D-methionine (D-met) as a Protective Agent:From Bench to Bedside

Kathleen Campbell, PhD

Professor & Director of Audiology Research

SIU School of Medicine

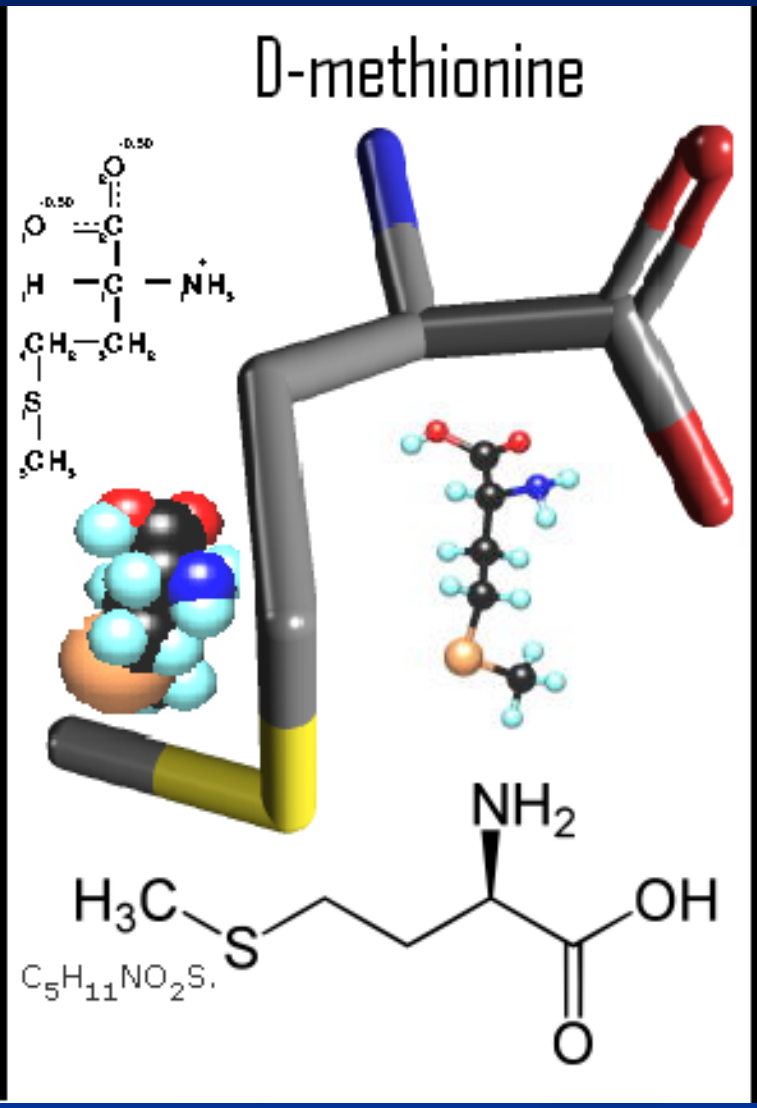
Technology Summary

- D-methionine (D-met) reduces platinum based chemotherapy induced hearing loss and other side effects without antitumor interference.
- D-met reduces radiation induced oral mucositis without antitumor interference.
- D-met reduces aminoglycoside induced ototoxicity and nephrotoxicity without antimicrobial interference.
- D-met prevents noise induced hearing loss if administered before, during or even if started up to 7 hours after noise exposure.

Technology Details

- D-methionine (D-met) is a direct and an indirect antioxidant
- D-met can be effectively delivered orally, or by injection. It can also be effectively delivered to the round window for auditory protection.
- In clinical trials to date we have used an orange-flavored oral preparation with flavor matched placebo.

Structure of Methionine



Current Developmental Status of D-met Research

- FDA approved our Investigational New Drug Application January 2005 for D-met protection from radiation induced oral mucositis.
- Phase 2 clinical trials manuscripts for cisplatin otoprotection and radiation induced oral mucositis are in preparation. Additional US clinical trials are being planned.
- The DoD has funded our clinical trials with US Army troops for protection from noise induced hearing loss and tinnitus. IND has been approved.
- Further bench work is in progress. NIH has funded funded further studies of aminoglycoside otoprotection and DoD has funded further NIHL studies .
- Currently seeking licensure partner.

