



3.1.3 Neuroprotective Strategies in Neurodegenerative Diseases



STRATEGIC OBJETIVES

- Oxidative stress is a key element in the aetiopathogenesis of neurodegenerative diseases and their comorbidities. Our laboratory studies the antioxidant protection mechanisms activated by extracellular signals and how this response could be regulated pharmacologically to provide a therapeutic benefit in these diseases.
- To meet these two objectives, we are studying signalling pathways that regulate antioxidant metabolism and provide a general protective response. An important finding of this group was the observation that the PI3K/AKT/GSK-3 survival pathway regulates the transcription factor NRF2, guardian of cellular redox homeostasis, that provides protection against oxidative, inflammatory and proteotoxic stress. For the past year we have been working on the validation this transcription factor as a new therapeutic target to modify progression of Parkinson's and Alzheimer's disease as well comorbid retinopathy and type II diabetes

RESEARCH LINES

- Role of oxidative stress in neuronal death and neuroinflammation in neurodegenerative diseases.
- Validation of NRF2 as a new therapeutic target in neurodegenerative diseases.
- Use of NRF2 transcriptional signature as a biomarker of prognosis, progression and therapeutic efficacy.
- Identification of NRF2 activating compounds by inhibiting their interaction with β -TrCP.
- Relevance of NRF2 transcriptional signature in altered molecular processes in ALS models.
- Molecular basis of the role of Nrf2 in type 2 diabetes and its complications (diabetic retinopathy and nephropathy).

RESEARCH ACTIVITY

Doctoral Theses

- Carracedo Sanchidrián D. Terapia Cognitiva Basada en Mindfulness frente a Intervención Psicoeducativa en Pacientes con Trastorno Bipolar con Síntomas Subsindrómicos Depresivos: Estudio Controlado Aleatorizado [dissertation]. Madrid: Universidad Autónoma de Madrid: 2024(14/10/2024). Director: Dios Perrino C, Lahera Forteza G

Publications

- Ardanaz CG, de la Cruz A, Minhas PS, Hernández-Martín N, Pozo MA, Valdecantos MP, Valverde AM, Villa-Valverde P, Elizalde

- Horcada M, Puerta E, Ramírez MJ, Ortega JE, Urbiola A, Ederra C, Ariz M, Ortiz-de-Solórzano C, Fernández-Irigoyen J, Santamaría E, Karsenty G, Brüning JC, Solas M. Astrocytic GLUT1 reduction paradoxically improves central and peripheral glucose homeostasis. *Sci Adv.* 2024; 10(42): eadp1115. Article. IF: 12.5; D1
- Caparrós E, García-Martínez I, Zapater P, Madero L, Valverde AM, Gutiérrez A, Francés R. An altered expression of miR-376a-3p and miR-20a-5p in peripheral blood exosomes regulates the autophagy and inflammatory systemic substrates, and relates to the smoking habit and age in Crohn's disease. *Faseb J.* 2024; 38(2): e23418.

Publications: 15 | Q1:14

COMPOSITION

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- Ángela Martínez Valverde. Científico titular CSIC. Instituto de Investigaciones Biomédicas Sols-Morreale
- Patricia Rada Llano. Investigadora Postdoctoral. CIBERNED

