Investigational medicines for the inner ear: clinical trial design considerations

Colleen G. Le Prell, Ph.D.
Emilie and Phil Schepps Professor of Hearing Science
Chair, Department of Speech, Language, and Hearing
School of Behavioral and Brain Sciences
University of Texas at Dallas

1

Disclosures

Co-inventor on patents owned by the University of Michigan

- Miller, J.M., Le Prell, C.G., and Yamashita, D. US 7,786,100 B2, Composition and method of treating hearing loss. Awarded August 31, 2010. (Delayed Treatment/Vitamin E, Salicylate)
- Miller, J.M., Le Prell, C.G., Schacht, J., and Prieskorn, D.M. US 7,951,845, Composition and method of treating hearing loss. Awarded May 31, 2011. (ACEMg)

Paid consultant on issues related to clinical trial design

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- 3M, Inc.
- Q30, Inc.
- MaxSound, Inc.
- Sound Pharmaceuticals, Inc.
- Edison Pharmaceuticals, Inc.

- **Emilie and Phil Schepps Distinguished Professorship in Hearing Science**

2

While many OTC dietary supplements are available online/in stores, there are NO products approved by the FDA for NIHL, DIHL, or SNHL prevention or hearing restoration at this time

OTC dietary supplements marketed with an FDA disclaimer do not have to be studied for safety or efficacy

3

Overview

- **Introduction**
- Auditory measures
  - Outcome, endpoint, and indication definitions
  - Objective and subjective test options
    - Systematic review of tests used in previous clinical trials
    - Hearing-in-noise test endpoints
- Possible participant populations for hearing loss prevention/hearing restoration studies
  - NIHL, DIHL, and SNHL indications require different populations
- Types of investigational medicines of interest for hearing loss prevention and hearing restoration

4

Development of Inner Ear Medicines: The Good News

- Extensive documentation of both *in vitro* and *in vivo* protection of hair cells and hearing sensitivity using various otoprotective drugs (antioxidant and other agents) to prevent various noise injuries as well as ototoxic drug insults
- Comparing effectiveness of agents across pre-clinical drug studies complicated by use of differences in species, treatment onset time, and duration of therapy, as well as use of different exposures with different injury severity
- This is active clinical trial space as evident from both PubMed searches and clinicaltrials.gov trial listings
- There are now more than 40 companies developing drugs for potential prevention of acquired hearing loss and/or hearing disorders (NIHL, DIHL, ARHL) as well as biologics for hair cell regeneration

5

The Not-So-Good News About Pre-Clinical Research

- Preclinical research has relied on multiple species
  - Guinea pigs, rats, chinchillas, mice
- With injury models that often fail to replicate the real-world condition
  - Noise exposures that induce profound pathology over hours, not years
  - Drug insults that induce profound pathology over days, not months or years
- With varying degrees of injuries for different species x drug combinations
  - How to compare prevention of 20 dB loss versus reduction of large (50-70 dB) loss?
- Using multiple treatment paradigms
  - Onset of treatment may be pre-injury (prevention) or post-injury (rescue, regeneration); duration of treatment varies, and very few dose response curves investigated for any drugs of interest
- Difficult, if not impossible, to draw conclusions on relative pre-clinical efficacy

6

How drugs are tested in humans

	Phase 1	Phase II	Phase III
Description	First test of new treatment to see if it is safe	Preliminary test of safe agents to see if benefit is provided	Assessment of agents that appear to provide benefit; frequently compares new agent to standard of care
Goals	-is treatment safe -how to deliver (pills, shot) -determine dose-related side effects in healthy volunteers	-does treatment "work" -do new side effects emerge when patients are treated	-is new treatment better than, equivalent to, or poorer than standard of care
Sample Size	Typically 20-30	Often 100 or more	Typically several hundred to several thousand
What to Expect	Physical exams and multiple laboratory tests	Physical exams and multiple laboratory tests; may be open-label or may be masked	Physical exams and blood tests; randomization, placebo control, double masking

Bhowmik, D., Chandira, M., Maharajganj, N., and Pradesh, U., Emerging Trends of Scope and Opportunities Clinical Trials in India. *International Journal of Pharmacy and Pharmaceutical Sciences.* Vol. 2, Suppl. 1. (2010).

7

Slow and expensive process

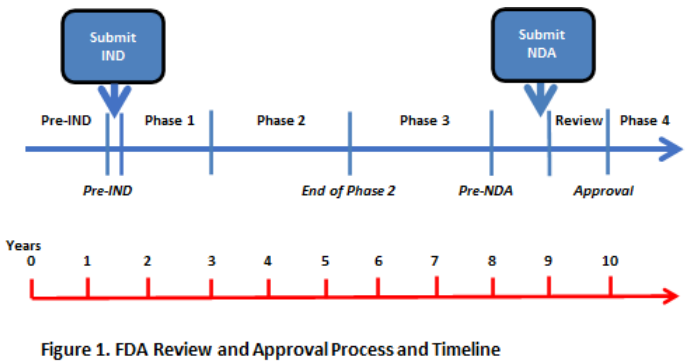


Figure 1. FDA Review and Approval Process and Timeline

Lynch, E., Kil, J., and Le Prell, C. G. (2016). Human clinical studies in noise-induced hearing loss. Le Prell, C. G., Lobarinas, E., Fay, R. R., and Popper, A. N. *Translational Research in Audiology and the Hearing Sciences, Springer Handbook of Auditory Research*. New York: Springer.

- 10+ years
- Greater than $100M cost across all years of this process
  - Animal studies (toxicology, safety, Pk, ADME, and efficacy)
  - Manufacturing processes
  - Validated chemical assays
  - Human Phase 1
  - Human Phase 2 – 2 smaller studies required (~50-100 subjects)
  - Human Phase 3- 600-1000 subjects, multi-site; typically must be repeated
  - New Drug Application then filed with requested health claims
- Successful drugs must cover company investments in failed drugs – estimated to be $1B cost per success achieved

For additional detailed discussion, see W.F. Crowley Jr., J.F. Gusella, The changing model of biomedical research. *Sci. Transl. Med.* 1, 1cm1 (2009).

