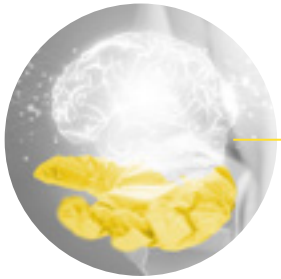
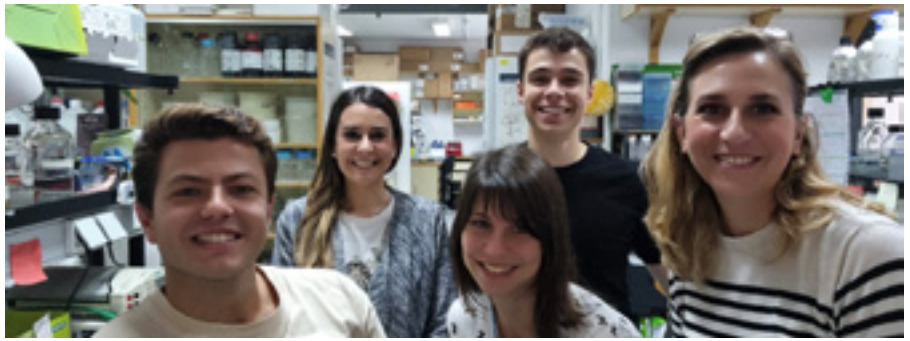


# 3.1.5 Mechanisms and Biomarkers in Neurodegenerative Diseases Group

Publications: 2
Q1: 2

## COMPOSITION

**Isabel Lastres Becker.** Profesora Titular. Universidad Autónoma de Madrid
**Marina Arribas Blázquez.** Investigadora Postdoctoral. Universidad Autónoma deMadrid
**Pablo Beceidero Macho.** Investigador Predoctoral. Universidad Autónoma de Madrid
**Alicia Berrojo Armisen.** Investigadora Predoctoral. Universidad Autónoma de Madrid
**Mirjam Brackhan.** Investigadora Postdoctoral. FIBHULP
**Ignacio Silva Llanes.** Investigador Predoctoral. Universidad Autónoma de Madrid



## STRATEGIC OBJECTIVE

The aging of the population poses a growing burden in society. This is associated with the increase in disability and diseases that have a high impact on health care, on patients and their families. Likewise, aging is associated with the appearance of different neurodegenerative diseases, among which include Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS). Therefore, the development of advanced biological markers, new drugs and appropriate technology is the key to establishing a treatment for these diseases, which is currently an important social challenge. In our laboratory we study the molecular basis of neurodegeneration. The research projects we develop have a multidisciplinary approach that combines basic and translational research, using cell culture techniques, murine models and postmortem samples from patients with AD, PD and ALS.

### Amyotrophic lateral sclerosis (ALS): Design and development of innovative drugs for the treatment of ALS

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease that affects motor neurons in the spinal cord and cerebral cortex. Patients have a loss of muscle strength and coordination that progressively progresses, preventing the performance of daily activities. Until now there is no treatment that cures ALS, and for this reason in our laboratory we are developing several lines of research that aim to address this challenge by designing and developing new therapies for the treatment of ALS. In collaboration with several laboratories in a project funded by the Community of Madrid (ELA_Madrid S2017/BMD-3813) we have generated and functionally and biochemically characterized cell models (lymphoblasts) based on human samples. In addition, we are developing new compounds that modulate the TDP-43 and NRF2 signaling pathways, respectively, validating them in cellular and mouse models of ALS. In this context, in a project funded by the Ministry of Science, Innovation and Universities (PID2019-105600RB-I00) we are also investigating the modulation of aging and neurodegeneration by small molecule protein kinase inhibitors, in collaboration with Dr. Ana Martínez . On the other hand, one of the main characteristics of ALS is that there are alterations in mRNA metabolism and deregulated axonal transport. For this reason, in a project financed by FUNDELA, we are determining if the TDP-43 aggregates kidnap the RNA-binding proteins, and do not let them carry out their function, in such a way that the mRNAs do not reach the synaptic connections and cannot be translate, causing there to be no connection between the neuron and the muscle, which ultimately leads

to loss of muscle function. So we are looking at RNA granule transport and protein translation in situ in ALS, determining the involvement of STAUFEN and TDP-43 proteins."

