Parte A. DATOS PERSONALES

Fecha del CVA	23/07/2024

Nombre y apellidos	Beatriz Pardo Merino		
Núm. identificación del investigador		Researcher ID	**C-3234-2016**
		Código Orcid	0000-0002-8219-5483

A.1. Situación profesional actual

Organismo	Universidad Autónoma Madrid (UAM)		
Dpto./Centro	Dept. de Biología Molecular/Centro de Biología Molecular Severo Ochoa (CBM)		
Dirección	c/ Nicolás Cabrera 1		
Teléfono		correo electrónico	bpardo@cbm.csic.es
Categoría profesional	Prof. Titular Universidad (UAM)		
Espec. cód. UNESCO			
Palabras clave	Mitochondria; mitochondrial carriers; Aralar/AGC1; ARALAR/AGC1 deficiency; mitochondrial aspartate- glutamate carrier; mitochondrial disorders; myelination		

A.2. Formación académica *(título, institución, fecha)*

Licenciatura/Grado/Doctorado	Universidad
Licenciatura en Biología "Bioquímica y Biología Molecular"	UAM
Doctorado en Ciencias	UAM

A.3. Actividades anteriores de carácter científico ó profesional

Period	Position/Institution/Country/Interruption cause
2020-present	Associate Professor (Titular Dept Biología Molecular), Universidad Autónoma de Madrid (UAM) , Spain
2010-2020	Associate Professor (PCD, Dept Biología Molecular), UAM, Spain
2007-2010	Indefinite Postdoctoral contract Rare Diseases Networking Biomedical Research Centre (CIBERER).
2006-2007	Postdoctoral Contract (UAM) Integrated European Project EuroDia
2004-2005	Postdoctoral contract "Comunidad de Madrid". CBM
2000-2003	Contract "Reincorporación para doctores en España". CBM
1996-2000	Contract of "First Assistant" Fac. of Medicine. Univ. de Lausanne (UNIL, Switzerland)
1994-1995	Contract of "Assistant". Fac. of Medicine. UNIL
1988-1993	Dpt. de Investigación. Hosp. Ramón y Cajal, Madrid. Pre-doctoral student, FISS. Advisor: Mari Angeles Mena Gómez/Justo García de Yébenes

A.4 Tesis doctorales dirigidas

"Implicación de aralar/agc1/Slc25a12, el transportador mitocondrial de aspartato-glutamato, y su dependencia funcional de Ca2+ en el metabolismo de la glucosa responsable de la secreción de insulina en las células β". Patricia Mármol Carrasco. Universidad Autónoma de Madrid. Noviembre 2009. Sobresaliente Cum Laude.
"New roles of Aralar, the brain mitochondrial aspartate-glutamate carrier, in dopamine handling, glutamate excitotoxicity and regulation of mitochondrial respiration" Irene Llorente Folch. Universidad Autónoma de Madrid. Junio 2013. Apto Cum Laude.
"Ca2+ modulation of mitochondrial function under physiological and pathological stimulation: role of the ATP-Mg/Pi Carrier, SCaMC-3" Carlos B. Rueda Díez. Universidad Autónoma de

Madrid. Diciembre 2014. Sobresaliente Cum Laude y Mención Doctorado Internacional.
"The mitochondrial aspartate-glutamate carrier Aralar/AGC1 controls neuronal respiration and (beta)-hydroxybutyrate rescues brain defects caused by AGC1 deficiency". Irene Pérez Liébana. Universidad Autónoma de Madrid. Junio 2020. Sobresaliente Cum Laude
"Calcium-regulated mitochondrial transporters in cellular metabolism and the pathophysiology of human diseases". Luis González Moreno. Universidad Autónoma de Madrid. En realización, fecha prevista 2024-25.
"Specific function of AGC1/Aralar in neurons and OPCs during neurodevelopment in mice". Eduardo Herrada Soler. Universidad Autónoma de Madrid. En realización, fecha prevista 2025.

A.5. Indicadores generales de calidad de la producción científica

- Tramos de investigación acreditados (sexenios): 5, el último (2014-2019).
- Miembro asociado a la unidad U-743 del CiBER de enfermedades raras desde 2006 hasta 2018.
- Miembro del Instituto de Investigación sanitaria Fundación Jimenéz Díaz desde 2013
- Revisor por pares de revistas internacionales con alto impacto del área de Biomedicina.
- Editorial Board de las revistas científicas Life y Frontiers in Cellular Neuroscience.
- De un total de 52 trabajos publicados en revistas internacionales, 27 han sido publicadas en revistas del primer cuartil (Q1), y dentro de éstas, 8 se encuentran entre las revistas pertenecientes al primer decil (D1) de sus categorias. Además de 5 capitulos de libro.
- El número de citas totales es de 3574. Indice **h**: 30; índice i10: 44 (Google Scholard)

