



## CURRICULUM VITAE (CVA)

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

Part A. PERSONAL INFORMATION		CV date	10/12/2021
First name	Alberto		
Family name	Pascual Bravo		
Gender (*)	Male	Birth date	26/10/1971
ID number	31265103F		
e-mail	apascual-ibis@us.es	URL Web	<a href="https://www.ibis-sevilla.es/investigacion/neurociencias/mecanismos-de-mantenimiento-neuronal/pascual-bravo-alberto.aspx">https://www.ibis-sevilla.es/investigacion/neurociencias/mecanismos-de-mantenimiento-neuronal/pascual-bravo-alberto.aspx</a>
Open Researcher and Contributor ID (ORCID) (*)	0000-0001-5459-6207		

(\*) Mandatory

### A.1. Current position

Position	Principal Investigator (“Científico Titular” CSIC)		
Initial date	2007		
Institution	CSIC		
Department/Center	Neuroscience	<a href="#">Instituto de Biomedicina de Sevilla (IBiS)</a>	
Country	Spain	Teleph.number	+34955923049
Keywords	Hypoxia, microglia, HIF, PHD, Alzheimer’s disease, endothelial cells, blood-brain barrier, vascular scars, angiogenesis		

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

Period	Position/Institution/Country/Interruption cause
2003-2006	“Ramón y Cajal” Investigator (Tenure). HUVR. Spain
1999-2002	Postdoctoral at “Institute Alfred Fessard”, CNRS, France
1995-1998	PhD student at IBVF, CSIC, Spain
1994-1994	Pre-graduated student fellowship. IBVF, CSIC, Spain

### A.3. Education

PhD, Licensed, Graduate	University/Country	Year
PhD in Biology	Universidad de Sevilla	1999
Graduated in Biology	Universidad de Sevilla	1994

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

I have been working for 26 years as a scientist. During those years I have been formed in (i) Biochemistry and molecular biology, PhD in the study of the ribonuclease P, an RNA enzyme involved in the maturation of tRNAs, 4 publications as a first author with only my PhD supervisor as an additional author, including a PNAS article; (ii) Genetics and learning and memory in *Drosophila*, postdoctoral at Dr. Thomas Preát laboratory, France, 5 first-author publications in *Science* (2x), *Nature*, *NAR*, and *Dev. Biol.*; (iii) Tenured scientist, mouse models of neurodegeneration and role of hypoxia in physiology and pathology, several first author articles, including a *Nat. Neurosci.* paper; and (iv) Principal Investigator at IBiS, we have unraveled new pathogenic mechanisms taking place in AD (1 and 2 from the publication list). During those years, the team has received financial support from autonomic, national, and international sources and both from public and private organizations.

The PI has developed a new and independent line of research in Alzheimer’s disease (AD) and the hypoxia signaling pathway. AD is characterized by a pathognomonic early decrease in brain blood flow, the accumulation of A $\beta$  peptide in the wall of brain vessels (amyloid angiopathy), and high local



inflammation surrounding senile plaques. These three circumstances lead to a decrease in oxygen concentration that could modify the progression of AD. We have shown that the human AD brain shows molecular markers of hypoxia. We have also shown that the accumulation of HIF1 $\alpha$  produces microglia cell cycle arrest and worsens AD pathology in animal models of AD. We have identified PHD3, a HIF target gene, as another contributor to the AD neurodegeneration. Genetic deletion of PHD3 recovers cognitive and behavioral phenotypes of an AD mouse model and change the activation profile of microglia. Actually, we are investigating the role of local hypoxia in the angiogenic processes taking place around A $\beta$  plaques. We have described a new structure associated with amyloid deposits that we have named vascular scars (VaS). VaS are complexes endothelium-derived structures characterized by low perfusion and high extracellular accumulation.

