Résumé du projet de thèse *Indiquer la participation de chaque co-directeur et structure dans la gestion du projet. Please indicate explicitely the specific contribution of each supervisor to the PhD project.*

Hearing and vision are essential for every major activity of daily life, ranging from communication, mobility and autonomy to an appreciation of music, art and nature. Today, about 466 and 285 million people currently suffer from serious hearing and vision impairments worldwide, respectively (see http://www.who.int/). **Untreated sensory decline severely impacts the quality of life is dramatic, impeding communication first, and in adults, leading to social isolation, depression, and reduced physical and cognitive functions.**

Congenital hearing loss affects 26 million people worldwide, with 60% (~ 15 million) attributed to genetic factors. However, an increasing number of cases (> 440 millions of cases), inherited or acquired, are postnatal and progressive. Among these, age-related hearing loss (or presbycusis) is one of the most prevalent and debilitating condition that significantly impact the quality of life for millions of individuals worldwide, with one in three adults over the age of 65 experiencing some degree of hearing loss. The underlying mechanisms driving these late hearing impairments remain elusive, hindering the development of effective, preventive and/or curative, therapeutic interventions.

Our work at the Institut Pasteur on the pathophysiology of the Usher Syndrome, the major cause of dual vision and hearing loss, have revealed that the molecular mechanisms underlying the development and function of the inner ear and the eye are remarkably similar. We here propose to investigate the mechanisms of progressive hearing impairments, capitalizing on recent progress showing the role of hypoxia and inflammation in age-related macular degeneration (AMD; worldwide recognized expertise of the team of Sennlaub F, Institut de la Vision). We will use animal models with progressive hearing loss (Instiut de l'Audition) to seek the underlying molecular mechanisms, with special emphasis on immune responses and inflammation homeostasis. Also, leveraging key animal model in which inflammatory homeostasis is affected (Institut de la Vision), we will explore the inner ear structure and function to unveil correlations between organ immune status and hearing decline. More specifically, our project includes 3 aims:

1. **Utilizing deafness animal models with progressive hearing loss (at the Institut de l'Audition, IP) to investigate pathways related to hypoxia and inflammation:** Ongoing work show that animal models, particularly clarin-deficient mice with inherited postnatal progressive hearing impairments, are valuable tools for elucidating the origin of progressive hearing loss. In-depth phenotyping of these mice models allowed us to establish precise structural and molecular alterations in both auditory hair cells and neurons. OMIC approaches, such as transcriptomics and proteomics, were carried out on distinct Clarin-deficient mice that depict various clinical situations observed in humans. Preliminary analyses helped identify various cellular pathways in hearing decline, including oxidative stress, vascular and inflammation pathways. Ongoing analyses of our OMIC data pinpoint specific inflammatory pathways and mediators that are dysregulated during the progression of hearing loss. Through the characterization of these pathways in health and disease conditions, we aim to provide key insights into the molecular mechanisms linking inflammation to age-related hearing decline.

2. **Investigating models with altered inflammatory homeostasis (at the Institut de la Vision, SU) to monitor changes in the inner ear structure and function:** Over the last years**,** the team of Sennlaub F has developed various hyperinflammatory mouse models targeting key immune-related genes and regulatory pathways. Notably, mice deleted for the immunosuppressive *TSP1* and its receptor *CD47*, were shown to present inflammation resolution deficit, age- and light-dependent chronic retinal inflammation and degeneration. Interestingly, *TSP1*$^{-/-}$ mice have recently been shown to be more susceptible to noise induced hearing loss, but neither the receptor involved, nor the exact mechanism have been identified. Using aged and noise-exposed TSP1$^{-/-}$ and CD47$^{-/-}$ mice as well as AAV-driven overexpression of a TSP1-derived CD47 agonist, we will perform phenotype characterization of hearing, and the integrity of hair cells and auditory neurons using our established multiscale phenotyping protocols, ranging from transcript, molecular, morphological (Confocal and electron microscopy), and physiological (ABR and DPOAEs) analyses. Additionally, immune cell infiltration and cytokine production will be analyzed.

3. **Targeting cochlear inflammation to prevent, slowdown and/or halt hearing damage (IP/SU):** We'll explore immune mechanisms and immunocompetent cells as therapy targets. Can treatments effective for AMD in the eye benefit inner ear hearing? Building on AMD success with TSP1, we'll test viral thrombospondin administration before noise exposure to mitigate immune dysregulation in hearing impairment models. Comparative studies using our animal models (Aims 1 and 2) may identify new testable factors or molecules. has expertise in delivery to the inner ear, using viral vectors as well as therapeutic molecule injections. For each model and intervention, we will monitor over time auditory sensitivity, morphology, and the molecular and cellular architecture of the auditory organ, including the hair bundles of hair cells, synapse with associated neurons, and inflammation within the cochlear canals.

To conclude, inflammation is recognized as a key element in neurosensory hearing impairments. Understanding the molecular and cellular mechanisms involved in the cochlea will pave the way to targeted therapeutic opportunities to selectively modulate cochlear inflammation, mitigate hearing damage, and restore auditory function.