PRINCIPAL INVESTIGATOR BIOGRAPHICAL SKETCH

NAME: **Inma Cobos**

eRA COMMONS USER NAME (credential, e.g., agency login): COBOSSILLERO

POSITION TITLE: Assistant Professor

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 Murcia School of Medicine, Murcia, Spain	M.D.	07/1996	Medicine
International University of Andalusia, Seville, Spain	Master's	11/1999	Neuroscience
University of Murcia School of Medicine, Murcia, Spain	Ph.D.	11/2000	Neuroanatomy and Development
University of California, San Francisco, San Francisco, CA	Postdoctoral	07/2007	Developmental Neurobiology
University of California, San Francisco, San Francisco, CA	Postdoctoral	06/2011	Neurodegeneration
Massachusetts General Hospital, Harvard Medical School, Boston, MA	Residency	06/2013	Anatomic Pathology
Massachusetts General Hospital, Harvard Medical School, Boston, MA	Fellowship	06/2015	Neuropathology

A. Personal Statement

My research focuses on understanding the basic mechanisms underlying the generation and maintenance of cell diversity in the brain and the cellular and molecular bases of selective vulnerability in neurodegeneration. As a neuropathologist with extensive experience in molecular, cellular, and developmental neuroscience, I am well positioned to contribute to our understanding of the pathogenesis of neurodegenerative disorders.

During my graduate and postdoctoral research, I studied the fundamental mechanisms that regulate neuronal specification, migration, and differentiation in the developing forebrain and how alterations in these mechanisms can lead to neuropsychiatric disorders. Our fate-mapping studies in avian embryos contributed to the discovery of the embryonic origins and migratory pathways of GABAergic interneurons and oligodendrocyte precursors in the developing forebrain (Cobos *et al*., 2001). My postdoctoral research at UCSF used mouse genetics to understand the complex organization of the cerebral cortex. We identified novel roles for *Dlx* homeobox transcription factors, master regulators of the GABAergic phenotype in the forebrain, in regulating dendritic and axonal morphogenesis, synaptogenesis, and apoptosis of cortical GABAergic interneurons. Our work established a new mouse model, the *Dlx1* knockout mouse, for delayed-onset epilepsy associated with interneuron loss (Cobos *et al*., 2005). Using molecular and cellular biology, genome-wide microarray, and cell transplantation approaches, we identified the fundamental Dlx-dependent molecular mechanisms that control cytoskeletal dynamics during early steps in interneuron differentiation and migration (Cobos *et al*., 2007).

After my postdoctoral studies, I pursued specialized training in Anatomic Pathology and Neuropathology. At MGH (2011–2015), I had the privileged opportunity to learn from world-class leaders in neuropathology, neurology, neuroimaging, and molecular pathology. As an Alzheimer Disease Research Center (ADRC) fellow, I was responsible for the processing, analysis, and completion of autopsy reports of over 100 brains received by the ADRC Brain Bank. This intensive training provided me with exceptional experience-based knowledge in the diagnosis and classification of neurodegenerative diseases and clinicopathological correlations.

In my research laboratory, I am applying my expertise in diagnostic neuropathology, neuroanatomy, and developmental neuroscience towards understanding selective vulnerability in neurodegenerative diseases, particularly, in Alzheimer's disease and related dementias. My ultimate goals are to advance our understanding of neurodegenerative disease pathogenesis at the cellular and molecular levels, develop novel models for the human

conditions that emphasize cell specificity, and identify therapeutic targets that can alleviate symptoms or modify disease progression.

