BIOGRAPHICAL SKETCH

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NAME: Lopez-Escamez, Jose Antonio

eRA COMMONS USERNAME (credential, e.g., agency login): ANTONIOLOPEZ

POSITION TITLES: 1 Professor of Meniere Disease Neuroscience, School of Medical Sciences, FMH, The University of Sydney, Australia 2 Visiting Scholar, Department of Surgery, University of Granada, Spain

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Granada, Spain	MD	1984-1990	Medicine & Surgery
University of Granada, Spain	PhD	1991-1993	Neuroscience
Kresge Hearing Research Institute, University of Michigan, USA	Postdoc	1993	Vestibular cell biology
Otolaryngology Residency, Hospital Virgen de las Nieves, Granada, Spain	Otolaryngology	1995-1998	Otolaryngology
LCSB, University of Luxembourg	-	2017-2018	Genomic/bioinformatics

A. Personal Statement

I am a Professor of Meniere's disease and Neuroscience at the University of Sydney and Visiting Scholar at the University of Granada, ranked in the Stanford World Top 2% Scientists in 2021-23. With >200 scientific publications in top scientific journals and >10,000 citations in GS, my research goal is to elucidate the genes and biochemical pathways involved in Meniere's Disease (MD) and severe tinnitus. I have a broad background in auditory neuroscience, clinical audiology and neurotology, with specific expertise in the clinical diagnosis and genetics of MD. As the PI of several multicenter-funded grants in Europe, I have laid the groundwork for the proposed research by assembling a network of experienced collaborators in audiology and neurotology, including hospitals in Australia (NSW, SA), Europe (Germany, Greece, Italy, Belgium, Spain, Sweden), USA and South Korea with the goal of obtaining standardized clinical data and DNA samples from patients with MD and tinnitus to recruit and track participants over time. With this effort, we have recruited more than 1500 MD patients with100 multiplex families and generated exome/genome sequencing data from > 450 MD and 400 tinnitus patients as documents in several publications. We have identified novel familial MD genes, including *OTOG, MYO7A, TECTA* genes and a burden of rare variants in several genes associated with severe tinnitus and hyperacusis such as *ANK2*. My current positions at the University of Sydney, with core facilities for genomic data analysis (Sydney Informatic Hub), animal and cell culture disease modelling (Kolling Research Institute) and University of Granada with a large network of clinical centers in Spain facilitate the development of translational research, including RCT for Meniere disease and tinnitus. I have successfully administered several projects (e.g., staffing, human research protections, budget), collaborated with other researchers, and produced over 200 peer-reviewed publications from each project. Due to this previous experience, I am aware of the importance of frequent communication among project members and of constructing a realistic research plan, timeline, and budget. The current application builds logically upon my prior work, and I have always chosen co-investigators who can provide additional expertise within the network. In summary, I have demonstrated a record of successful and productive research projects in MD and tinnitus genetics, and I have the expertise. leadership, motivation and discipline necessary to successfully carry out the proposed project.

Highly cited publications that I would like to highlight:

a. Requena T, Espinosa-Sanchez JM, Cabrera S, Trinidad G, Soto-Varela A, Santos-Perez S, Teggi R, Perez P, Batuecas-Caletrio A, Fraile J, Aran I, Martin E, Benitez J, Pérez-Fernández N, **Lopez-Escamez JA** (2014) Familial clustering and genetic heterogeneity in Meniere's Disease. ***Clinical Genetics*** 85 (3): 245-52. http://dx.doi.org/10.1111/cge.12150

b. **Lopez-Escamez JA,** Carey J, Chung WH, Goebel JA, Magnusson M, Mandalà M, Newman-Toker DE, Strupp M, Suzuki M, Trabalzini F, Bisdorff A, Classification Committee of the Barany Society, Japan Society for Equilibrium Research, European Academy of Otology and Neurotology (EAONO), Equilibrium Committee of the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS), Korean Balance Society (2015) Diagnostic criteria for Menière's Disease. ***J Vestibular Research*** 25: 1–7. http://dx.doi.org/10.3233/VES-150549

c. Roman-Naranjo P, Gallego-Martinez A, Soto-Varela A, et al. (2020) Burden of rare variants in the *OTOG* Gene in Familial Meniere's Disease. ***Ear Hearing*** 2020 Nov/Dec;41(6):1598-1605. http://dx.doi.org/10.1097/AUD.0000000000000878

