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Response to “Drug diffusion to the apex of the human cochlea?”

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We appreciate the opportunity to clarify several points raised by the letter writer regarding the experiments we performed and our report of those experiments.

First, the writer declares the absence of Reissner’s membrane, the organ of Corti, and other soft tissue components in our images to be evidence of “morphological disintegration” after death. The bisphosphonates we have analyzed bind avidly to bone, an action fundamental and intrinsic to their therapeutic effect. Histological processing to visualize cochlear soft tissue removes bone through decalcification. Visualization of cochlear bone instead requires embedding the specimen in resin and grinding the bone away until the mid-modiolar region of the cochlea is reached. This process, which we describe in detail in the methods section, destroys most of the soft tissue, but leaves the bone (and the bisphosphonate that has bound to it) intact. Thus, lack of soft tissue is not evidence of “putrefactive processes” as the writer imagines, but rather a consequence of the procedure necessary to image and quantify the drug bound to bone. This misunderstanding of our procedure may have also led to the writer questioning why soft tissue was not present in our measurements of the lateral cochlear wall.

Second, the writer objects to our use of cadaveric human tissue to analyze bisphosphonate distribution, suggesting that postmortem redistribution of drug may have significantly influenced the results. However, as cited in the paper, our findings in the cadaveric human cochlea are remarkably similar to previously published findings in the live guinea pig ear generated by our group and others, supporting the idea that work in the human cadaveric ear is indeed relevant. The ability to confirm and extend observations made in the live animal to the human, even in a cadaveric ear, is invaluable.

Third, the writer strongly disagrees with our statement that “...fresh cadaveric human temporal bones have clear advantages relative to animal models” and states that we failed to make clear that distribution in the live ear will differ from that in the cadaveric ear. In fact, our actual statement was, “Although fresh human cadaveric temporal bones have clear

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advantages relative to animal models... dynamics within the sealed living human cochlea are likely to be complex and may confound efforts at description in a cadaveric system,” and the rest of the lengthy paragraph discusses the many limitations. Such limitations aside, no existing *in vitro* system captures the three-dimensional intricacies of bony anatomy of the human cochlea, underscoring the importance of a cadaveric approach.

Finally, use of cadaveric cochlear tissue has proven not to be as misguided a proposition as the writer suggests. Von Békésy deduced the strikingly complicated physiological mechanisms by which the cochlea decodes auditory signals using cadaveric tissue. Studies of human cadaveric temporal bones have further revealed fundamental elements of middle ear physiology, leading to successful modification of human middle ear surgery. Detailed electron microscopic images of the fine structure of subcellular processes have been acquired from cadaveric specimens, allowing volumes of animal work to be interpreted in the human. Decades of human temporal bone histopathological analyses in cadaveric specimens have provided critical insights into mechanisms of cochlear function, both in health and disease.

In sum, while we agree a cadaveric human cochlea cannot replicate all the functions of a living human cochlea – a point that we emphasize in our paper – we stand by our assertion that the thoughtful use of cadaveric tissue can yield important insights and bridge the gap between animal experiments and human application.

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