NICE Week of Sound – June 9, 2021, 9:45 am - 6 pm
"Ear & Sound" Scientific Workshop

9:45 - 10:00 am Welcome & introduction

A- AUDITORY GENETICS & PHYSIOLOGY

1 - 10:00 - 11:00 am **Prof Jonathan GALE,** University College LONDON UK
"Cellular and molecular mechanisms of damage, repair & regeneration in the inner ear."

2 - 11 :00 - 11:30 am **Dr Didier DULON,** Université de BORDEAUX Fr
"Neurophysiology of the auditory synapse."

3 - 11:30 - 12:00 am **Dr Fabrice GIRAUDET,** Université CLERMONT AUVERGNE Fr
"Towards new audiological tools used to decipher the functioning of the hearing system, from Mouse to Human.

12:00 - 1:00 pm Lunch break

B- AUDITORY PATHOPHYSIOLOGY THERAPIES

4 - 1:00 - 2:00 pm **Prof Jean-Luc PUEL,** Université de MONTPELLIER Fr
"Neurobiology, physiology & pathophysiology of hearing: deafness, tinnitus & therapies."

5 - 2:00 - 2:30 pm **Dr Aziz El AMRAOUI,** PASTEUR Institute PARIS Fr
"Progressive sensory disorders: pathophysiology & therapy."

6 - 2:30 - 3:00 pm **Dr Saaid SAFIEDDINE, PhD,** PASTEUR Institute PARIS Fr
"Gene therapy & reversal of hearing damages."

3:00 – 3:15 pm Coffee break

C- EAR & SOUND IN ANIMALS – The transdisciplinary session

7 - 3:15 - 3:45 pm **Dr Anne Le Maître**, University of VIENNA Austria & University of POITIERS Fr
"Evolution of the Mammalian Ear: An Evolvability Hypothesis."

8 - 3:45 - 4:15 pm **Dr Travis PARK**, The national History Museum of LONDON UK
"Convergent evolution in toothed whale cochleae".

9 - 4:15 - 5:15 pm
Prof Paolo GUIDETTI, ECOSEAS Université Côte d'Azur NICE Fr
Dr Jérome LEBRUN, I3S Université Côte d'Azur SOPHIA-ANTIPOLIS Fr
Dr Audrey GALVE, GEOAZUR Université Côte d'Azur SOPHIA-ANTIPOLIS Fr
"NAUTILUS" – Marine Noise in the ligurian sea: From systematic signal analysis to impact on Marine Species.

5:15 – 5:30 pm: Final conclusions & acknowledgements

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A - AUDITORY GENETICS & PHYSIOLOGY

1 - 10:00 – 11:00 am
Prof Jonathan GALE, PhD, Professor in Auditory Cell Biology and Interim Director of the UCL Ear Institute, University College LONDON, UK
Infos: https://www.ucl.ac.uk/ear/research/gale-lab

Cellular and molecular mechanisms of damage, repair & regeneration in the inner ear.

2 - 11:00 – 11:30 am
Dr Didier DULON, PhD, Research Director INSERM, Audition Institute & University of BORDEAUX, Fr
Head of research Unit "Clinical and Translational Exploration of Sensorineural Hearing Loss",.
Infos: https://www.bordeaux-neurocampus.fr/team/neurophysiology-of-the-auditory-synapse/

Neurophysiology of the auditory synapse.
Hair cell ribbon synapse dysfunction (synaptopathy) in Age-related Hearing loss.
Age-related hearing loss (ARHL or presbycusis) is the most prevalent form of sensory disability in human populations and this pathology adversely affects the quality of life of many individuals at various ages. Simultaneously with ARHL, chronic tinnitus and hyperacusis often develop due to abnormal neural activity in the central auditory system whose origin arises from peripheral cochlear pathologies. During ARHL or after noise trauma, hearing thresholds can often remain normal, but speech intelligibility becomes hampered, especially in noisy environment. This pathology is referred as hidden hearing loss and is explained in mice models by a specific degeneration of the ribbon synapses contacting the inner hair cells (synaptopathy), in absence of any major loss of hair cells and spiral ganglion neurons. Oxidative damage due to an increase in Reactive Oxygen Species seems to play a crucial role in this synaptic degeneration. I will discuss here our recent findings characterizing the morphological and functional changes of the auditory hair cell afferent synapses occurring with aging in mice models.