- Article. IF: 4.2; Q1
- **Cazalla E, Cuadrado A, García-Yagüe AJ.** Role of the transcription factor NRF2 in maintaining the integrity of the Blood-Brain Barrier. *Fluids Barriers Cns.* 2024; 21(1): 93. Review. IF: 6.2; Q1
 - **Fernández-Ginés R, Encinar JA, Escoll M, Carnicero-Senabre D, Jiménez-Villegas J, García-Yagüe AJ, González-Rodríguez A, García-Martínez I, Valverde AM, Rojo AI, Cuadrado A.** Specific targeting of the NRF2/β-TrCP axis promotes beneficial effects in NASH. *Redox Biol.* 2024; 69: 103027. Article. IF: 11.9; D1
 - **Ferreira V, Folgueira C, Lorenzo AMS, Rodríguez-López A, González-Iglesias E, Zubiaur P, Abad-Santos F, Sabio G, Rada P, Valverde AM.** Estrogens prevent the hypothalamus-periphery crosstalk induced by olanzapine intraperitoneal treatment in female mice: Effects on brown/ beige adipose tissues and liver. *BBA-Mol Basis Dis.* 2024; 1870(5): 167227. Article. IF: 4.2; Q1
 - **Gallardo-Villanueva P, Fernández-Marcelo T, Villamayor L, Valverde AM, Ramos S, Fernández-Millán E, Martín MA.** Synergistic Effect of a Flavonoid-Rich Cocoa-Carob Blend and Metformin in Preserving Pancreatic Beta Cells in Zucker Diabetic Fatty Rats. *Nutrients.* 2024; 16(2): 273. Article. IF: 5; Q1
 - **García-Sáez J, Figueroa-Fuentes M, González-Corrales C, Roncero C, Lazcanoiturburu N, Gutiérrez-Uzquiza A, Vaquero J, González-Sánchez E, Bhutia K, Calero-Pérez S, Maina F, Traba J, Valverde AM, Fabregat I, Herrera B, Sánchez A.** Uncovering a Novel Functional Interaction Between Adult Hepatic Progenitor Cells, Inflammation and EGFR Signaling During Bile Acids-Induced Injury. *Int J Biol Sci.* 2024; 20(7): 2339-55. Article. IF: 10; Q1
 - **González-Sánchez E, Vaquero J, Caballero-Díaz D, Grzelak J, Fusté NP, Bertran E, Amengual J, García-Saez J, Martín-Mur B, Gut M, Esteve-Codina A, Alay A, Coulouarn C, Calero-Pérez S, Valdecantos P, Valverde AM, Sánchez A, Herrera B, Fabregat I.** The hepatocyte epidermal growth factor receptor (EGFR) pathway regulates the cellular interactome within the liver fibrotic niche. *J Pathol.* 2024; 263(4-5): 482-95. Article. IF: 5.2; D1
 - **Jurado-Aguilar J, Barroso E, Bernard M, Zhang MJ, Peyman M, Rada P, Valverde AM, Wahli W,**

- Palomer X, Vázquez-Carrera M.** GDF15 activates AMPK and inhibits gluconeogenesis and fibrosis in the liver by attenuating the TGF-β1/SMAD3 pathway. *Metabolism.* 2024; 152: 155772. Article. IF: 11.9; D1
- **Marañón P, Rey E, Isaza SC, Wu HH, Rada P, Choya-Foces C, Martínez-Ruiz A, Martín MA, Ramos S, García-Monzón C, Cubero EJ, Valverde AM, González-Rodríguez A.** Inhibition of ALK3-mediated signalling pathway protects against acetaminophen-induced liver injury. *Redox Biol.* 2024; 71: 103088. Article. IF: 11.9; D1
- **Morgenstern C, Lastres-Becker I, Demirdogen BC, Costa VM, Daiber A, Foresti R, Motterlini R, Kalyoncu S, Arioz BI, Genc S, Jakubowska M, Trougakos IP, Piechota-Polanczyk A, Mickael M, Santos M, Kensler TW, Cuadrado A, Copple IM.** Biomarkers of NRF2 signalling: Current status and future challenges. *Redox Biol.* 2024; 72: 103134. Article. IF: 4.2; Q1
- **Patibandla C, van Aalten L, Dinkova-Kostova AT, Honda T, Cuadrado A, Fernández-Ginés R, Mcneilly AD, Hayes JD, Cantley J, Sutherland C.** Inhibition of glycogen synthase kinase-3 enhances NRF2 protein stability, nuclear localisation and target gene transcription in pancreatic beta cells. *Redox Biol.* 2024; 71: 103117. Article. IF: 11.9; D1
- **Rada P, Carceller-López E, Hitos AB, Gómez-Santos B, Fernández-Hernández C, Rey E, Pose-Utrilla J, García-Monzón C, González-Rodríguez A, Sabio G, García A, Aspichueta P, Iglesias T, Valverde AM.** Protein kinase D2 modulates hepatic insulin sensitivity in male mice. *Mol Metab.* 2024; 90: 102045. Article. IF: 6.6; Q1
- **Uruno A, Kadoguchi-Igarashi S, Saito R, Koiso S, Saigusa D, Chu CT, Suzuki T, Saito T, Saido TC, Cuadrado A, Yamamoto M.** The NRF2 inducer CDDO-2P-Im provokes a reduction in amyloid β levels in Alzheimer's disease model mice. *J Biochem.* 2024; 176(5): 405-14. Article. Not Indexed
- **Valdecantos MP, Ruiz L, Folgueira C, Rada P, Gomez-Santos B, Solas M, Hitos AB, Field J, Francisco V, Escalona-Garrido C, Zagmutt S, Calderon-Dominguez M, Mera P, García-Martínez I, Maymó-Masip E, Grajales D, Alen R, Mora A, Sainz N, Vides-Urrestarazu I, Villarasa N, Arbones-Mainar JM, Zaragoza C, Moreno-**

