hearing loss:

- **Hearing Aids, often effective**
 - Frequency-limited to surviving sensory cells
 - Amplifies noise, poor frequency discrimination
 - Accessibility limited to cost and need for fitting to HL
 - Social stigma
- **Cochlear or Bone-anchored Implants, can be outstandingly effective**
 - Invasive, needs surgery, no guarantee of efficacy
 - Limited by battery life
 - Limited to surviving cochlear neurons

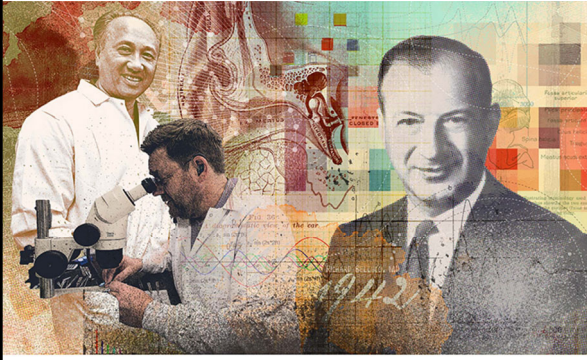
Vestibular Implants:

- **Still at translational stage in humans, very small clinical trials**

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established in June 2019



Creighton Magazine, August 2019

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Severe bacterial infections are treated with life-saving aminoglycoside antibiotics

- Severe infections induce systemic inflammatory responses and can modulate permeability of blood-brain barrier (Abbot et al., 2006)
- Systemic inflammation increases the cochleotoxicity and hearing loss induced by aminoglycosides (*iatrogenic drug-induced hearing loss*)
- **Thus, those in need of aminoglycoside therapy are those most at risk of drug-induced hearing loss**
- *Yet, ~95% of nonclinical ototoxicity studies to date use healthy subjects*

Thus, candidate othotherapeutics must be also be efficacious in models of the medical setting in which they are to be employed

Koo et al., 2015

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Overall Goal

Build a critical mass of Center-affiliated Investigators that identify strategies and candidate compounds (ototherapeutics) to preserve or restore hearing and vestibular function (all reference to hearing include vestibular (dys)function)


Rationale:

- **Hearing loss affects at least 500 million worldwide**
 - Noise-induced hearing loss (millions at risk each year; m/o/rec)
 - >400 genomic and mitochondrial polymorphisms lead to HL
 - Iatrogenic causes of hearing loss (hospital/medication based)
 - Age-related hearing loss, including neurodegenerative disease
 - Teratogenic-induced hearing loss (e.g., alcohols and solvents)
 - Tinnitus and central auditory processing disorders

Consequences:

- Prelingual: >\$1.5 mil. socioeconomic cost, diminished relationships
- Accelerates aging, diminished relationships, falls, cognitive decline

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Develop therapeutics to preserve or restore hearing and vestibular function (peripherally or centrally)

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graph TD
    A[Identify genetic or clinical settings that lead to hearing loss] --> B[Design and screen candidate othotherapeutics]
    B --> C[Identify optimal local or systemic delivery mechanisms]
    C --> D[Drug trafficking/PK/PD (ADME, local or systemic)]
    D --> E[Validate lead othotherapeutic hits to prevent hearing loss in clinically-relevant scenarios (mechanisms of protection in preclinical models)]
    E --> F[Clinical trials in humans (with BTRNH and UNMC; Phase II?)]
    E --> G[Commercialization (SBIRs and STTRs)]
    
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Initial Funding: Bellucci DePaoli Family Foundation

- 11 competitively-awarded Pilot Projects (2019-2021; \$610k) resulting in at least 3 federally-sponsored studies (>\$3 m) to date
- Infrastructure enhancements
- One 4-year PhD studentship
- Post-doc and graduate student research awards (\$55k)
- Currently negotiating a multi-year gift to fund:
 - 3 PhD and 2 post-doctoral trainees annually
 - 4 post-doc and 4 PhD research awards
 - 1 (clinical) faculty pilot project per year
 - Additional infrastructure enhancements



