THE ROLE OF PHARMACEUTICAL AGENTS IN HEARING LOSS MANAGEMENT AND PREVENTION

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Disclosure

- Dr. Campbell is the inventor on the patents for D-methionine as a protective agent.
- The patents are owned by her employer Southern Illinois University School of Medicine.
- The patents are licensed to MetArmor Inc where Dr. Campbell is co-founder and Chief Scientific Officer
- A commercial entity for sales and distribution is required for New Drug Application at the FDA.

A Thank You

- National Institutes of Health
- US Department of Defense
- SIU School of Medicine

Otoprotective Agents

- Already in or approaching clinical trials for:
- Protection from Cisplatin-Induced Ototoxicity
- Protection from Noise Induced Hearing Loss: TTS and PTS
- Clinical trials to prevent Aminoglycoside Induced Hearing Loss are being planned

D-methionine (D-met)

- Provides virtually complete protection from cisplatin-induced ototoxicity, also reduces other side effects
- No anti-tumor interference in appropriate tumor model and dosing ratio
- Provides excellent protection against aminoglycoside-induced hearing loss
- Excellent protection from noise-induced hearing loss for pre- only, pre/peri- and even initial post exposure administration up to 24-36 hours
- Excellent protection from radiation-induced oral mucositis

ORAL D-METHIONINE (MRX-1024) SIGNIFICANTLY PROTECTS AGAINST CISPLATIN-INDUCED HEARING LOSS: A PHASE II STUDY IN HUMANS

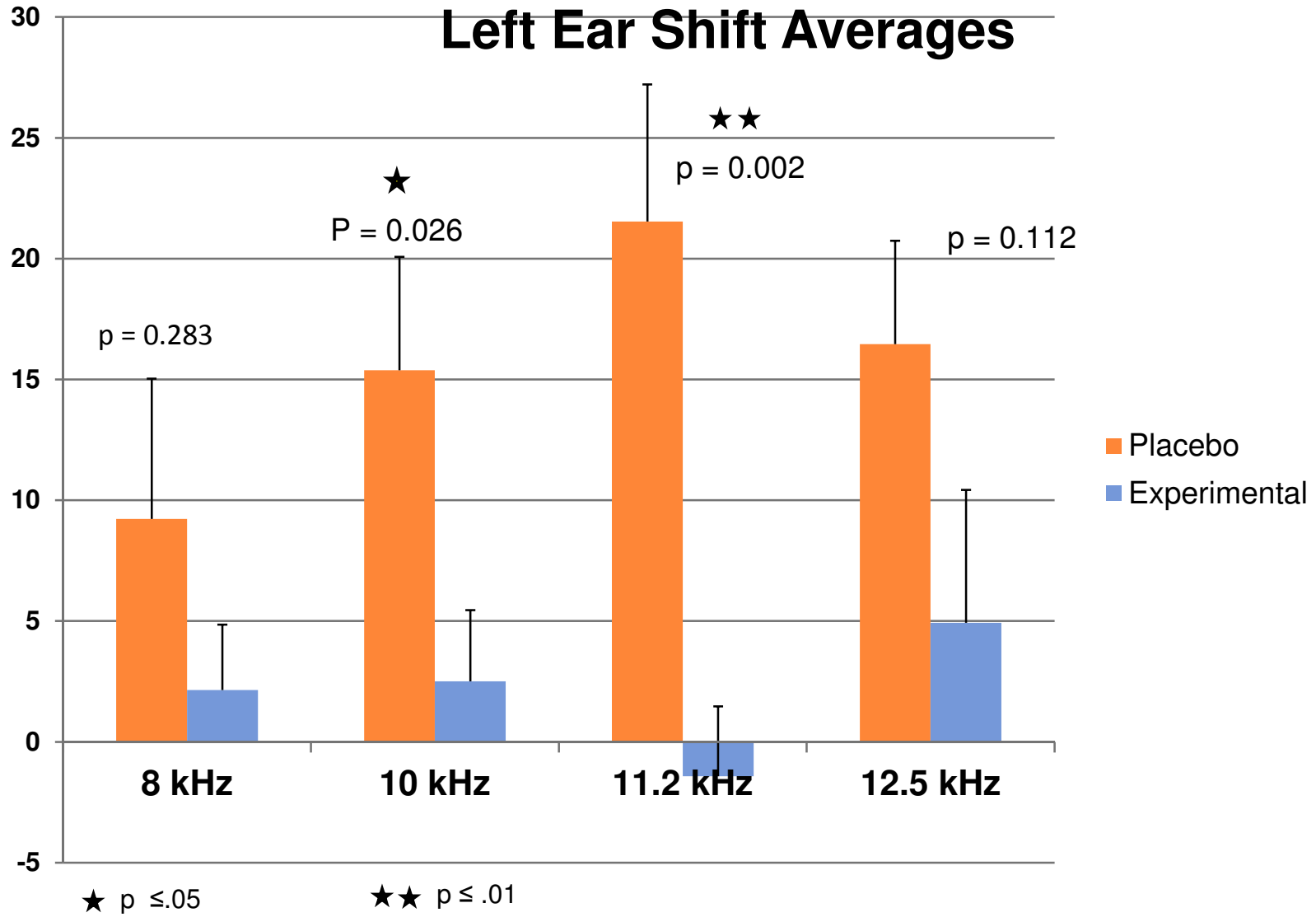
Kathleen C.M. Campbell, Ravi Nayar, Sudhir Borgonha, Larry Hughes, Alnawez Rehemtulla, Brian Ross, Prasad Sunkara
Southern Illinois University School of Medicine, Springfield, IL
St. John's National Academy of Sciences, Bangalore, India
Molecular Therapeutics, Ann Arbor, Michigan