Current Funding for D-met Otoprotection (Campbell)

- 2007-2012 R01 DC008412-01A1 NIH/NIDCD **($1,941,684)**"Developing D-methionine as an Aminoglycoside Otoprotectant'.R01.PI Kathleen Campbell, PhD Co investigators: M. Cooper PhD, L. Rybak, MD, PhD, L. Hughes, PhD, N. Khardori, MD. M El-Azizi
- 2009-2013 R01DC008412-03S1 **($274,527)** "Developing D-methionine as a Kanamycin Otoprotectant"ARRA Supplement to R01 DC008412-01A1 NIH/NIDCD "Developing D-methionine as an Aminoglycoside Otoprotectant'.R01.PI Kathleen Campbell, PhD Co investigators: M. Cooper PhD, L. Rybak, MD, PhD, L. Hughes, PhD, N. Khardori, MD. M El-Azizi MD
- 2009-2012 3R01DC008412-03S2 **($72,750)** "Developing D-methionine as a Neomycin Otoprotectant"Supplement to R01 DC008412-01A1 NIH/NIDCD "Developing D-methionine as an Aminoglycoside Otoprotectant'.R01.PI Kathleen Campbell, PhD Co investigators: M. Cooper PhD, L. Rybak, MD, PhD, L. Hughes, PhD, N. Khardori, MD. M El-Azizi
- 2010-2015 Department of Defense **($2,568,585)** "Phase 2 Clinical Trials; D-methionine to Reduce Noise-Induced Hearing Loss". Kathleen Campbell PhD, PI, Co-Is L Rybak, MD. PhD J Milbrandt,PhD Cpt J Curry-Mathis AuD, C Redlich, MD, M Slade MPH
- 2011-2014 Department of Defense: **($1,206,303.42**) Research in Prevention and Treatment of Noise-Induced Hearing Loss (NIHL) Kathleen CM Campbell PI, S Verhulst, J Qin
- **Total: $6,063,849.42**
- **A Licensure Partner Could Move Our Research Forward More Quickly**

The Competition

- Currently no drug is FDA approved to prevent noise-induced, aminoglycoside-induced or platinum-based chemotherapy induced hearing loss.
- This lecture is focusing on preventing noise induced hearing loss and tinnitus. Currently 2 other oral compounds are in or approaching clinical trials to prevent NIHL. Another compound is approaching clinical trials but can only be safely given to the round window which will severely restrict its use. N-acetylcysteine (NAC) was tested in DoD clinical trials and was ineffective.

The Competition: Oral Agents

- ACE Mg: Approaching clinical trials to prevent temporary threshold shift the at the University of Florida. They are seeking funding for further studies in Spain for protection from permanent threshold shift. Disadvantages: Cannot be used in smokers as the beta carotene can increase risk of lung cancer. Also Mg content may increase risk of loose stools. These limitations may affect military and industrial use.
- Ebselen: Approaching clinical trials to prevent temporary threshold shift at UF. No clinical trial site yet for permanent threshold shift. Disadvantages: Must be given for up to 14 days for partial protection from a single noise exposure. Selenium may be toxic.
- NAC: Did not work in 2 DoD clinical trials and DoD.
- D-met : is the only agent funded by the DoD for clinical trials with the US military at this time.

Market for Protective Agent for Noise Induced Hearing Loss and Tinnitus

- Noise Induced Hearing loss (NIHL) is the leading cause of hearing loss world wide.
- The US Department of Defense and Veteran's Administration alone spend over 4 billion dollars per year on NIHL and noise induced tinnitus.
- Prevention of NIHL has moved to the top of the DoD research funding priorities.
- RNID states the potential value of novel otoprotectants for NIHL is $1.9 billion per year.
- Currently no approved drugs exist to prevent NIHL and tinnitus. D-met is the only agent funded for DoD clinical trials.