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CoBRES and similar IDeA programs in Omaha

Center for the Molecular Biology of Neurosensory Systems
Shelley Smith, UNMC, recently completed Phase III in 2020

Center for Research in Human Movement Variability
Nikolaos Stergiou, UNO, Phase II (human)

Center for Perception and Communication in Children
Lori Leibold, BTRNH, Phase II (human)

Cognitive Neuroscience of Development and Aging Center
Anna Dunaevsky, UNMC, Phase I (human and preclinical)

Great Plains IDeA-Clinical & Translational Research Network
Matthew Rizzo, UNMC, Phase II (human and preclinical)

Nebraska INBRE Program
Paul Sorgen, UNMC (undergrads)










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- The Center is also a tri-institutional Center, consisting of:
 - CU: focus on developing oth^{er}apeutics to prevent drug- or noise-induced HL loss
 - BTRNH: focus on gene therapy to reverse congenital hearing loss
 - UNMC: focus on central neural mechanisms of hearing loss
- Train next generation of researchers and clinicians
- Commercialize discoveries (e.g., Ting Therapeutics)
- Become an academic leader in translational auditory neuroscience

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Funding: National Institute of General Medical Sciences




- Center of Biomedical Research Excellence (CoBRE) Award from NIGMS, March 4th, 2021, for 5 years (phase 1); \$1.5m dc funds:
- Administrative Core: coordinates all activities, funds 4x \$50k faculty Pilot Projects, and multiple Research Vouchers each year, recruit new junior faculty, coordinates mentorship to obtain R01-level funding, facilitate sustainability
- Drug Discovery & Delivery Core: med chem, in silico, in vitro and in vivo screening, PK and PD in inner ear tissues via fee-for-service model to increase sustainability
- Auditory & Vestibular Technologies Core: cellular and non-invasive electrophysiology, advanced imaging, molecular biology and mass spectrometry via fee-for-service model to increase sustainability
- Promote Auditory-Vestibular research via 3 Research Project Leaders at any 1 time
 - Goal: obtain R01-level funding within 3 years
 - Mentored by Internal and External mentors to gain independent research funding
 - Enhance research excellence and capacity to increase potential for start-up spin-offs

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Funding: National Institute of General Medical Sciences



- Center of Biomedical Research Excellence (CoBRE) Award from NIGMS, for 5 years (phase 1); \$1.5m dc funds:

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Overall Aims

Aim 1: Establish translational auditory & vestibular research by bringing junior and senior researchers and clinicians together with an oth^{er}apeutic approach to preserve or restore these sensory modalities.



Aim 2: Support junior investigator projects in hearing loss & vestibular deficits.

- Three contemporaneous research project leaders (RPLs)
- A CoBRE-supported tenure-track hire (UNMC, CND and hearing loss)
- Four Pilot Projects per year
- Research vouchers to support "bench" for Pilot Projects and RPL slots

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Research Project Leader: **Tejbeer Kaur**
Biomedical Sciences, SoM

Role of macrophages and fractalkine in degeneration and repair of cochlear synapses



NIHL occurs due to loss of synapses between cochlear sensory cells and afferent neurons
Noise-induced synaptic loss precedes hair cell loss or threshold elevations, i.e., *cochlear synaptopathy or hidden hearing loss*
Immune-mediated fractalkine (FKN) signaling is a positive regulator of SGN survival and synaptic repair in other systems.