Main scientific responsibilities: **IBiS**: 1) General coordinator of scientific infrastructures/core facilities. 2020-to date; 2) Scientific coordinator IBiS's proteomic service, 2011-to date; 3) Scientific coordinator IBiS's sterilization and cleaning service, 2011-2016; 4) Scientific coordinator IBiS's biomedical research support facility, 2011-2018; 5) Secretary of IBiS's Neuroscience Department, 2014-2021; 6) Organizer of the IBiS's Neuroscience department seminar series (weekly, international), 2014-2021; Organizer of the IBiS's Seminar series (international), 2011-12. **Networks**: 1) Secretary of the Spanish network of researchers in hypoxia, 2014-to date. 2) European Neuroscience Institute-NET Alumni investigator, 2014-to date; 3) European Neuroscience Institute-NET Young investigator, 2008-2013; iv) Participant in COST action Hypoxia sensing, signaling, and adaptation, 2009-2013. **Evaluation**: 1) "Comisión Evaluación" RyC2015, JdIC-I2017, and JdIC-F&I2018; 2) "Comisión de Evaluación Plan Nacional" 2020; 3) "Adjunto evaluación Fundación Progreso y Salud" 2021; 4) ANEP 2006, 2008-to date; 5) EMBO LTF 2008; 6) ANR (France) 2012 & 2020; 7) "Junta de Andalucía" 2010-2011; 8) Parkinson's disease society 2010-2011; 9) Parkinson's UK 2012, 2013, 2015- 2016; 10) COST 2014; 11) Fundación Progreso y Salud, 2016, 2018-to date. **Collaborations** (with publications): 1) Ratcliffe, P.J., Crick/University of Oxford; 2) Körbelin, J. University of Eppendorf/Hamburg; 3) Berra, E., CICbioGUNE; 4) de Castro, F., Insituto Cajal; 5) Herrera, E., Instituto de Neurociencias; 6) Vitorica, J., IBiS; 7) López-Barneo, J., IBiS; 8) Escudero, L.M., IBiS; 9) Scholl, F.G., IBiS. **Thesis**: 7 (2 ongoing; all of them with FPU (6)/FPI (2)/Andalusia (1) fellowships). **Supervision of Postdoctoral researchers**: 1) Marie Curie Fellowship: Macías, D., 2022-23; 2) Juan de la Cierva Incorporación: Rosales-Nieves, A.E., 2018-19; 3) Ramón y Cajal (sharing space): Escudero, L.M., 2011-16; 4) Miguel Servet (sharing space): Escudero, L.M., 2007-10; 5) Sara Borrell: March-Díaz, R., 2008; 6) Sara Borrell: Romero-Ruiz, A. 2006. **TFM/TFG supervision**: 26+3 ongoing. **Fellowships**: 1) Chaire Joliot, Paris Sciences 2011 and 2013; 2) "Ramon y Cajal" at Hospital Virgen del Rocío, 2003-2007; 3) Fellowship "Foundation pour la Recherche Medicale", 2002-2002; 4) EMBO-LTF, 2000- 2002; Fellowship "Foundation pour la Recherche Medicale", 1999- 2000; 5) FPU, CSIC, 1995-1998; 6) Undergraduate student fellowship for starting investigators, 1994. **Research abroad**: 1) Sidney Altman (1989 Nobel prize in Chemistry), Yale University, 3 months in 1996/FPU; 2) Thomas Pr at, Institut Alfred Fessard, France. 1999-2002; 3) Thomas Pr at, ESPCI, France (1 month) 2011; 4) Dr. Thomas Pr at, ESPCI, France (1 month) 2013.

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

### C.1. Publications (CA: corresponding author, a selection from 24 articles in the period 2012-2021, see ORCID for full CV)

1. Alvarez-Vergara, M.I., Rosales-Nieves, A.E., March-Díaz, R., ... and Pascual, A.\* (\*CA; 30/30) 2021. Non-productive angiogenesis disassembles A $\beta$  plaque-associated blood vessels. *Nat. Commun.* 12, 3098
2. March-Díaz, R., Lara-Urena, N., Romero-Molina, C., ..., Vitorica, J.\*, and Pascual, A.\* (\*CA; 25/25) 2021. Hypoxia compromises the mitochondrial metabolism of Alzheimer's disease microglia via HIF1. *Nat. Aging.* 1(4) 385-399
3. Ortega-de San Luis, C., Sanchez-Garcia, M., Nieto-Gonzalez, J.L., Garcia-Junco-Clemente, P., Montero-Sanchez, A., Fernandez-Chacon, R., Pascual, A.\* (\*CA) 2018. Substantia nigra dopaminergic neurons and striatal interneurons are engaged in three parallel but interdependent postnatal neurotrophic circuits. *Aging Cell* 17(5):e12821
4. Serrano-Pozo, A.\*, Sánchez-García, M.A., Heras-Garvín, A., Pascual, A.\* (\*CA; 9/9) 2017. Acute and Chronic Sustained Hypoxia Do Not Substantially Regulate Amyloid- $\beta$  Peptide Generation In Vivo. *PLoS ONE* 12(1):e0170345
5. Ortega-de San Luis, C., Pascual, A.\* (\*CA) 2016. Simultaneous detection of both GDNF and GFR $\alpha$ 1 expression patterns in the mouse central nervous system. *Frontiers in Neuroanatomy* 10:1-24