Parte B. RESUMEN LIBRE DEL CURRÍCULUM

During the PhD, at the "Ramón y Cajal" Hospital (Madrid) my investigations were focused on the mechanisms of L-DOPA toxicity by using neurons from human and murine origin, emphasizing its effect on the mitochondrial function involved in the ethiopathology of PD. I studied the mechanisms responsible for dopaminergic neurodegeneration and tried several pharmacological approaches in rats and primates *in vivo*. The most relevant findings were related to: 1) the role of L-DOPA on mitochondrial function, and 2) the effect of antioxidant molecules on the metabolism and survival of dopaminergic neurons. I obtained the Ramón y Cajal prize of the Spanish Society of Neurology to PhD thesis in Neurosciences (1994).

During postdoctoral training at the University of Lausanne (Paul Honegger's group, 1994-2000) my research activity was focused on the study of the differentiation potential of stem cells from embryonic rat and mouse brain, and on the metabolic and structural alterations in neuronal and glial cells induced by ischemic conditions in an organotypical three-dimensional brain cell culture system. Also I worked on the identification of apoptosis-inducing signals during neurodevelopment, when the numerical balance between excitatory and inhibitory neurons is actively regulated. We found that GABAergic interneurons with low excitatory input are eliminated by apoptosis mediated by the $GABA_A$ receptor stimulation. The immature GABAergic neurons appeared to be very vulnerable to calcium deprivation by L- and T-VGCCs blockers; indicating that these channels play a critical role in the survival of inhibitory GABAergic neurons during maturation.

Attracted by the pivotal role of mitochondria function in neurophysiopathology, I joined the group of Jorgina Satrústegui (year 2000). The most outstanding achievements during this period correspond to the identification of Aralar/AGC1 and citrin/AGC2 as the mitochondrial aspartate-glutamate transporters stimulated by calcium, in mammalian and human cells. Both working as the regulatory component of the NADH malate-aspartate shuttle (MAS). The identification of a mechanism of mitochondrial activation by cytosolic

Ca^{2+} (nanomolar) through Aralar/AGC1-MAS was revealed as a new Ca^{2+} signaling pathway to mitochondria. Global Aralar-deficient mice were phenotypically characterized, which was inspiring for the discovery of humans with Aralar/AGC1 deficiency. Aralar was found to be implicated in the synthesis of glutamate and glial glutamine; and the nigrostriatal system as a target of Aralar-MAS deficiency. During this period our scientific results were published in very high impact journals such as **The EMBO J.** or **Physiol. Reviews**.

Actually, my work pursuit deciphering the relevance of Aralar-MAS in physiological processes as brain myelination (postnatal, and adult remyelination), brain energetics and neurotransmission. We aim to advance the mechanistic understanding of the actions of AGC1-MAS to develop therapies applicable to AGC1 deficiency and other metabolic, hypo-desmyelinating conditions in the CNS. Neuronal and oligodendroglial contributions to the drastic phenotype observed in global AGC1 deficiency in humans and mice are being addressed to decipher the molecular mechanisms responsible for brain affectation in AGC1/Aralar deficiency and neuroenergetic failure.

Parte C. MÉRITOS MÁS RELEVANTES

C.1. Publicaciones relevantes de los últimos 10 años

1. **Pardo B** (2024) Neuronal hypoglycolysis sustains body health***. Nature Metab.*** 6 (7): 1197-1199.

2. Del Arco A, González-Moreno L, Pérez-Liébana I, Juaristi I, González-Sánchez P, Contreras L, **Pardo B**, Satrústegui J. (2023) Regulation of neuronal energy metabolism by calcium: Role of MCU and Aralar/malate-aspartate shuttle. ***BBA Mol Cell Res.*** 1870(5):119468.

3. **Pardo B**, Herrada-Soler E, Contreras L, del Arco A, Satrústegui J. (2022) AGC1 deficiency: Pathology and molecular and cellular mechanisms of the disease" ***Int. J. Mol. Sci.*** 23 (1): 528.

4. Pérez-Liébana I, Jauristi I, González-Sánchez P, González-Moreno L, Rial E, Poduvanac M, Zakarian A, Molgó J, Vallejo-Illarramendi A, Mosqueira-Martín L, Lopez de Munain A, **Pardo B,** Satrústegui J, Del Arco A. (2022) A Ca^{2+}-Dependent Mechanism Boosting Glycolysis and OXPHOS by Activating Aralar-Malate-Aspartate Shuttle, upon Neuronal Stimulation. ***J. Neurosci.*** 42(19):3879-3895.