8

Most drugs do not survive this process

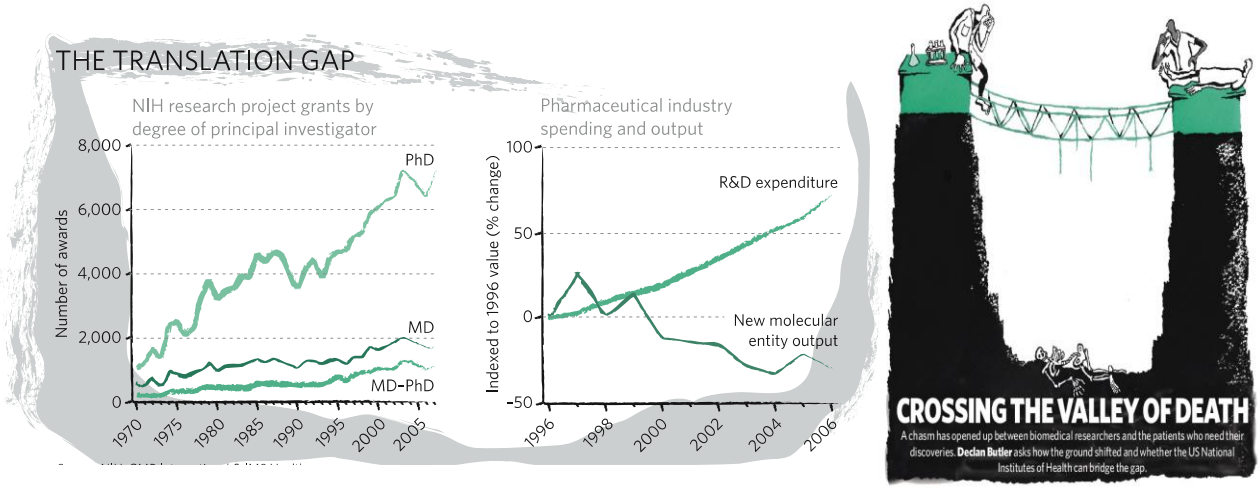
- Failure at Phase I: clinical safety issue or a Pk/Pd/ADME issue (doesn't get to right target, doesn't act at right receptor, etc.)
- Failure at Phase II or III: clinical safety or efficacy issue, commercial issues
- Commercial issues can include high bureaucracy, low flexibility, mergers and acquisitions, cash flow, cost-benefit ratio, fear of failure, etc.

"Failures could be linked to incomplete understanding of the human diseases and mechanisms investigated, lack of correlation of animal models to human diseases, poor biomarkers and surrogate endpoints, selection of non-optimal drug molecules (pharmacokinetics/ pharmacodynamics profile, off-target effects, among others), idiosyncratic drug toxicity and poor clinical trials design."

Khanna, I. Drug discovery in pharmaceutical industry: productivity challenges and trends. *Drug Discovery Today.* Volume 17 (2012).
Cousins, R. P. (2019). "Medicines discovery for auditory disorders: challenges for industry," J. Acoust. Soc. Am. 146, 3652-3667.

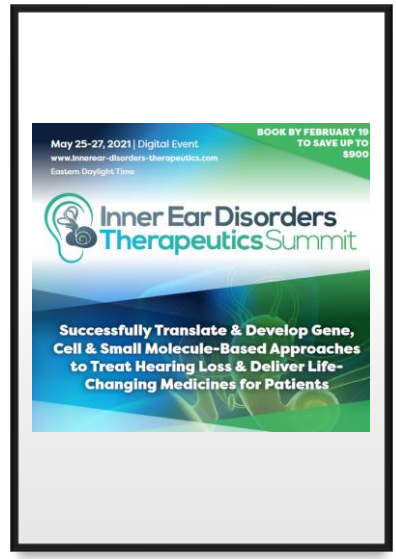
9

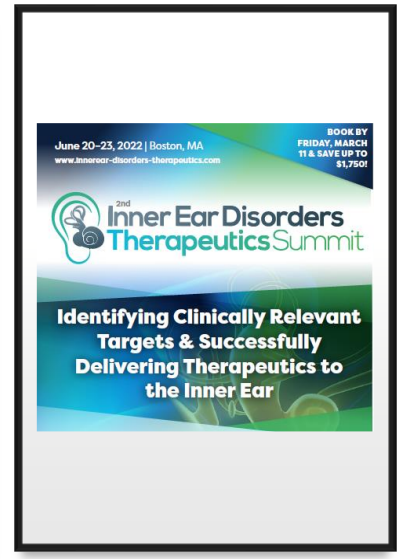
Investing greater financial resources, but getting fewer drugs through the approval process



Butler, D. *Crossing the Valley of Death.* Nature Vol 453 (2008).

10





11

Facilitating Success: DoD HCE Open-Access Resources

- Pharmaceutical Interventions for Hearing Loss Clinical Research Guidance Papers; In: Otology and Neurotology, 37(8), 2016.
- Noise in the Military; In: Hearing Research 349, 2017.
- Cellular Mechanisms of Ototoxicity; In: Frontiers in Neuroscience, 2017.
- Special Topics in Clinical Monitoring; In: International Journal of Audiology 57(Suppl. 4), 2018.
- Pharmacology and Ototoxicity. Seminars in Hearing, Volume 40, Issue 2, 2019.
- Noise-Induced Hearing Loss: Translating Risk from Animal Models to Real-World Environments, Journal of Acoustical Society of America, 146(4), 2019

Closed to new submissions; 16 articles accepted and 15 articles in various stages of peer review

12

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13

Key Definitions

- Outcome: measured variable
  - e.g., audiometric threshold, DPOAE amplitude
- Endpoint: analyzed parameter (e.g., change from baseline)
  - Primary endpoint – typically will be the most important outcome; addresses whether a new treatment prevents disease, or is better at preventing disease than the standard therapy
  - Secondary endpoint – other relevant questions to be answered by study; can build on primary endpoint with mechanistic insights (e.g., a drug for osteoporosis with fractures as the primary endpoint could include improved bone density as a secondary endpoint)
- Indication: use of a drug for treating a particular disease (e.g., use of a drug for NIHL prevention or ARHL treatment)
  - Multiple endpoints may be used to evaluate clinical benefit when (1) there are several important aspects of a disease or several ways to assess an important aspect, (2) there is no consensus about which one will best serve the study purposes, and (3) an effect on any one will be sufficient as evidence of effectiveness to support 501 approval.

