showed significant changes in frequencies >8 kHz that were not detected with the routine pure tone audiometry and distortion product otoacoustic emission audiodiagnostic tests.4

In conclusion, although the idea of such studies about the otoprotective effect of intratympanic injections against cisplatin-induced ototoxicity seems magnificent and deserves more modifications, a careful revision in evaluating their results and moving them forward from animal models to human studies is suggested.

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Response to “A Revision in Evaluating the Results of Intratympanic Otoprotective Injections against Cisplatin-Induced Ototoxicity”
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We thank you for your interest and comments regarding our article “Cisplatin-Induced Ototoxicity and the Effects of Intratympanic Diltiazem in a Mouse Model.” We are grateful for the opportunity to address your comments. We acknowledge some of the shortcomings of working with animal models, and we share the objective of refining animal models of cisplatin ototoxicity.

The first point that you suggest is that cisplatin ototoxicity is not the same bilaterally, thus making comparison between a treatment ear and a control ear of the same mouse unreliable. We are aware that cisplatin may not have the same ototoxic effect on each ear. We were able to account for this in the key portion of our study (phase II), where otoprotective effects of intratympanic diltiazem and saline controls were evaluated in separate animals, not in contralateral ears.

Second, you raise the point that that the ototoxic effects of cisplatin can occur long after the last dose is administered. Many notable cisplatin animal model studies do not evaluate its long-term effects.1,2 In fact, we are one of the few laboratories that has explored the effects of cisplatin on audiodiagnostic testing over an extended period. Our laboratory’s experience has shown that in a mouse model, ototoxic effects from cisplatin stabilize after 3 weeks, and audiodiagnostic evaluations carried out up to 90 days do not show progression of ototoxicity.3,4

Finally, you discuss the concept that traditional audiometric measures, such as pure tone audiometry and distortion product otoacoustic emissions, may not be adequate measures of cisplatin ototoxicity, as the high frequencies are often more sensitive to the effects of cisplatin. We certainly agree with this point. We recognize the limitations of traditional audiometric measurements, and we are currently evaluating the utility of an outer hair cell–specific protein, prestin, as an otologic biomarker that has the potential to act as early indicator of inner ear damage that presents before audiometric changes.5 We anticipate that this current work will afford new, more sensitive techniques to detect effects of inner ear damage.

In conclusion, we agree that there is more work that needs to be performed, and ultimately, we hope to have the opportunity to translate some of our work to the clinical setting. This is a clinical problem that has remained unsolved, and one of our goals with this work was to demonstrate that novel therapeutic agents such as diltiazem may provide a paradigm shift in approach to potential therapies. Although the mouse model has certain limitations, it provides a medium through which novel concepts can be evaluated. We look forward to contributing more to this topic in the future.

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References