Select peer-reviewed publications:

Cobos I, Calcagnotto ME, Vilaythong AJ, Thwin MT, Noebels JL, Baraban SC, Rubenstein JL. Mice lacking Dlx1 show subtype-specific loss of interneurons, reduced inhibition and epilepsy. Nat Neurosci. 2005, 8:1059–68. PMID: 16007083

Cobos I, Borello U, Rubenstein, JL. Dlx transcription factors promote migration through repression of axon and dendrite growth. Neuron. 2007, 54:873–88. PMID: 17582329

Cobos I, Seeley WW. Human von Economo neurons express transcription factors associated with layer V subcerebral projection neurons. Cereb Cortex. 2015, 1:213–20. PMID: 23960210

B. Positions and Honors

Positions and Employment

1996–2000 **Ph.D. Student**
Department of Anatomy, University of Murcia, Murcia, Spain

2001–2007 **Postdoctoral Researcher**
Laboratory of Dr. John Rubenstein, Department of Psychiatry, UCSF, San Francisco, CA

2007–2009 **ICREA Junior Investigator** (Catalan Institution for Research and Advanced Studies)
Department of Cell Biology, University of Barcelona, Barcelona, Spain

2009–2010 **Ramon y Cajal Investigator**
CSIC & UMH, Neuroscience Institute, Alicante, Spain

2010–2011 **Postdoctoral Researcher**
Laboratory of Dr. William Seeley, Department of Neurology, UCSF Memory and Aging Center, San Francisco, CA

2011–2013 **Resident in Anatomic Pathology**
Massachusetts General Hospital, Harvard Medical School, Boston, MA

2013–2015 **Clinical Fellow in Neuropathology**
Massachusetts General Hospital, Harvard Medical School, Boston, MA

9/15–5/19 **Assistant Professor, Ladder Rank**
Department of Pathology and Laboratory Medicine, Division of Neuropathology, UCLA, Los Angeles, CA

6/1/2019– **Assistant Professor of Pathology & Neuropathology, MCL**
Department of Pathology, Stanford University School of Medicine, Palo Alto, CA

Medical Licensure and Specialty Board Certification

2015– Medical Board of California, Physician license no. A139333
2015– Board certification in Anatomic Pathology and Neuropathology, American Board of Pathology

Honors and Awards

1995–1996 Undergraduate Research Fellowship from the Spanish Ministry of Education and Science
1996–2000 Predoctoral Fellowship from the Local Government of Murcia, Spain
1997 Master's Student Fellowship from the International University of Andalusia, Spain
1999 Short-Term Research Fellowship from the Spanish/French Picasso Project
2001 Doctoral Extraordinary Prize, University of Murcia, Murcia, Spain
2001 Fulbright Postdoctoral Fellowship (declined)
2001–2003 Postdoctoral Fellowship from the Spanish Ministry of Education and Science
2003–2005 NARSAD Young Investigator Award (National Alliance for Research on Schizophrenia and Depression)
2004–2006 NAAR Postdoctoral Fellowship (National Alliance for Autism Research/Autism Speaks)
2009 Short-Term Visiting Fellowship from the Alicia Koplowitz Foundation
2016 Stop Cancer Research Career Development Award
2018 Ben Barres Early Career Acceleration Award, Chan Zuckerberg Initiative

C. Contribution to Science

1. Forebrain Development. My graduate work contributed to our understanding of early forebrain development. I used fate-mapping studies in avian embryos to unravel the topological organization of the main forebrain

structures in the rostral neural plate. Our fate map is a reference in many laboratories for interpreting the topography of gene expression patterns in the neural plate and neural tube. Since we established the topography of telencephalic subdivisions with respect to patterning centers (e.g., the neural ridge), our fate map has helped other studies in elucidating the mechanisms that regulate the patterning of the rostral neural plate and telencephalon. Using cell transplantation, I mapped the embryonic origins and migratory pathways of GABAergic interneurons and oligodendrocytes in the developing telencephalon. We discovered that cortical interneurons are generated in the ventral forebrain from where they migrate tangentially to reach their final positions in cortex. Our studies demonstrated evolutionarily conserved mechanisms for the origin and migration of cortical GABAergic interneurons in birds and mammals.

