



## SEMINARIO PRESENCIAL

Viernes, 14 de Febrero de 2025  
12:30 h. Instituto Cajal - CSIC

### **Dra. María Ángeles Moro**

Centro Nacional de Investigaciones Cardiovasculares (CNIC)

## **NEUTROPHIL-DRIVEN IMMUNOTHROMBOSIS IN ACUTE STROKE: FROM MICE TO HUMANS**

### **Abstract**

Ischemic stroke has high morbidity and mortality, emphasizing the need for effective therapies. Despite promising preclinical neuroprotective treatments, translation to clinical success remains elusive, an effect in which variations due to circadian rhythms could be involved. Recent evidence shows that infarct volumes and stroke outcomes vary with diurnal oscillations, with worse outcomes during the inactive circadian phase. Neutrophils, which are key players in post-stroke inflammation, have been shown to exhibit circadian fluctuations in phenotype and function that may influence damage and repair in several pathophysiological settings. In the case of stroke, they contribute to pathology via oxidative stress, blood-brain barrier disruption, and immunothrombosis through neutrophil extracellular traps (NETs). However, neutrophils show a remarkable phenotypic heterogeneity, with an impact in the final outcome. This heterogeneity can be regulated by different factors such as microbiota products and circadian influences. In this context, studies reveal that neutrophil circadian dynamics regulate infarct size, with higher NET release and reduced collateral circulation during the inactive phase. In this talk we will discuss how neutrophils and circadian rhythms are critical factors in ischemic damage and suggest targeting these mechanisms for personalized stroke therapies.

### **Affiliation and short bio**

Graduated in Pharmacy (UAH), María Ángeles Moro obtained her PhD in Pharmacology in 1990 (Extraordinary Degree and PhD awards). She has carried out stays at Centre de Neurochimie-Unité 44 (CNRS-INSERM; Strasbourg), Wellcome Research Laboratories (Beckenham, UK; as a Fleming and Marie Curie Fellow) and Mass Gen Hospital/Harvard Medical School (Boston, USA; 2010, as a Real Colegio Complutense Fellow). In 1995 she joined the Dept. Pharmacology and Toxicology, Faculty of Medicine, Complutense University (UCM), where she held consecutive positions of Assistant, Titular (Associate) and Full Professor (Catedrática). In November 2019 she moved to the Spanish Centre for Cardiovascular Research (Centro Nacional de Investigaciones Cardiovasculares; CNIC) as Full Professor, where she set up the Neurovascular Pathophysiology group focused on stroke and vascular-driven cognitive impairment. She is also Co-coordinator of the CNIC "Cardiovascular Risk factors and Brain Health" programme. She also co-leads the Neurovascular Research Unit (UCM) and the Neurovascular Diseases Group of the i+12 Health Research Institute (Health Research Institute of Hospital 12 de Octubre). She participates in several consortia such as the Leducq Foundation Grants "Stroke-Impact" and "Leducq Circadian Network", the latter included in the Consortium International pour la Recherche Circadienne sur l'AVC (CIRCA), and in the Spanish Neurovascular Network (RICORS-ICTUS).

With over 25 years of expertise, she has identified therapeutic targets for stroke, such as TLRs, transcription factors, and glutamate transporters. Her translational work includes developing a TLR4 antagonistic aptamer that successfully completed a Phase Ib/IIa clinical trial, reducing mortality rates. Her research spans vascular neuroplasticity, immunothrombosis, NETosis, and circadian regulation, with applications in cerebrovascular diseases and Alzheimer's.

She has published nearly 200 papers ([MyBibliography](#)), authored books and chapters, and achieved an h-index of 67/81 (WoS/GS). Currently President-Elect of the ISCBFM, she is a member of the Spanish Royal Academy of Pharmacy and serves on editorial boards and scientific advisory panels globally. She has supervised 25 PhDs and is the editor of *Velázquez. Basic and Clinical Pharmacology*.

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## Related publications with the topic

Di G, Vazquez S, Díaz B, Peña-Martínez C, García-Culebras A, Cuartero MI, Moraga A, Pradillo JM, Esposito E, Lo EH, Moro MA\*, Lizasoain I\*. Daytime DNase-I administration protects mice from ischemic stroke without inducing bleeding or tPA-induced hemorrhagic transformation, even with aspirin pretreatment. *Stroke* (in press).

Zeng Q, Oliva VM, Moro MÁ, Scheiermann C. Circadian Effects on Vascular Immunopathologies. *Circ Res.* 2024; 134:791-809.

Tiedt S, Buchan AM, Dichgans M, Lizasoain I, Moro MA, Lo EH. The neurovascular unit and systemic biology in stroke - implications for translation and treatment. *Nat Rev Neurol.* 2022;18:597-612.

Endres M, Moro MA, Nolte CH, Dames C, Buckwalter MS, Meisel A. Immune Pathways in Etiology, Acute Phase, and Chronic Sequelae of Ischemic Stroke. *Circ Res.* 2022;130:1167-1186.

Peña-Martínez C, Durán-Laforet V, García-Culebras A, Cuartero MI, Moro MÁ\*, Lizasoain I\*. Neutrophil Extracellular Trap Targeting Protects Against Ischemic Damage After Fibrin-Rich Thrombotic Stroke Despite Non-Reperfusion. *Front Immunol.* 2022 Feb 16;13:790002.

Adrover JM, Aroca-Crevillén A, Crainiciuc G, Ostos F, Rojas-Vega Y, Rubio-Ponce A, Cilloniz C, Bonzón-Kulichenko E, Calvo E, Rico D, Moro MA, Weber C, Lizasoain I, Torres A, Ruiz-Cabello J, Vázquez J, Hidalgo A. Programmed 'disarming' of the neutrophil proteome reduces the magnitude of inflammation. *Nat Immunol.* 2020;21:135-144.

Peña-Martínez C, Durán-Laforet V, García-Culebras A, Ostos F, Pérez-Ruiz A, Bravo-Ferrer I, Hernández-Jiménez M, Ballenilla F, Díaz-Guzmán J, Pradillo JM, Lizasoain I\*, Moro MA\*. Pharmacological modulation of neutrophil extracellular traps reverses thrombotic stroke t-PA-resistance. *Stroke.* 2019;50:3228-3237.

García-Culebras A, Durán-Laforet V, Peña-Martínez C, Moraga A, Ballesteros I, Cuartero MI, de la Parra J, Palma-Tortosa S, Hidalgo A, Corbí AL, Moro MA\*, Lizasoain I\*. Role of TLR4 (Toll-Like Receptor 4) in N1/N2 Neutrophil Programming After Stroke. *Stroke.* 2019 Aug 27:STROKEAHA119025085.

Adrover JM, Del Fresno C, Crainiciuc G, Cuartero MI, ..., Ballesteros I, Martín-Salamanca S, Aroca-Crevillén A, Chong SZ, Evrard M, Balabanian K, López J, Bidzhekov K, Bachelier F, Abad-Santos F, Muñoz-Calleja C, Zarbock A, Soehnlein O, Weber C, Ng LG, Lopez-Rodriguez C, Sancho D, Moro MA, Ibáñez B, Hidalgo A. A Neutrophil Timer Coordinates Immune Defense and Vascular Protection. *Immunity.* 2019;50:390-402.e10.