14

Majority of Clinical Tests provide quantitative data – generate a numeric score that can be monitored for change

- Tympanometry – status of tympanic membrane; how well it moves
- Acoustic Reflex – measures stapedius muscle contraction in response to loud sound
  - Threshold – how loud sound must be to elicit response
  - Amplitude of response – strength of neural signal
- Audiogram
  - Pure-tone air-conduction thresholds
  - Speech reception threshold (SRT): correlates well with PTA512
- Word recognition – identification of words in quiet
- Hearing-in-Noise – identification of words in noise background (babble, speech-shaped noise, etc.)
- Otoacoustic Emissions – reflects health of outer hair cells, assuming normal conduction
  - Useful in diagnosis of auditory neuropathy (OAEs present, ABR reduced or absent)
- Electrocochleography (eCochG)/Auditory brainstem response (ABR) – reflects health of afferent neural pathway, assuming normal conduction and intact outer hair cells
  - Useful in diagnosis of auditory neuropathy (OAEs present, ABR reduced or absent)

15

Quantitative tests can be objective or subjective

Objective (Does not require patient participation)

- Tympanometry
  - Pressure, admittance, volume
- Otoacoustic emissions
  - Threshold, amplitude
- Sound-evoked cochlear potentials (ABR, eCochG)
  - Threshold, amplitude, latency
- Central auditory processing (MLR, LLR)
  - Present/absent, amplitude, latency

Subjective (Patient report)

- Audiogram
  - Threshold (tones, words)
- Hearing-in-noise
  - WIN, QuickSin, HINT, BKB-SIN
- Tinnitus matching
  - Pitch, level
- Tinnitus surveys
  - Tinnitus Functional Index (TFI)
  - Tinnitus Handicap Inventory (THI)
- Hearing surveys
  - SSQ/SSQ12
  - Hearing Handicap Inventory (HHI-A, HHI-E)
  - Hearing Screening Inventory (HSI)
- Patient reported outcomes
  - Patient Global Impression of Change

16

Challenges in Matching Endpoints to Indications

- Clinical Benefit: A therapeutic intervention may be said to confer clinical benefit **if it prolongs life, improves function, and/or improves the way a patient feels**
  - Changes in OAE amplitude or ABR amplitude may be earliest outcomes of disease or injury process; however, if there are no measurable perceptual deficits associated with those changes, clinical benefit and medical indication may be difficult, to establish making them more appropriate secondary endpoints
  - Changes in audiogram are the most common outcome but the specific endpoint definition for clinically significant changes in the audiogram vary significantly
  - Hearing-in-noise is receiving increased discussion
- Systematic review strategy used to identify common endpoints

17

ClinicalTrials.gov

- All clinical trials funded by NIH must be listed
- 42 CFR 11.22 requirements broadly include registration for any U.S. clinical trial with one or more arms that (i) is interventional, (ii) is other than Phase 1, and/or (iii) studies an FDA-regulated drug product.
- The criteria for U.S. clinical trials further include (i) having at least one clinical trial location within the U.S. or one of its territories, (ii) product manufacturing in and export from the U.S. or one of its territories for study in another country, and/or (iii) the clinical trial has an FDA IND Number.
- Thus, all efficacy-based U.S. clinical trials submitted to FDA for review through IND (investigational new drug application) process and any clinical trial using drugs manufactured in the U.S. must be listed
- Not every trial listed on ClinicalTrials.gov is overseen by FDA but there is no publicly available list of clinical trials making this website the best available proxy for drugs in development for possible future U.S. FDA approval

18

Endpoint measures in 61 hearing loss prevention/hearing restoration clinical trials posted on ClinicalTrials.gov

Primary, Secondary, or Other Endpoint	NIHL (n = 9)	DIHL (n = 30)	SNHL (n = 13)	SSNHL (n = 9)
Threshold Shift	7; 78%	14; 47%	8; 62%	9; 100%
Rate of ASHA SOC	0	6; 20%	0	0
Rate of CTCAE	0	3; 10%	0	0
Rate of Brock	0	1; 3%	0	0
Rate of Boston SIOP	0	1; 3%	0	0
Rate of Tune	0	1; 3%	0	0
Other STS Rate	1; 11%	8; 27%	1; 8%	0
DPOAE Shift	5;56%	10; 33%	1; 8%	0
EHF Threshold shift	1; 11%	5; 17%	2; 15%	0
Word Recognition Change	0	2; 7%	6; 46%	4; 44%
Hearing in Noise Change	2; 22%	2; 7%	5; 38%	0
Change in Tinnitus	5; 56%	7; 23%	5; 38%	1;11%
Change in Hearing Status	0	6; 20%	2; 15%	1; 11%
ABR Shift	0	0	2; 15%	0

Le Prell CG. 2021. Investigational Medicinal Products for the Inner Ear: Review of Clinical Trial Characteristics in ClinicalTrials.gov, J Am Acad Audiol, 32(10):670–694.

19

Various definitions for pure-tone threshold shift across trials

NIHL	DIHL	SNHL	SSNHL
"pure tone audiometry"	"pure-tone audiometry"	"pure-tone audiometry"	"pure-tone audiometry"
4 kHz	HFPTA, 6-16 kHz	Average of 2 and 4 kHz	PTA 5124
2, 3, 4, or 6 kHz	Frequencies from 0.25 to 16 kHz		Change at 3 most affected frequencies
PTA346	9, 10, 12.5 and 14 kHz		
"group mean hearing level"	Degree or incidence of hearing loss using pure tone audiometry		
Absolute change in pure tone thresholds	Pure tone audiometry in conventional and high frequency ranges		

Le Prell CG. 2021. Investigational Medicinal Products for the Inner Ear: Review of Clinical Trial Characteristics in ClinicalTrials.gov, J Am Acad Audiol, 32(10):670–694.

20

Summary of ClinicalTrials.gov data

- Information available in ClinicalTrials.gov often lacked precision in the definition of outcome measures and endpoints
- Where detail was provided:
  - Audiogram was by far the most used outcome measure; however, study endpoints (definitions for threshold shift) varied widely within and across indications
  - DPOAEs were more common outcome measure in NIHL (56%) and DIHL (33%) trials than those for other indications (0-8%) – but with no consistent endpoint used
  - Hearing-in-noise was more common outcome measure in SNHL amelioration (33%) and NIHL prevention (22%) trials than those for other indications (0-8%) – but with no consistent endpoint used
- What about reports in scientific literature?

