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

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 ototherapeutics must be also be efficacious in models of the medical setting in which they are to be employed

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

- Identify genetic or clinical settings that lead to hearing loss
- Design and screen candidate ototherapeutics
- Identify optimal local or systemic delivery mechanisms
- Drug trafficking/PK/PD (ADME, local or systemic)
- Validate lead ototherapeutic hits to prevent hearing loss in clinically-relevant scenarios (mechanisms of protection in preclinical models)

 Clinical trials in humans [with STTR and UNMC; Phase IV]
 Commercialization [SBIRs and STTRs]

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 [dis]function)

Rationale:
- Hearing loss affects at least 500 million worldwide
- Noise-induced hearing loss (millions at risk each year; m/o/rec)
- >400 genic and mitochondrial polymorphisms lead to HL
- Iatrogenic causes of hearing loss (hospital/medication based)
- Age-related hearing loss, including neurogenerative 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

Peter S. Steyger, PhD
Director, Translational Hearing Center
Creighton University
1. 11 competitively-awarded Pilot Projects (2019-2021; $150k) resulting in at least 3 federally-sponsored studies (~$3 m) to date
2. Infrastructure enhancements
3. One 4-year PhD studentship
4. Post-doc and graduate student research awards ($55k)
5. Currently negotiating a multi-year gift to fund:
   a. 3 PhD and 2 post-doctoral trainees annually
   b. 4 post-doc and 4 PhD research awards ($55k)
   c. 1 (clinical) faculty pilot project per year
   d. Additional infrastructure enhancements

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**Initial Funding: Bellucci DePaoli Family Foundation**

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**Translational Hearing Center**

- The Center is also a tri-institutional Center, consisting of:
  - UNMC: focus on developing ototherapeutics to prevent drug- or noise-induced HL loss
  - BTNRR: 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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**Translational Hearing Center**

**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
  - Nikolai Stengou, UNO, Phase II (human)
- Center for Perception and Communication in Children
  - Lori Letondor, BTNRR, Phase II (human)
- Cognitive Neuroscience of Development and Aging Center
  - Anna Danzovsky, UNMC, Phase II (human and preclinical)
- Great Plains IDeA Clinical & Translational Research Network
  - Matthew Reznik, UNMC, Phase II (human and preclinical)
- Nebraska INBRE Program
  - Paul Sorgen, UNMC (undergrads)

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**Translational Hearing Center**

**Funding: National Institute of General Medical Sciences**

1. 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: 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
   - Developmental 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
   - Auditory & Vestibular Technologies 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

2. Administrative Core:
   - Mentored by Internal and External mentors to gain independent research funding
   - Aims:
     a. Goal: obtain R01-level funding within 3 years (~$1.75m over 5 years)
     b. Mentored by Internal (5% FTE) and External mentors to gain independent research funding
     c. Enhance research excellence and capacity to increase potential for start-up spin-offs

3. Drug Discovery & Delivery Core:
   - Mentored by Internal (5% FTE) and External mentors to gain independent research funding
   - Aims:
     a. 3 PhD and 2 post-doctoral trainees annually
     b. 4 post-doc and 4 PhD research awards
     c. Enhance research excellence and capacity to increase potential for start-up spin-offs

4. Auditory & Vestibular Technologies Core:
   - Mentored by Internal (5% FTE) and External mentors to gain independent research funding
   - Aims:
     a. 3 PhD and 2 post-doctoral trainees annually
     b. 4 post-doc and 4 PhD research awards
     c. Enhance research excellence and capacity to increase potential for start-up spin-offs

5. Promote Auditory-Vestibular research via 3 Research Project Leaders at any 1 time
   a. Goal: obtain R01-level funding within 3 years
   b. Mentored by Internal and External mentors to gain independent research funding
   c. Enhance research excellence and capacity to increase potential for start-up spin-offs

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**Translational Hearing Center**

**Overall Aims**

Aim 1: Establish translational auditory & vestibular research by bringing junior and senior researchers and clinicians together with an ototherapeutic 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)
   - Forty Pilot Projects per year
   - Research vouchers to support “bench” for Pilot Projects and RPL slots
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 ototrophic against CIHL and NHL 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 NHL in vivo

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

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-mycobacterial with high potency, no ototoxicity, and optimized physicochemical properties.
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

5) Proposal reviewed by Executive Team

6) Potential 2nd year funding via competitive review and need

7) Pass a proposal and project feasibility

8) Mentor to provide feedback

9) Proposals recommended for funding by EAC with NIH benchmarks

10) Must meet typical NIH compliance criteria, e.g., IACUC approvals etc.

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

5) Proposal reviewed by Executive Team

6) Preparatory and postdoctoral proposals

7) Vouchers to be spent in Center Cores (see below)

Drug Development and Delivery (DDD Core)

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 ototoxicants against cisplatin-, aminoglycoside antibiotic- and noise-induced hearing loss, including many FDA-approved drugs for other indications that can be re-purposed.

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 ototoxicants.

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; He, R21 (EVR)

6) Startup companies: Ting Therapeutics has received SBIR phase I/II awards from NIDCD (~$2 million)

Auditory & Vestibular Technology (AVT) Core

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 and super-resolution confocal microscopy.

Satellite noninvasive electrophysiology facility in Durham Behavioral Core (Samuelson)

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

Innovation

Theme: Valid ototherapeutics 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,
- Overall Center performance

Sustainability

Institutional Commitments from:
- Creighton, BTNRMH 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

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

Apply for patents:
- Zuo/Salehi: Provisional Patent Application 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)

Attract sponsored research contracts from Big Pharma:
- Novartis
- Boehringer Ingelheim
- Decibel Therapeutics
- Frequency Therapeutics
- Manros Therapeutics

Build revenue stream for longer-term Center sustainability

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
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)

Interactive Discussion

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 as 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

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)

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

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