

La Semaine du Son de l'UNESCO NICE 2022
Fondation LENVAL – Grand Amphithéâtre
26 janvier - 14h

**Late-onset and progressive hearing and balance impairments:
disease mechanisms and therapeutic options**

Aziz El-AMRAOUI, PhD

Progressive Sensory Disorders, Pathophysiology and Therapy Unit
Institut Pasteur, Institut de l'Audition
63 rue de Charenton, F75012, Paris, France

Abstract:

Progressive hearing impairment, the most frequent sensory deficit, causes communication difficulties, often associated with social isolation, depression and reduced physical and cognitive function, with a dramatic economic impact on healthcare systems worldwide. According to World Health Organization estimates, approximately 466 million people — 5% of the world's population — have a disabling hearing impairment, and this number will have increased to more than one billion by 2050. Whether of genetic origin or due to aging and/or environment, the hearing loss can affect people of any age and manifest in various forms that range from mild hearing impairment to severe and profound deafness, with or without balance deficit. So far, tremendous progress has been made regarding the mechanisms of congenital and early hearing loss, but we know very little about the key hearing pathways critical in late-onset, progressive hearing impairments, with and without balance deficits.



Our recent work on two tetraspan-like proteins, member of the clarin family, highlights the key role of clarin-1 and clarin-2 in the inner ear, with defects of either clarin leading to hearing impairment, sometimes associated with variable balance and vision deficits, in mouse and humans. Using these mutant deaf mice as model systems for late-onset hearing loss, we set interdisciplinary and multi-scale approaches that allow us to study inner ear disorders, from disease mechanisms to therapy. Owing to the properties of the deafness genes' encoded proteins, their molecular network, and characterization of related animal models, our work help:

- 1- Determine where, when and how inner ear abnormalities manifest in the available defective mice to elucidate the precise molecular and cellular mechanisms underlying the hearing and balance sensory deficits (disease signature).
- 2- Decipher if (& how) external factors, notably exposure to intense sound, impacts the onset, progression and/or severity of the disease.
- and 3) evaluate gene therapy interventions aimed to restore normal sensory modalities in the appropriate disease animal models.

Short Bio:

After a PhD in Neuroscience from the University of Lyon-I in 1995, he joined the Institut Pasteur (Paris) where resorting to dozen identified deafness genes as entry points has enabled him to enlighten both fundamental and medical aspects of hearing & vision functioning and

related disorders (<https://orcid.org/0000-0003-2692-4984>). Building on accurate and well-documented disease molecular underpinnings and pathogenic mechanism, his team current efforts are focused on late-onset and/or progressive hearing and vision impairments, from pathogenesis to treatment solutions, aiming to i) elucidate the precise underlying pathogenic pathways, and ii) identify therapeutic targets and solutions to delay, prevent and/or cure progressive sense deterioration in animal preclinical models, and accelerate their transfer into clinics.

Orcid : <https://orcid.org/0000-0003-2692-4984>

Research gate profile: https://www.researchgate.net/profile/Aziz_El-Amraoui

Website : <https://research.pasteur.fr/en/team/progressive-sensory-disorders-pathophysiology-and-therapy/>

Relevant Bibliography:

1. Delmaghani S, **El-Amraoui A.** (2020) Inner ear gene therapies take off: current promises and future challenges. *J Clin Med.* Jul 21;9(7):E2309. doi: 10.3390/jcm9072309.
2. Dunbar L, Patni P, Aguilar C, Mburu P, Corns L, Wells H, Delmaghani S, Parker A, Johnson S, Williams D, Esapa C, Simon M, Chessum L, Newton S, Dorning J, Jeyarajan P, Susan Morse S, Lelli A, Codner G, Peineau T, Gopal S, Alagramam K, Hertzano R, Dulon D, Wells S, Williams F, Petit C, Dawson S, Brown S, Marcotti W, **El-Amraoui A***, Bowl M* (2019) Clarin-2 is essential for hearing by maintaining stereocilia integrity and function. *EMBO Mol. Med.* 11(9): e10288. doi: 10.15252/emmm.201910288. # cover article, *Co-senior/corresponding authorships.
3. Dulon D*, Papal S, Patni P, Cortese M, Vincent P, Tertrais M, Emptoz A, Tlili A, Bouleau Y, Michel V, Delmaghani D, Aghaie A, Pepermans E, Allegria-Prevot O, Akil O, Lustig L, Avan P, Safieddine S, Petit C*, **El-Amraoui A ***. (2018) Clarin-1 defect results in a rescuable auditory hair cell synaptopathy. *J. Clin. Invest.* 128(8):3382-3401. doi:10.1172/JCI94351.
4. Michel V, Booth K, Patni P, Cortese M, Azaiez H, Bahloul A, Kahrizi K, Labbé M, Emptoz A, Lelli A, Dégardin J, Dupont T, Aghaie A, Oficyalska D, Picaud S, Najmabadi H, Smith RJ, Bowl MR, Brown SDM, Avan P, Petit C, **El-Amraoui A *** (2017) CIB2, defective is isolated deafness, is key to auditory hair cells mechanotransduction and survival. *EMBO Mol. Med.* 9:1711-1731.
5. Cortese M, Papal S, Pisciotto F, Elgoyhen AB, Hardelin J.-P, Petit C, Franchini LF*, & **El-Amraoui A***. (2017) Spectrin β V adaptive mutations and changes in subcellular location correlate with emergence of hair cell electromotility in mammals. *Proc. Natl Acad. Sci. USA.* 114(8):2054-2059. *Co-senior authorships.

