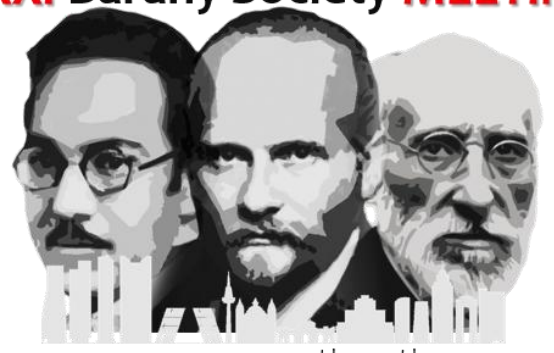
XXXI Bárány Society MEETING



MADRID, MAY 9th-11th 2022

SP05

SYMPOSIUM FORM

- ORGANIZER'S NAME and SURNAME: Maria Teresa Requena Navarro
- ORGANIZER'S E-MAIL: mrequena@ed.ac.uk
- ACADEMIC/HOSPITAL AFFILIATION: Edinburgh University
- SESSION TITLE: Exciting new approaches to studying Meniere's Disease

3 or 4 SPEAKERS PER SYMPOSIUM:

- SPEAKER 1
  NAME AND SURNAME: Jose Antonio Lopez-Escamez
  TOPIC DESCRIPTIVE TITLE: A multiallelic model of inheritance for Meniere disease
  ACADEMIC / HOSPITAL AFFILIATION: Instituto de Investigación Biosanitaria de Granada, Spain

- SPEAKER 2
  NAME AND SURNAME: Andreas H.Eckhard
  TOPIC DESCRIPTIVE TITLE: Emerging endotype-phenotype patterns based on inner ear pathologies in Meniere's Disease
  ACADEMIC / HOSPITAL AFFILIATION: University Hospital Zurich, Switzerland

- SPEAKER 3
  NAME AND SURNAME: Anna Lysakowski
  TOPIC DESCRIPTIVE TITLE: Mouse models of familial Meniere's Disease
  ACADEMIC / HOSPITAL AFFILIATION: University of Illinois at Chicago, USA

- SPEAKER 4
  NAME AND SURNAME: Maria Teresa Requena Navarro
  TOPIC DESCRIPTIVE TITLE: Drosophila and zebrafish models for understanding the basis of Meniere's Disease
  ACADEMIC / HOSPITAL AFFILIATION: University of Edinburgh, UK

- **A BRIEF** (<300 WORDS) DESCRIPTION OF THE THEME AND TARGET AUDIENCE:

Meniere's Disease (MD) has a long and prominent history in the world of neuroscience as a loss of balance and hearing. An interesting challenge for MD research today is a lack of knowledge of the mechanisms involved, especially genetic backgrounds, the inner ear cells that are affected, and the molecular pathways involved.

MD can be characterized as follows: recurrent episodes of vertigo, fluctuating and progressive sensorineural hearing loss (SNHL) and tinnitus. MD is a heterogeneous clinical syndrome. The prevalence of MD is about 0.5-1/1000. The usual age of onset ranges from 30-50 years. Both ears are affected, leading to severe hearing impairment and chronic imbalance, resulting in a huge burden for patients and a significant impact on health-related quality of life. Because of a lack of knowledge of the molecular mechanisms involved, it is difficult to generate treatments for these patients. We are interested in developing new approaches to understand how the inner ear cells might be degraded to generate the disease phenotype at a relatively young age in these adult patients.

To be effective, we propose research that integrates four different approaches: 1) genetic studies in familial Meniere's patients; 2) neuroimaging and histopathology of the human temporal bone focusing on the

endolymphatic sac; 3) mice as an animal model to understand the molecular basis behind the human disease; and 4) the use of flies and fish as animal models to filter potential candidate genes.

The purpose of this symposium is to explore a variety of cutting-edge approaches. We suggest that the target audience could be the leading researchers and clinicians who have worked with different paradigms (emphasizing approaches from the clinic to basic science) to explore a synergy that will exploit the best of each.