Intellectual Property Protection

- US Patents #6,187,817 (2/13/01) & #7,557,142 (7/7/09)
  - Covers ototoxicity, neurotoxicity, gastrointestinal toxicities, weight loss, and alopecia induced by platinum anti-tumor drugs
  - Patents issued in Australia, Canada, Europe, Japan
- US Patent #6,265,386 (7/24/01)
  - Covers aminoglycoside-induced ototoxicity
  - Patents issued in Australia, Canada, Europe
- US Patents #7,071,230 (7/4/06) & #7,423,065 (9/8/08)
  - Covers noise-induced ototoxicity
- Patents/Applications in Australia, Canada, Europe, Japan
  - Cover radiation-induced oral mucositis

D-methionine Protection for Noise-Induced Hearing Loss

Samples of our published data.

Study Funding and Approvals

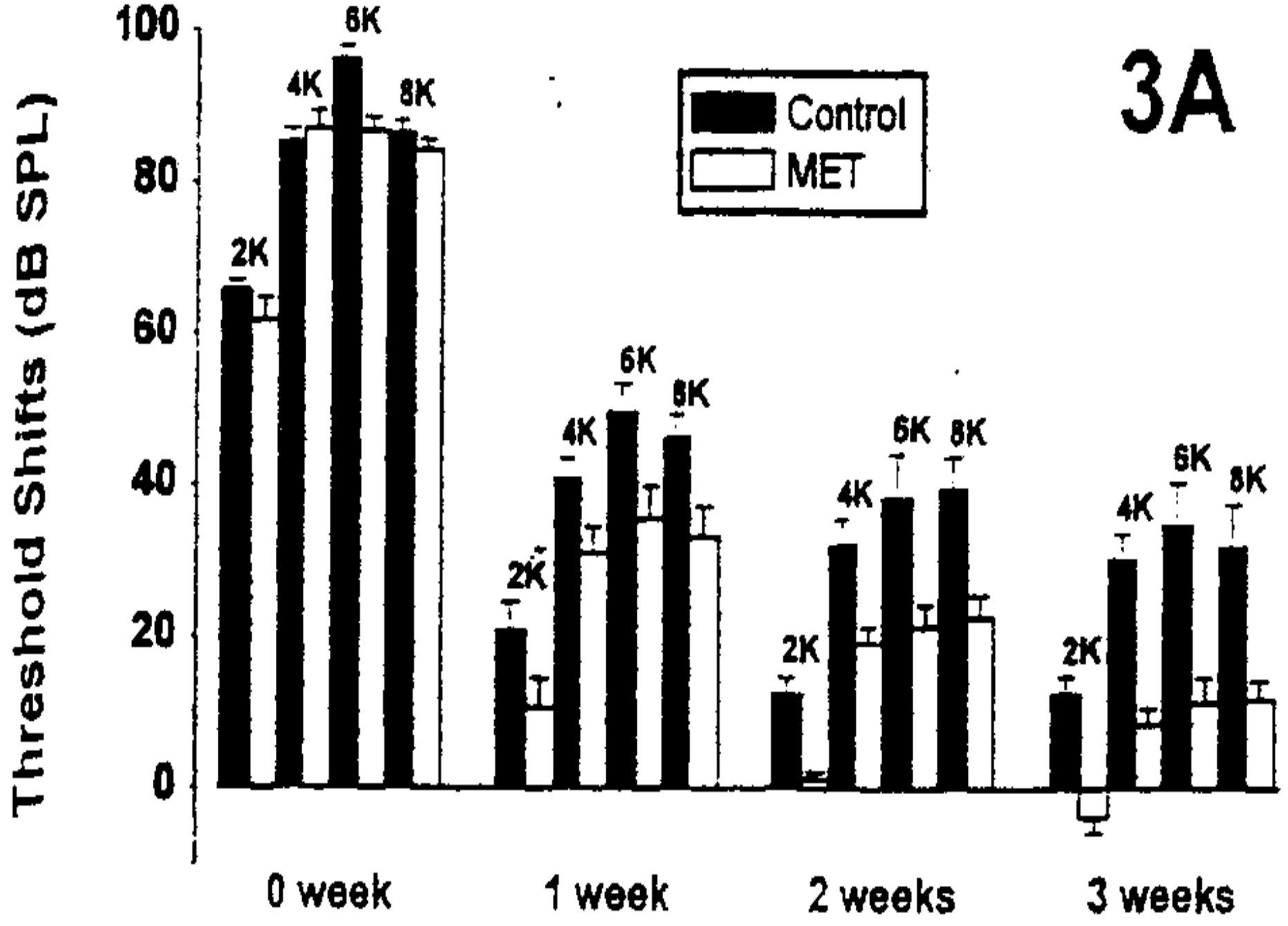
- Funded by the Department of Defense, U. S. Army Research and Materiel Command
- Reviewed and authorized to begin by the FDA