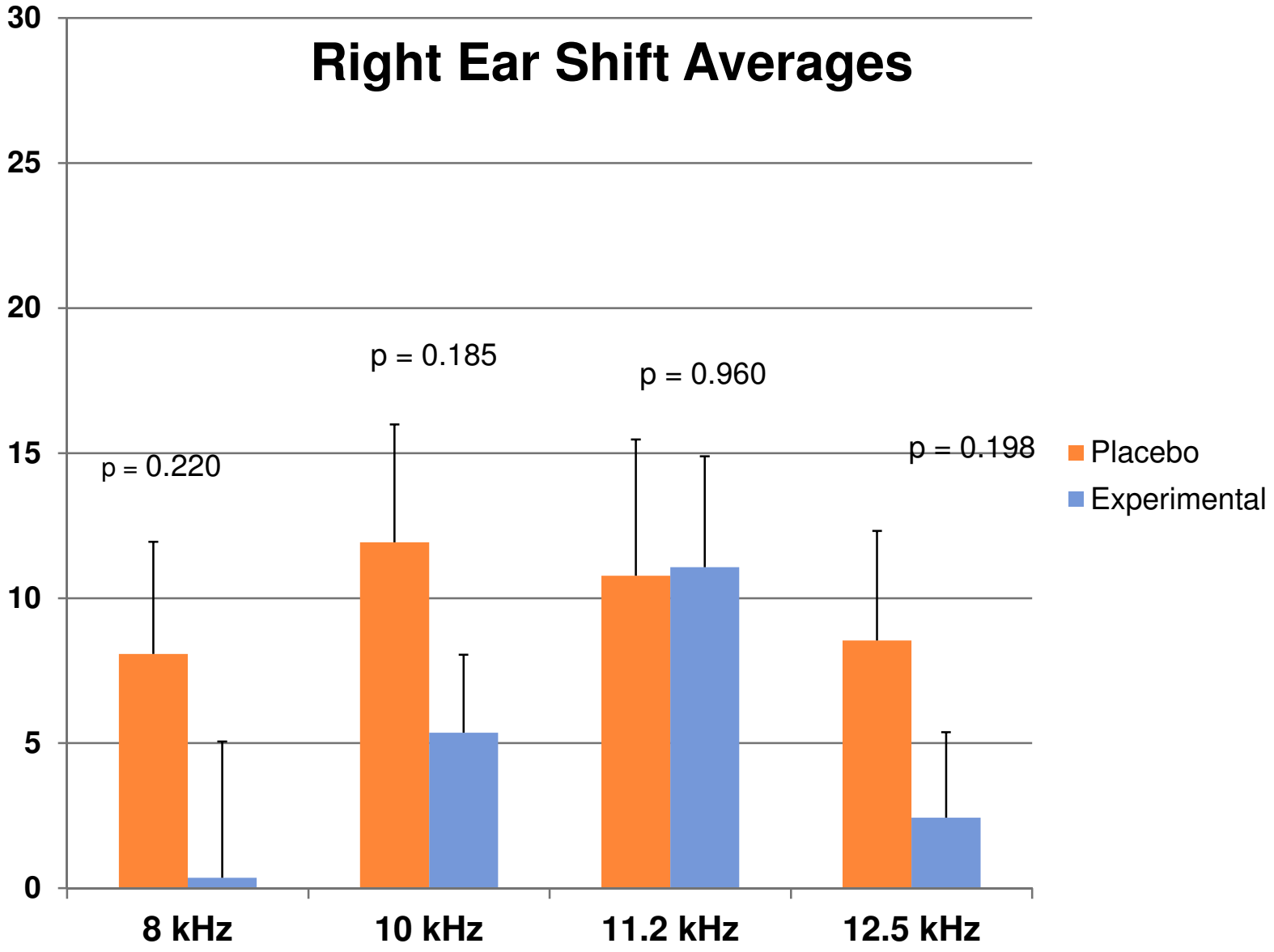
Study Design:Subjects

- Double blind randomized study
- 14 adults received 100mg/kg MRX 1024 1 hour prior to each dose of 50 mg/M2 cisplatin (Mean 263.57, SD 74.79)
- 13 adults received flavor matched placebo (Mean 253.85, SD 56.94)
- Primary tumor sites ranged from genitourinary tract to head and neck cancers
- Some patients also received radiation to the head and neck area but patients with radiation to the auditory pathway were excluded

Audiologic Procedures:

- All testing conducted with GSI 61 audiometers with appropriate earphones (TDH 39 for 8 kHz and below, Sennheiser HDA 200 for 10 kHz and above)
- Double walled sound booth
- Baseline audiometry 8, 10, 11.2, 12.5 kHz replicability within 5 dB, tympanometry, word recognition
- Modified Hughson-Westlake procedures for threshold determination
- Testing performed by licensed audiologists