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2023-Present Professor of Meniere disease Neuroscience, SoMS, FMH, University of Sydney, Australia.
2019-23 Assoc. Prof. Otorhinolaryngology, Dept. of Surgery, Div. Otolaryngology, Univ. of Granada, Spain.
2018-20 Scientific Director, Health Research Institute of Granada (IBS-Granada), Granada, Spain.
2017-18 Visiting Researcher, Bioinformatic Core, Center System Biomedicine, Univ. du Luxembourg. Luxembourg.
2015-23 Consultant in Otolaryngology, Hospital Universitario Virgen de las Nieves, Granada, Spain
2012-23 PI, Dept. Genomic Medicine, Centre for Genomics and Oncology (GENyO), Granada, Spain
2011-12 Res. Assoc., Dept. Genomic Medicine, Ctr. for Genomics and Oncology (GENyO), Granada, Spain
2008-09 Director of Research, Hospital de Poniente, El Ejido, Almería, Spain
2002-15 Head of Otology & Neurotology Group CTS495, Hospital de Poniente, El Ejido, Almeria, Spain
1999-15 Consultant in Otolaryngology, Hospital de Poniente, El Ejido, Almeria, Spain
1999-99 Consultant in Otolaryngology, Hospital Universitario Virgen de las Nieves, Granada, Spain
1995-98 Residency in Otolaryngology Head and Neck Surgery. Hospital Virgen de las Nieves. Granada.
1993 Postdoctoral Research Fellow, Kresge Hearing Research Institute, University of Michigan, US
1992 Research Scholar Exchange Visitor, Kresge Hearing Research Institute, University of Michigan, US
1991 Honorary Research Fellow, Dept. of Physiology, St. Thomas' Hospitals, University of London, UK.
1986-90 Medical Internship, Dept. Cell Biology, Faculty of Medicine, University of Granada, Granada, Spain

Honors

2024 Hallpike-Nylen Medal. Barany Society. Uppsala
2024 American Tinnitus Association Scientific Advisory Committee.
2023 Kolling Discovery Science Research Award Best publication by a researcher at any career stage.
2021-23 Chair, Education Committee and Member of the Executive Board of the Spanish Society Otorhinolaryngology (SEORL)
2018 Frontiers Spotlight Award 2018. Research Topic: Vestibular contribution to health and disease
2018 Global Otology Research Forum- Vestibular Research Prize. Politzer Society meeting 2018. Genetic Diagnosis of Autoimmune Meniere's Disease.
2018 Joan Gasso Best publication Award: Extended phenotype and clinical subgroups in unilateral Meniere disease. Clinical Otolayngology. 2017;1-9. DOI:10,1111/coa.12844. 2018.
2016-20 Member, Program Committee, Association for Research in Otolaryngology (ARO).
2016 Member, Collegium Oto-Rhino-Laryngologicum Amicitae Sacrum (CORLAS).
2015-21 Chair, Research Committee of the Spanish Society Otorhinolaryngology (SEORL)
2011-15 Chair of Meniere's Disease subcommittee of Barany Society, Member of International Classification for Vestibular Disorders.
2011 3th award Ulyssess to best Medical Staff paper Best Spanish Research to "Immunogenetic profile and endophenotypes in Meniere disease. CTO Foundation. 2011.

2010 Award Fundacion Juan Gasso to best Oral Presentation SEORL Congress.
2009 Awarded Bronze medal of the SEORL. Meniere disease: from basic science to clinical medicine.
2009 First Prize Solvay Pharma to best publication in Otoneurology.
1998 Outstanding PhD Award, University of Granada, Spain.

