1 Introduction
2 Executive summary
3 Research areas and groups
4 Associated clinicians

3.1.5 Molecular Mechanisms and Biomarkers of Neurodegenerative Diseases

Publications: 3 | Q1: 2

COMPOSITION

Isabel Lastres Becker.
Profesora Titular. Universidad Autónoma de Madrid

- **Marina Arribas Blázquez.** *Investigadora Postdoctoral. Universidad Autónoma de Madrid*
- **Pablo Beceiredo Macho.** *Investigador Predoctoral. Universidad Autónoma de Madrid*
- **Daniel Flores Téllez.** *Investigador Predoctoral. Universidad Autónoma de Madrid*
- **Ignacio Silva Llanes.** *Investigador Predoctoral. Universidad Autónoma de Madrid*
- **Virginia Solar Fernández.** *Investigadora Postdoctoral. Universidad Autónoma de Madrid*
- **Javier Suárez Fonseca.** *Investigador Predoctoral. Universidad Autónoma de Madrid*

STRATEGIC OBJETIVES

- As our society's population grows older, we face mounting challenges in healthcare and social support systems. The rise in age-related conditions brings increased physical limitations and illnesses, creating significant strain not only on medical resources but also on those affected and their loved ones. Among the most concerning aspects of aging are neurodegenerative conditions, particularly frontotemporal dementia (FTD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS). A critical societal priority is developing effective treatments for these conditions, which requires advances in biomarker identification, pharmaceutical development, and technological innovation. Our laboratory focuses on understanding neurodegeneration at the molecular level. We employ a comprehensive research strategy that bridges fundamental science with clinical applications, utilizing various experimental approaches including cell cultures, mouse models, and analysis of tissue samples from individuals who had FTD, PD and ALS

RESEARCH LINES

- **Targeting pyroptosis in TAU-induced neurodegeneration: mechanisms and modulation.** Frontotemporal dementia (FTD) is an early-onset progressive neurodegenerative disease primarily characterized by neuronal degeneration in the frontal and temporal lobes, followed by hippocampal atrophy. FTD is the second most common cause of dementia in adult patients and the most frequent in patients under 65 years of age. From a molecular perspective, FTD is mainly characterized by aggregates of TAU or TDP-43 proteins. There is also a dysregulation of redox homeostasis and low-grade chronic neuroinflammation. Recent research has revealed a strong connection between neuroinflammation and TAU protein-related neurodegeneration. A key discovery shows that the NLRP3 inflammasome, when activated, can significantly impact TAU pathology and subsequent neuronal death. This process involves pyroptosis - a specific form of cell death that occurs when the NLRP3 inflammasome assembles, leading to GASDERMIN D (GSDMD) cleavage and the subsequent release of inflammatory molecules IL-1β and IL-18. To better understand this relationship, our laboratory investigated pyroptosis's role in TAU-driven neurodegeneration using two distinct experimental approaches.
- **CB2 Cannabinoid Receptor Modulation as a New Therapeutic Strategy to Protect Against TAU-dependent FTD Neurodegeneration.** TAU protein is the main component of intracellular filamentous deposits that define a series of neurodegenerative diseases called tauopathies. Generally, tauopathies are characterized by alterations in synaptic plasticity, cell death, proteinopathy, and neuroinflammation. Despite enormous efforts to find a cure for these diseases, an effective treatment does not yet exist. In our laboratory, we approach this challenge with two different approaches. We have demonstrated both in vitro and in vivo that neurons with TAU accumulation induce the expression of the CB2 cannabinoid receptor, which enhances neurodegeneration. Therefore, in our first approach, we focus on studying the pharmacological modulation of the CB2 receptor and its effects on TAU-induced neurodegeneration. Currently, there are no specific biomarkers for tauopathies that would allow for prognosis/diagnosis of these diseases.
- **Differential Function of Mitochondria in Neuron and Astrocyte α-synuclein-dependent Parkinson's Disease.** Parkinson's Disease (PD) is the most prevalent neurodegenerative disease with motor alterations characterized by the degeneration of dopaminergic (DA) neurons in the substantia nigra and the accumulation of protein aggregates in so-called Lewy bodies, where the most abundant protein is alpha-synuclein (α-SYN). In addition to the neurodegenerative process and protein accumulation, PD is characterized by low-grade chronic inflammation and oxidative stress, which are associated with mitochondrial alterations. PD has been predominantly approached from a neuron-centric point of view, without considering other cell types, such as astrocytes, which are part of the tripartite synapse. However, we cannot rule out that mitochondrial dynamics and function may also be altered in astrocytes and differently from DAergic neurons, contributing to the onset and propagation of the disease. Therefore, in this research project, we aim to address the hypothesis that mitochondrial dynamics and function may be different between neurons and astrocytes in α-SYN-associated PD.
- **Fighting against Parkinson's Disease with SGK1 inhibitors.** Parkinson's disease (PD) is the second most common neurodegenerative disorder characterized by the degeneration of dopaminergic neurons of the substantia nigra and the accumulation of protein aggregates, called Lewy bodies, where the most abundant is alpha-synuclein (a-SYN). In addition to the neurodegeneration and the accumulation of proteins, PD is characterized by chronic low-grade inflammation and mitochondrial alterations that lead to oxidative stress. Currently, PD patients are only treated with dopamine replacement therapy (levodopa), with serious side effects and which also does not stop the degenerative condition. or this reason, in this innovative research project we want to address this challenge by developing new SGK1 kinase inhibitors to alleviate the 3 main hallmarks: neuroinflammation, autophagy/mitophay and oxidative stress. Preliminary results of our research groups support this hypothesis. For this, we will carry

