Histopathology of a Mouse Model of Kanamycin/Furosemide-induced Cochlear Hair Cell Injury

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1 INTRODUCTION
Ototoxicity is a known adverse effect of several drugs, including antibiotics, loop diuretics, platinum-based chemotherapy agents and several nonsteroidal anti-inflammatory drugs (NSAIDS). The potential for sensorineural hearing loss, balance impairment, or both in patients has gradually resulted in increased interest in screening of new chemical entities during early drug development. We characterized a mouse model of cochlear hair cell injury using two known ototoxic compounds, kanamycin and furosemide, as a tool to screen for ototoxicity.

2 MATERIALS AND METHODS
Four groups of 4 C57BL6 female mice/group were administered a single dose of kanamycin (1 mg/g) by subcutaneous injection and furosemide (0.08, 0.10, 0.25 or 0.40 or mg/g) by intraperitoneal injection. Animals were monitored for 10 days. At necropsy, the tympanic bulla was opened, the temporal bone was trimmed off and the tissues were fixed and decalcified using a solution of picric acid and formic acid (PFF). Decalcification was monitored by x-rays. The inner ears were then embedded in paraffin, step-sectioned at 75 μm intervals and stained with hematoxylin and eosin.

3 RESULTS AND DISCUSSION
Microscopic evaluation of the cochlea revealed loss and/or degeneration of various cell populations of the organ of Corti. There was a dose-dependent increase in the severity of those findings in the cochlea of animals administered furosemide at ≥ 0.10 mg/g. Outer hair cells were the most susceptible to degenerative changes induced by kanamycin/furosemide, followed by, in a decreasing order of sensitivity, the inner hair cells and the supporting cells (i.e. pillar cells and phalangeal cells). Atrophy of the stria vascularis was also noted in some animals.

4 CONCLUSION
In conclusion, our mouse model of ototoxicity was characterized by degeneration and loss of hair cells and supporting cells of the organ of Corti 10 days after systemic administration of kanamycin and furosemide. This model can be used as a comparative tool in the assessment of ototoxicity of new drugs.