D-Methionine (D-met)

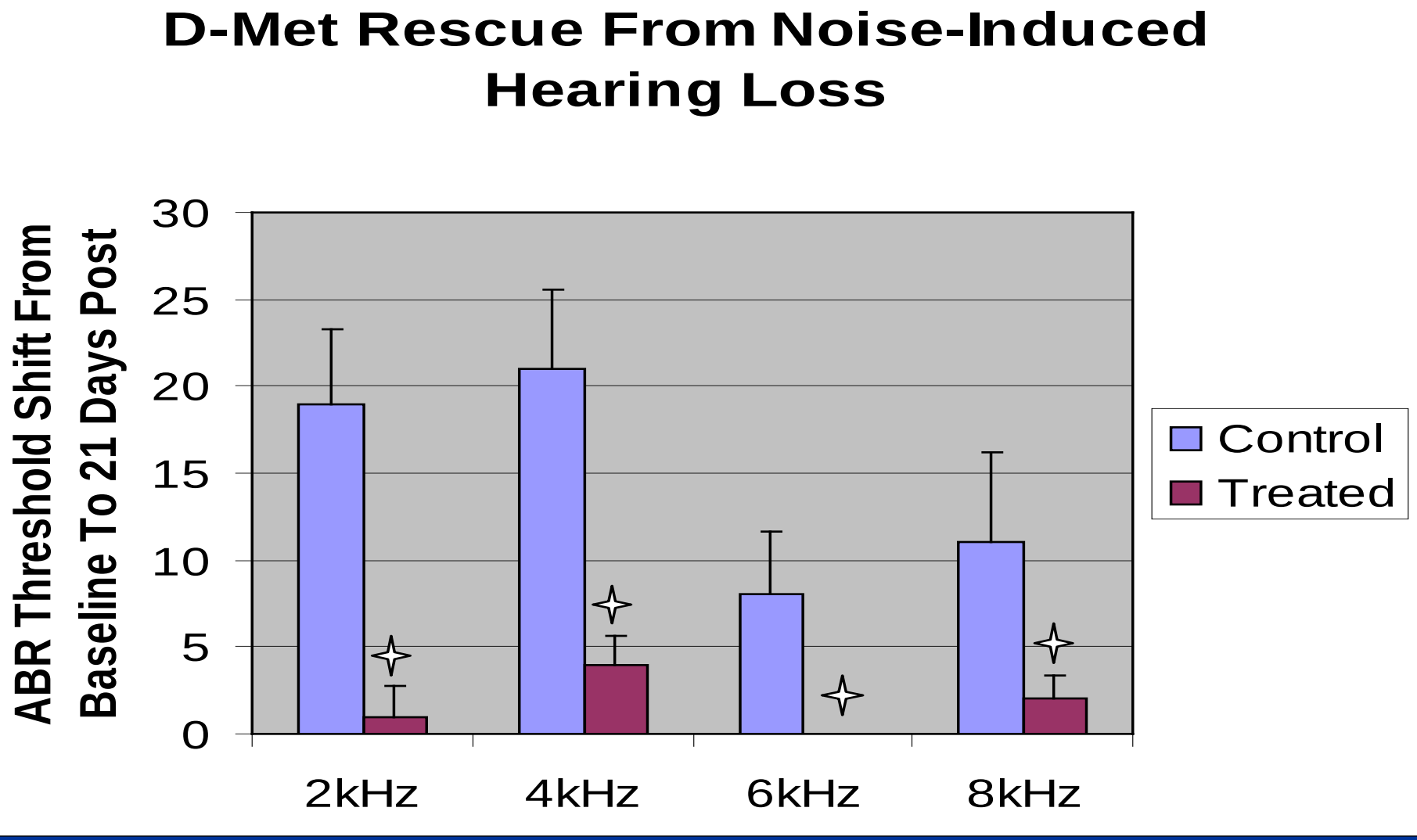
- D-met was first discovered to protect against hearing loss caused from a chemotherapy drug (cisplatin) in 1996 by Dr. Kathleen Campbell at Southern Illinois University School of Medicine (Campbell, et al., 1996).
- Methionine is a micronutrient, (i.e. found in cheese and yogurt) and is not alien to the human system.
- Methionine comprises 26 mg/g high quality protein in the diet (National Academy of Sciences 1980).
- D-met has been studied in human clinical trials (India) for chemotherapy (cisplatin) induced hearing loss with no side effects greater in the D-met group than in the placebo group at the same dosing level proposed for this study (100 mg/kg/day).
- Methionine has been studied for decades as a part of human and animal nutrition.

