MINISTERIO DE CIENCIA E INNOVACIÓN

Cofinanciado por la Unión Europea

AGENCIA ESTATAL DE INVESTIGACIÓN

CURRICULUM VITAE (CVA)

IMPORTANT – The Curriculum Vitae cannot exceed 4 pages. Instructions to fill this document are available in the website.

CV date	25/11/2021

Part A. PERSONAL INFORMATION

First name	Raúl		
Family name	Estévez Povedano		
Gender (*)	Male	Birth date (dd/mm/yyyy)	21/12/1971
Social Security, Passport, ID number	37381932D		
e-mail	restevez@ub.edu	URL Web http://www.neurociencies.ub.edu/molecular-bases-of-rare-brain-diseases-and-channelopathies/	
Open Researcher and Contributor ID (ORCID) (*)		0000-0003-1579-650X	

(*) Mandatory

A.1. Current position

Position	Full Professor of Physiology			
Initial date	21 April 2021			
Institution	University of Barcelona			
Department/Center	Physiological Sciences	Faculty of Medicine. Campus de Bellvitge		
Country	Spain		Teleph. number	34934039781
Key words	Physiology, chloride, channels, regulation, rare diseases			

A.2. Previous positions (research activity interuptions, art. 14.2.b))

Period	Position/Institution/Country/Interruption cause
01/01/1995-01/03/2000	PhD in Biochemistry (Extraordinary Prize)/University of Barcelona/Spain
02/04/2000-31/03/2003	EMBO and Marie Skolodowska-Curie Postdoc/Zentrum Molekulare Neurobiologie/Germany
01/04/2003-31/12/2006	Ramón y Cajal researcher/University of Barcelona/Spain
01/01/2007-15/04/2021	Associate Professor of Physiology/University of Barcelona/Spain
25/11/2007-Actual date	Group leader/CIBERER/Spain
15/04/2021-Actual date	Full Professor of Physiology/University of Barcelona/Spain

A.3. Education

PhD, Licensed, Graduate	University/Country	Year
Licensed in Biochemistry (Extraordinary Prize)	University of Barcelona/Spain	1994
MBA (Master's in business and Administration)	University of Barcelona, University Autonomous of Barcelona, University Politècnica de Cataluña/Spain	1999
PhD in Biochemistry (Extraordinary Prize)	University of Barcelona/Spain	2000

Part B. CV SUMMARY *(max. 5000 characters, including spaces)*

In 1994, I got the degree in Biochemistry obtaining the Extraordinary Degree Award. Then, I started my PhD in the group of Dr. Manuel Palacín, who had recently identified two proteins (rBAT and 4F2hc) related in an unknown manner with amino acid transport. My work discovered that these proteins were auxiliary subunits of different amino acid transporters, contributing to the identification of the LAT family of transporters (FASEB J 1998, JBC 1998, JBC 1999). My PhD also contributed to explain the pathogenesis of two rare diseases: cystinuria and lysinuria with protein intolerance (JBC 1996, JBC 1997, Nature Gen 1999a, 199b, Physiological Reviews 1998, Curr Opin Cell Biol 1998). My PhD obtained the Extraordinary Degree Award.

I continued my formation with membrane proteins and transport processes performing a postdoctoral stay funded by an EMBO and Marie Sklodowska-Curie fellowships, at the Zentrum für Molekulare Neurobiologie (Germany), under the supervision of Dr. Thomas Jentsch in 2000. In a similar manner to the work performed in my PhD, I identified the first auxiliary subunit of the kidney chloride channel ClC-K (Nature 2001). Moreover, I learnt to perform molecular modelling and structure-function studies, which were used to map an inhibitor binding site and to understand the crosstalk between the C terminus and the TM part in the skeletal muscle chloride channel ClC-1 (Curr Opin Struct Biol 2002, Neuron 2003, J Physiol 2004).