Martinez S, Crossley PH, **Cobos I**, Rubenstein JL, Martin GR. FGF8 induces formation of an ectopic isthmic organizer and isthmocerebellar development via a repressive effect on Otx2 expression. Development. 1999, 126:1189–200. PMID: 10021338

Olivier C*, **Cobos I***, Perez-Villegas EM*, Spassky N, Zalc B, Martinez S, Thomas JL. Monofocal origin of telencephalic oligodendrocytes in the anterior entopeduncular area of the chick embryo. Development. 2001, 128:1757–69. (*Equal contributions). PMID:11311157

Cobos I, Shimamura K, Rubenstein JL, Martinez S, Puelles L. Fate map of the avian anterior forebrain at the four-somite stage, based on the analysis of quail-chick chimeras. Dev Biol. 2001, 239:46–67. PMID: 11784018

Cobos I, Puelles L, Martinez S. The avian telencephalic subpallium originates inhibitory neurons that invade tangentially the pallium (dorsal ventricular ridge and cortical areas). Dev Biol. 2001, 239:30–45. PMID: 11784017

2. Cortical GABAergic Interneuron Development. We identified novel roles for the *Dlx* family of homeobox transcription factors, master regulators of the GABAergic phenotype in the forebrain, in regulating dendritic and axonal morphogenesis, synaptogenesis, and apoptotic cell death of cortical GABAergic interneurons. Our work established a new mouse model, the *Dlx1* knockout mouse, for delayed-onset epilepsy associated with interneuron loss, now widely used as a mouse model for epilepsy. Through microarray, cellular and molecular biology, and cell transplantation approaches, we identified the key Dlx-dependent mechanisms that control cytoskeletal dynamics during early stages of interneuron differentiation and migration and in later stages of synapse formation. We demonstrated that Dlx genes promote interneuron migration in part by preventing the premature expression of PAK3, a serine/threonine kinase that is later involved in neurite outgrowth and interneuron maturation, introducing the concept that transcription factors dynamically coordinate migration and neuronal differentiation programs during brain development.

Cobos I, Calcagnotto ME, Vilaythong AJ, Thwin MT, Noebels JL, Baraban SC, Rubenstein JL. Mice lacking Dlx1 show subtype-specific loss of interneurons, reduced inhibition and epilepsy. Nat Neurosci. 2005, 8:1059–68. PMID: 16007083

Cobos I, Broccoli V, Rubenstein JL. The vertebrate ortholog of Aristaless is regulated by Dlx genes in the developing forebrain. J Comp Neurol. 2005, 483:292–303. PMID: 15682394

Cobos I, Borello U, Rubenstein, JL. Dlx transcription factors promote migration through repression of axon and dendrite growth. Neuron. 2007, 54:873–88. PMID: 17582329

Le TN, Zhou QP, **Cobos I**, Zhang S, Zagozewski J, Japoni S, Vriend J, Parkinson T, Du G, Rubenstein JL, Eisenstat DD. GABAergic interneuron differentiation in the basal forebrain Is mediated through direct regulation of glutamic acid decarboxylase isoforms by Dlx homeobox transcription factors. J Neurosci. 2017, 37:8816–8829. PMID: 28821666

3. Methods to Study Cell Diversity in the Brain. My expertise in cellular and developmental neuroscience, neuroanatomy, and histology over the past 15 years has contributed to our understanding of cell diversity in the forebrain. I developed and optimized methods for mRNA detection in a wide array of tissues, including postmortem human brain. We characterized the expression patterns of many genes in the avian, murine, and human forebrain, including most transcription factors in the developing basal ganglia and cortical GABAergic interneurons of mice (Cobos *et al*., 2006; Long *et al*., 2009). My expertise is used to assist many laboratories in characterizing the phenotypes of diverse transgenic and mutant mice. We also applied this knowledge to develop methods for identifying and producing neural stem and progenitor cells and their progeny in the forebrain.