3 - 11:30 – 12:00 pm
Dr Fabrice GIRAUDET, PhD, Assistant Professor (MCU HDR)
Laboratoire de Biophysique Neurosensorielle, UFR de Médecine et des Professions Paramédicales NEURO-DOL, University CLERMONT AUVERGNE Fr
Infos: https://scholar.google.com/citations?user=yUP4DkgAAAAJ&hl=fr

Pathophysiological mechanisms of pain & hearing disorders.
Towards new audiological tools used to decipher the functioning of the hearing system, from Mouse to Human.
Hearing loss is typically described by elevated hearing thresholds associated with outer hair cells alterations. However, some patients have difficulties with speech intelligibility in context of "normal hearing. This complain is commonly labelled as "auditory neuropathy" with or without electrophysiological evidence. In this talk, we'll propose, based upon animal models and human case studies, to illustrate the possible tools to assay the vulnerability of the auditory pathways (highlighted by non-traumatic noise exposure) using noninvasive functional-exploration strategies as electrophysiology.

B - AUDITORY PATHOPHYSIOLOGY THERAPIES

4 - 1:00 – 2:00 pm
Prof Jean-Luc PUEL, PhD, Professor in Neurosciences and Director of Montpellier Neurosciences Institute, University of MONTPELLIER, Fr
Infos: https://www.cochlea.org/content/view/full/587

Neurobiology, physiology & pathophysiology of hearing: deafness, tinnitus & therapies.

5 - 2:00 – 2:30 pm
Dr Aziz El AMRAOUI, PhD, Research Director INSERM PASTEUR Institute PARIS Fr
Head of research Unit "Progressive Sensory Disorders, PathoPhysiology and Therapy", Audition Institute.
Infos: https://www.institut-audition.fr/en/progressive-sensory-disorders-pathophysiology-and-therapy

Progressive sensory disorders: pathophysiology & therapy.
From hearing and/or balance disease mechanisms to adapted gene therapies.
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.
Recently, we characterized the role of clarin-1, a tetraspan-like protein whose defect is responsible for post-lingual hearing loss (occurring after language acquisition), and variable balance and vision deficits in humans. Focusing on this clarin protein family, we did find that defects in the clarin-2 gene also cause hearing impairment in mouse and humans, supporting a key role of this clarin family in the inner ear. Using these mutant deaf mice as model systems for late-onset hearing loss in humans, we set and 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.
3- evaluate gene therapy interventions aimed to restore normal sensory modalities in the appropriate disease animal models.

6 - 2:30 – 3:00 pm

Dr Saaid SAFIEDDINE, PhD, Research Director CNRS PASTEUR Institute PARIS Fr
Head of research Unit "Technologies & Gene Therapy for Deafness", Audition Institute.
Infos: https://www.institut-audition.fr/en/technologies-and-gene-therapy-deafness

Gene therapy & reversal of hearing damages.

Viral gene therapy prevents and cures deafness and balance defect.

Hearing loss is a major concern and a serious burden for Public Health as it is affecting 466 million worldwide according to the World Health Organization. Approximately one in 500 children and 4% of the population before 45 years are affected. This proportion increases markedly with age, to reach over 50% of individuals above 80 years. In France, one child out of 700 suffers from profound deafness at birth. About 80% of these congenital deafness cases are attributed to a genetic cause, 30% of which are associated with other anomalies such as balance defect and blindness. As yet no curative therapies exist and the progress in assisting patient with technical aids and prostheses is limited. Gene therapy based on adeno-associated virus (AAV) technology has emerged as a promising strategy to treat hereditary diseases. Because of their distinct tropism and high levels of transgene expression, AAV gene therapy approaches are now being utilized for several inherited disorders in a number of pre-clinical and clinical trials including Parkinson's disease, blindness and metabolism disorders. To date more than 100 deafness genes have been identified but several hundred are awaiting identification, highlighting the potential of gene therapy for the treatment of inherited inner ear defects. The use of gene therapy for the treatment of inherited inner ear defects has nevertheless not been attempted so far in clinical trials. During the last eight years, we focused our efforts on the development of gene therapy for restoring hearing and balance in mouse model for human inner ear defects. As a result, we identified the AAV8 serotype with a hybrid promoter composed of CMV enhancer/chicken β-actin (CAG promoter) as specifically targeting the cochlear and vestibular hair cells. Using this AAV configuration, we could restore hearing in a mouse model for DFNB59, and both hearing and balance in mouse models for two types of Usher's syndrome, 1G and IIIA. Recently, we reported, in the profoundly deaf DFNB9 mouse model, the first proof-of-principle that cochlear delivery of a fragmented cDNA via a dual-AAV vector approach can effectively restore production of the full-length protein, leading to a reversal of the deafness phenotype at a stage where the maturation of the auditory organ is complete. I will briefly discuss these results that raise strong hopes for future gene therapy trials.