C. Contributions to Science

1. Since 2002, my major research interest has been to understand the **molecular underpinnings of Meniere's Disease (MD)**, a chronic disorder of unknown etiology. During the last 25 years we have recruited clinical data and DNA samples in a large cohort of Spanish patients. Our major contribution has been the identification of *OTOG, MYO7A* and *TECTA* in multiple families with MD, OTOG being the most common gene with recessive inheritance that support a higher frequency of familial MD in European population.

a. Requena T, Cabrera S, Martin-Sierra C, Price SD, Lysakowski A, **Lopez-Escamez JA** (2015) Identification of two novel mutations in FAM136A and DTNA genes in autosomal-dominant familial Meniere's disease. ***Human Molecular Genetics*** 24(4):1119–26. http://dx.doi.org/10.1093/hmg/ddu524
b. Martin-Sierra C, Gallego-Martinez A, Requena T, Frejo L, Batuecas-Caletrío A, **Lopez-Escamez JA** (2017) Variable expressivity and genetic heterogeneity involving DPT and SEMA3D genes in autosomal dominant familial Meniere's disease. ***Eur J Human Genetics*** 25(2):200-207. http://dx.doi.org/10.1038/ejhg.2016.154
c. Roman-Naranjo P, Gallego-Martinez A, Soto-Varela A, et al. (2020) Burden of Rare Variants in the OTOG Gene in Familial Meniere's Disease. ***Ear Hearing*** 41(6):1598-1605. http://dx.doi.org/10.1097/AUD.0000000000000878
d. Roman-Naranjo P, Parra-Perez AM, Escalera-Balsera A, Soto-Varela A, Gallego-Martinez A, Aran I, Perez-Fernandez N, Bächinger D, Eckhard AH, Gonzalez-Aguado R, Frejo L, **Lopez-Escamez JA.** (2022). Defective α-tectorin may involve tectorial membrane in familial Meniere disease. ***Clin Transl Med.*** 2022 Jun;12(6):e829. http://dx.doi.org/10.1002/ctm2.829.
e. Parra-Perez AM, Gallego-Martinez A, Lopez-Escamez JA. (2024). An overload of missense variants in the OTOG gene may drive a higher prevalence of familial Meniere disease in the European population. ***Hum Genet.*** Mar 22 http://dx.doi.org/10.1007/s00439-024-02643-8.

2. In 2014, I joined TINNET, http://tinnet.tinnitusresearch.net/, a European Network for tinnitus research, as leader of the genetic working group. The aim of our group was to define the **genetic contribution to tinnitus** using twin studies, familial aggregation studies and genomic app in patients with extreme phenotype. We have been able to demonstrate a moderate heritability in bilateral tinnitus in a Swedish twin cohort, upsetting the dogma that tinnitus has no genetic contribution. In 2017, I took part of ESIT, https://esit.tinnitusresearch.net, a H2020-MSC-ITN funded proposal to create an European School for Interdisciplinary Tinnitus Research, an international doctoral training programme offered by the ESIT network to integrate of academic, clinical, and industrial partners together with patient organisations and public health authorities. By exome sequencing and selecting MD patients with extreme phenotype for tinnitus, we were able to identify a significant enrichment of missense rare variants in synaptic genes including *ANK2, TSC2 and AKAP9* in patients with tinnitus extreme phenotype in MD. We also replicated these findings in an independent cohort of tinnitus patients from Sweden. Gene ontology (GO) and gene-set enrichment analyses revealed several pathways and biological processes involved in severe tinnitus, the top GO terms being membrane trafficking and cytoskeletal protein binding in neurons.

a. **Lopez-Escamez JA**, Bibas T, Cima RFF, Van de Heyning P, Knipper M, Mazurek B, Szczepek AJ, Cederroth CR (2016) Genetics of tinnitus: an emerging area for molecular diagnosis and drug development. ***Front Neuroscience*** http://dx.doi.org/10.3389/fnins.2016.00377
b. Maas IL, Brüggemann P, Requena T, Bulla J, Edvall NK, Hjelmborg JvB, Szczepek AJ, Canlon B, Mazurek B, **Lopez-Escamez JA***, Cederroth CR* (2017) Genetic susceptibility to bilateral tinnitus in a Swedish twin cohort. ***Genetics Medicine*** 19(9):1007-1012. http://dx.doi.org/10.1038/gim.2017.4
c. Amanat S, Gallego-Martinez A, Sollini J,…Lopez-Escamez JA (2021) Burden of rare variants in synaptic genes in patients with severe tinnitus: An exome based extreme phenotype study. ***EBioMedicine***v66:103309. http://dx.doi.org/10.1016/j.ebiom.2021.103309
d. Escalera-Balsera A, Parra-Perez AM, Gallego-Martinez A, Frejo L, Martin-Lagos J, Rivero de Jesus V, Pérez-Vázquez P, Perez-Carpena P, **Lopez-Escamez JA** (2023). Rare Deletions or Large Duplications

Contribute to Genetic Variation in Patients with Severe Tinnitus and Meniere Disease. ***Genes (Basel)*** 15(1):22. http://dx.doi.org/10.3390/genes15010022.