21

Primary/Co-Primary endpoints in NIHL prevention studies published in scientific literature (n=24) or posted on ClinicalTrials.gov (n=7)

	PTS (pre-Tx) (n = 4 trials)	PTS (Post-tx) (n = 5 trials)	TTS (pre-tx) (n = 20 trials)	TTS (post-tx) (n = 2 trials)	Total (n = 31 trials)
Average threshold shift	1/4; 25%	2/5; 40%	17/20; 85%	2/2; 100%	22/31; 71%
Duration of threshold shift	0	0	1/20; 5%	0	1/31; 3%
Rate of ASHA SOC	1/4; 25%	0	0	0	1/31; 3%
Other STS (unspecified)	1/4; 25%	0	1/20; 5%	0	2/31; 6%
Rate of threshold shift ≥ 25 dB	1/4; 25%	0	0	0	1/31; 3%
Rate of threshold shift ≥ 5, 15, or 25 dB	1/4; 25%	0	0	0	1/31; 3%
Rate of threshold shift ≥ 15 dB	0	1/5; 20%	0	0	1/31; 3%
Rate of threshold shift ≥ 10 dB	1/4; 25%	2/5; 40%			3/31; 10%
DPOAE amplitude change	0	0	4/20; 20%	0	4/31; 13%
TEOAE amplitude change	0	0	1/20; 5%	0	1/31; 3%
Word recognition change ≥15%	0	1/5; 20%	0	0	1/31; 3%

Le Prell, C. G. (2022). "Prevention of noise-induced hearing loss using investigational medicines for the inner ear: previous trial outcomes should inform future trial design," Antioxid. Redox Signal., 36(16-18):1171-1202.

22

Threshold-based secondary endpoint measures

	PTS pretreatment (n = 4 trials)	PTS post-treatment (n = 5 trials)	TTS pretreatment (n = 20 trials)	TTS post-treatment (n = 2 trials)	Total (n = 31 trials)
Average Threshold Shift	1/4; 25%	1/5; 20%	8/20; 40%	0	10/31; 32%
Duration of Threshold Shift	0	0	3/20; 15%	0	3/31; 10%
Rate of ASHA SOC	1/4; 25%	0	0	0	1/31; 3%
Rate of OSHA/DOEHRSHC STS	1/4; 25%	0	0	0	1/31; 3%
Rate of NIOSH/ DOEHRSHC Early Warning	1/4; 25%	2/5; 40%	0	0	3/31; 10%
Rate of Modified Navy STS	1/4; 25%	0	0	0	1/31; 3%
Rate of threshold shift $\geq$ 10 dB	0	0	1/20; 5%	0	1/31; 3%
Average EHF threshold shift	1/4; 25%	2/5; 40%	1/20; 5%	0	4/31; 13%

Le Prell, C. G. (2022). "Prevention of noise-induced hearing loss using investigational medicines for the inner ear: previous trial outcomes should inform future trial design," Antioxid. Redox Signal., 36(16-18):1171-1202.

23

DPOAE, ECochG, Hearing-in-noise as secondary outcome measures

	PTS pretreatment (n = 4 trials)	PTS post-treatment (n = 5 trials)	TTS pretreatment (n = 20 trials)	TTS post-treatment (n = 2 trials)	Total (n = 31 trials)
DPOAE amplitude shift	2/4; 50%	2/5; 40%	3/20; 15%	0	7/31; 23%
DPOAE threshold shift	0	0	1/20; 5%	0	1/31; 3%
DPOAE unspecified shift	0	0	1/20; 5%	0	1/31; 3%
TEOAE amplitude shift	0	0	1/20; 5%	1/1; 100%	2/31; 6%
CAP/ECochG amplitude shift	1/4; 25%	2/5; 40%	1/20; 5%	0	4/31; 13%
Change in Hearing-in-Noise	1/4; 25%	2/5; 40%	1/20; 5%	0	4/31; 13%

Le Prell, C. G. (2022). "Prevention of noise-induced hearing loss using investigational medicines for the inner ear: previous trial outcomes should inform future trial design," Antioxid. Redox Signal., 36(16-18):1171-1202.

24

Tinnitus secondary outcome measures

	PTS pretreatment (n = 4 trials)	PTS post-treatment (n = 5 trials)	TTS pretreatment (n = 20 trials)	TTS post-treatment (n = 2 trials)	Total (n = 31 trials)
Tinnitus Handicap Inventory	0	0	1/20; 5%	0	1/31; 3%
Tinnitus incidence	0	0	3/20; 15%	0	3/31; 10%
Tinnitus loudness/annoyance	1/4; 25%	0	1/20; 5%	0	2/31; 6%
Tinnitus severity	1/4; 25%	0	0	0	1/31; 3%
Tinnitus intensity	0	1/5; 20%	0	0	1/31; 3%

Le Prell, C. G. (2022). "Prevention of noise-induced hearing loss using investigational medicines for the inner ear: previous trial outcomes should inform future trial design," Antioxid. Redox Signal., 36(16-18):1171-1202.

25

Summary of NIHL study data

- Audiometric threshold shift was primary outcome in ~70% of studies, and secondary outcome in remaining 30%
  - Rate of STS was only rarely used - however, rate of NIOSH or OSHA STS are of high interest as “accepted” definitions of noise-injury
- Changes in objective outcomes only used as primary endpoint in about 15% of studies (OAEs), and secondary endpoint in about 30% of studies (OAEs in ~25%, ABR/eCochG in about 15%)
- Tinnitus measures not used as primary endpoint in NIHL prevention studies and appear as secondary endpoint in just 10% of studies
- Hearing-in-noise changes have not been used as primary endpoint in NIHL prevention studies and appear as secondary endpoint in just 13% of NIHL studies

26

Hearing in background noise

- Difficulties hearing-in-noise are one of most common complaints; can occur with or without hearing loss
- Out of 100,000 patient records reviewed at one clinic, 10% seen for hearing-in-noise complaints with no audiometric loss at testing (Parthasarathy et al., 2020)
- Some jobs critically rely on hearing-in-noise ability; important for social reasons as well
- No agreed-on gold standard test, but there are multiple standardized published tests
- Emerging literature shows hearing in noise deficits can occur with damage to OHCs or damage to synapses – deficits are NOT a diagnostic for synapse loss

For detailed reviews, see:
Le Prell C.G. & Clavier O.H. 2017. Effects of noise on speech recognition: Challenges for communication by service members. Hear. Res., 349, 76-89.
Le Prell, C. G. (2019). Effects of noise exposure on auditory brainstem response and speech-in-noise tasks: A review of the literature. *International Journal of Audiology*, *58*(sup1), S3-S32.

