D-methionine (D-met) as a Protective Agent

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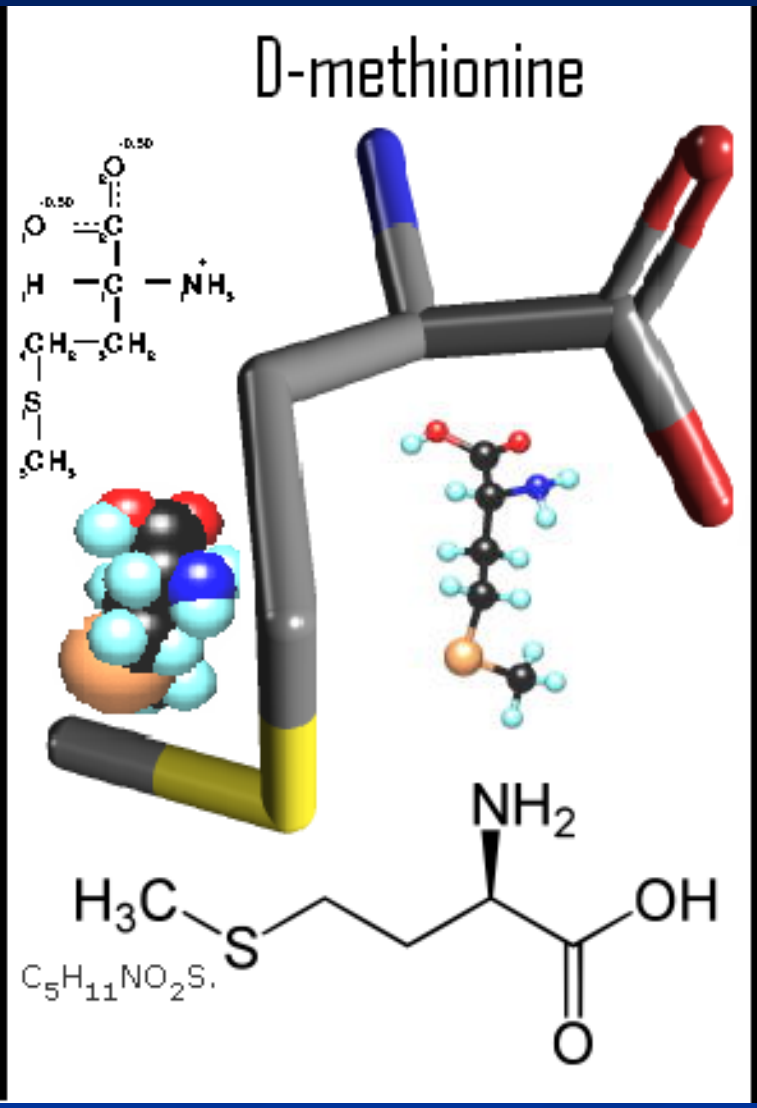
Technology Summary

- 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.
- 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 is in progress.
- 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