3. In 2016, we started to identify the best predictors to define **clinical endophenotypes** with a potential different etiology in bilateral and unilateral MD. We have already identified 5 subgroups for bilateral and unilateral MD that is helping to improve phenotyping in MD and facilitating the selection of patients for randomised clinical trials.

a. Frejo L, Soto-Varela A, Santos-Perez S, Aran I, Batuecas-Caletrio A, Perez-Guillen V, Perez-Garrigues H, Fraile J, Martin-Sanz E, Tapia MC, Trinidad G, Garcia-Arumi AM, Gonzalez-Aguado R, Espinosa-Sanchez JM, Marques P, Perez P, Benitez J, **Lopez-Escamez JA** (2016) Clinical subgroups in bilateral Meniere's disease. ***Front Neurology*** http://dx.doi.org/10.3389/fneur.2016.00182
b. Frejo L, Martin-Sanz E, Teggi R, Trinidad G, Soto-Varela A, Santos-Perez S, Marique R, Perez N, Aran I, Almeida-Branco MS, Batuecas-Caletrio A, Fraile J, Espinosa-Sanchez JM, Perez-Guillen V, Perez-Garrigues H, Oliva-Dominguez M, Aleman O, Benitez J, Perez P, **Lopez-Escamez JA** (2017) Extended phenotype and clinical subgroups in unilateral Meniere disease: A cross-sectional study with cluster analysis. ***Clin Otolaryngol*** 42(6):1172-1180. http://dx.doi.org/10.1111/coa.12844

4. From 2017 to 2024, we documented biological markers to define different subgroups of MD patients according to single cell immunoprofiling and transcriptomics.

a. Frejo L, Requena T, Okawa S, Gallego-Martinez A, Martinez-Bueno M, Aran I, Batuecas-Caletrio A, Benitez-Rosario J, Espinosa-Sanchez JM, Fraile-Rodrigo JJ, García-Arumi AM, González-Aguado R, Marques P, Martin-Sanz E, Perez-Fernandez N, Pérez-Vázquez P, Perez-Garrigues H, Santos-Perez S, Soto-Varela A, Tapia MC, Trinidad-Ruiz G, Del Sol A, Alarcon Riquelme ME, **Lopez-Escamez JA** (2017) Regulation of Fn14 receptor and NF-κB underlies inflammation in Meniere's Disease. ***Front Immunology*** 8:1739. http://dx.doi.org/10.3389/fimmu.2017.01739
b. Frejo L, Gallego-Martinez A, Requena T, Martin-Sanz E, Amor-Dorado JC, Soto-Varela A, Santos-Perez S, Espinosa-Sanchez JM, Batuecas-Caletrio A, Aran I, Fraile J, Rossi-Izquierdo M, **Lopez-Escamez JA** (2018) Proinflammatory cytokines and response to molds in mononuclear cells of patients with Meniere disease. ***Scientific Reports*** 8:5974. http://dx.doi.org/10.1038/s41598-018-23911-4
c. Flook M, Rojano E, Gallego-Martinez A, Escalera-Balsera A, Perez-Carpena P, Moleon MDC, Gonzalez-Aguado R, Rivero de Jesus V, Domínguez-Durán E, Frejo L, G Ranea JA, **Lopez-Escamez JA.** (2024). Cytokine profiling and transcriptomics in mononuclear cells define immune variants in Meniere Disease. ***Genes Immun.*** Feb 23. http://dx.doi.org/10.1038/s41435-024-00260-z.
d. Frejo L, Cara FE, Flook M, Robles-Bolivar P, Escalera-Balsera A, Montilla-Ibañez MA, Dominguez-Duran E, Martinez-Martinez M, Perez-Carpena P, Lopez-Escamez JA. Allergy and autoinflammation drive persistent systemic inflammatory response in Meniere Disease: A longitudinal study. **Clin Immunol. 2025** Feb;271:110413. http://dx.doi.org/10.1016/j.clim.2024.110413