27

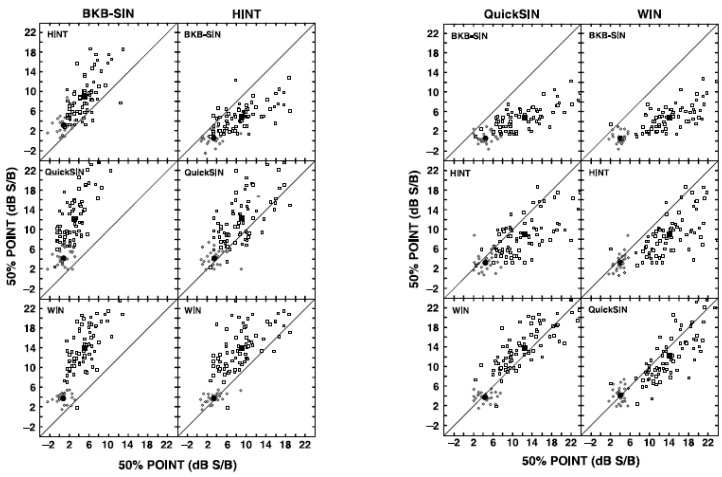
Multiple validated speech-in-noise tests are available

Test	Test Items	SNR range	Sentence Sound Levels	Target Voice	Noise/Babble Background/Level
HINT	25 sentence lists, 10 sentences per list, 6 target words per sentence	SNR step size begins at 4-dB, and changes to 2-dB. Sentence level is manipulated up/down to determine lowest level at which all words are correctly repeated.	Sentence presentation level at either 90 dB SPL (PTA≤40 dB HL) or 100 dB SPL (PTA>40 dB HL); level is increased in 4-dB steps until listener correctly repeats sentence	Male talker	Speech-spectrum noise fixed at 65-dBA (or 72-dBA)
BKB-SIN	18 pairs of lists, 10 words per list	Sentences presented at SNRs of +21, +18, +15, +12, +9, +6, +3, 0, -3, and -6 (3-dB decrements)	Sentence presentation level varies from 96 dB SPL (first 8 sentences) to 93 (9th sentence) and 90 dB SPL (10th sentence)	Male talker	Multi-talker babble with 4 voices (“Auditech babble”); Background babble increases by 3-dB per sentence
QuickSin	12 sentence lists, 6 sentences per list, 5 target words per sentence	SNR levels of 0 (hardest), +5, +10, +15; can also include +20 and +25 (easiest)*	70-dB HL sentence presentation level (100-dB SPL)	Female talker	4-talker babble; babble level increases from 75 dB SPL to 100 dB SPL to increase difficulty of task
WIN	2 word-lists, with 35 NU-6 words per list. Five words per SNR	SNR decreasing from 24 (easiest) to 0 (most difficult) in 4-dB decrements*	Word level varies from 104 dB SPL to 80 dB SPL to increase difficulty of task	Female talker	Multi-talker babble with 6 female voices, fixed at 80 dB SPL

* If no correct words are achieved within a level, then harder SNRs are not tested.

28

Tests are related to each other



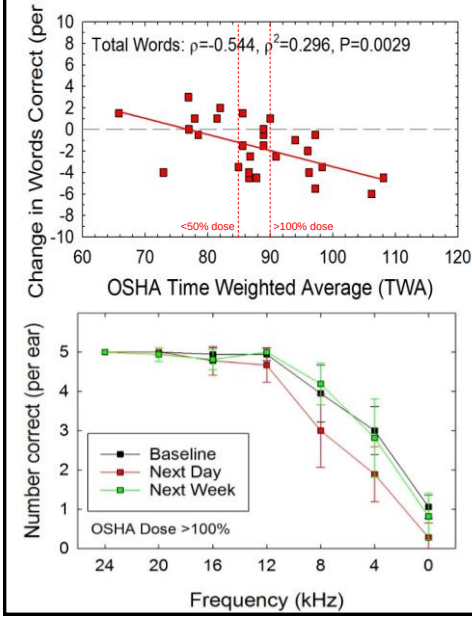
Figures 2 and 3: Test named at top is test plotted on x-axis; test named in upper left corner is test plotted on y-axis. 24 listeners with normal hearing (circles) and 72 listeners with hearing loss (squares).

- All listeners do better on BKB-SIN and HINT than QuickSin or WIN.
  - BKB-SIN and HINT sentences provide more context than QuickSin sentences
  - WIN is word-based not sentence based; reduces role of memory, cognition, and linguistic context, with greater emphasis on acoustic cues
- QuickSin and WIN better than BKB-SIN and HINT for separating normal and hearing impaired listeners
- Wilson et al. recommend either the QuickSin or WIN for clinical use

From: Wilson RH, McArdle RA, Smith SL. An evaluation of the BKB-SIN, HINT, QuickSin, and WIN materials on listeners with normal hearing and listeners with hearing loss. J Spch Lang, Hear Res, 50, 844-857 (2007).

29

Sound exposure results in temporary hearing-in-noise deficits the next day, at difficult SNRs (≤8 dB SNR) using WIN



- 28 participants attended recreational event they deemed loud
  - Level: 93.3±7.8 dBA (range 73.1–104.2 dBA)
  - Duration: 4.2±3.5 hrs (range 1.5–16.0 hrs)
- Average dose and TWA calculated using 29 CFR 1910.95 (OSHA)
  - 168.4%±276% (range 3.5%–1,230.8%)
  - 87.8 dBA TWA±9.5 dBA (range 65.8–108.1 dBA TWA)
- Participants generally equally divided into groups with < 50% dose (4M, 5F), 50-100% dose (4M, 6F), and > 100% dose (3M, 6F)
- Among participants with >100% OSHA dose, hearing in noise deficits were observed at 0, 4, and 8 dB SNRs

Grinn, S., Baker, J., Wiseman, K., and Le Prell, C. G. Hidden hearing loss? No effect of common recreational noise exposure on cochlear nerve amplitude in humans. *Frontiers in Neuroscience, 11:465;* https://doi.org/10.3389/fnins.2017.00465

