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 calrin-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 mechanotransductioin and survival. ***EMBO Mol. Med.*** 9:1711-1731.
5. Cortese M, Papal S, Pisciottano F, Elgoyhen AB, Hardelin J.-P, Petit C, Franchini LF*, & **El-Amraoui A*. (2017)** Spectrin βV adaptive mutations and changes in subcellular location correlate with emergence of hair cell electromotility in mammalians. ***Proc. Natl Acad. Sci. USA.*** 114(8):2054-2059. *Co-senior authorships.

La Semaine du Son de l'UNESCO NICE 2022
Fondation LENVAL – Grand Amphithéâtre
26 janvier – 15h

Targeted deletion and in vivo rescue uncover critical roles of the neuronal t-SNARE SNAP-25 in hearing function

Saaid SAFIEDDINE, PhD
Technologies & Gene Therapy for Deafness Unit
Institut Pasteur, Institut de l'Audition
63 rue de Charenton, F75012, Paris, France

Abstract:
The auditory sensory inner hair cells (IHCs) encode sound into nerve impulses with high temporal precision and sensitivity over a wide range of stimulus intensities[1] . A striking structural and functional feature of IHC synapses is the presence of an electron-dense presynaptic organelle of submicron diameter called a ribbon, marking the centre of the synaptic active zone. Despite their structural differences, IHC ribbon synapses and conventional central nervous system (CNS) synapses share several key mechanisms of regulated synaptic vesicle exocytosis. IHC and CNS synapses are both equipped with the presynaptic scaffold proteins, bassoon and RIM. The presence of the neuronal SNARE (soluble N-ethylmaleimide sensitive factor attachment protein receptor) complex in auditory hair cell is well documented, including syntaxin 1, SNAP25 and synaptobrevin1/2 [3–6].

These observations led to the notion that vesicle fusion at both synapses involves similar SNARE proteins [1,7,8]. However, the study of null mutant mouse models failed to reveal functional role for the neuronal SNARE proteins in IHC synaptic transmission. This finding led to the proposal that IHC synapse operate without neuronal SNARE [3]. It worthy to note that the null mutant mouse models for many of the neuronal SNARE proteins, die at birth or shortly after. Therefore, the IHC function in these mutants could only be analysed in organotypic culture, wherein the findings may not reproduce the functioning of IHC synapse in a healthy and mature hearing organ. To untangle this issue, we focused on SNAP-25, a key component of the canonical synaptic SNARE complex. We generated a hair cell-specific *Snap-25* knockout (*Snap-25* cKO) mouse model allowing to study the effect of acute inactivation of *Snap-25* in IHCs at both neonatal and mature stages. We found that the mice subjected to *Snap-25* inactivation at mature

stage, i.e., after the hearing onset, developed a severe to profound deafness which was associated with a defective exocytosis at IHC synapses followed by ribbon degeneration and a progressive loss of hair cells. Viral mediated transfer of SNAP25 cDNA rescued all these phenotype aspects. These results demonstrated that SNAP-25 is essential for normal hearing function by ensuring the rapid fusion of vesicles at the IHC ribbon synapse and strongly suggest that this fusion is governed by the canonical neuronal SNARE complex

Bio:
Auditory physiopathology has been Dr. Saaid Safieddine's area of research for almost 30 years now. In the 1990's, Saaid Safieddine spent seven years as staff scientist in Robert Wenthold's laboratory at the National Institutes of Health in Bethesda, Maryland, USA. During that time, he made a determinant contribution toward the elucidation of the molecular architecture of the auditory hair cell synapse. In the late 1990's he joined the Pasteur Institute in Paris, wherein he has been working during the last 19 years. His achievements during that time have had still greater impact on our understanding of the molecular anatomy and function of hearing organ. In addition to pursing pioneering basic research aimed at understanding the molecular genetics of hearing and deafness, Dr. Safieddine's recently started a translational research project focusing on the development of innovative therapies for deafness, especially gene therapy. His team conducted several proof-of-concept studies demonstrating for the first time that not only gene therapy can prevent deafness, but that it can also treat it once installed. These studies are raising unexpected new hopes for gene replacement therapy in deaf patients and open the way to future clinical trials. He is now the leader of the team Technologies and gene therapy for deafness at the Institut de l'Audition, Paris. Safieddine's team is one of the three investigators of the University Hospital Research Project (RHU) *AUDINNOVE*. The goal is to develop gene therapy for one of the most frequent form of congenital deafness. This project has been selected for funding under the French State's Major Investment Programs involves tight collaboration between Dr. Safieddine's team and ENT clinicians at the Necker Hospital of Paris (Necker-Sick Children Hospital, Public Assistance - Hospitals of Paris).