Specific hypotheses:
Aim 1. FKN treatment can repair damaged ribbon synapses in hair cells after noise trauma
Aim 2. Macrophages attenuate synaptic loss and/or repair damaged synapses after noise trauma

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Research Project Leader: **Jeffery North**
Pharmacy Sciences

Development of novel therapeutics for treatment of mycobacterial infections



No FDA-approved therapeutics for hospital-prescribed medication-induced HL
HTS screening revealed two compounds that target mycobacterial proteins only, with negligible toxicity in mammalian cells
Development of these compounds will reduce dependence on aminoglycosides with their known ototoxic effects

Specific Aims:
Aim 1. In vitro and in vivo assessment of the potential ototoxic and cytotoxic effects of a novel series of antimycobacterial agents
Aim 2. Design and synthesis of novel and selective anti-mycobacterials with high potency, no ototoxicity, and optimized physicochemical properties

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Research Project Leader: **Padmashri Ragunathan**
UNMC: Neurological Sciences

Effects of prenatal alcohol exposure on synaptic plasticity and auditory processing

Fetal alcohol spectrum disorders (FASD) is a major teratogen (1-5%) inducing central auditory processing disorders
Growing evidence that neuronal plasticity is impaired in FASD including reduction in the number of dendritic spines and alterations in AMPA receptor function



Hypothesis: Does prenatal alcohol exposure (PAE) impair auditory processing?

Specific Aims:
Aim 1. Is central auditory processing altered in mice with PAE?
Aim 2. Does PAE impair synaptic AMPAR dynamics and AMPAR-mediated synaptic transmission in the primary auditory cortex?
Aim 3. Can activation of TrkB normalize AMPA Receptor function, dendritic spines and auditory processing in a mouse model of FASD?

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Research Project Leader: **eligibility**






- 1) Meritorious proposals will have a focus aligned with Center's mission: *mechanisms of hearing loss or strategies that preserve/restore hearing*
- 2) 2 RPL slots at Creighton, 1 slot alternates between BTNRH and UNMC
- 3) RPL slot = \$200,000 per year, direct costs for up to 3 years
- 3) Mentored by an Internal (5% FTE) and an External Mentor
- 4) Must be a junior investigator (<\$215,000 in funds from single agency)
- 5) Must submit proposal for R01-level funding (≥\$250k) by end of Year 2
- 6) Must meet typical NIH compliance criteria, e.g., IACUC approvals etc.
- 7) Year 3 funding dependent on R01-level proposal submission
- 8) Success is receipt of R01-level funding, rolls off RPL position
- 9) Replacement RPL proposals requested when slot opens up
- 10) Total RPL funding cannot exceed 3 years

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Research Project Leader: **Tal Teitz**
Pharmacology & Experimental Neuroscience, SoM

Repurposing a B-Raf kinase inhibitor to prevent cisplatin- and noise-induced hearing loss

No FDA-approved therapeutics for hospital-prescribed medication-induced HL
HTS screening identified several kinase-inhibitors as cytoprotective
B-Raf kinase inhibitor is an FDA-approved compound
In silico screening suggests that B-Raf be re-purposed as an othotherapeutic against CIHL and NIHL and pilot data supports this screen.


Specific Aims:
Aim 1. B-Raf inhibitor dabrafenib is effective against CIHL *in vivo*
Aim 2. B-Raf inhibitor dabrafenib is effective against NIHL *in vivo*

Graduated with R01 (~\$1.5 million over 5 years) to expand these specific aims

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COBRE-funded junior investigator hire at UNMC



Criteria similar to RPL eligibility:

- 1) Search begins in Year 3, starts beginning Year 4, max 2 years
- 2) Hired on tenure-track with \$200k per year, + UNMC-matching funds
- 3) Focus: *mechanisms of hearing loss during Central Neurodegenerative Disease*
- 4) Internal Mentor to provide project and proposal feedback
- 5) Shortlist of preferred candidates presented to Center's External Advisory Committee
- 6) Hire to be in Neurological Sciences or Pharmacology & Experimental Neuroscience
- 7) Hire to prepare RPL and/or R01-level proposals
- 8) COBRE start-up ends when RPL slot or R01-level funding begins

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Eligibility for Pilot Projects

Similar to RPL eligibility:

