Summary

In the scientific study “A Single Dose of AC102 Reverts Tinnitus by Restoring Ribbon Synapses in Noise-Exposed Mongolian Gerbils” we could show for the first time that the recovery of ribbon synapses at the inner hair cells by a single application of the drug AC102 does not only revert minor hearing loss but also redeems the animals from their tinnitus percept.

Like most scientists in the field, we think that tinnitus develops primarily after some kind of hearing loss. Reducing the hearing deficit, e.g., by hearing aids or cochlea implants, has proven to be effective in reducing the tinnitus burden for some patients. Nevertheless, these devices cannot restore hearing completely. We and other scientists speculate that the full recovery of hearing would also lead to the relief of tinnitus.

In our animal model, the Mongolian gerbil (*Meriones unguiculatus*), we could already show that tinnitus develops only in animals with a synaptopathy of the ribbon synapses of the inner hair cells after a mild acoustic trauma. The percept is independent of the development of a “clinical hearing loss”, i.e., also animals with “hidden hearing loss” show the percept, if a synaptopathy is present. The newly developed small-molecule pyridoindole drug AC102 has been shown to rescue ribbon synapses in other animal models and is currently in a multicentric clinical phase 2 study for treating sensorineural hearing loss in humans. AC102 is one of the most promising drugs for hearing recovery and therefore also a candidate for successful treatment of the cause of tinnitus. Therefore, the questions of this study were simple: Can AC102 rescue the ribbon synapses in the cochleae of gerbils after a mild acoustic trauma? If so, is the hearing loss reduced and the animal relieved of a possible tinnitus percept?

For that, we choose two approaches: First, three successive applications of the drug / placebo over the cause of three weeks starting immediately after the monaural acoustic trauma. And second, only one application of the drug / placebo immediately after the monaural acoustic trauma. The two approaches were chosen to elucidate, if multiple applications have a higher success rate or a stronger effect on the hearing thresholds and tinnitus. Over five weeks after the acoustic trauma, hearing threshold development was monitored by auditory brainstem response (ABR) audiometry, tinnitus development by the behavioral paradigm of the gap prepulse inhibition of the acoustic startle (GPIAS) response and synaptopathy was investigated with immunofluorescence histology of the whole cochleae (trauma ear and control ear of each animal) after the sacrifice of the animals at the end of the fifth week after trauma. The drug was delivered into the cochlea via the round window membrane of the trauma ear by a AC102 loaded gel or in the placebo case without the drug in the gel by surgery at one or the three timepoints. Overall 51 adult male Mongolian gerbils were used in the study.

Over the cause of the first two to three weeks after trauma, the animals treated with AC102 recovered their ABR hearing thresholds completely, even with only one application of the drug. The single application approach resulted in even better hearing threshold recovery compared to the triple application approach, as only one surgery was needed. The tinnitus percept vanished over the same timeframe and did not come back till the end of the experiment in both approaches. Both positive developments were not visible in the placebo-

treated animal groups. The cause of the recovery was found to be the reduction (single application approach) or complete lack of frequency dependent synaptopathy (triple application approach) in the AC102-treated animals' trauma ears. The synaptopathy was clearly visible in the placebo groups' trauma ears in both experimental approaches, especially in those with a persistent tinnitus percept.

As the drug is already in a phase 2 clinical study, we expect a huge impact of this treatment for tinnitus patients with sensorineural hearing loss, if it is as successful in humans as it is in rodent animal models. We expect it to be especially effective in early-on treatment, which would be similar to the approaches used in our study, but could also provide some benefit in more chronic hearing loss cases, which should be the focus of follow up-studies.