EAR & SOUND IN ANIMALS – The transdisciplinary session

7 - 3:15 – 3:45 pm
Dr Anne Le Maître PhD, Postdoctoral researcher and lecturer at Department of Evolutionary Biology - Unit for Theoretical Biology University of VIENNA, Austria & Associated researcher PALEVOPRIM - UMR 7262 CNRS University of POITIERS, Fr
Infos: https://theoretical.univie.ac.at/people/associated-scientists-and-postdocs/anne-le-maitre/

Evolution of the Mammalian Ear: An Evolvability Hypothesis.
Compared to other vertebrates, the mammalian ear is a complex structure, because it comprises more elements, with multiple embryonic origins. This complexity arose at the dawn of mammalian evolution in the Mesozoic era, when several bones of the primary jaw joint were incorporated in the ear system. This major transition enabled the decoupling of hearing and chewing modules, hence their independent evolution and adaptation. The *evolvability hypothesis of the mammalian ear* states that, besides this decoupling, the incorporation of new components in the ear of mammals hugely increased the genetic, regulatory, and developmental complexity of this sensory organ. As a consequence, the evolutionary range of possible independent adaptation for each functional unit of the ear would have widened. This increased *evolvability* of the ear might have been a critical factor in the rapid diversification of ecological and behavioural niches of placental mammals, after the extinction of the dinosaurs. In this presentation, I will review the main arguments supporting this hypothesis.

8 - 3:45 – 4:15 pm
Dr Travis PARK PhD, Postdoctoral researcher at the national History Museum of London, UK
Infos: www.travisparkpalaeo.com ; http://orcid.org/0000-0002-9492-8859

Convergent evolution in toothed whale cochleae.
Odontocetes (toothed whales) are the most species-rich marine mammal lineage. The catalyst for their evolutionary success is echolocation - a form of biological sonar that uses high-frequency sound, produced in the forehead and ultimately detected by the cochlea. The ubiquity of echolocation in odontocetes across a wide range of physical and acoustic environments suggests that convergent evolution of cochlear shape is likely to have occurred. We tested this hypothesis using statistical models that incorporate information on the relationships between species, using the shape of the cochlea as a proxy for hearing ability. We then tested whether convergence was significantly greater than expected by chance. We identified three convergent regimes: (1) True's (Mesoplodon mirus) and Cuvier's (Ziphius cavirostris) beaked whales; (2) sperm whales (Physeter macrocephalus) and all other beaked whales sampled; and (3) pygmy (Kogia breviceps) and dwarf (Kogia sima) sperm whales and Dall's porpoise (Phocoenoides dalli). The first two regimes were significantly convergent, with habitat type and dive type significantly correlated with membership of the sperm whale + beaked whale regime. The extreme acoustic environment of the deep ocean likely constrains cochlear shape, causing the cochlear morphology of sperm and beaked whales to converge. This study adds support for cochlear morphology being used to predict the ecology of extinct cetaceans.

9 - 4:15 – 5:15 pm

Prof Paolo GUIDETTI PhD, Professor of Ecology Université Côte d'Azur & Director of ECOSEAS laboratory, NICE, Fr
Infos: http://ecoseas.unice.fr/index.php/people/faculty-and-researchers/16-paolo-guidetti-professeur-d-universite-aires-marines-protegees

Dr Jérome LEBRUN PhD, CNRS Research Scientist I3S, Head of research Team "SIGNAL", Université Côte d'Azur, SOPHIA-ANTIPOLIS, Fr
Infos: https://www.i3s.unice.fr/signal/

Dr Audrey GALVE PhD, CNRS Research Scientist GEOAZUR, Université Côte d'Azur, SOPHIA-ANTIPOLIS, Fr
Infos: https://sites.google.com/view/audreygalve/accueil

"NAUTILUS" – Marine Noise in the ligurian sea: From systematic signal analysis to impact on Marine Species.

The NAUTILUS project brings together experts in marine biology and ecology, geosciences, acoustic signal processing and artificial intelligence to observe and evaluate a major ecological hazard: marine noise, and its impacts on key marine species in coastal and offshore habitats in the Ligurian Sea.