- Any changes replicated within 24 hours to confirm


Left Ear Shift Averages
30
25
20
15
10
5
0
-5
★★
p = 0.002
★
P = 0.026
p = 0.112
p = 0.283
8 kHz
10 kHz
11.2 kHz
12.5 kHz
Placebo
Experimental
★ p ≤.05
★★ p ≤ .01


Right Ear Shift Averages
30
25
20
15
10
5
0
p = 0.220
p = 0.185
p = 0.960
p = 0.198
8 kHz
10 kHz
11.2 kHz
12.5 kHz
Placebo
Experimental

No Difference Between groups for:

- SIDE EFFECTS MONITORED:
- Weight loss
- Digestive/Gastrointestinal
- Blood/Bone Marrow
- Constitutional (eg fever, fatigue, dizzyness)
- Musculoskeletal system
- Pulmonary
- Dermatologic
- Neurologic
- Body as a whole

Anti-tumor interference

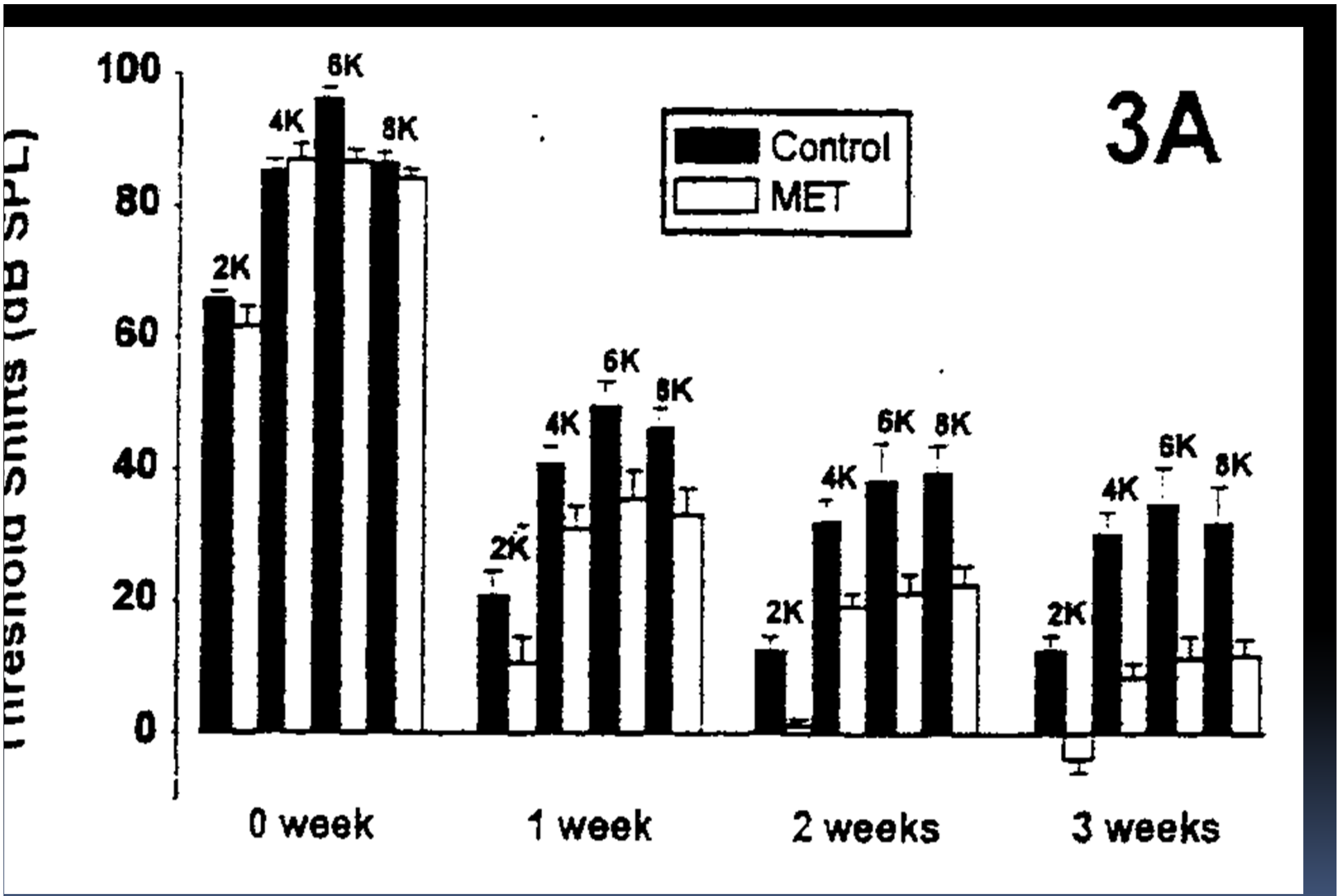
- No difference between groups in tumor response or survival during the course of the study.
- Long term survival data not available because subjects returned to their homes across India at the end of the study.

