Detailed knowledge of the role that particular genes and factors play during the development and in the normal function of the auditory system is necessary to develop successful regenerative inner ear therapies. Islet1 transcription factor and brain derived neurothrophic factor (BDNF) have great potential to play a role in regenerative inner ear therapy as both have been shown to be sufficient for self-repair regeneration in cochlea in animal studies. In this study we looked at the roles these two factors play in the development and function of the auditory system.

In the transgenic mice used in the study, overexpression of Isl1 affected cell specification during embryonic development, leading to enlargement of the cochleovestibular ganglion and accelerated nerve fiber extension and branching in mutant embryos. The hearing of young transgenic mice was not affected. However, it started to decline in 1-month-old animals. This early onset of age-related hearing loss was found to be a consequence of the neurodegeneration of the olivocochlear system caused by Pax2-driven Isl1 misexpression in the hindbrain. Our data provide the first evidence that the alternation of the olivocochlear system efferent system accelerates the age-related functional decline of hearing without the loss of OHCs.

The functional role of BDNF in the mature auditory system was studied using mutant mice with conditional deletion of BDNF in the lower parts of the auditory pathway. The deletion of BDNF impaired frequency and intensity coding, and affected the inhibitory circuitry in the inferior colliculus, suggesting the importance of BDNF for normal sound processing in the ascending auditory pathway.

Another important step in regenerative therapy is the atraumatic delivery of an active agent to the specific cochlear tissue for targeted action. We tested three types of nanoparticles (NPs; liposomes, polymersomes and polylysine) as a potential tool for minimally invasive intracochlear drug delivery after middle ear application in adult animals. All NPs penetrated the round window membrane and were identified in the spiral ganglion, the organ of Corti and the lateral wall, producing no distinct morphological or functional damage to the inner ear. Using a model neurotoxic drug, liposomes and polymersomes were shown to be capable of carrying into the inner ear an active drug that elicits a detectable biological effect.

Results presented in this thesis contribute to knowledge about the role of Islet1 and BDNF in the development and function of the auditory system. Together with results of nanoparticle testing these data may contribute to the development of regenerative therapy for the inner ear.