30

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31

Our NIHL clinical trial populations

- Completed: TTS after Weapons Training/Swedish Military
  - **ACEMg, funded by NIH U01 DC008423.** Le Prell, C. G., Johnson, A.-C., Lindblad, A.-C., Skjönsberg, A., Ulfendahl, M., Guire, K., Green, G. E., Campbell, K. C. M., and Miller, J. M. (2011). Increased vitamin plasma levels in Swedish military personnel treated with nutrients prior to automatic weapon training. Noise Health 13, 432-443.
- Completed: Music Player TTS studies
  - **ACEMg, funded by NIH U01 DC008423.** Le Prell, C.G., Fulbright, A., Spankovich, C., Griffiths, S., Lobarinas, E., Campbell, K.C.M., Antonelli, P.J., Green, G.E., Guire, K., and Miller, J.M. (2016). Dietary supplement comprised of β-carotene, vitamin C, vitamin E, and magnesium: failure to prevent music-induced temporary threshold shift. *Audiology & Neurotology EXTRA, 6: 20-39.*
  - **Ebselen, funded by Sound Pharmaceuticals.** Kil J, Lobarinas E, Spankovich C, Griffiths SK, Antonelli PJ, Lynch ED, Le Prell CG. 2017. Safety and efficacy of ebselen for the prevention of noise-induced hearing loss: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet. 390(10098):969-979.
  - **Vincerinone, funded by Edison Pharmaceuticals.** NCT02257983 conducted at University of Florida with Drs. Patrick Antonelli, Chris Spankovich, Ed Lobarinas, Scott Griffiths. Results masked by sponsor.
- Recruiting: PTS after Surgical Skull-Based Drilling Noise, Safety Officer Weapons Training
  - **Zonisamide, funded by Department of Defense W81XWH-19-C-0054.** NCT04768569 conducted at University of Washington in St. Louis with Drs. Craig Buchman, Jianxin Bao, Amanda Ortmann; NCT04774250 conducted at University of Akron with Drs. Craig Buchman, Jianxin Bao, Kristine Sonstrom-Malowski

32

Endpoint measures in our studies

Endpoints	Swedish Soldiers	MP3 players, ACEMg	MP3 players, Ebselen	MP3 players, Vincerinone	Skull-based drilling	Safety Officers
Primary Endpoint	Max shift at 3, 4, 6 kHz in either ear	Change in 4kHz threshold	Change in 4 kHz threshold	Change in 4kHz threshold	Proportion of patients with ≥10 dB shift between 2-6 kHz	Proportion of officers with ≥10 dB shift between 2-6 kHz
Secondary endpoint	Shift at each frequency	Shift at each frequency	Shift at at 3, 4, 6 kHz	Shift at each frequency	Proportion of patients meeting NIOSH red flag	Proportion of officers meeting NIOSH red flag
Secondary endpoint		Shift at 0.5, 1, 2 kHz	Shift at 4, 6, 8 kHz		EHF threshold shift (10-14 kHz)	EHF threshold shift (10-14 kHz)
Secondary endpoint		Shift at 3, 4, 6 kHz	Average shift from 0.25 to 8 kHz			
Secondary endpoint			Proportion of participants with TTS ≥10 dB at any frequency			
DPOAEs	F2=2,3,4,6,8 kHz; L1=25-65 dB SPL	F2=2,3,4,6,8 kHz; L1=25-65 dB SPL	No	F2=2,3,4,6,8 kHz; L1=35,45,55 dB SPL	F2=1-6 kHz; L1=65 dB SPL	F2=1-6 kHz; L1=65 dB SPL
Hearing-in-noise	4k PMTF	No	No	WIN	WIN	WIN
Tinnitus	Incidence, loudness, bothersomeness	Incidence, loudness, bothersomeness	No	Incidence, loudness, bothersomeness	Tinnitus Functional Index (TFI)	Tinnitus Functional Index (TFI)
ABR/eCochG	No	No	No	No	ABR	ABR

33

Another PTS Population: U.S. Service Members

- Camp Pendleton Marine Corps Base, STS after 16 days of basic training including weapons training
  - "As part of routine weapons training, all subjects were uniformly exposed to various noises including impulse, steady-state noise, as well as simulated explosions. The most common noise exposure was M-16 rifle fire, with every trainee firing 325 rounds during the training."
  - Primary endpoint: ASHA Significant Ototoxic Change - increase ≥20 dB at any test frequency or average increase ≥10 dB at any two consecutive test frequencies)
  - Secondary endpoint: US Navy STS rate in trigger-hand ear (increase of ≥15 dB at any test frequency or average increase of ≥10 dB at any two consecutive test frequencies)
- Fort Jackson Drill Sargent instructor training, STS after 11 days of weapons training with minimum of 500 rounds of M-16 weapon fire
  - Rate of ASHA SOC, OSHA STS (average shift ≥ 10 dB at 2, 3, and 4 kHz), and DoD Early warning (15 dB shift at 1, 2, 3, or 4 kHz in either ear) all reported

Kopke R, Slade MD, Jackson R, Hammill T, Fausti S, Lonsbury-Martin B, Sanderson A, Dreisbach L, Rabinowitz P, Torre P 3rd, Balough B. Efficacy and safety of N-acetylcysteine in prevention of noise induced hearing loss: a randomized clinical trial. Hear Res. 2015 May;323:40-50. doi: 10.1016/j.heares.2015.01.002.

Campbell, K.C.M. 2016. Final Report on AWARD NUMBER: W81XWH-11-C-0033. Phase 2 Clinical Trials: D-Methionine to Reduce Noise-induced Hearing Loss. Prepared for U.S. Army Medical Research and Materiel Command, Fort Detrick, Maryland 21702-5012.https://apps.dtic.mil/docs/citations/AD1028742

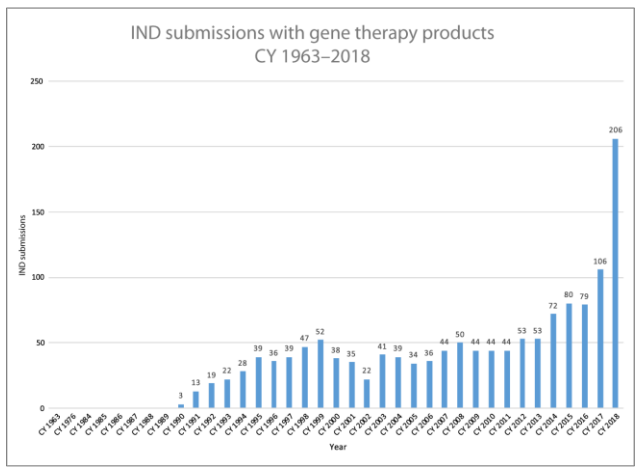
34

Gene therapy across tissues

- Over 1800 human clinical trials in the 2013 review by Ginn et al. – no hearing loss trials reported
  - GINN SL, ALEXANDER IE, EDELSTEIN ML, ABEDI MR, WIXON J (2013) Gene therapy clinical trials worldwide to 2012—an update. J Gene Med 15:65–77. doi:10.1002/jgm.2698
- 2017 review by Ahmed et al noted that there were no trials in the human inner ear yet
- Over 2600 human clinical trials in the 2018 review by Ginn et al. – hearing loss was included as part of "other diseases" – which comprised a combined 58 trials (2%) out of the >2600 trials reported
  - GINN SL, AMAYA AK, ALEXANDER IE, EDELSTEIN ML, ABEDI MR (2018) Gene therapy clinical trials worldwide to 2017: An update. J Gene Med 20:e3015. doi: 10.1002/jgm.3015