Conclusions:

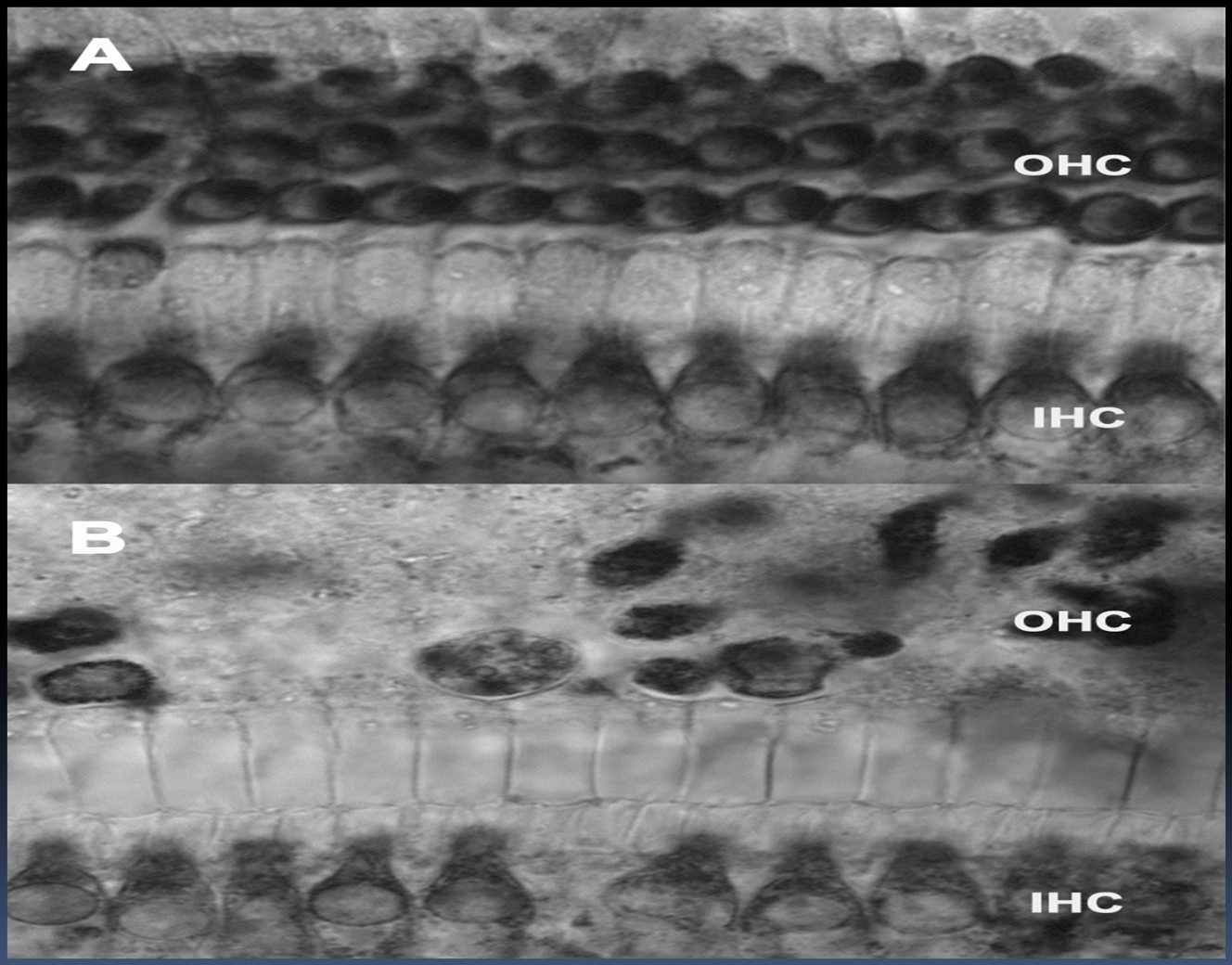
- Oral D-methionine can protect against cisplatin induced hearing loss in humans
- Further large scale clinical trials studies are needed to confirm these findings in larger patient populations