5. Esparza-Moltó PB, Romero-Carramiñana I, Núñez de Arenas C, Pereira MP, Blanco N, **Pardo B**, Bates GR, Sánchez-Castillo C, Artuch R, Murphy MP, Esteban JA, Cuezva JM (2021) Generation of mitochondrial reactive oxygen species is controlled by ATPase inhibitory factor 1 and regulates cognition. ***PLOS Biol.*** 19(5): e3001252.

6. Perez-Liébana I, Casarejos MJ, Alcaide A, Llorente-Folch I, Contreras L, Satrústegui J, **Pardo B** (2020) "ßOHB protective pathways in Aralar-KO neurons and brain: an alternative to ketogenic diet". ***J. Neurosc.*** 40(48):9293-9305.

7. Puertas-Frías G, del Arco A, **Pardo B**, Satrústegui J, Contreras L (2019) Mitochondrial movement in Aralar/Slc25a12/AGC1 deficient cortical neurons. ***Neurochem. Int.*** 131: 104541.

8. Juaristi I, Contreras L, González-Sánchez P, Pérez-Liébana I, González-Moreno L, **Pardo B**, del Arco A, Satrústegui J (2019) The response to stimulation in neurons and astrocytes. ***Neurochem Res.*** 44(10): 2385-2391.

9. Juaristi I, García-Martín ML, Rodrigues TB, Satrústegui J, Llorente-Folch I, **Pardo B** (2017) "ARALAR/AGC1 deficiency, a neurodevelopmental disorder with severe impairment of neuronal mitochondrial respiration, does not produce a primary increase in brain lactate". ***J. Neurochem.*** 142 (1), pp. 132-139.

10. Llorente-Folch I, Rueda CB, Pérez-Liébana I, Satrústegui J and **Pardo B** (2016) "L-Lactate-mediated neuroprotection against glutamate-induced excitotoxicity requires ARALAR/AGC1". ***J. Neurosc.*** 36 (16): 4443-56.

11. Rueda CB, Llorente-Folch I, Traba J, Amigo I, Gonzalez-Sanchez P, Contreras L, Juaristi I, Martinez-Valero P, **Pardo B**, del Arco A, Satrústegui J. (2016) "Glutamate excitotoxicity and Ca^{2+} regulation of respiration: Role of the Ca^{2+} activated mitochondrial transporters (CaMCs)". ***BBA*** 1857 (8), pp. 1158-66.

12. Del Arco A, Contreras L, **Pardo B**, Satrústegui J (2016) Calcium regulation of mitochondrial carriers. ***Biochim. Biophys. Acta (BBA)*** 1863: 2413-21.

13. Llorente-Folch I, Rueda CB, **Pardo B**, Szabadkai G, Duchen MR, Satrústegui J. (2015) "The regulation of neuronal mitochondrial metabolism by calcium". ***J. Physiol.*** 593(16), pp. 3447-62.

14. Rueda CB, Llorente-Folch I, Amigo I, Contreras L, González-Sánchez P, Martínez-Valero P, Juaristi I, **Pardo B**, del Arco A, Satrústegui.J (2014). "Ca^{2+} regulation of mitochondrial function in neurons". ***Biochim. Biophys. Acta*** 1837 (10), pp. 1617-24.

15. Llorente-Folch I, Rueda CB, Amigo I, del Arco A, Saheki T, **Pardo B**, Satrústegui J (2013) Calcium-regulation of mitochondrial respiration maintains ATP homeostasis and requires Aralar/AGC1-malate aspartate shuttle in intact cortical neurons. ***J Neurosci.*** *33*: 13957-71.

16. Llorente-Folch I, Sahún I, Contreras L, Casarejos MJ, Grau JM, Saheki T, Mena MA, Satrústegui J, Dierssen M, **Pardo B.** (2013) AGC1-malate aspartate shuttle activity is critical for dopamine handling in the nigrostriatal pathway. ***J Neurochem****.* 124:347-62.

C.2. Proyectos. Se indican los últimos 10 años:

A. Investigador principal:

1. **"***Roles of AGC1/Aralar in neurons and proliferating OPCs; myelination, cytosolic redox state and aspartate levels***" IP: *Beatriz Pardo*** *and Araceli del Arco***. PID2023-146837OB-I00**. Período: 2024-2027.

2. **"***Calcium-regulated mitochondrial transporters: Role of SCaMC3 and citrin in calcium signaling in the liver and of Aralar in intercellular communication in the CNS"* **IP: *Beatriz Pardo*** *and Araceli del Arco***. PID2020-114499RB-I00**. Período: 2021-2024.