35

Investigational new drug applications (INDs) in gene therapy by year to US FDA



- First clinical trial of gene therapy, for a rare inherited form of immunodeficiency, began at NIH in 1990
- The first approved gene therapy in the US wasn't until 2017 when FDA approved treatment of a rare form of congenital blindness caused by autosomal recessive mutations in the gene RPE65

Katherine A. High. 2020. Turning genes into medicines—what have we learned from gene therapy drug development in the past decade? Nature Communications, 11:5821; https://doi.org/10.1038/s41467-020-19507-0

36

Gene therapy is more advanced for the eye than the ear

- Pharmaceutical industry once neglected the eye (just like the ear) but now there are blockbuster drugs injected into the eye to prevent blindness from retinal diseases
  - Gene therapy for the eye: retinal RPE65 gene therapy
    - Spark Therapeutics Luxturna https://luxturnahcp.com/id-appropriate-patients/rpe65-gene/
  - Genentech Lucentis and Regeneron Eylea are vascular endothelial growth factor-A (VEGF-A) drugs injected into the retina for wet macular degeneration and diabetic retinopathy indications
  - Multiple companies are in the process of developing gene therapies in which VEGF production is stimulated by delivering genes responsible for VEGF production
    - https://www.brightfocus.org/macular/article/gene-therapy-eye-dis
  - Excellent overview of lessons learned from studies of the eye are available in Zhang et al. (2018)
    - Zhang W, Kim SM, Wang W, Cai C, Feng Y, Kong W, Lin X. Cochlear Gene Therapy for Sensorineural Hearing Loss: Current Status and Major Remaining Hurdles for Translational Success. Front Mol Neurosci. 2018 Jun 26;11:221. doi: 10.3389/fnmol.2018.00221

37

Current barriers to gene therapy in the eye

- Each treatment can only fix a single gene
  - Retinal RPE65 gene therapy via Luxturna
  - Retinitis pigmentosa can be caused by 100 different mutations in the RHO gene, making it difficult to develop gene therapy for this disease
- Developing a gene therapy is expensive
  - It is not financially feasible to develop gene therapies for every mutation, especially for extremely rare mutations
  - One strategy in progress is to "silence" the RHO gene whether mutated or not and then use gene therapy to introduce a replacement copy that is immune to the RNA silencing
- Gene therapy is not cheap.

  "In the US, Luxturna costs a whopping $425,000. Per eye. That makes Luxturna one of the most expensive drugs in the world (along with other gene therapies such as Novartis' Zolgensma or bluebird bio's Zynteglo)."

https://www.labiotech.eu/features/gene-therapy-blindness-cure/

38

Gene therapy/small-molecule regeneration therapy trials: Adults with severe SNHL

Clinical Trial ID	Inclusion Criteria	Primary Outcome	Secondary Outcomes	Status
NCT02132130	21-75 yrs; non-fluctuating severe-to-profound unilateral or bilateral HL	Adverse events, conventional audiometry, bone conduction audiometry	BAER, vestibular function (HIT, VEMP, SVV), speech recognition	Completed
NCT03300687	18 or older; severe to profound SNHL of 80 dB HL or poorer at 500 Hz, meets criteria for CI; has chosen CI surgery	Adverse events (tinnitus, vertigo, perforation)	plasma pharmacokinetics over 24 and 72 hours; perilymph pharmacokinetics within 24 hours	Completed
NCT04629664	18-65 yrs; acquired, non-genetic, severe sensorineural hearing loss; PTA5124 of 71-90 dB HL in ear to be injected	Number of CTCAE v5.0 adverse events; abnormal otoscopic changes; abnormal change in tympanometry; suicide risk	speech in quiet, speech in noise (BKB-SIN), conventional and high frequency audiometry, tinnitus (TFI)	Completed

Le Prell, C. G., Brewer, C., and Campbell, K. C. (2022). The Audiogram: Detection of pure-tone stimuli in ototoxicity monitoring and assessments of investigational medicines for the inner ear. J. Acoust. Soc. Am., 152(1): 470-490; DOI: 10.1121/1110.0011739.

39

Gene therapy/small-molecule regeneration therapy trials: older populations

Clinical Trial ID	Inclusion Criteria	Primary Outcome	Secondary Outcomes	Status
NCT04462198	66-85 yrs; age-related SNHL; PTA5124 of 26-70 dB HL in ear to be injected	Treatment emergent adverse events	Pharmacokinetics; other outcomes include speech in noise, audiometry, auditory brainstem response	Completed
NCT04601909	66-85 yrs; age-related SNHL; PTA5124 of 26-70 dB HL in ear to be injected	Number of CTCAE v5.0 adverse events; abnormal otoscopic changes; abnormal change in tympanometry; suicide risk (C-SSRS)	speech in quiet, speech in noise (WIN), conventional and high frequency audiometry, tinnitus (TFI)	Active, Not yet recruiting

Le Prell, C. G., Brewer, C., and Campbell, K. C. (2022). The Audiogram: Detection of pure-tone stimuli in ototoxicity monitoring and assessments of investigational medicines for the inner ear. J. Acoust. Soc. Am., 152(1): 470-490; DOI: 10.1121/1110.0011739.

40

Gene therapy/small-molecule regeneration therapy trials: Adults with intact hearing

Clinical Trial ID	Inclusion Criteria	Primary Outcome	Secondary Outcomes	Status
NCT04120116	18-65 yrs; stable hearing loss due to NIHL or sudden SNHL; PTA5124 26-70 dB HL in the injected ear	Speech in quiet, speech in noise (WIN), audiometry, CTCAE v5.0 adverse events, abnormal otoscopic changes; abnormal change in tympanometry	high frequency audiometry, tinnitus assessment (TFI), patient reported outcome measures (HHIA, HIS)	Completed
NCT03616223	18-65 yrs; stable hearing loss due to NIHL or sudden SNHL; PTA5124 better than 70 dB HL	Number of CTCAE v5.0 adverse events	drug concentration in plasma within first 24 hours	Completed
NCT04129775	21-64 yrs; normal or up to moderately severe hearing impairment, self-reported difficulty hearing in noise for at least 6 months and a speech-in-noise deficit in at least one ear	Number of adverse events; abnormal otoscopic changes; abnormal change in audiometry	speech in noise, auditory brainstem response, and patient global impression of change	Recruiting
NCT05086276	18-65 yrs; acquired, adult onset, SNHL (NIHL or sudden SNHL); PTA5124 of 35-85 dB HL in ear to be injected	Speech perception	standard and high frequency audiometry, tinnitus assessment, and multiple patient reported outcome measures	Recruiting
NCT05061758	18-65 yrs; minimum of 6 months stable hearing loss (<80 dB HL) and stable word recognition test for approximately 6 months	Number of responders with at least 2 dB improvement in an adaptive sentence in noise test (international matrix test) compared to placebo		Not yet recruiting

Le Prell, C. G., Brewer, C., and Campbell, K. C. (2022). The Audiogram: Detection of pure-tone stimuli in ototoxicity monitoring and assessments of investigational medicines for the inner ear. J. Acoust. Soc. Am., 152(1): 470-490; DOI: 10.1121/1110.0011739.