- Aliaga MJ, Aspichueta P, Fernández-Veledo S, Vendrell J, Serra D, Herrero L, Schreiber R, Zechner R, Sabio G, Hornigold D, Rondinone CM, Jermutus L, Grimsby J, Valverde AM.** The dual GLP-1/glucagon receptor agonist G49 mimics bariatric surgery effects by inducing metabolic rewiring and inter-organ crosstalk. *Nat Commun.* 2024; 15(1): 10342. Article. IF: 15.7; D1

Research projects

- **Cuadrado Pastor A, Seabra M .** NRF2 as a novel therapeutic target in age-related macular degeneratio (HR22-00569). Fundación La Caixa. 2022-2026. **Managment centre: UAM**
- **Cuadrado Pastor A.** Activation of NRF2 by 6-MISTC, role in AD (2021/0175). Kinjirushi Ltd. Co. 2021-2023. **Managment centre: Fundación UAM**
- **Cuadrado Pastor A.** Bench to bedside transition for pharmacological regulation of NRF2 in noncommunicable diseases (1004040104). European Union - Programa COST. 2021-2025. **Managment centre: "Victor Babes" National Institute of Pathology**
- **Cuadrado Pastor A.** Optimización y validación in vivo de fármacos innovadores para el tratamiento de taupatías (1004020195). CAM. 2023-2026. **Managment centre: UAM**
- **Cuadrado Pastos A, Rojo Sanchís AI.** Desarrollo de nuevos fármacos antiinflamatorios basados en la activación del factor de transcripción NRF2 (PDC2021-121421-100). Agencia Estatal de Investigación. 2021-2023. **Managment centre: UAM**
- **Cuadrado Pastos A, Rojo Sanchís AI.** El factor de transcripción NRF2 en la patofisiología de la enfermedad de Alzheimer (1004020167). MICIN. 2020-2023. **Managment centre: UAM**
- **Cuadrado Pastos A, Rojo Sanchís AI.** Optimización de un nuevo activador del factor de transcripción NRF2 para frenar la progresión de NASH (1004020190). Agencia Estatal de Investigación. 2022-2024. **Managment centre: UAM**
- **Cuadrado Pastos A, Rojo Sanchís AI.** Papel del factor de transcripción NRF2 en protección sináptica en las Taupatías (1004020200). MICIN. 2023-2026. **Managment centre: UAM**
- **Martínez Valverde A.** Extracelular vesicles: new insights into their role in liver-pancreas interactome

3 Research areas and groups

3.1. Neurosciences Area

in T2D. European Association for the Study of Diabetes. 2021-2023. **Managment centre: CIBER**

Cibers and Retics

- **Cuadrado Pastor A.** Centro de Investigación Biomédica en Enfermedades Neurodegenerativas (CIBERned). ISCIII. (31/12/2024). UAM
- **Martínez Valverde A.** Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERdem). ISCIII. (31/12/2024). CSIC
- **Cuadrado Pastor A, Rojo Sanchís AI.** Bench to bedside transition for pharmacological regulation of NRF2 in noncommunicable diseases (BenBedPhar). EU European COST Action. (18/10/2025). Victor Babes Research Institute (Romania)

Patents and Trademarks

- **Cuadrado Pastor A, Innamorato NG,** inventors: CSIC, UAM. Use of sulforaphane as supplementary therapy for early-stage neurodegenerative disease. P201231693; 2012 November 06.
- **León Martínez R, Egea Maíquez J, Buendía Abaitua I, Parada Pérez E, Navarro González de Mesa E,** inventors; Fundación para la Investigación Biomédica del Hospital Universitario de La Princesa, UAM, CSIC, DNS NEUROSCIENCE S.A., assignees. Use of 3-(2-isothiocyanatoethyl)-5-methoxy-1H-indole for the treatment of neurodegenerative diseases. P201300667; 2013 July 17.
- **León Martínez R, Buendía Abaitua I, Navarro González de Mesa E, Michalska P, Gameiro Ros I, López Vivo A, Egea Maíquez J, García López M, García García A,** inventors; Fundación para la Investigación Biomédica del Hospital Universitario de La Princesa, UAM, DNS NEUROSCIENCE S.A., assignees. Compounds derived from 3-alkylamine-1H-indolyl acrylate and its use for the treatment of neurodegenerative diseases. P201400810, PCT/ES2015/000139, CA2964309; 2014 October 15.
- **Cuadrado Pastor A, Fernández-Ginés R, León Martínez R, Encinar JA, Rodríguez Franco MI, García López MG, Rojo Sanchís AI,** inventors. UAM, CSIC, UMH y Fundación de Investigación Biomédica del Hospital Universitario de la Princesa, assignees. Treatment of NRF2-Related diseases. PCT/2022/382025.1.