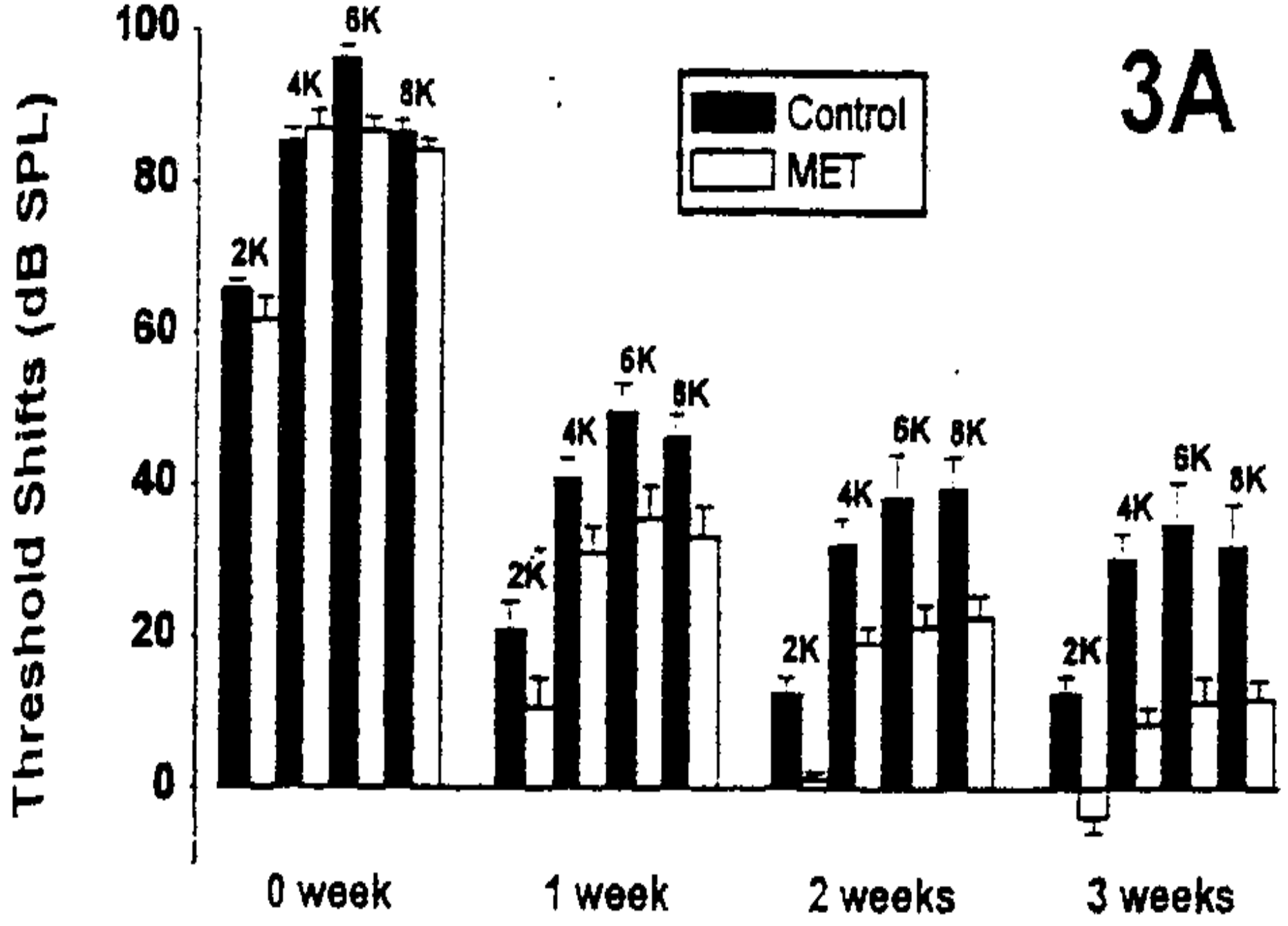
- US Patents #6,187,817 (2/13/01) & #7,557,142 (7/7/09)
  - Covers ototoxicity, neurotoxicity, gastrointestinal toxicities, weight loss, and alopecia induced by platinum anti-tumor drugs
  - Patents issued in Australia, Canada, Europe, Japan
- US Patent #6,265,386 (7/24/01)
  - Covers aminoglycoside-induced 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