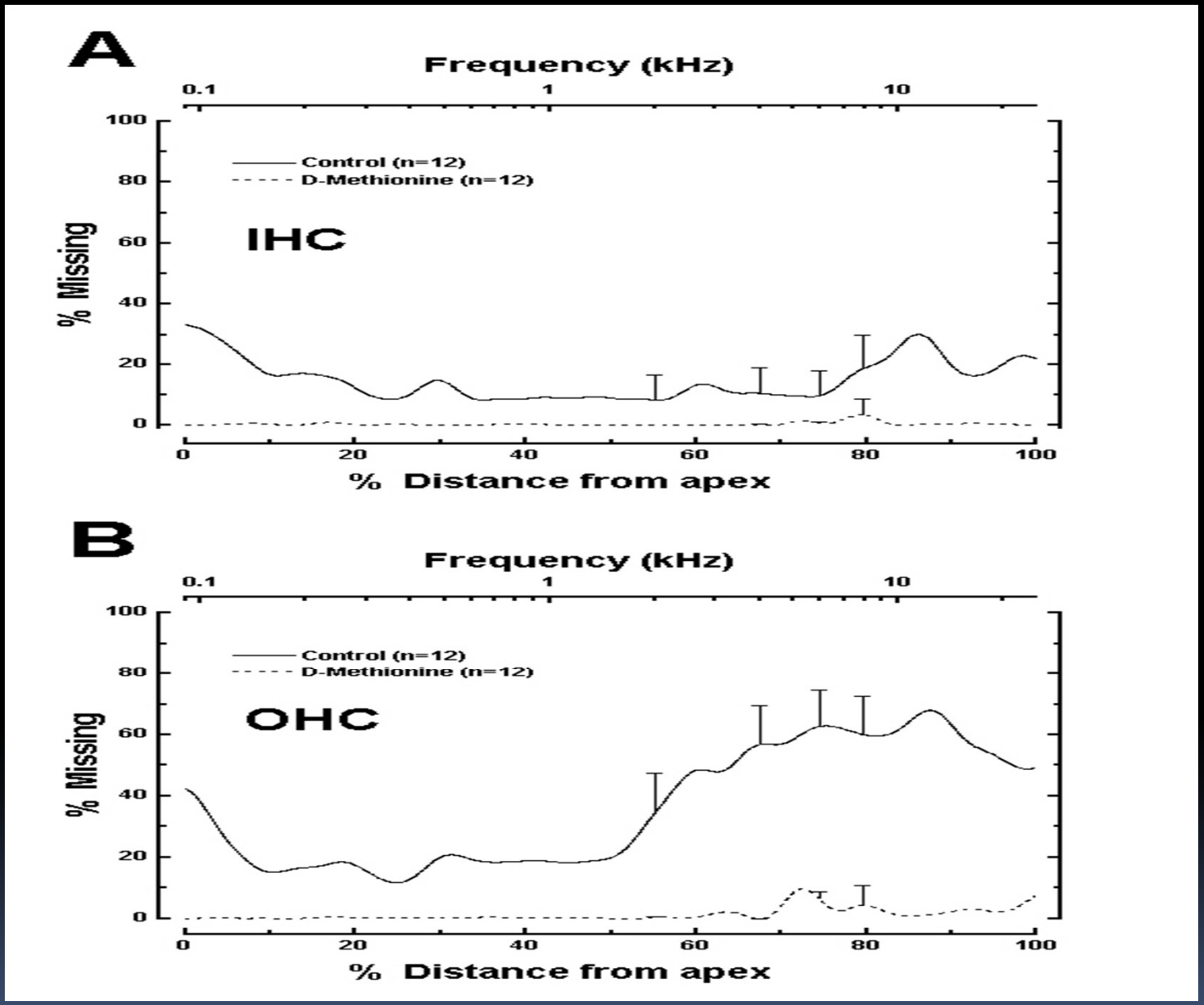
Kopke et al 2002

- Chinchilla model
- 105 dB SPL noise band centered at 4kHz
- D-met or ALCAR administered at 200mg/kg ip,
- Administered every12 hours starting 48 hours prior to noise and 1 hour prior to the noise and then twice per day for 2 days following noise exposure


3A
Control
MET
100
80
60
40
20
0
2K
4K
6K
8K
0 week
1 week
2 weeks
3 weeks

Met HC protection




A
Frequency (kHz)
0.1
1
10
Control (n=12)
D-Methionine (n=12)
IHC
% Missing
100
80
60
40
20
0
0
20
40
60
80
100
% Distance from apex
B
Frequency (kHz)
0.1
1
10
Control (n=12)
D-Methionine (n=12)
OHC
% Missing
100
80
60
40
20
0
0
20
40
60
80
100
% Distance from apex

SIU School of Medicine

D-methionine (D-met) Administration, Delayed up to 36 Hours Post-Noise Cessation, Significantly Rescues Permanent Steady State or Impulse Noise Induced Auditory Threshold Shift in the Chinchilla

Kathleen Campbell, Robert Meech, Tim Hargrove, Steve Verhulst, Daniel Fox

First presented at
MHSRS Symposium Fort Lauderdale, FL
August 20, 2015

Background

- Noise-induced hearing loss (NIHL) is the most common cause of hearing loss worldwide.
- NIHL costs billions of dollars to the US alone. The US Department of Defense spends 2-4 billion dollars per year on NIHL and noise-induced tinnitus.
- NIHL also renders the soldier more vulnerable to attack and less effective in locating the enemy.
- Battlefield communications require excellent word recognition in the presence of background noise.
- Currently, no protective agent is FDA-approved to prevent or treat NIHL.

Study Purpose

Determine maximum time delay for effective D-met post-noise rescue protection from steady state or impulse NIHL



Methods

- Auditory brainstem responses at baseline and 21 days post-noise
- Outer hair cell quantification
- Steady state noise exposure
  - 6 hours at 105 dB SPL centered at 4 kHz
- Impulse noise exposure
  - 150 simulated M16 weapon fire impulses at 155 dB and 2/second