D-met Protection from NIHL

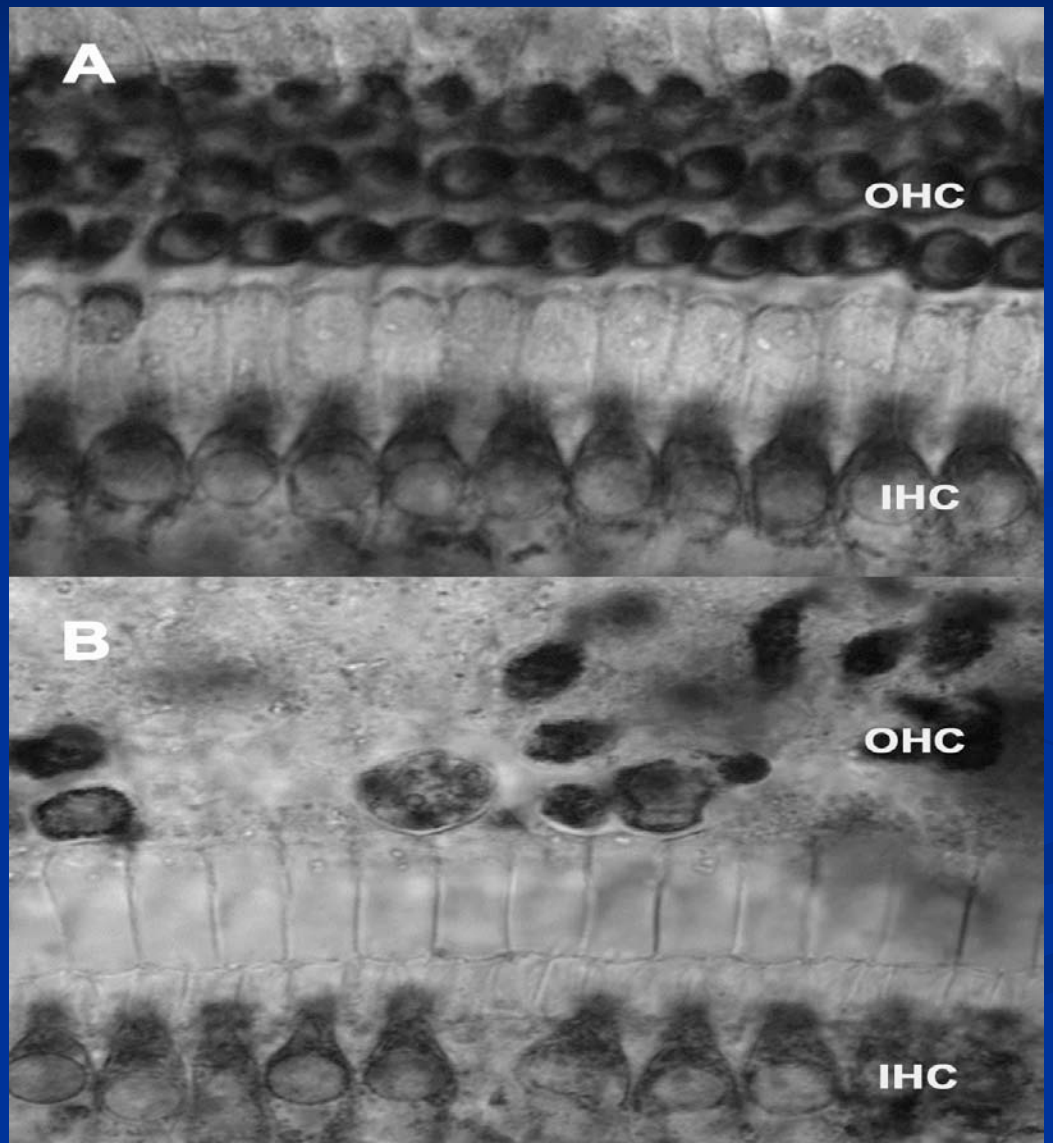
- Protects from permanent threshold shift (PTS) in chinchillas when given 2 days before and after, noise exposure (Kopke 2002, Clifford et al 2011) and when given 1 hour before and after (Samson et al 2008)
- Protects from PTS when first started 1,3,5,or 7 hours after noise cessation (Campbell et al 2007, 2011)
- Protects from temporary threshold shift when given just 1 hour before noise (Cheng et al 2008)