41

Summary of Populations

- NIHL studies have included both TTS and PTS populations
  - Studies in which noise is unavoidable are preferred for ethical (risk) reasons
  - Studies in which HPDs are required due to noise exposure have observed less than expected rate of NIHL
  - Occupational studies have focused on post-shift TTS however the overarching clinical need is prevention of PTS that develops over years of exposure
- DIHL studies recruit participants who are required to receive cisplatin or aminoglycoside antibiotics for therapeutic indications
  - Caution is required as otoprotective drugs have the potential to bind to and inactivate therapeutic agent of interest
  - Interest in DIHL prevention has seen significant shift from systemic treatment (pre-clinical) to middle ear delivery (clinical)
- Gene therapy and small molecule regeneration therapies have emerged and populations enrolled in clinical trials are shifting to populations with less hearing loss as safety studies show hearing can be preserved from injection-related trauma

42

Overview

- Introduction
- Auditory measures
  - Outcome, endpoint, and indication definitions
  - Objective and subjective test options
    - Systematic review of tests used in previous clinical trials
    - Hearing-in-noise test endpoints
- Possible participant populations for hearing loss prevention/hearing restoration studies
  - NIHL, DIHL, and SNHL indications require different populations
- **Types of investigational medicines of interest for hearing loss prevention and hearing restoration**

43

Commercial Activity

June 2018 search to identify companies working in the field of therapeutics for inner ear and central hearing disorders

43 companies with pre-clinical or clinical research programs identified

- 24 in United States, 4 in France, 4 in Germany, 3 in Switzerland, 2 in the United Kingdom, 1 each in Japan, Israel, Sweden, Denmark, Belgium and the Netherlands

Otoprotection
- 24 companies, 37 therapeutic programs
- Ototoxicity, noise injury, aging, ISSNHL, CI insertion trauma
- 20 programs preclinical, 4 Phase I programs, 5 Phase 2 programs (2 failed), 3 Phase 3 programs

Regeneration
- 15 companies, 16 therapeutic programs
- 13 programs pre-clinical, 2 Phase I programs, 1 Phase I/2 program

Tinnitus Reduction
- 12 companies, 13 therapeutic programs
- 8 programs preclinical, 2 Phase I programs, 1 Phase 2 (failed), 2 Phase 3 programs (failed)

Central Hearing Disorders
- 1 company, 1 therapeutic program
- Preclinical

Balance
- 5 companies, 5 therapeutic programs
- 2 programs preclinical, 1 Phase I programs, 1 Phase 2 programs, 1 Phase 3 programs

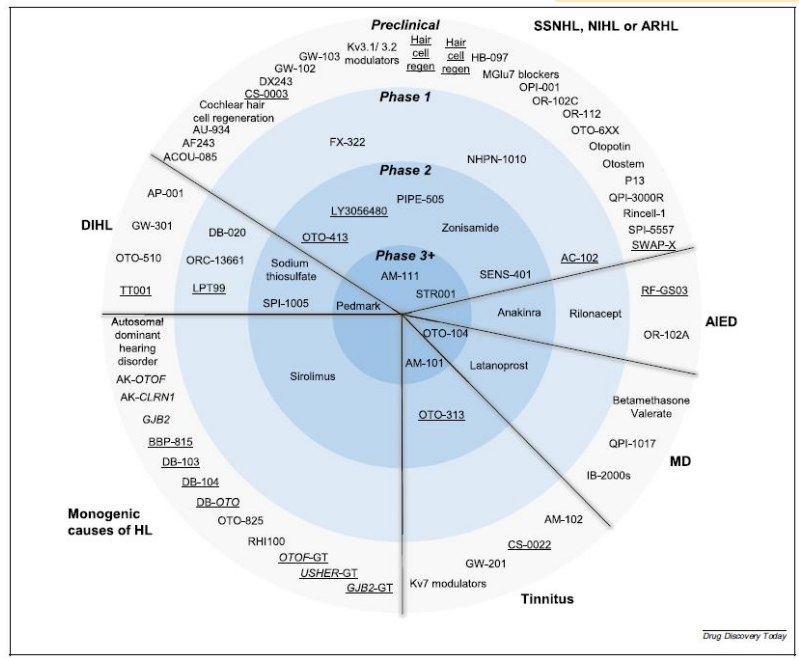
Schilder AGM et al. (2019). Hearing protection, restoration, and regeneration: An overview of emerging therapeutics for inner ear and central hearing disorders. Otol Neurotol, 40(5), 559-570.

44

Investigational medicines have diverse mechanisms of action and are being assessed for diverse clinical indications

- Preclinical: Animal models
- Phase 1: Safety endpoints
- Phase 2: Safety and efficacy endpoints
- Phase 3: Large efficacy studies
- Phase 4: Post-marketing

- Exciting time for inner ear medicine development with multiple promising agents, growth in companies, and growth in investment



Isherwood, B., Gonçalves, A. C., Cousins, R., and Holme, R. (2022). The global hearing therapeutic pipeline: 2021. Drug Discov Today 27, 912-922.

45

Summary

- Pre-clinical test paradigms highly variable; so are clinical trial protocols to date
  - Pure tone audiometry better reflects OHC loss than IHC loss or peripheral neuropathy
  - Hearing-in-noise ability not well predicted by audiometric PTA thresholds
  - OAEs assess integrity of OHCs; no agreed-on definitions of clinically significant change
  - ABRs of significant interest but uncertain value for human “hidden hearing loss”
  - Audibility (threshold) and clarity (identification) may be distinct and both are of significant clinical value
  - Self-reported hearing difficulty has no gold standard but patient-reported outcomes and global measures of function are of high interest to FDA
- As additional drugs enter and complete Phase II testing, standardization may emerge – FDA will play significant role as they review proposed endpoints as part of study approval
- Once a first inner ear medication is approved, there will be a benchmark for other drugs seeking to establish non-inferiority

46

Questions and Discussion

47