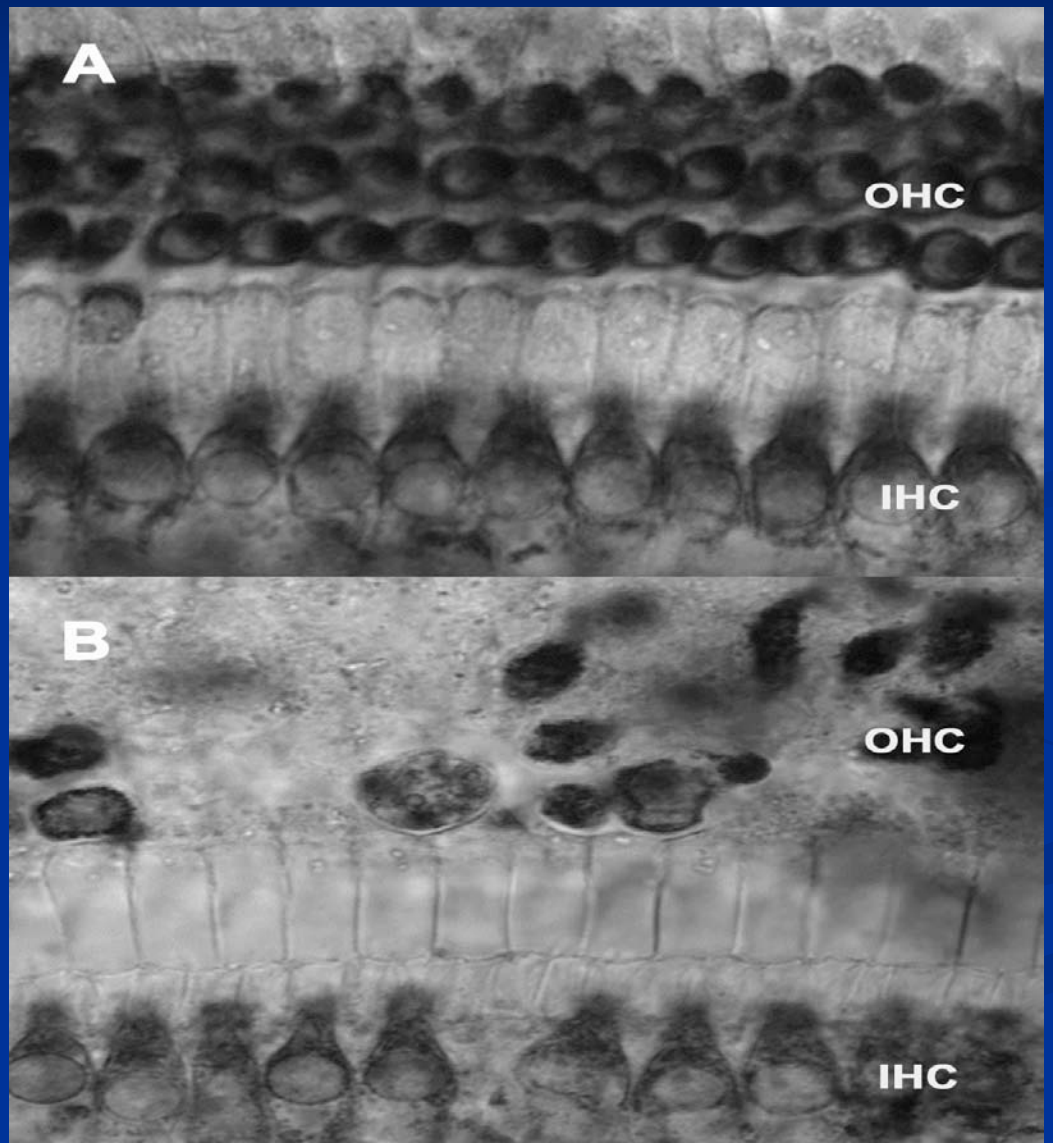
Samples of our published data.

