

Auris Medical News Release

January 4, 2012 – Publication showing AM-111's otoprotective effect in cochlear ischemia

The December 2011 issue of the renowned scientific journal *Otology & Neurotology*¹ presented new data on the otoprotective effects of AM-111, Auris Medical's intracellular JNK ligand. In an article titled "Protection Against Ischemic Cochlear Damage by Intratympanic Administration of AM-111" a research group around Prof. Kiyofumi Gyo from the Department of Otolaryngology of Ehime University, Japan, showed the results of a study with AM-111 in an animal model of transient cochlear ischemia. Vascular disturbances such as an acute interruption of the blood supply to the cochlea are one of the factors that can trigger sudden sensorineural hearing loss.

The Japanese scientists used a previously established model of transient cochlear ischemia for the study. In this model the vertebral artery of gerbils is occluded for 15 minutes in order to provoke transient cochlear ischemia, followed by reperfusion. As presented in earlier publications, this leads to irreversible loss especially of inner hair cells and permanent hearing loss especially at higher frequencies. 10 µl of AM-111 at a concentration of 1, 10 or 100 µM and formulated in a gel was placed onto the round window membrane 30 minutes after the insult. The gel without active substance served as control. For the evaluation of the auditory function, auditory brainstem responses (ABRs) were measured at 2, 4 and 8 kHz before ischemia, as well as 4 days and 7 days after the temporary arterial occlusion. Animals were sacrificed on day 7 for histopathology and counting of hair cells.

In control ears mean ABR thresholds increased substantially to day 4 (+31 dB at 8 kHz, the most sensitive frequency) and from there recovered slightly to day 7 (+25 dB at 8 kHz). In contrast, ears treated with AM-111 showed less hearing loss the higher the applied concentration was. At the highest concentration, mean ABR thresholds in AM-111 protected ears rose by only 7 dB to day 4 and were elevated by 3 dB on day 7. Statistical analysis (one-way analysis of variance followed by Fisher's post hoc test) revealed statistical significance of the otoprotective effect of AM-111 at all 3 concentrations ($p < 0.01$ at 100 and 10 µM, and $p < 0.05$ at 1 µM). The protective effect was confirmed by histopathology: inner hair cell loss on Day 7 in the most affected basal turn amounted to $13.3 \pm 2.7\%$ in controls and $3.1 \pm 0.6\%$ in the highest concentration AM-111 group. The difference was statistically significant in a concentration dependent fashion ($p < 0.01$ at 100 and 10 µM, and $p < 0.05$ at 1 µM).

About acute sensorineural hearing loss

Acute sensorineural hearing loss (ASNHL) or inner ear hearing loss is the consequence of various insults to the cochlea. It may result e.g. from overexposure to noise, bacterial or viral infections, inflammation, vascular compromise, or a variety of other factors. In ASNHL, sensorineural structures of the inner ear – inner and outer hair cells, neurons – are damaged, as well as other structures such as supporting cells or vascular tissues. The common observation is a temporary increase in hearing thresholds, i.e. hearing loss. Thanks to cellular defences and intrinsic repair mechanisms, a certain amount of such hearing loss is frequently re-

¹ Omotehara Y, Hakuba N, Hato N, Okada M, Gyo K (2011), Protection Against Ischemic Cochlear Damage by Intratympanic Administration of AM-111, *Otology & Neurotology* 32(9): 1422-1427.

covered in the subsequent days and weeks. The remaining hearing loss however is irreversible. ASNHL may be accompanied by other disorders of the inner ear such as dizziness or tinnitus.

When ASNHL develops into permanent hearing loss, it may have chronically debilitating consequences. Hearing loss may have serious impacts on professional and personal lives, e.g. through avoidance or withdrawal from social situations, reduced alertness and increased risk to personal safety, impaired memory and ability to learn new tasks, or reduced job performance and earning power. Unfortunately, there exists no standard therapy with proven efficacy for ASNHL so far.

About AM-111

AM-111 is a cell-permeable peptide that selectively blocks JNK MAPK mediated apoptosis of stress injured hair cells and neurons in the cochlea. Major cochlear stress incidents that may result in irreversible hearing loss include exposure to excessive noise, disturbances of the blood supply, viral or bacterial infections, and exposure to certain ototoxic substances. When administered within a therapeutic window after the incident, AM-111 can effectively protect cochlear hair cells and neurons that would otherwise undergo apoptosis and be lost forever. AM-111's otoprotective properties have been extensively tested and confirmed in various animal models so far, including acute acoustic trauma, acute labyrinthitis, surgery trauma, aminoglycoside ototoxicity, semicircular canal injury in otitis media and cochlear ischemia. AM-111 has been granted orphan drug status in both the European Union and the USA for the treatment of acute sensorineural hearing loss. The active substance of AM-111 has been in-licensed by Auris Medical from Swiss biotechnology company Xigen S.A.

About Auris Medical

Auris Medical is a Swiss biotechnology company developing specific pharmaceutical compounds for the prevention or treatment of inner ear disorders, an area of great unmet medical need. Around the world, many million people are suffering permanently from severe hearing loss and / or tinnitus, still lacking truly effective and safe treatments for their disorders. Auris Medical is currently focusing on the development of treatments for acute inner ear tinnitus (AM-101) and for acute sensorineural hearing loss (AM-111).

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