- 1) Meritorious proposals will have a focus aligned with Center's mission: *mechanisms of hearing loss or strategies that preserve/restore hearing*
- 2) 4-5 1-year Pilot Projects each year, each @ \$50,000
- 3) Preferably, applicants eligible for an RPL position
- 4) Must have tenure-track position at **Creighton**, **BTNRH** or **UNMC**
- 3) Meet weekly with *Internal Mentor* regarding progress
- 4) Mentor to provide proposal and project feedback
- 5) Proposals are recommended for funding by **EAC** with NIH benchmarks
- 6) **Potential 2nd year funding via competitive review and need**
- 7) Prepares applicant for RPL proposals
- 8) **Senior faculty eligible for new directions for 1 year only**
- 9) **Must meet typical NIH compliance criteria, e.g., IACUC approvals etc.**

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DDD Core

- 2) Establish a medicinal chemistry pipeline to optimize chemical entities used in research projects or discovered in 1) or in RPLs
The DDD Core has utilized existing medicinal chemistry facilities to optimize multiple drugs and synthesize new drugs (e.g., PROTACs) as otoprotectants.
- 3) Establish drug delivery and pharmacokinetic/pharmacodynamic (PK/PD) methodologies
The DDD Core has developed perilymph collection and UPLC-MS/MS analysis from guinea pigs, and further developed new techniques for cochlear cellular biodistribution of drugs using MALDI-MSI
- 4) Developed a sustainability plan for DDDC services
The DDD Core has published a website and presented seminars to introduce our capabilities and services with a **fee structure** for all services provided; weblinks to be provided by email after the seminar
- 5) Training and mentoring
NIDCD grant awards include Fleegel, F30; Ingersoll, F32; Hati, R21 (ECR)
- 6) Startup companies: Ting Therapeutics has received SBIR phase I/II awards from NIDCD (~\$2 million)

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Research Vouchers: eligibility




Criteria to be eligible to submit Pilot Projects (similar to RPL eligibility):

- 1) Meritorious proposals will have a focus aligned with Center's mission: *mechanisms of hearing loss or strategies that preserve/restore hearing*
- 2) Available in \$1,000 increments, to a max of \$5,000 per cycle (every six months)
- 3) To acquire data to be competitive for a Pilot Project award or an RPL slot
- 4) Has a tenure-track position
- 3) Proposal reviewed by **Executive Team**
- 4) Prepares applicant for Pilot and RPL proposals
- 5) **Must have typical NIH compliance criteria, e.g., IACUC approvals etc.**
- 6) **Vouchers to be spent in Center Cores (see below)**

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Translational Hearing Center

Auditory & Vestibular Technology (AVT) Core







David He Director Michael Nichols Co-Director David Smith Co-Director

To provide Core services to RPLs, Center investigators, outside investigators, companies, etc on a fee-for-service basis

- 1) Provide state-of-the-art methodologies and instrumentation for auditory and vestibular studies in preclinical models
Auditory and vestibular neurophysiology and noninvasive electrophysiology, (confocal) imaging, molecular biology (including single cell RNAseq) and mass spectrometry (LC/MS), with plans to add new imaging equipment, including confocal microscopy clone and super-resolution confocal microscopy.





Satellite noninvasive electrophysiology facility in Durham Behavioral Core (Samuelson)

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Drug Development and Delivery (DDD) Core

Jian Zuo Director Sandor Lovas Co-Director Alekha Dash Co-Director Gopali Jadhav Core Manager

To provide Core services to RPLs, Center investigators, outside investigators, companies, etc on a fee-for-service basis

- 1) Develop in silico, in vitro and in vivo high-throughput screening paradigms to discover and validate novel therapeutics for auditory disorders.
The DDD Core has successfully employed in silico screens to identify a large number of candidate otoprotectants against cisplatin-, aminoglycoside antibiotic- and noise-induced hearing loss, including many FDA-approved drugs for other indications that can be re-purposed