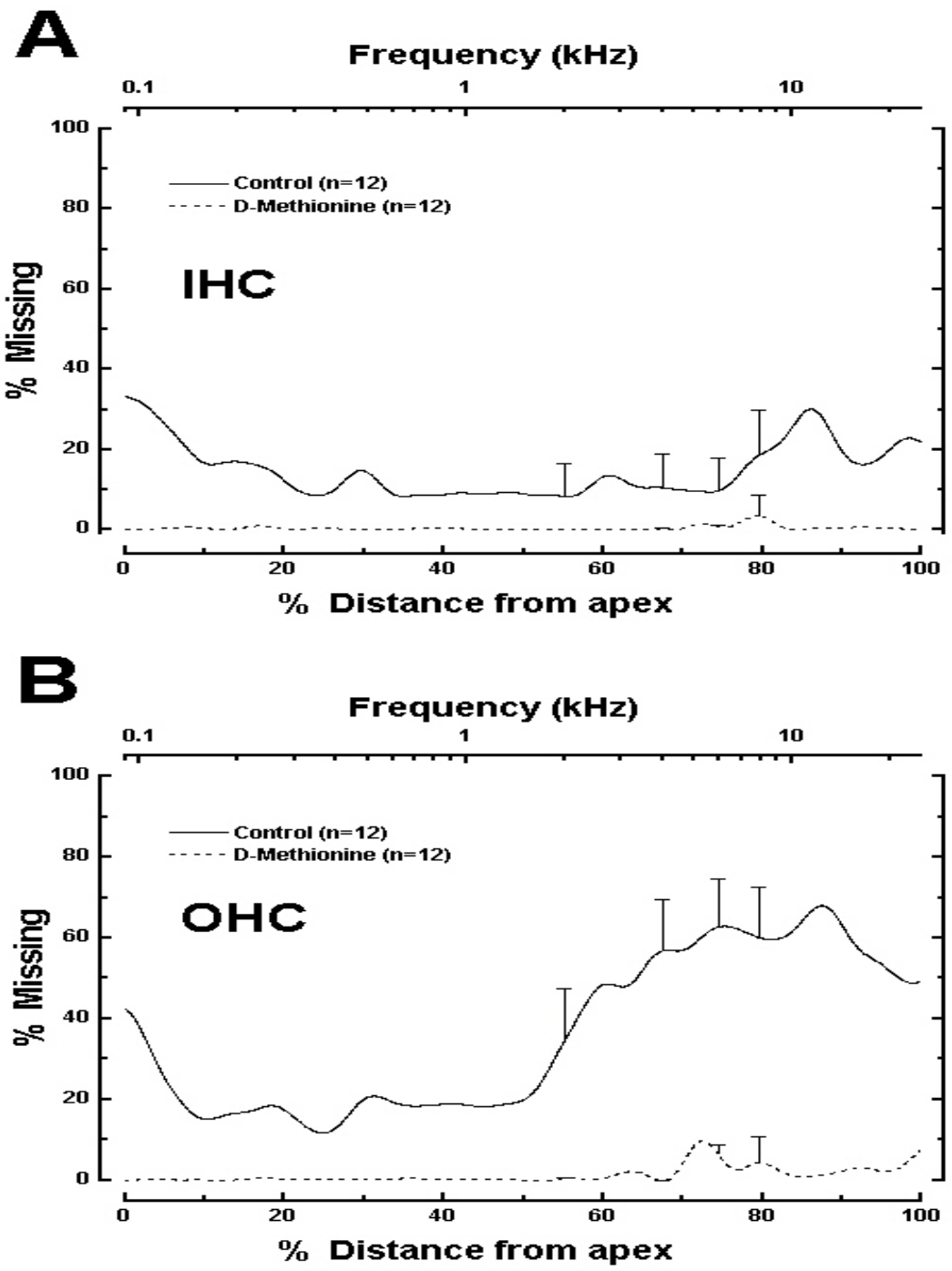
Kopke et al 2000, 2002

- Chinchilla model
- 105 dB SPL noise band centered at 4kHz
- D-met or ALCAR administered at 200mg/kg ip, NAC at 325mg/kg plus salicylate
- 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
Threshold Shifts (dB SPL)
100
80
60
40
20
0
Control
MET
2K
4K
6K
8K
0 week
1 week
2 weeks
3 weeks