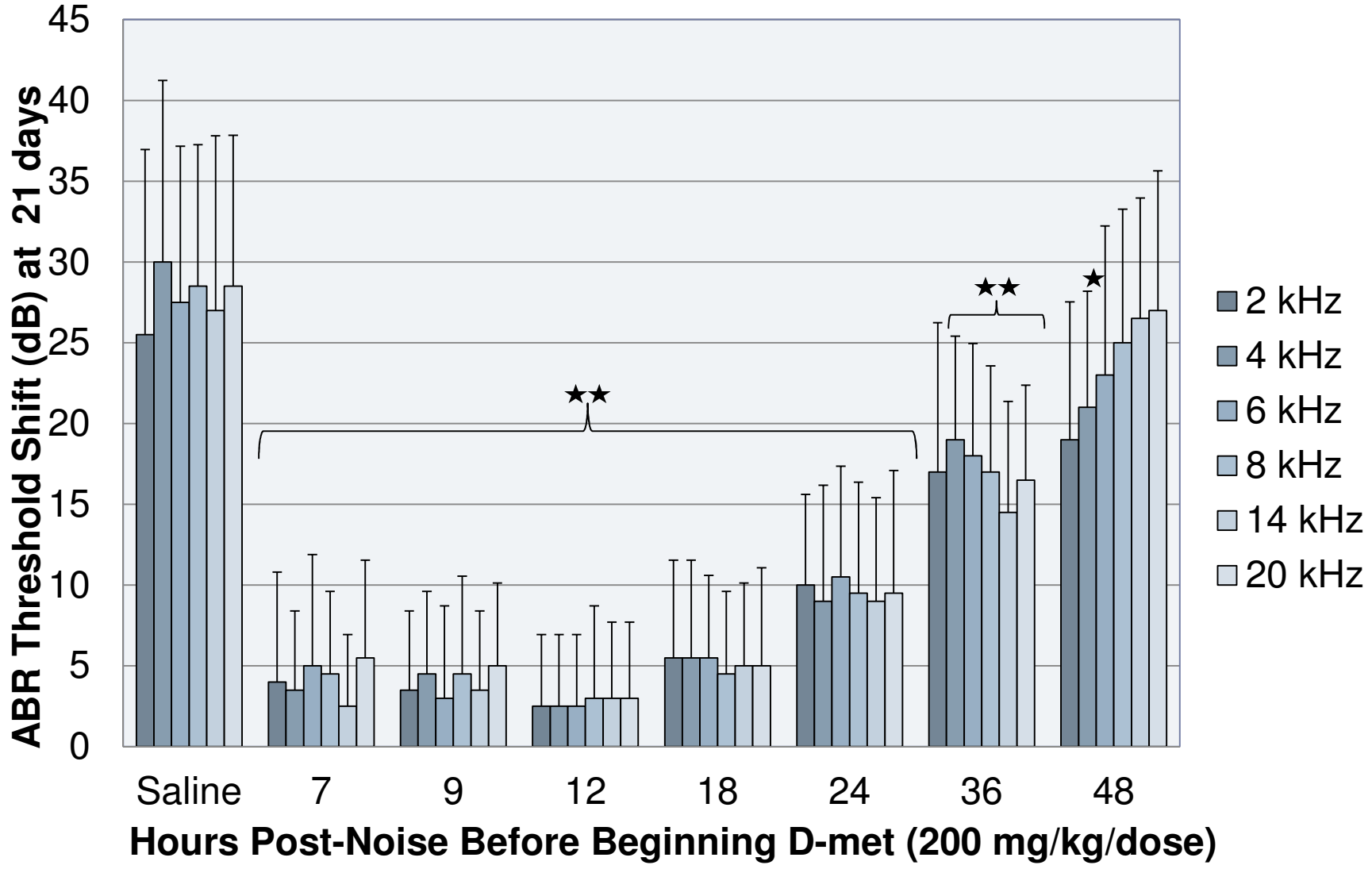
Statistical Analysis

- ABR and histological data were analyzed with a factorial ANOVA
  - Between: rescue interval
  - Within: test days and frequencies
- Tukey's post-hoc follow up tests were performed at the 0.05 or 0.01 level as indicated.