Complete list of published work in MyBibliography (193 publications):
https://www.ncbi.nlm.nih.gov/myncbi/jose%20antonio.lopez-escamez.1/bibliography/public/

D. Research Support
Ongoing Research Support
2024 NHMRC Ideas Grant. Flinders University, Bionic Institute of Australia, University of Sydney, Soterix Medical, University of South Australia
2025-2029 Novel Tinnitus Management Combining Brain Stimulation and Hearing Aids with Genetic and Epigenetic Biomarkers. CIA Raj Shekhawat CIB Mehrnaz Shoushtarian **CIC Jose Antonio Lopez Escamez** CID Abhishel Datta CIE Adrian Esterman CIF Malcom Battersby CIG Kenneth Pope. **AU$ 2,237,869.40**
2024 American Tinnitus Association Innovative Grant Research Program. University of Sydney.
2024-2026 Genetics and epigenetics of severe tinnitus. **CI Jose Antonio Lopez-Escamez**. **US$ 120.000.** This project will study the rare genetic variation and DNA methylation in patients with severe tinnitus
B3413. Lopez-Escamez (PI) 2023-27.
Meniere disease Neuroscience Program, University of Sydney. AUD 3,000,000. Deciphering the genetics and inflammatory bases of Meniere's Disease and Tinnitus Disorder by combining multi-omic data and cellular models.

Completed Research Support (last 5 years)

H2020-MSCA-ITN 722046. Schlee (Chair)/Lopez-Escamez (PI, Granada) 01/03/2017– 31/03/2021
EU-H2020 PhD Initial Training Network. € 3,823,897
European School for Interdisciplinary Tinnitus Research (ESIT)
ESIT is a European network for training PhD student in tinnitus research. They will implement innovative research methods, perform the first genetic studies on tinnitus, and establish the largest pan-European tinnitus dataset, which will allow the implementation of innovative solutions for personalized tinnitus treatment.

EU-H2020-SC1-BHC-2019 848261. Schlee (Chair)/Lopez-Escamez (PI, Granada) 01/01/2020 – 31/03/2023
EU-H2020 Research and Innovation Action. € 5,989,343.75
Unification of treatments and Interventions for Tinnitus patients (UNITI)
UNITI's overall aim is to deliver a predictive computational model, based on existing and longitudinal data, attempting to address the question of which treatment approach is optimal for a specific patient based on specific parameters. Clinical, epidemiological, medical, genetic and audiological data, including signals reflecting ear-brain communication, will be analyzed from existing databases.

GNP-180-2018. Cederroth (PI) 2019-2021
Gender-NET plus. €1,000,000
The combined role of genetic and environmental risk factors in the gender-specific development of severe tinnitus (TIGER).
The aim of this study is to determine the gender-specific genetic contribution to an extreme phenotype of tinnitus.

PE-0356-2018. Lopez-Escamez (PI) 2019-2021
Health Andalusian Regional Government. €176,487.80
In Vitro Clinical Trial with BIIB023 and monitoring of clinical response in Meniere Disease (CLINMON-MD)
The aims of this study are to monitor soluble TWEAK and pro-inflamatory cytokines in a multicenter longitudinal study in patients with MD, and to conduct preclinical studies *in vitro* using different genotype-conditioned cell lines to evaluate the effect of rs4947296 in their expression profiles and to reduce NFkB-mediated inflammation with BIIB023.

PI20.00303. Lopez-Escamez (PI) 2021-23
University and Research Andalusian Regional Government. € 153.170
Role of epigenomic regulation on penetrance and expressivity in Meniere disease (EPIMEN)
EPIMEN aim to investigate genetic and epigenetic mechanisms in patients with early onset, sporadic MD that would lead to differences in penetrance and expressivity by analysis of genome, epigenome and transcriptome datasets.

PI-0027-2020 Lopez-Escamez (PI). 2021-24
Health Andalusian Regional Government. €146,522
Pro-inflammatory cytokines and epigenetic signature to improve molecular diagnosis and personalized medicine in patients with episodic vertigo and migraine (EPIVERT)
EPIVERT aim to perform a systematic clinical assessment including cytokines and genome methylation profiling in patients with MD, vestibular migraine and migraine through a prospective, multicenter longitudinal study.