Met HC protection

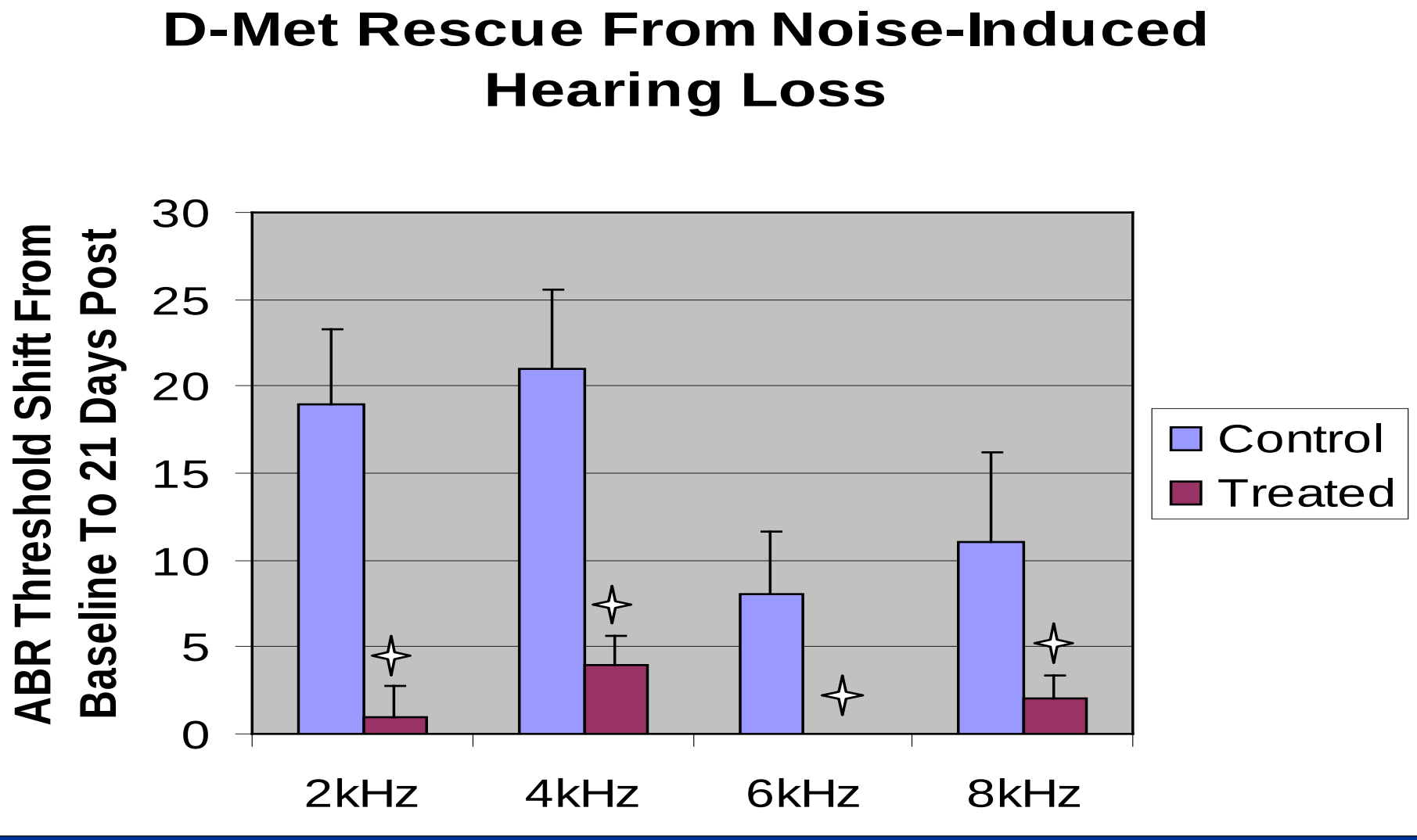



A
Frequency (kHz)
0.1
1
10
Control (n=12)
D-Methionine (n=12)
IHC
% Missing
% Distance from apex
B
Frequency (kHz)
0.1
1
10
Control (n=12)
D-Methionine (n=12)
OHC
% Missing
% Distance from apex

D-met Post-Noise Rescue Mitchell, Meech, Campbell

- D-met can be started 1-7 hours after noise exposure and provide protection from permanent NIHL.
- D-met consistently prevents permanent noise induced hearing loss across studies for pre-or post administration. Protection for temporary hearing loss is variable across studies.
- Methods: 6 hour: 105dB SPL 4kHz octave band noise, 200 mg/kg D-met 1 hour after exposure and 2 days BID.
- With 10 animals per group, significant protection at 2, 4, 6 & 8 kHz for 1 hour post administration.

D-met rescue from NIHL



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?