3. "*Calcium regulated mitochondrial carriers: Role of Aralar/AGC1 in metabolic regulation and intercellular traffic in brain and role of SCaMC1 in tumor metabolism*". **IP: *Beatriz Pardo*** *and Araceli del Arco***. SAF2017-56929-R**. Período: 2018-2020.

4. "*Calcium signaling to the mitochondria and metabolic regulation in neurons and glia: therapeutic implications*". **IP:** *Jorgina Satrústegui and* ***Beatriz Pardo*****. SAF2014-56929-R**. Período: 2015-2017.

B. Miembro del equipo investigador:

5. "*AGC1 deficiency and calcium signaling to mitochondria: a new model of the disease for the study of pathogenic mechanisms and development of therapeutic strategies*". **IP: *Jorgina Satrústegui*.** Entidad: Fundación Ramón Areces. Período: 2017-2019.

6. Participación en **Programa de I+D en Biomedicina de la Comunidad de Madrid**. "*La mitocondria y su implicación en patología humana*". Coordinador: José M. Cuezva Marcos. Responsable grupo CAMIT (al que pertenezco): J.Satrústegui Gil-Delgado. Centro de Biología Molecular "Severo Ochoa". Universidad Autónoma, Madrid. Referencia: P2010/BMD-2402, S2011/BMD-2402. Período: 2012-2015.

C.3 Congresos y Conferencias invitadas (**selección de entre los últimos años**):

1. E. Herrada-Soler, M.A. Serrano-Lope, M.J. Casarejos, M.P. Pereira, A. del Arco, J. Satrústegui, **B. Pardo** (2023) "*Corticostriatal metabolic rewiring and social reward deficits in adult mice lacking neuronal Aralar, the mitochondrial aspartate-glutamate Carrier1*" SENC/IBRO 11th IBRO World Congress of Neuroscience (Granada, 9-13 septiembre 2023).

2. E. Herrada-Soler, M.A. Serrano-Lope, M.J. Casarejos, M.P. Pereira, A. del Arco, J. Satrústegui, **B. Pardo** (2023) "*Aralar/AGC1 mitochondrial carrier ablation in NG2-Cre mice exhibit myelination defects affecting behavior*" SENC/IBRO 11th IBRO World Congress of Neuroscience (Granada, 9-13 septiembre 2023).

3. E. Herrada-Soler, M.A. Serrano-Lope, A. del Arco, T. Aguado, J. Satrústegui, J. Palazuelos, **B. Pardo** (2022) "*Dissecting the role of Aralar/AGC1 in the brain: generation and characterization of oligodendroglial-specific Aralar-KO mice*". 44th SEBBM Meeting (Malaga, 6-9 septiembre 2022).

4. I. Pérez-Liébana, M.J. Casarejos, M. Caamaño, A. Alcaide, J. Satrústegui, **B. Pardo** (2019) *"ARALAR/AGC1 deficiency: Therapeutic approaches"*. ISN-ASN (International Society for Neurochemistry-American Society for Neurochemistry) Meeting (Montreal, 4-8 Agosto 2019)

5. I. Pérez-Liébana, M.J. Casarejos, M. Caamaño, A. Alcaide, J. Satrústegui, **B. Pardo** (2019) *"ARALAR/AGC1 deficiency: Therapeutic approaches"*. 18th National Meeting of the Spanish Society of Neuroscience (SENC) (Santiago de Compostela, España, 4-6 septiembre 2019).

7. María Traka, Miles Barney, **Beatriz Pardo** and Brian Popko. (2018) *"NAA depletion rescues myelin degeneration in the Canavan disease mouse model Aspa^{nur7} but results to hypomyelination and lethality"*. Society for Neuroscience Meeting (San Diego, USA, 3-7 Noviembre 2018).
8. **7. Beatriz Pardo** (2017) "The AGC1 Knockout mouse" International Symposium: Amino acid transport defects. Fundación Ramón Areces (Madrid, 20-21 Noviembre 2017). (invited conference).

9. **Beatriz Pardo Merino**, Irene Llorente-Folch, Carlos B Rueda, Irene Pérez-Liébana, Jorgina Satrústegui. (2016) *"L-lactate mediated neuroprotection against glutamate-induced neurotoxicity requires ARALAR-MAS pathway"*. 39th SEBBM Meeting (Salamanca, 5-8 septiembre 2016). (invited conference).

9. Beatriz Pardo Merino, Irene Llorente-Folch, Sara Laine-Menéndez, Laura Contreras, Carlos B Rueda, Paloma González-Sánchez, Inés Juaristi, Paula Martínez-Valero, Araceli del Arco, Jorgina Satrústegui (2014) *"Mitochondrial glutamate transporter (Aralar): influence over myelin formation and dopamine metabolism"*. 37th SEBBM Meeting (Granada, 9-12 septiembre 2014) (invited conference).