Education:
Since 2011: Accreditation to supervise research, Neuroscience Sorbonne université (Paris, France)
1990-1993: Ph.D in "Biology & Health", (Université de Montpellier II, France)
1988-1990: Master's degree in cell biology (Université de Montpellier II, France)

Research & Work History:
2019-present: Visiting Researcher, University of Sheffield, UK
2019-present: group leader "Technologies and gene therapy for deafness"
2012-present: Scientific Director CNRS, Institut Pasteur
2017-present: President of the "Intranational Society for Inner Ear Therapeutics"
2000-2012: Researcher at CNRS, Institut Pasteur (Paris, France)
1997-1999: Researcher associate, NIH (Bethesda, USA)
1994-1997: Visiting Fellow, NIH (Bethesda, USA)

Relevant Bibliography:

1. Safieddine, S., El amraoui, A. & Petit, C. The auditory hair cell ribbon synapse: from assembly to function. *Annu Rev Neurosci* vol. Vol. 35 in press (2012).
2. Beurg, M. *et al.* Control of exocytosis by synaptotagmins and otoferlin in auditory hair cells. *J. Neurosci.* 30, 13281–13290 (2010).
3. Nouvian, R. *et al.* Exocytosis at the hair cell ribbon synapse apparently operates without neuronal SNARE proteins. *Nat Neurosci* 14, 411–413 (2011).
4. Safieddine, S. & Wenthold, R. J. The glutamate receptor subunit delta1 is highly expressed in hair cells of the auditory and vestibular systems. *J Neurosci* vol. 17 7523–31 (1997).
5. Scheffer, D. I., Shen, J., Corey, D. P. & Chen, Z.-Y. Gene Expression by Mouse Inner Ear Hair Cells during Development. *J Neurosci* 35, 6366–6380 (2015).
6. Uthaiah, R. C. & Hudspeth, A. J. Molecular Anatomy of the Hair Cell's Ribbon Synapse. *J Neurosci* 30, 12387–12399 (2010).
7. Johnson, C. P. & Chapman, E. R. Otoferlin is a calcium sensor that directly regulates SNARE-mediated membrane fusion. *J Cell Biol* vol. 191 187–97 (2010).
8. Ramakrishnan, N. A., Drescher, M. J. & Drescher, D. G. The SNARE complex in neuronal and sensory cells. *Mol Cell Neurosci* 50, 58–69 (2012).

La Semaine du Son de l'UNESCO NICE 2022
Fondation LENVAL – Auditorium
26 janvier - 16h

Noise & World:
Exploring the Poetic and Cognitive Richness of Noise

Frank DUFOUR, EUR HEALTHY, Université Côte d'Azur

Abstract:
The goal of this workshop is to present noise as the central theme of a multimodal ecology of perception. Through the presentation of various examples borrowed from the domains of artistic expression, psychology of perception and urban design, the workshop will allow participants to understand some of the positive contributions of noise in human communications, and interactions with natural as well as technological environments. This workshop wishes to invite participants to consider noise beyond the traditional and paradoxical attitude that is frantically attempting to limit noise all the while contributing to its inflation, and to further engage in an ecological reflection upon this highly meaningful component of our environments.

Bio:
Frank DUFOUR is currently the pedagogical engineer in charge of the redesign of the graduate programs at the graduate school HEALTHY, Université Côte d'Azur. He holds a Ph.D. in Sciences of Information and Communication from the University of Paris VIII and is Emeritus Professor at the University of Texas at Dallas in the school of Arts, Technology and Emerging Communication (ATEC). As a sound designer and new media artist, Frank creates interactive audiovisual installations exploring multimodal perceptions. Together with Prof. Xtine BURROUGH, Frank created in the school of ATEC at UT Dallas, the independent Laboratory of Synthetic and Electronic Poetry (LabSynthe) destined to observe, study, and create poetic experiences in the context of digital technologies.