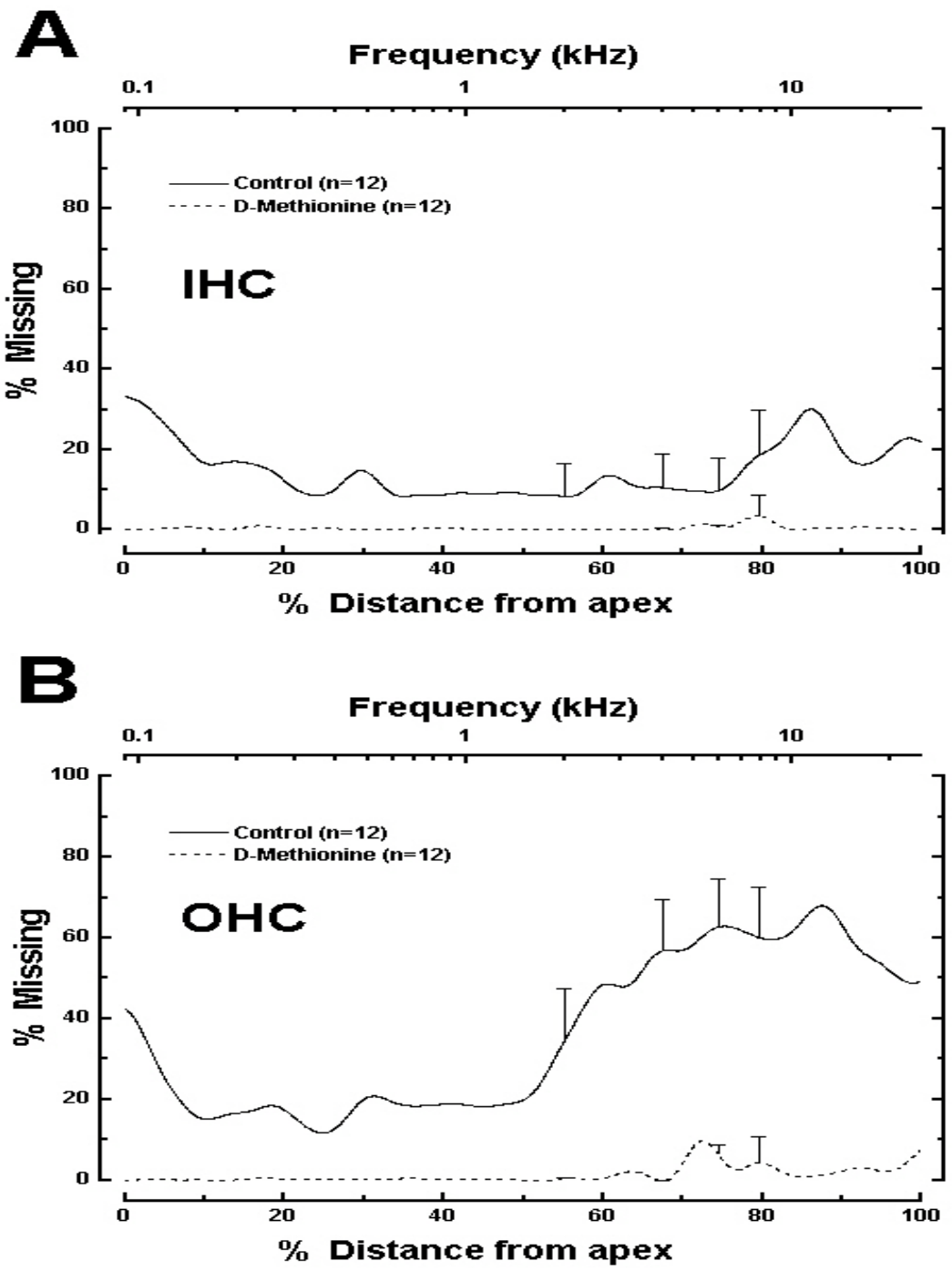

3A
Threshold Shifts (dB SPL)
100
80
60
40
20
0
Control
MET
2K
4K
6K
8K
0 week
1 week
2 weeks
3 weeks

D-met rescue from NIHL



Met HC protection




A
Frequency (kHz)
0.1
1
10
Control (n=12)
D-Methionine (n=12)
IHC
% Missing
% Distance from apex
B
Frequency (kHz)
0.1
1
10
Control (n=12)
D-Methionine (n=12)
OHC
% Missing
% Distance from apex

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.
- Application included GMP 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)
- We have been invited to submit for Special Protocol Review (SPA)

Current Clinical Trial Study Design

- Data collected on 600 soldiers during M-16 weapons training (500 rounds in less than 2 weeks)
- 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

Advantages of Military Site Clinical Trials

- Very disciplined and motivated study team
- The training situation offers a very regimented environment for better controls
- Easy to add on study protocol as all weapons training already standardized for the Soldiers
- Drug dispensing can be readily dispensed and monitored

Possible Challenges of Military Site Clinical Trials

- Conducting studies within the US military presents unique challenges differing from private/academic facilities
  - Multiple approvals needed for clinical protocol. Approvals must be vetted up the chain of command
  - Civilian researchers (like us) unfamiliar with military hierarchy, procedures, language and general culture (we are learning)
  - Requires multiple collaborators, credit will be needed for everyone
  - Military sites/personnel may be unfamiliar with clinical trials research
  - Deployments cause staff turnovers

Additional Challenges

- Cooperative Research and Development Agreement (CRADA)
- Transferring Funds and hiring personnel on base
- Subjects have very limited time
- Space for equipment, testing and drug storage can be an issue
- Institutional Review Board (IRB)
- Multiple Military Divisions under Different Commands Involved
- Multiple levels of scientific review needed before study commencement
- FDA and IRB can require more measures but grant funding is limited

D-Met Protection

- For more information stop by our display table.
- Visit our website: www.siumed.edu/adrfa/techtransfer.html
- Or E-mail: Kathleen Campbell, PhD kcampbell@siumed.edu
- Or Office of Technology Transfer techtransfer@siumed.edu
- Questions?