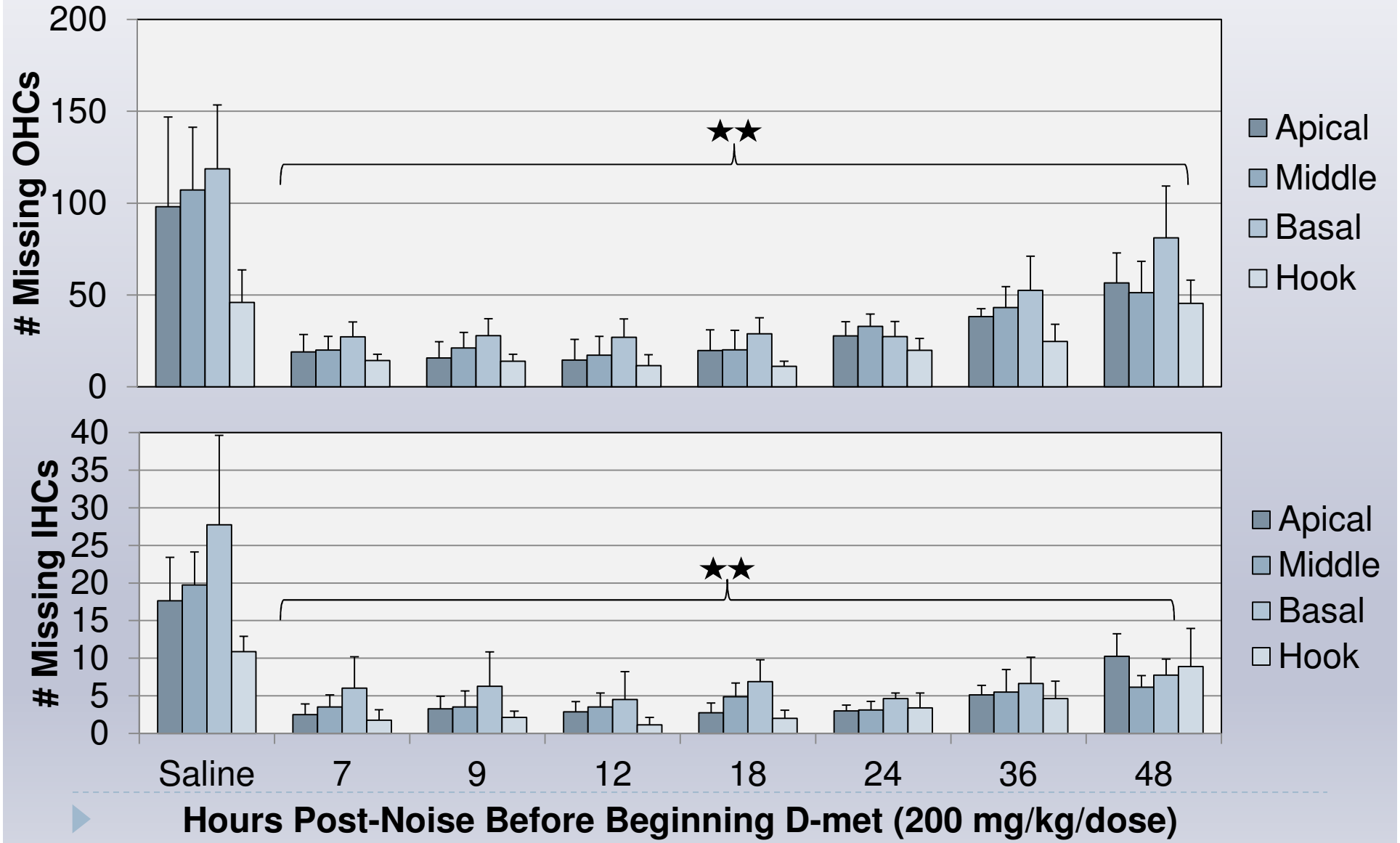
Results



D-met significantly reduced ABR permanent threshold shifts in steady state noise-exposed chinchillas when first administered as late as 36 hours post-steady state noise exposure.



Rescue D-met administration significantly reduced missing outer and inner hair cells in steady state noise-exposed chinchillas.



Conclusions

- D-met significantly rescues from both steady state and impulse noise exposures.
- Study results support clinical trial design by defining D-met's optimal rescue dose and therapeutic window.



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D-METHIONINE (D-MET) CLINICAL TRIALS FOR NOISE-INDUCED HEARING LOSS

Study Funding and Approvals

- Funded by the Department of Defense, U. S. Army Research and Materiel Command
- Reviewed and authorized to begin by the FDA





Previous D-met Clinical Trials (Phases 1-2)

- Study #1: Phase 1a: Pharmacokinetic Evaluation of D-met included 12 normal human adult volunteers.
- Study #2: Phase 1b: Open-label, multiple-dose, phase 1study of D-met concurrent with radiation therapy with or without cisplatin. Purpose of the study was to evaluate the effect of D-met on radiation-induced oral mucositis in head and neck cancer. This study included 25 adult subjects with head and neck cancer (15 male/10 female; mean age 47 years).
- Study #3: Phase 2: Multi-center, randomized, double-blind, placebo-controlled, phase 2 study to evaluate the safety and effectiveness of D-met for mucosal protection in head and neck cancer patients. This study included 58 adult subjects (44 male/14 female; mean age 49 years).