- A 150-WORD **ABSTRACT FROM EACH OF THE SPEAKERS:**

ABSTRACT 1

The genetic underpinnings of Meniere's disease (MD) include some rare monogenic forms in isolated families and a polygenic contribution in most familial and sporadic cases. So, familial MD has been reported in 6-8% of sporadic cases and several genes have been described in single Familial MD including FAM136A, DTNA, PRKCB, SEMA3D and DPT, suggesting genetic heterogeneity. Multiplex rare missense variants in OTOG gene have been reported in 33% of familial MD, supporting a multiallelic inheritance. Moreover, the genetic landscape of sporadic MD is more complex and it involves multiplex rare variants in several SNHL genes such as GJB2, USH1G, SLC26A4, ESRRB, and CLDN14 and axonal-guidance signalling genes such as NTN4 and NOX3. Here, we proposed a multiallelic model to explain the hearing loss phenotype in MD. The interaction of common cis-regulatory variants located in non-coding regions and rare variants in coding regions in one or more target genes will determine the variation on the phenotype in MD, explaining the incomplete phenotype and variable expressivity in the condition.

ABSTRACT 2

Meniere's disease (MD) is commonly associated with a pathological accumulation of endolymphatic fluid, termed "idiopathic" endolymphatic hydrops (iEH). Although numerous precipitating/exacerbating factors have been proposed for MD, its etiology remains elusive. Here, using immunohistochemistry and in situ protein–protein interaction assays, we demonstrate regulated sodium and calcium transport mechanisms in the epithelium of the extraosseous portion of the endolymphatic sac (eES) in murine and human inner ears. Histological analysis in an extensive series of human temporal bones consistently revealed pathological changes in the eES in cases with iEH and a clinical history of MD, but no such changes were found in cases with "secondary" EH, due to other otological diseases, or in healthy controls. Notably, two etiologically different pathologies—degeneration and developmental hypoplasia—that selectively affect the eES in MD were distinguished. Clinical records from MD cases with degenerative and hypoplastic eES pathology revealed distinct intergroup differences in clinical disease presentation. Overall, we have identified two inner ear pathologies consistently present in MD that are directly linked to EH pathogenesis and which potentially affect the phenotypical presentation of MD.

ABSTRACT 3

We have been working with one mouse model, Fam136a knockout (KO), using biochemical, immunohistochemical and behavioural approaches, to understand how its inner ear might be degraded to generate the disease phenotype. Fam136a is a protein localized in mitochondria that is highly conserved across species (from plants to humans), and it is coded for by a gene on Chromosome 2. We have reported its presence in the rodent inner ear (Requena et al. 2014). Through whole exome sequencing, this gene was found in multiple generations of a human family with familial MD (fMD). In wild type (WT) and KO mice, we have found significantly reduced differences in both Rotarod performance over time and mitochondrial function, supporting the hypothesis of its role in the dysfunction occurring in fMD. A second mouse model, a DTNA KO (coding for the cytoskeletal protein alpha-dystrobrevin, also found in inner ear), is also being tested and analyzed.

ABSTRACT 4

Multiple genes and variants are arising as candidate targets for Meniere's disease (MD). These genes must be screened using functional animal models able to reproduce both the hearing and vestibular phenotypes. Zebrafish inner ears contain the semicircular canals and utricular maculae, concerned with balance, acceleration and gravity-sensing, whereas saccular and lagenar maculae manage the hearing function. The fly's 'inner ear', the Johnston's organ, is a chordotonal organ localized in the 2nd-antennal segment, which mediates the sensations of hearing,

gravity and wind. In both organisms, MD candidate gene orthologues are predicted to be found in cells of the auditory/proprioceptive chordotonal sensory organs. Given the large number of candidate genes, a mammal model can be expensive, experimentally laborious and time consuming. In contrast, development of a zebrafish or drosophila model to investigate the role of MD candidate genes in hearing and balance would significantly reduce both costs and time for preliminary screening.