As a Ramón y Cajal researcher starting in 2003 at the University of Barcelona, I started a new line of research to get insights into the pathophysiology of MLC disease, a type of leukodystrophy (myelin alteration), which I suspected that might be caused by chloride channels dysfunction, as the disease is characterized by water accumulation in the brain, and normally water movement is coupled to chloride fluxes. I have been working in this disease now for nearly 20 years, first as Ramón y Cajal, but continuing in 2007 as an Associate Professor in the Faculty of Medicine, University of Barcelona, and since 2021, as a Full Professor. During this time, we have achieved different milestones in the study of this disease: A) Localization and expression of MLC1 protein, the first disease gene (Hum Mol Gen 2004, Hum Mut 2006, Neurob Dis 2007, Acta Neuropat 2007, Hum Mol Gen 2008); B) Identification of GlialCAM as the second protein involved in MLC and its relationship with chloride channels (Am J Hum Gen 2011, Neuron 2012, Hum Mol Gen 2013); C) Generation and analyses of different models of the disease (Nature Communic 2014, Hum Mol Genet 2014, Orphanet J Rare Dis 2019); D) The relationship of GlialCAM/MLC1 with signaling (Hum Mol Gen 2017, Neurobiology of Disease 2018, Hum Mol Gen 2021, Neuron 2021, ELife 2021); E) The first structural studies using molecular modelling (Hum Mol Gen 2020) and finally, F) The first therapeutical studies using gene therapy (Neurotherapeutics 2020). In this last aspect, we have recently obtained the designation as approved orphan designation by the European Medical Agency (EMA/OD/0000059436) for the treatment of MLC in September 2021.

During these years, I have received different grants that supported my research, including national and international grants, from public and private agencies. Within

these, I have obtained 5 consecutive MICINN grants (2006, 2009, 2012, 2015, 2018), Fundació La Caixa (2004), 1 Ramón Areces Foundation (2007), 1 AFM grant (2010), 1 Marato TV3 grant (2017), 5 European Leukodystrophy Association (2017, 2015, 2014, 2011, 2008) and 2 European ERARE Grants (2010, 2014). We have also obtained funds from the company MEDDAY to test a compound in preclinical models of MLC disease.

Due to all this work, I have been awarded two consecutive times with the ICREA Academia Prize, an initiative from the Government of Catalonia to reward University teachers that perform excellent science. Moreover, I belong to CIBERER (Spanish center for rare diseases) since 2007, from which I obtained also funding for my research. I am also a member of the Board of Directors of the Institute of Neurosciences of the University of Barcelona and a member of the Health Institute IDIBELL. I belong to the scientific committee of the European Leukodystrophy Association. I am a member of the SEBBM, of the Glia network in the Spanish Society of Neuroscience, the International Biophysical Society, and the Society of General Physiologists.

Finally, during all this work I have contributed to the formation of new PhDs, and thus I directed 11 theses, and there are also now three in progress. Two of these theses obtained the mention of Extraordinary Prize of the Faculty of Medicine. I also contributed to the formation of 7 Postdoc students, and three of them have a stable position at the University of Barcelona.

Part C. RELEVANT MERITS *(sorted by typology)*

C.1. Publications *(see instructions)*

I include here 10 selected publications from the last 10 years about our research on MLC disease.

1: Alonso-Gardón M, Elorza-Vidal X, Castellanos A, et al, **Estévez R*.** (16/16). Identification of the GlialCAM interactome: the G protein-coupled receptors GPRC5B and GPR37L1 modulate megalencephalic leukoencephalopathy proteins. Hum Mol Genet. 2021 Aug 12;30(17):1649-1665. doi: 10.1093/hmg/ddab155.

2: Baldwin KT, Tan CX, Strader ST, et al, **Estévez R**, Ji RR, Eroglu C. (10/12) HepaCAM controls astrocyte self-organization and coupling. Neuron. 2021 Aug 4;109(15):2427-2442.e10. doi: 10.1016/j.neuron.2021.05.025. *Comment by the editor.*

3: Sánchez A, García-Lareu B, Puig M, et al, **Estévez R***, Bosch A* (8/9) (*Equal contribution). Cerebellar Astrocyte Transduction as Gene Therapy for Megalencephalic Leukoencephalopathy. Neurotherapeutics. 2020 Oct;17(4):2041-2053. doi: 10.1007/s13311-020-00865.