6. Fernandez-Aguera, M.C., Gao, L., Gonzalez-Rodriguez, P., ..., Lopez-Barneo, J. (8/10) 2015. Mitochondrial Complex I Ndufs2 is Required for Acute O<sub>2</sub> Sensing by Arterial Chemoreceptors. *Cell Metabolism* 22: 825-837
7. Gao, L.\*, Hidalgo-Figueroa, M., Escudero, L.M., Lopez-Barneo, J. and Pascual, A.\* (\*CA) 2013. Age-mediated transcriptomic changes in adult mouse substantia nigra. *PLoS ONE*. 8:e62456(1-12)
8. Hidalgo-Figueroa, M., Bonilla, S., Gutiérrez, F., Pascual, A.\*, and López-Barneo, J.\* (\*CA) 2012. GDNF is predominantly expressed in the PV<sup>+</sup> neostriatal interneuronal ensemble in normal mouse and after injury of the nigrostriatal pathway. *The Journal of Neuroscience*. 32:864-872
9. Romero-Ruiz A, Bautista L, Navarro V, ..., Lopez-Barneo J.\*, and Pascual A.\* (\*CA; 11/11) 2012. Prolyl hydroxylase-dependent modulation of eukaryotic elongation factor 2 activity and protein translation in acute hypoxia. *J. Biol. Chem.* 287: 9651-9658
10. Marcos-Almaraz, M.T., Rodriguez-Gomez, J.A., Lopez-Barneo, J., Pascual, A.\* (\*CA) 2012. Alpha-hemoglobin regulates sympathoadrenal cell metabolism to maintain catecholaminergic phenotype. *Biochem J*. 441:843-850

### C.2. Congress (Only invited conferences and congress organization)

1. Non-productive angiogenesis in Alzheimer's disease: a tale of three friends. VI UIMP-IBIS SCHOOL OF BIOMEDICINE. MECHANISMS OF NEURODEGENERATION: from genes to neural networks. Plenary Conference, Seville, December 2021.
2. Microglial and endothelial cells in Alzheimer's disease, a hypoxic perspective. Instituto de Investigaciones Biomédicas Alberto Sols/Departamento de Medicina UAM, March, 24<sup>th</sup> 2021. Madrid.
3. Hypoxia, Microglia, and Endothelial Cells in Alzheimer's Disease Pathogenesis. Hypoxia: Molecules, Mechanisms and Disease, Keystone Symposia Plenary Conference, January 23<sup>th</sup> 2020. Keystone, USA.
4. Niche factors compromise the metabolism of A $\beta$  plaque-associated microglia. Achucaro Basque Center for Neuroscience, July, 2019. Derio.
5. A $\beta$  plaques induce progressive blood vessel loss by non-productive angiogenesis, a new pathologic mechanism in Alzheimer's disease. Congreso de la Sociedad Española de Neurología, November, 2018. Seville.
6. A $\beta$  plaques induce progressive blood vessel loss by non-productive angiogenesis, a new pathologic mechanism in Alzheimer's disease. Instituto Cajal, Madrid, January, 2019.
7. Analysis of the HIF1 $\alpha$ -PHD3 pathway reveals modular and distinctive microglial responses to Alzheimer's disease. XL SEBBM Congress, Barcelona, 2017.
8. Hypoxia and microglia, the innate immune system of the brain. ConsEPOC International Meeting "Hypoxia and Inflammation in Physiology and Disease". 4<sup>th</sup> May, UAM, Madrid, 2015.
9. International workshop: Hypoxia, molecular mechanisms and clinical translation. Organizer. Seville, Spain. Invited speakers included two Nobel Prizes in Physiology or Medicine (Peter. J. Ratcliffe and Gregg L. Semenza). 2014.
10. Microglia and Hypoxia: Implications for Alzheimer's disease. CIC bioGUNE, Derio, Bilbao. 2013.