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AVT Core

- 2) Mentor Core users in multidisciplinary research to successfully compete for research funding
NIDCD grant awards include Teitz, R01; Fleegel, F30; Ingersoll, F32.
R01 proposal under review, RPL Kaur, scored highly, potentially fundable (>\$2 m over 5 years)
- 3) Developed a sustainability plan for DDDC services
The AVT Core has published a website and presented seminars to introduce our capabilities and services with a **fee structure** for all services provided; weblinks to be provided by email after the seminar

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Translational Hearing Center

Bellucci Symposium 2021

Friday, June 4, 2021
Two-Day Virtual Event

Annual Bellucci Symposium on Hearing Research
Focus on Drug Therapeutics
Creighton University, Omaha, Nebraska
Free Registration

Keynote Address by 2021 Bellucci Prize Winner:
Hilal V. Vignithan, PhD
UNC/NIH

<p>Podium Presentations:</p> <p>Joseph Cude, PhD, University College London</p> <p>Richard Sakic, PhD, State University of New York at Buffalo</p> <p>Alan Cheng, MD, FACS, Stanford Hearing Lab</p> <p>Robert Frisoux, Jr, PhD, University of South Florida</p> <p>David Spiller, PhD, University of Washington</p>	<p>Corporate/Academic Speakers:</p> <p>John DyrWald Software, PhD, Chief Development Officer, Azeusa Therapeutics</p> <p>Hubert Dzwonkiewicz, MD, PhD, University of Subjerg</p> <p>Marisa Zullo, PhD, The Therapeutic Ltd</p> <p>Michelle D. Valdes, PhD, Alkermes Inc</p> <p>Debashree Mukherjee, PhD, Founder and CEO, Nance Therapeutics</p>	<p>2021 Trainee Award:</p> <p>Roopam Singh, Indiana University, PT, PhD, Northwestern University</p> <p>Call for Abstracts:</p> <p>Learn more: https://belluccisymposium.weebly.com/</p>
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Sponsored by the Bellucci DePaul Society Foundation.
Honored by Richard J. Bellucci, MD, PhD, a national leader in the utilization of our surgical techniques to treat conductive hearing loss.

Theme for Bellucci Symposium 2022 (early June): Age-related hearing loss



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Commercialize othotherapeutics hits to be a global leader in preserving or restoring hearing

Apply for patents:


- Zuo/Salehi - Provisional Patent Applications filed by Creighton
- Licensing can also generate new income streams

Establish an incubator at Creighton for startups (STTR/SBIR)

- Support from University/Consultant hired
- Participate in SHARPhub (Kansas City/Michigan)




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Innovation

Thematic: Valid othotherapeutics will be efficacious in the medical settings in which they are employed

Mentorship Plan to integrate RPLs with Internal Mentors, and External Mentors to guide translation into human studies

External Advisory Committee for review of:

- Research Project Leader proposals, and
- Overall Center performance

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Translational Hearing Center

Commercialize othotherapeutics hits to be a global leader in preserving or restoring hearing

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Establish an incubator at Creighton for startups (STTR/SBIR)

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Attract sponsored research contracts from Big Pharma:

- Novartis
- Boehringer Ingelheim
- Decibel Therapeutics
- Frequency Therapeutics
- Manros Therapeutics

Build revenue stream for longer-term Center sustainability

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Translational Hearing Center

Sustainability



Institutional Commitments from:

- Creighton, BTNRH and UNMC to recruit eligible faculty hires for bench
- Interaction with local CoBREs and IDEA-funded Awards for increased efficacy


Replace COBRE funding with other support:

- Independent federal research funding (R01s, DoD, etc)
- Industry Licensing
- Patents Sales?