**Tauopathies: new biomarkers and targets against neurodegeneration**

The TAU protein is the main component of the intracellular filamentous deposits that define a series of neurodegenerative diseases called tauopathies. In general, tauopathies are characterized by alterations in synaptic plasticity, cell death, proteinopathy, and neuroinflammation. Despite enormous efforts to find a cure for these diseases, there is still no effective treatment. That is why in my laboratory we face this challenge with two different approaches. In our laboratory we have shown in vitro and in vivo that neurons with accumulation of TAU induce the expression of the cannabinoid receptor CB2, which enhances neurodegeneration. Therefore, in a first approach we focus on the study of the pharmacological modulation of the CB2 receptor and its effects on TAU-induced neurodegeneration, with a project funded by the Fundación Tatiana Pérez de Guzmán el Bueno (2021-2024). There are currently no specific biomarkers for tauopathies that allow a prognosis/diagnosis of these diseases. "

**Implication of alterations at the mitochondrial level and mitophagy in Parkinson's disease**

We are interested in elucidating the molecular aspects that underlie Parkinson's Disease (PD). PD is the second most common multisystem neurodegenerative disorder associated with aging. Most cases of PD are sporadic and of unknown aetiology, but mutations in genes such as PARKIN and PINK1 have been associated with familial forms of the disease. Mitochondrial impairment is a well-established pathological hallmark of PD, but whether mitophagy is impaired in this disease remains a subject of intense debate. Therefore, in this research project we are determining the role of mitophagy and the differential alterations in mithocondria between neurons and astrocytes in a-synuclein associated-PD.

## RESEARCH LINES

- Research on targeted therapies to modulate neurodegeneration-associated TDP-43 and TAU proteins.
- Analysis of RNA transport and protein translation in situ: implication of STAUFEN 1/2?.
- Modulation of cannabinoid CB2 receptor as a new therapeutic strategy to protect against TAU-induced neurodegeneration.
- Differential function of mitochondria in neuron-astrocyte-dependent a-synuclein protein in Parkinson's disease.

## RESEARCH ACTIVITY

### Doctoral theses

**Castro Sánchez S.** Neuroinflamación y mitofagia en la enfermedad de Parkinson y posibles estrategias terapéuticas para las tauopatías [dissertation]. Madrid: UAM: (19/04/2022).

**Director:** Lastres Becker I.

### Master theses

**Rodríguez López SM.** Characterization of the neuroprotective effects of CB2 cannabinoid receptor antagonist's treatment in a TAU-dependent Frontotemporal Dementia mouse models[dissertation]. Madrid: UAM: (2022).

**Director:** Lastres Becker I.

### Publications

- Lastres-Becker I, de Lago E, Martínez A, Fernández-Ruiz J. New Statement about NRF2 in Amyotrophic Lateral Sclerosis and Frontotemporal Dementia. Biomolecules. 2022; 12(9): 1200. Article. IF: 5.5; Q1
- Martín-Cámara O, Arribas M, Wells G, Morales-Tenorio M, Martín-Requero A, Porras G, Martínez A, Giorgi G, López-Alvarado P, Lastres-Becker I, Menéndez JC. Multitarget hybrid fasudil derivatives as a new approach to the potential treatment of amyotrophic lateral sclerosis. J Med Chem. 2022; 65(3): 1867-82. Article. IF: 7.3; D1

### Research projects

**Martínez A, Lastres-Becker I.** Diseño y desarrollo de fármacos innovadores para el tratamiento de la esclerosis lateral amiotrófica (B2017/BMD-3813 ELA-Madrid ). CM. 2018-2022.

**Managment centre:** CSIC-UAM

**Martínez A, Lastres-Becker I.** Aging and neurodegeneration targeting by protein kinase small molecules inhibitors (PID2019-105600RB-I00). MICIN. 2020-2023.

**Managment centre:** CSIC

**Lastres-Becker I.** Modulación del receptor cannabinoide CB2 como nueva estrategia terapéutica para proteger contra la neurodegeneración inducida por TAU (2021/00072/001). Fundación Tatiana Pérez de Guzmán el Bueno. 2021-2024.

**Managment centre:** UAM

**Martínez A, Lastres-Becker I.** Luchando contra la enfermedad de Parkinson con inhibidores de SGK1 (PDC2022-133774-I00 ). MICIN. 2022-2024.

**Managment centre:** CSIC

**Martínez A, Lastres-Becker I.** TTBK1 inhibitors as new therapeutic approach for FTD and other related disorders (ADDF-AFTD RA-202205-2023343). ADDF. 2022-2024.

**Managment centre:** CSIC-UAM

### Patents and trademarks

**López-Rodríguez ML, Viso A, Ortega S, Lastres-Becker I, González S, Fernández-Ruiz JJ, Ramos JA,** inventors; Universidad Complutense de Madrid, assignees; Nuevos derivads de ácido araquidónico con afinidad por el transportador de anandamide. P200001920. 2020 nov 5