- Study #4: Phase 2: Randomized, double-blind, placebo-controlled, phase 2 study to evaluate D-met protection in cisplatin-induced hearing loss. This study included 27 adult subjects (6 male/21female; mean age 55 years).

Investigational New Drug Application (IND)

- IND application has been filed.
- We are approved to proceed and are collecting data.
- Application included drug formulation and testing, 2 species toxicology studies, 3 species PK studies, our published Phase I, all previous published animal and human data, all of our unpublished data, copies of all manuscripts (6,429 pages single copy)

Current Clinical Trial Study Design

- Randomized, double-blind, parallel, placebo-controlled study
- Pure-tone air-conduction thresholds at .5, 1, 2, 3, 4, 6, 8 kHz
- Bone conduction at thresholds exceeding 15 dB HL
- Testing for permanent threshold shift only
- Tinnitus questionnaires modified from Tinnitus Ototoxicity Monitoring Interview (TOMI), Tinnitus Loudness Index, Tinnitus Handicap Index (THI)
- Independent statistical analysis at Yale: Carrie Redlich,MD, Marty Slade statistician

Next step?

- The first goal of our research program is to obtain FDA approval of D-methionine to prevent and treat noise induced hearing loss for clinical use within the next 5 years.
- The second goal is to obtain FDA approval of D-methionine to prevent and treat cisplatin induced hearing loss in the near future.

DISCUSSION AND QUESTIONS