The undersea environment has long been described as a silent world. Research carried out in recent decades, however, has raised a growing awareness about sounds and noises as important components of the marine environment. Marine noise consists of biotic (produced by animals such as fish and mammals), abiotic (e.g., breaking waves, currents, ice breaking), and anthropogenic sounds (e.g., sonar, seismic prospecting, drilling, recreational and fishing vessels, shipping). The sum of these noise sources is referred to as the soundscape. The rise of global urbanization, industrialization and trading has resulted in a dramatic increase in anthropogenic noise, recognized as a major global pollutant in the 21st century. Anthropogenic noise may impact a large variety of marine animal species, with consequences ranging from no effect to major repercussions (e.g., behavioral alterations or stress induction, negatively impacted co-specific interactions, survival and reproduction) or even immediate death. The NAUTILUS project builds upon a multidisciplinary collaboration among researchers in marine biology and ecology, geosciences and acoustic signal analysis to provide essential information on the soundscape in the Ligurian Sea and its impacts on marine organisms that play key roles in the local marine ecosystems (i.e., bony fish and cetaceans).

The project started recently, and in the summer 2019, we deployed two types of instruments (some of which are usually used for earthquake recording), offshore Villefranche-sur-Mer, Saint-Jean-Cap-Ferrat and Eze: short-term listening and high frequency hydrophones, and long-term listening, lower frequency hydrophones. These instruments recorded the soundscape (i.e., acoustic waves) for the first time in the Ligurian Sea, at sites that were Natura 2000 labeled by the EU. Meanwhile, we collected juvenile sparid fish data and samples in the three sites. Based on these data and on earlier seismological datasets (acoustic and seismic waves), we are currently developing machine-learning-based algorithms to automatically extract the signal information from marine noise and marine mammal activity in the Ligurian Sea (along with other type of relevant information in the recordings). This automatic extraction should help us to discriminate, estimate and map the various sources of marine noise in the Ligurian Sea, and examine their local impact on key species.

The Week of SOUND ORGANIZATION COMMITTEE IN NICE

Renaud DAVID is a medical doctor, psychiatrist, at the CHU of Nice. His areas of expertise, within Université Côte d'Azur and the CHU of Nice, are the diagnosis and management of Alzheimer's disease and related pathologies; neurodegenerative pathologies of the young subject and rare diseases; screening and management of physical and cognitive fragility of the elderly subject; screening, monitoring and management of post-concussion symptoms in high level athletes. He also participates in the activities of the GDR O3 (Odorants-Odeur-Olfaction) with Prof J GOLEBIOWSKI (Institut de Chimie de Nice) and is interested in the links between olfaction and neurodegenerative diseases as well as the use of odorant molecules in the management of emotional and affective disorders and motivation.

Carole BARON has a PhD in Molecular and Cellular Pathophysiology and has studied signal transduction in the central nervous system, intracellular transport and ciliogenesis. She is also a project engineer, in charge at Université Côte d'Azur Academy of excellence 4 "Complexity and Diversity of the Living Systems".

Nicolas CAPET is a physician, neurologist, head of clinic in the neurology department of the Nice University Hospital (Prof P THOMAS). He works in the Clinical Research Unit of the Central Nervous System of the Clinical Neurosciences pole (URCSNS). He participates in the MNC3 research group (digital medicine, brain and cognition) with INRIA Sophia-Antipolis. He is interested in the study and management of post-concussion syndrome in high-level athletes.

Nicolas GUEVARA MD PhD is an ENT and face and neck surgeon, specialized in hearing rehabilitation techniques, and is responsible for the Otology and audio-vestibular explorations department at the University Institute of Face and Neck (CHU of Nice). One of his main research themes is devoted to cochlear implants. He has developed a digital model of the cochlea in partnership with INRIA (Sophia-Antipolis) and one of the manufacturers of cochlear implants, Oticon Medical.

Alice GUYON is a former student of the "École Normale Supérieure" and holds a PhD in Neuroscience. She was an assistant professor for 10 years at the University of Paris 6 and then a researcher at the Institute of Molecular and Cellular Pharmacology (IPMC) in Sophia Antipolis. She is currently a Research Director at CNRS. She has been interested in the interactions between the brain and the immune system in physiological and pathological conditions, in the beneficial effects of environmental enrichment, and more recently in the effects of non-drug interventions in prevention and care.

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