### C.3. Research projects (PI: Principal Investigator)

1. "Characterization of the local vascular component in Alzheimer's disease, an update of the gamma secretase loss of function hypothesis" Junta de Andalucía (2021-2022) PI: **Dr. Pascual. 79,900 €**
2. "Plataformas de organoides, impresión 3D y biomodelos del Instituto de Biomedicina de Sevilla". ISCIII (2021-2023) PI: Dr. Enrique de Álva, **Dr. Pascual: coordinator of the sub-platform "mouse models". 428,560 €**
3. "CARACTERIZACION DE LA PERDIDA PROGRESIVA DE VASOS POR ANGIOGENESIS NO PRODUCTIVA, UN NUEVO MECANISMO PATOLOGICO EN LA ENFERMEDAD DE ALZHEIMER". Plan Nacional Retos. 3 years (2019-2021) PI: **Dr. Pascual. 193,600 €**
4. "Uso de hiperoxia combinada con agentes normalizadores de la vasculatura para el tratamiento de la enfermedad de Alzheimer, una prueba de concepto". Fundación Domingo Martínez. (2018-2021) PI: **Dr. Pascual. 150,000 €**
5. "Role of the HIF/PHD signaling pathway in microglia: Implications for Alzheimer's disease". Spanish Ministry of Science ("Plan Nacional-SAF-Retos"). 2016-2018. PI: **Dr. Pascual. 217,800 €**
6. "Caracterización de los mecanismos intrínsecos implicados en el mantenimiento de las neuronas dopaminérgicas de la SNpc. Papel de GDNF y de genes modulados por el envejecimiento" CICE (Andalusian government). 2014-2018. PI: **Dr. Pascual. 256,750 €**



7. "Improving Translational Research Potential at the Institute of Biomedicine of Seville ". REGPOT-2012-2013-1 FP7 (Grant agreement no: 316151). (2013-2017) PI: Dr. José López Barneo. Coordinator Work Package 4: **Dr. Pascual. 4,218,197 €**

8. "TRANSLATING HYPOXIA RESEARCH TO A CLINICAL SETTING: O<sub>2</sub> DEFICIENCY TOLERANCE, BRAIN DYSFUNCTION, INFECTION, AND CANCER". ISCIII. "Proyectos integrados de excelencia 2013". (2014-2016) PI: Dr. José López Barneo. 8 Principal investigators, one of them **Dr. Pascual, 825,000 €** (For 8 different teams)

9. "CHARACTERIZATION OF INTRINSIC MECHANISMS INVOLVED IN DOPAMINERGIC SNPC NEURON MAINTENANCE. ROLE OF GDNF AND AGING-MODULATED GENES." Spanish Ministry of Science ("Plan Nacional-SAF"). (2013-2015) PI: **Dr. Pascual. 187,200 €**

10. "INDISPENSABLE GLIAL CELL LINE-DERIVED NEUROTROPHIC FACTOR (GDNF)-MEDIATED MECHANISMS OF THE MAINTENANCE OF ADULT CATECHOLAMINERGIC NEURONS" Spanish Ministry of Science ("Plan Nacional-SAF"). (2010-2012). PI: **Dr. Pascual. 175,450 €**

#### **C.4. Contracts, technological or transfer merits (Patents)**

1. Nicolas, A., Peciña, A. **Pascual, A.**, Smith, K., Mezard, C. Rassoulzadegn, M. Methods for inducing targeted stimulation of meiotic recombination and kit for performing said methods. 10/199,762 PET/PRO3/08834. France and USA. 19/07/2002. Institute Curie and Centre National Recherche Scientifique (CNRS)-

2. **Pascual, A.**, Hidalgo-Figueroa, M., Piruat, J.I., Pintado, C. O., Gomez-Diaz R., and López-Barneo, J. Animal model for neurodegenerative diseases. EP07380344.7. Europe. 7/12/2007. Universidad de Sevilla/Hospital Virgen del Rocío

3. Escudero, LM, Montero, A, Paradas, C, Rivas, E, **Pascual, A**, Saez, A, Serrano, C, Acha, B. Método para obtener información útil para el diagnóstico de enfermedades neuromusculares. P201131840. Spain. 15/12/2011. Servicio Andaluz de Salud.

4. **Pascual, A**, Rosales-Nieves, A.E., Alvarez-Vergara, M.I. Non-productive angiogenesis inhibitor for use in the treatment of Alzheimer's disease. 20382318.2 – 1112. Europe. 27/10/2021. CSIC