4: Elorza-Vidal X, Xicoy-Espaulella E, Pla-Casillanis A, Alonso-Gardón M, Gaitán-Peñas H, Engel-Pizcueta C, Fernández-Recio J, **Estévez R***. Structural basis for the dominant or recessive character of GLIALCAM mutations found in leukodystrophies. Hum Mol Genet. 2020 May 8;29(7):1107-1120. doi:10.1093/hmg/ddaa009. *Cover of the journal.*

5: Sirisi S, Elorza-Vidal X, Arnedo T, et al, **Estévez R*** (12/12). Depolarization causes the formation of a ternary complex between GlialCAM, MLC1 and ClC-2 in astrocytes: implications in megalencephalic leukoencephalopathy. Hum Mol Genet. 2017 Jul 1;26(13):2436-2450. doi:10.1093/hmg/ddx134.

6: Arnedo T, López-Hernández T, Jeworutzki E, Capdevila-Nortes X, Sirisi S, Pusch M, **Estévez R***. Functional analyses of mutations in HEPACAM causing megalencephalic leukoencephalopathy. Hum Mutat. 2014 Oct;35(10):1175-8. doi:10.1002/humu.22622. *Selected as a video by the editor.*

7: Sirisi S, Folgueira M, López-Hernández T, et al, **Estévez R*,** Barrallo-Gimeno A*. (16/17) (*Equal contribution). Megalencephalic leukoencephalopathy with subcortical

cysts protein 1 regulates glial surface localization of GLIALCAM from fish to humans. Hum Mol Genet. 2014 Oct 1;23(19):5069-86. doi: 10.1093/hmg/ddu231.
8: Hoegg-Beiler MB, Sirisi S, Orozco IJ, et al, **Estévez R***, Jentsch TJ*. (11/12) (*Equal contribution). Disrupting MLC1 and GlialCAM and ClC-2 interactions in leukodystrophy entails glial chloride channel dysfunction. Nat Commun. 2014 Mar 19;5:3475. doi:10.1038/ncomms4475.
9: Capdevila-Nortes X, López-Hernández T, Apaja PM, et al, **Estévez R**. (11/11) Insights into MLC pathogenesis: GlialCAM is an MLC1 chaperone required for proper activation of volume-regulated anion currents. Hum Mol Genet. 2013 Nov 1;22(21):4405-16. doi: 10.1093/hmg/ddt290.
10: Jeworutzki E, López-Hernández T, Capdevila-Nortes X, et al, **Estévez R***. (16/16) GlialCAM, a protein defective in a leukodystrophy, serves as a ClC-2 Cl(-) channel auxiliary subunit. Neuron. 2012 Mar 8;73(5):951-61. doi: 10.1016/j.neuron.2011.12.039. *Comment by the editor and Selected as a video by the editor.*

C.2. Congress
1. Presentation at American Society Neurochemistry (ASN) Meeting 2021. Glial Chloride channel and transporters. Oral meeting (Virtual). ”The crosstalk between MLC1, GlialCAM and the glial chloride channels ClC-2 and LRRC8 in leukodystrophies”
2. Presentation at SINS (Italian Society of Neuroscience). Astroglial cells in disease. 2019. Perugia (Italy). Oral presentation. ”Regulation of astrocytic chloride channels in health and disease”

C.3. Research projects
1. “Regulation of chloride channels in health and disease”. IP: Raúl Estévez. MICINN 2019-2021. 242000 €.
2. “Estudios iniciales para determinar la estructura 3D de MLC1”. IP and coordinator: Raúl Estévez. CIBERER 2020. 40000 €
3. “Characterization of a zebrafish model of myotonia congenita”. IP and coordinator: Raúl Estévez. CIBERER 2021. 40000 €.
4. “Development of novel inhibitors of the chloride channel LRRC8/VRAC, a novel player in ischemia”. IP and coordinator. Raúl Estévez. Fundació La Marató de TV3. 2018-2020. 199936,53 €.
5. “Misslocalization of astrocytic VCAM-1 in MLC” European Leukodystrophy Association. ELA 2017-012F4. IP Raúl Estévez. ELA International. 2018-2019. 71288 €.
6. ICREA Academia Prize. Raúl Estévez. 2015-2019. 200000 €.

C.4. Contracts, technological or transfer merits
1. Approved Orphan Drug Designation (EMA/OD/0000059436) for the treatment of MLC. September 2021.
2. Transfer agreement between AstraZeneca UK Limited of the compound AZD0530 (Saracatinib) as a novel therapy for MLC. November 2021.