Relevant Bibliography:
-AUGOYARD J-F. & Torgue H. A l'écoute de l'environnement Répertoire des effets sonores, Marseille, Ed. Parenthèses,1998.
-BREGMAN, A. Auditory Scene Analysis: The Perceptual Organization of Sound. Cambridge, MA: MIT Press, 1990.

-CLARKE, E. Ways Of Listening: An Ecological Approach to the Perception of Music. Oxford: Oxford University Press, 2005.
-CONTI S et al. "Measurement of the scattering and absorption cross sections of the human body." Applied Physics Letters 85, no. 5 (April): 2004.
-DELALANDE. F. Les Unités Sémiotiques Temporelles, éléments nouveaux d'analyse musicale, Laboratoire Musique et Informatique de Marseille,1990.
-DEWEY, J., Art as Experience. New York, USA. Minton, Balch & Company, 1934.
-DUFOUR, F. "Acoustic Shadows an Auditory exploration of the Sense of Space", Sound Effects, an Interdisciplinary Journal of Sound and Sound experience. Volume 1. Aarhus University Press. Denmark. (August 2011) 83-97
-DUFOUR, F. "DreamArchitectonics. The Other Dream Work".: Leonardo Journal. MIT Press. Cambridge. MA. Volume 51. Issue 2. April 2018
-DUFOUR, F. "A Study of Sound Objects and Structures". Interference Journal. Issue 5. May 2016. 58-71Trinity College. Dublin. Ireland.
-DUFOUR, F. "La Composition Musicale comme Expérience". LINKs. Séries 3-4. Novembre 2019
-GIBSON, J. The ecological Approach to Visual Perception. Hillsdale, NJ: LawrenceErlbaum Associates, Inc, 1979.
-GIBSON, J. The Senses Considered as Perceptual Systems. Westport, CT: Greenwood Press, 1966.
-GIBSON, James, J. The Perception of the Visual World. Boston, MA: Houghton Mifflin, 1950.
-GORDON, M S, and Rosenblum L D. "Perception of Sound-Obstructing Surfaces Using Body Scaled Judgments." Ecological Psychology (Routledge) 16, no. 2 (2004): 87-113.
-GRIFFIN, Donald R. Echoes of Bats and Men. New York, NY: Anchor Book Doubleday & Company, Inc, 1959.
-IHDE, D., Acoustic Technics. Lanham, Md, USA, Lexington Books, 2016.
-IHDE, D., Listening and Voice: Phenomenologies of Sound. Second edition. Albany NY, USA State University of New York Press. 2007
-LE GUERN Ph. « Sound Studies. Sons de l'histoire et histoire du son ». Revue de la BNF. 2017/2 n° 55 | pages 21 à 29
-MERLEAU-PONTY, M., Phénoménologie de la Perception. Paris, France, La Librairie Gallimard. NRF, 1945
-ROSENBLUM L D. See What I'm Saying: The Extraordinary Powers of Our Five Senses. New York, NY: W. W. Norton & Company, 2010.
-ROSENBLUM L. "Perceiving Articulatory Events: Lessons for an Ecological Psychoacoustics." In Ecological Psychoacoustics, edited by John G. Neuhoff, 219-248. San Diego, CA: Elsevier Academic Press, 2004.
-VAN MANNEN, M., « Phenomenology of Practice », in Phenomenology & Practice, Volume 1 (2007), No. 1, pp. 11 – 30. Open Journal System, 2007
-VION-DURY, J., "L'Homonculus Musical, ou le Contenu des Vécus Préréflexifs dans l'écoute de la Musique", Chroniques Phénoménologiques, AHEX, No3-4, 2016. P.5

CONCERT

17h

Sebastien DELHAYE / ZANNALEE

Chanteur Compositeur Interprète et chercheur IPMC Université Côte d'Azur, Répertoire Pop Rock.

ZANNALEE est un jeune chanteur/guitariste et compositeur niçois. Gagnant de la finale niçoise "Emergenza" en groupe, il se produit dans de nombreux bars et événements de la Côte d'Azur. Son univers funk rock est influencé par PRINCE, David BOWIE et QUEEN.

ZANNALEE is a young singer/guitarist and composer from Nice. Winner of the "Emergenza" final in Nice as a group, he performs in many bars and events on the French Riviera. His funk rock universe is influenced by PRINCE, David BOWIE and QUEEN.

NICE 2022
LA SEMAINE DU SON
UNESCO
Organisation des Nations Unies pour l'Education, la Science et la Culture