IdiPAZ Instituto de Investigación Hospital Universitario La Paz

1 Introduction
2 Executive summary
3 Research areas and groups
4 Associated clinicians

out a multidisciplinary approach from in vitro assays, evaluate new small molecules capable of selectively inhibit SGK1 and finally, we will evaluate the efficacy of these molecules in preclinical trials in a murine model of PD. The results obtained from this project have an immediate projection as a possible clinical tool for the treatment of patients with PD

- **Exploring the Pathophysiological Links Between Parkinson's Disease, Hypertension, and Acute Lung Inflammation**. This research line examines the interplay between PD, hypertension, and acute lung inflammation (ALI), aiming to elucidate shared pathophysiological mechanisms and their impact on disease progression and patient outcomes. The project focuses on how systemic processes, particularly inflammation, vascular dysfunction, and altered autonomic regulation, may contribute simultaneously to neurodegeneration, cardiovascular dysregulation, and pulmonary injury. By integrating molecular profiling with functional assessments across brain, cardiovascular, and lung systems, the study seeks to clarify whether acute inflammatory events in the lung and chronic blood pressure alterations can exacerbate PD-related pathology or symptom severity. Ultimately, this work aims to identify convergent biological pathways and potential therapeutic strategies capable of addressing neurological, cardiovascular, and respiratory complications in a unified framework.

RESEARCH ACTIVITY

Doctoral Theses

- **Silva Llanes I.** Nuevas estrategias terapéuticas para el tratamiento de la demencia frontotemporal. [dissertation]. Madrid: UAM: 2025(28/09/2025). Director: Lastres Becker I.

Master Theses

- **Suárez Fonseca J.** Analysis of the pyroptosis process in Amyotrophic Lateral Sclerosis: comparative study between a murine model and patient samples[dissertation]. Madrid: UAM: 2025(01/06/202). Director: Lastres Becker I.
- **Mihaila G.** Análisis del efecto de la hipertensión arterial sobre el proceso neurodegenerativo en un modelo murino de la enfermedad de Parkinson[dissertation]. Madrid: UAM: (01/06/2025). Director: Lastres Becker I.

Final Degree Theses

- **León Alonso LT.** Evaluación de PMI y Omaveloxolona como moduladores de NRF2 en un modelo celular de α-SINUCLEÍNA para la enfermedad de Parkinson. [dissertation]. Madrid: UAM: 2025(01/05/2025). Director: Lastres Becker I.

Publications

- **Rojo AI, Buttari B, Cadenas S, Carlos AR, Cuadrado A, Falcao AS, López MG, Georgiev MI, Grochot-Przeczek A, Gumeni S, Jimenez-Villegas J, Horbanczuk JO, Konu O, Lastres-Becker I, Levonen AL, Maksimova V, Michaeloudes C, Mihaylova L, Mickael ME, Milisav I, Miova B, Rada P, Santos M, Seabra MC, Strac DS, Tenreiro S, Trougakos IP, Dinkova-Kostova AT.** Model organisms for investigating the functional involvement of NRF2 in non-communicable diseases. Redox Biol. 2025; 79: 103464. Article. IF: 16.2; D1
- **Silva-Llanes I, Madruga E, Martínez A, Lastres-Becker I.** RIPK1 expression and inhibition in tauopathies: implications for neuroinflammation and neuroprotection. Front Neurosci. 2025; 18: 1530809. Article. IF: 4.0; Q2
- **Silva-Llanes I, Rodríguez-López S, González-Naranjo P, del Sastre E, López MG, Páez JA, Campillo N, Lastres-Becker I.** Targeting CB2 receptor with a novel antagonist reverses cognitive decline, neurodegeneration and pyroptosis in a TAU-dependent frontotemporal dementia mouse model. Brain Behav Immun. 2025; 127: 251-68. Article. IF: 7.5; D1

Research projects

- **Lastres-Becker I.** A-Synuclein-dependent neuron-astrocyte differential function of mitochondria in Parkinson's disease (PID2022-137065OB-I00). MICIN. 2023-2026. Managment centre: UAM
- **Lastres-Becker I.** Receptor cannabinoide CB2: Validación como Biomarcador en Demencias TAU-dependientes. FIBHULP. 2024-2026. Managment centre: FIBHULP
- **Lastres-Becker I.** Targeting SGK1: Bridging Therapies for Parkinson and Cardiovascular Diseases (SGK1-4PDCar) (NED24PI02/2024). CIBER. 2024-2026. Managment centre: CIBERNED

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
- **Martínez Gil A, Gil Ayuso-Gontán C, Madruga Mayordomo E, Garcia-Rubia A, Oliver Pérez E, Briones Alonso AM, Lastres-Becker, inventors; CSIC-UAM.** assignees; Compuestos inhibidores de SGK1 y su uso para el tratamiento de enfermedades neurodegenerativas y/o cardiovasculares. PCT/ES2025/070297. España 2024 jun 7

IdiPAZ Instituto de Investigación Hospital Universitario La Paz