



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 co-morbid 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

- **Alén Alonso, RM.** Vesículas extracelulares de tamaño pequeño derivadas de hepatocitos en el interactoma intrahepático e hígado-páncreas en el contexto de la enfermedad de hígado graso no alcohólico [dissertation]. Madrid: UAM: 2023(14/07/2023). Director: Martínez Valverde A, García Martínez I.
- **Da Silva Ferreira VM.** La modulación de AMPK y de JNK1 en el hipotálamo por Olanzapina controla el balance energético y la lipogénesis hepática: beneficios adicionales de la inhibición de PTIP1B [dissertation]. Madrid: UAM: 2023(06/10/2023). Director: Martínez Valverde A, Rada Llano PP.
- **Diego Martínez D.** Análisis de la función del factor de transcripción NRF2 en la progresión tumoral [dissertation]. Madrid: UAM: 2023(13/01/2023). Director: Cuadrado Pastor A, Escoll Guerrero MI.

Master Theses

Debasa Mouce M. 6-MSITC (wasabi-isocyanate) as a modulator of NRF2 and protector against tauopathy [dissertation]. Madrid: UAM: 2023(4/5089). Director: García Yagüe AJ, Cuadrado Pastor A

Publications: 12 | Q1:11

COMPOSITION

Ana Isabel Rojo Sanchís.
Profesor Permanente (Profesor Contratado Doctor). Dpto. Bioquímica. Facultad Medicina. Universidad Autónoma de Madrid

- **Daniel Carnicero Senabre.** Investigadora Predoctoral. Universidad Autónoma de Madrid
- **Eduardo Cazalla Ibáñez.** Investigadora Predoctoral. Universidad Autónoma de Madrid

- **Antonio Cuadrado Pastor.** Catedrático. Dpto. Bioquímica. Facultad Medicina. Universidad Autónoma de Madrid
- **María Isabel Escoll Guerrero.** Investigadora Postdoctoral. CIBERNED
- **Raquel Fernández Ginés.** Investigadora Postdoctoral. Universidad Autónoma de Madrid
- **Ángel Juan García Yagüe.** Investigador Postdoctoral. Universidad Autónoma de Madrid
- **José Jiménez Villegas.** Investigador Predoctoral. Universidad Autónoma de Madrid
- **Ángela Martínez Valverde.** Científico titular CSIC. IIB "Alberto Sols"/UAM-CISC
- **Patricia Rada Llano.** Investigadora Postdoctoral. CIBERNED



3.1 Neurosciences Area

Publications

- Bourdakou MM, Fernández-Ginés R, Cuadrado A, Spyrou GM. Drug repurposing on Alzheimer's disease through modulation of NRF2 neighborhood. *Redox Biol.* 2023; 67: 102881. Article. IF: 10.7; Q1
- Bourgonje AR, Kloska D, Grochot-Przeczek A, Feelisch M, Cuadrado A, van Goor H. Personalized redox medicine in inflammatory bowel diseases: an emerging role for HIF-1 α and NRF2 as therapeutic targets. *Redox Biol.* 2023; 60: 102603. Article. IF: 10.7; Q1
- Crisman E, Duarte P, Dauden E, Cuadrado A, Rodríguez-Franco MI, López MG, León R. KEAP1-NRF2 protein-protein interaction inhibitors: Design, pharmacological properties and therapeutic potential. *Med Res Rev.* 2023; 43(1): 237-87. Review. IF: 10.9; D1
- Ferreira V, Folgueira C, García-Altares M, Guillén M, Ruiz-Rosario M, DiNunzio G, García-Martínez I, Alen R, Bookmeyer C, Jones JG, Cigudosa JC, López-Larrubia P, Correig-Blanchar X, Davis RJ, Sabio G, Rada P, Valverde AM. Hypothalamic JNK1-hepatic fatty acid synthase axis mediates a metabolic rewiring that prevents hepatic steatosis in male mice treated with olanzapine via intraperitoneal: Additional effects of PTP1B inhibition. *Redox Biol.* 2023; 63: 102741. Article. IF: 10.7; Q1
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- García-Yagüe AJ, Cuadrado A. Mechanisms of NURR1 regulation: Consequences for its biological activity and involvement in pathology. *Int J Mol Sci.* 2023; 24(15): 12280. Review. IF: 4.9; Q1
- Laiglesia LM, Escoté X, Sáinz N, Félix-Soriano E, Santamaría E, Collantes M, Fernández-Galilea M, Colón-Mesa I, Martínez-Fernández L, Quesada-López T, Quesada-Vázquez S, Rodríguez-Ortigosa C, Arbones-Mainar JM, Valverde AM,