SharpHUB will guide this latter process

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Closing Comments on COBRE:

Funding opportunities exist for UNMC investigators within the Center's theme mechanisms of hearing loss or strategies that preserve/restore hearing

Writing proposals/manuscripts forges closer interactions and collaborations between investigators and institutions

Challenges Institutional Administrations to act, deadlines matter

Enables research growth and translation into clinic to impact lives

Theme, funds, and oversight challenges Center investigators to remain focused on the mission

COBRE can re-direct resources to specialized topics of actual need

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Translational Hearing Center Acknowledgements

Executive Team
 Peter S Steyger (PD/PI)
 Jian Zuo (Drug Discovery & Delivery Core)
 David He (Auditory & Vestibular Technology Core)
 Anna Dunaevsky (Site Director, UNMC)
 Dominic Cosgrove (Site Director, BTNRH)
 Stacy Barney (Program Administrator)
 Jacob Walker (Admin Assistant)

Administrative Advisory Committee
 Laura Hansen (CU)
 Nick Stergiou (UNO)
 Ryan McCreery (BTNRH)
 Anna Dunaevsky (UNMC)

Internal Advisory Committee
 Dominic Cosgrove (BTNRH)
 Jason Bartz (CU)
 Howard Fox (UNMC)
 Evan Robinson (CU)

External Advisory Committee
 Daniel Tollin (U Colorado, Chair)
 Ronna Hertzano (U Maryland)
 Amanda Lauer (JHU)
 Alain Daboub (Toronto)
 Lisa Hunter (Cincinnati Children's)

Creighton Institutional Officials
 Fr. Hendrickson (President)
 Thomas Murray (then-Provost)
 Robert Dunlay (Dean, SoM)
 Ray Stoupa (SoM Dean's Office)
 Jerrod Lawrence (BMS)
 Rebecca Scott (BMS)
 Olivia Shope (BMS)

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Admin Core: External Mentor

- 1) Must have had R01-level funding
- 2) Must have active research laboratory
- 3) Must have experience in RPL research topic
- 4) Must (have) serve(d) on study section as member or ad hoc
- 5) Must meet/discuss weekly with RPL regarding project progress
- 6) Must respond to **evaluation questionnaires**
- 7) Will provide Career Guidance
- 8) **Be a practicing translational or clinical researcher to guide direction**
- 9) **Will receive a significant fee for effort**
- 10) **May visit Omaha, as needed**

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Interactive Discussion

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Admin Core: External Advisory Committee

Cannot be named in proposal, nor contact with potential members

All members will

- 1) the capability to serve at least one 5-year term, and
- 2) extensive grant-review experience in topics relevant to the Center.

In addition, at least one will be:

- 3) Familiar with managing proposal and Center reviews (Tollin, chair)
- 4) A clinician-scientist familiar with hearing loss and rehab (Hertzano, UMd)
- 5) Auditory nerve and central physiology (Lauer, JHU)
- 6) A research audiologist (TBA)
- 7) **experienced in translating candidate therapeutics towards clinical trials and into clinical practice (Daboub, Toronto, and Hertzano, UMd)**

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Admin Core: Internal Mentor

- 1) Must have had R01-level funding
- 2) Must have active research laboratory
- 3) Must have experience in topic of RPL
- 4) Must (have) serve(d) on study section as member or as ad hoc
- 5) Meet/discuss weekly with RPL regarding project progress
- 6) Must respond to **evaluation questionnaires**
- 7) Will provide Career Guidance
- 8) Will have access to Center Research Cores
- 9) **Will receive 5% salary support for effort**

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Admin Core: External Advisory Committee

Primary roles are to monitor or review:

- 1) Proposals from replacement RPLs, using AUD criteria
- 2) RPL Progress (milestones: personnel, abstracts, papers, proposals)
- 3) Efficacy of Mentorship of RPLs and trainees
- 4) Pilot Projects
- 5) Research Cores (equipment, usage, voucher system)
- 6) Proposals for COBRE-supported Faculty hire, eligible for RPL
 Initial: **translational auditory disorders with central neural degeneration**
- 7) Overall progress in establishing and sustaining the Center
- 8) Will visit Omaha at least once a year, with at least Zoom meetings

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