Cobos I, Long J, Thwin MT, Rubenstein JL. Cellular patterns of transcription factor expression in developing cortical interneurons. Cereb Cortex. 2006, 16 Suppl 1:i82–8. PMID: 16766712

Long JE, **Cobos I**, Potter GB, Rubenstein JL. Dlx1&2 and Mash1 transcription factors control MGE and CGE patterning and differentiation through parallel and overlapping pathways. Cereb Cortex. 2009, Suppl 1:i96–106. PMID: 19386638

Palop JJ, Roberson ED, **Cobos I**. Step-by-step *in situ* hybridization method for localizing gene expression changes in the brain. Book chapter in "Alzheimer's Disease and Frontotemporal Dementia." Methods in Molecular Biology, 2011, Volume 670, Part 2, p 207–230. DOI: 10.1007/978-1-60761-744-0_15. PMID: 20967593

Intellectual property:
Title: Methods for identifying and producing neural stem and progenitor cells and their progeny
Inventors: John Rubenstein, Jason Long, Inma Cobos, Greg Potter
Publication number: WO2010053522 A3
Application number: PCT/US2009/005881
Publication date: 9/16/ 2010

4. Neurodegeneration. I recently began applying my expertise in developmental neuroscience towards understanding selective vulnerability in neurodegenerative diseases. My studies contributed to the molecular identification of human von Economo neurons (VENs), large bipolar neurons located in the anterior cingulate and frontoinsular cortices and linked to frontotemporal dementia. We found that VENs are layer V projection neurons with a molecular identity similar to that of the corticospinal neurons that degenerate in ALS (Cobos *et al*., 2015). My collaborative work with Dr. Palop at UCSF contributed to the understanding of GABAergic interneuron dysfunction in Alzheimer's disease (AD) mouse models. We showed that impaired inhibition contributes to epileptiform activity and cognitive decline in mouse models of AD. Transplants of parvalbumin interneuron precursors from the medial ganglionic eminence (ventral forebrain) overexpressing the voltage-gated sodium channel Nav1.1 reduce epileptiform activity and improve behavioral and cognitive deficits in AD mice.

Cobos I, Seeley WW. Human von Economo neurons express transcription factors associated with layer V subcerebral projection neurons. Cereb Cortex. 2015, 1:213–20. PMID: 23960210

Verret L, Mann EO, Hang GB, Barth AM, **Cobos I**, Ho K, Devidze N, Masliah E, Kreitzer AC, Mody I, Mucke L, Palop JJ. Inhibitory interneuron deficit links altered network activity and cognitive dysfunction in Alzheimer model. Cell. 2012, 149:708–21. PMID: 22541439

Mitchell SB, Lucente D, Larvie M, **Cobos I**, Frosch MP, Dickerson BC. A 63-year-old man with progressive visual symptoms. JAMA Neurology 2017, 74(1):114–118. PMID: 27842190

Martinez-Losa M, Tracy TE, Ma K, Verret L, Clemente-Perez A, Khan AS, **Cobos I**, Ho K, Gan L, Mucke L, Alvarez-Dolado M, Palop JJ. Nav1.1-Overexpressing Interneuron Transplants Restore Brain Rhythms and Cognition in a Mouse Model of Alzheimer's Disease. Neuron, 2018; 98:75-89.e5. PMID: 29551491

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1Reh5NH0zuOkL/bibliograpahy/50344170/public/?sort=date&direction=descending

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

R01AG059848 **Cobos (PI)** **8/2018 – 4/2023**
National Institute on Aging- NIH
Resolving selective vulnerability and disease progression in human Alzheimer's brain via single-cell RNA-seq

AARG-17-528298 **Cobos (PI)** **9/2017–8/2020**
Alzheimer's Association International Research Grant
Single-cell RNA-seq in human AD to define selective cell vulnerability

A2017346S **Cobos (PI)** **7/2017–6/2020**
BrightFocus
A cell-type focused approach to define selective vulnerability in human AD

Chan Zuckerberg Initiative **Cobos (PI)** **5/2019–4/2024**
Ben Barres Early Career Acceleration Award.
Investigating mechanisms of tau-mediated neurodegeneration in human brain