- Martínez JA, Dalli J, Herrero L, Lorente-Cebrián S, Villarroya F, Moreno-Aliaga MJ. Maresin 1 activates brown adipose tissue and promotes browning of white adipose tissue in mice. *Mol Metab.* 2023; 74: 101749. Article. IF: 7.0; D1
- Marsal-Beltrán A, Rodríguez-Castellano A, Astiarraga B, Calvo E, Rada P, Madeira A, Rodríguez-Peña MM, Llauro G, Núñez-Roa C, Gómez-Santos B, Maymó-Masip E, Bosch R, Frutos MD, Moreno-Navarrete JM, Ramos-Molina B, Aspichueta P, Joven J, Fernández-Real JM, Quera JC, Valverde AM, Pardo A, Vendrell J, Ceperuelo-Mallafre V, Fernández-Veledo S. Protective effects of the succinate/SUCNR1 axis on damaged hepatocytes in NAFLD. *Metabolism.* 2023; 145: 155630. Article. IF: 10.8; D1
- Palomino-Antolín A, Decouty-Pérez C, Farré-Alins V, Narros-Fernández P, López-Rodríguez AB, Álvarez-Rubal M, Valencia I, López-Muñoz F, Ramos E, Cuadrado A, Casas AI, Romero A, Egea J. Redox regulation of microglial inflammatory response: Fine control of NLRP3 inflammasome through Nrf2 and NOX4. *Antioxidants.* 2023; 12(9): 1729. Article. IF: 6.0; Q1
- Peyman M, Barroso E, Turcu AL, Estrany F JR, Smith D, Jurado-Aguilar J, Rada P, Morisseau C, Hammock BD, Valverde AM, Palomer X, Galdeano C, Vázquez S, Vázquez-Carrera M. Soluble epoxide hydrolase-targeting PROTAC activates AMPK and inhibits endoplasmic reticulum stress. *Biomed Pharmacother.* 2023; 168: 115667. Article. IF: 6.9; Q1
- Valverde Araceli M, Naqvi Raza A, Naqvi Afsar R. Global profiling of differentiating macrophages identifies novel functional long non-coding mas regulating polarization and innate immune responses. *Biorxiv.* 2023; 536159. Preprint. Not indexed
- Zhang MJ, Barroso E, Ruat M, Peña L, Peyman M, Aguilar-Recarte D, Montori-Grau M, Rada P, Cugat C, Montironi C, Zarei M, Jurado-Aguilar J, Camins A, Balsinde J, Valverde AM, Wahli W, Palomer X, Vázquez-Carrera M. Elafibranor upregulates the EMT-inducer S100A4 via PPAR β / δ . *Biomed Pharmacother.* 2023; 167: 115623. Article. IF: 6.9; Q1

Research projects

- Cuadrado Pastor A, Seabra M. NRF2 as a novel therapeutic target in age-related macular degeneration (HR22-00569). Fundación La Caixa. 2022-2026. *Management centre: UAM*
- Cuadrado Pastor A. Activation of NRF2 by 6-MISTC, role in AD (2021/0175). KINJIRUSHI Ltd. Co. 2021-2023. *Management centre: Fundación UAM*
- Cuadrado Pastor A. Bench to bedside transition for pharmacological regulation of NRF2 in noncommunicable diseases (1004040104). Europeo. Programa COST. 2021-2025. *Management 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. *Management centre: UAM*
- Cuadrado Pastros A, Rojo Sanchis AI. Desarrollo de nuevos fármacos antiinflamatorios basados en la activación del factor de transcripción NRF2 (PDC2021-121421-I00). Agencia Estatal de Investigación. 2021-2023. *Management centre: UAM*
- Cuadrado Pastros A, Rojo Sanchis AI. El factor de transcripción NRF2 en la patofisiología de la enfermedad de Alzheimer (1004020167). MICIN. 2020-2023. *Management centre: UAM*
- Cuadrado Pastros A, Rojo Sanchis AI. Optimización de un nuevo activador del factor de transcripción NRF2 para frenar la progresión de NASH (1004020190). Agencia Estatal de Investigación. 2022-2024. *Management centre: UAM*
- Cuadrado Pastros A, Rojo Sanchis AI. Papel del factor de transcripción NRF2 en protección sináptica en las Taupatías (1004020200). MICIN. 2023-2026. *Management centre: UAM*
- Martínez Valverde A. Extracellular vesicles: new insights into their role in liver-pancreas interaction in T2D. European Association for the Study of Diabetes. 2021-2023. *Management centre: CIBER*

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- Martínez Valverde A. Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERdem). ISCIII. (31/12/2023). CSIC
- Cuadrado Pastor A, Rojo Sanchis AI. Bench to bedside transition for pharmacological regulation of NRF2 in noncommunicable diseases (BenBed-Phar). EU. (18/10/2025). Victor Babes Research Institute (Romania)

Patents and trademarks

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- 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.
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