SUMMARY OF RESEARCH GROUP

Our research group has a longstanding interest in the molecular and cellular mechanisms of synaptic plasticity, and their contribution to cognitive processes such as learning and memory. Using electrophysiological, imaging and molecular techniques, we have made important contributions to understand how the membrane trafficking machinery of the neuron controls synaptic function by shuttling neurotransmitter receptors in and out of the synaptic membrane. For example, and most recently, we have identified different kinesin motors and adaptor proteins that steer endosomal compartments to drive synaptic insertion of neurotransmitter receptors during long-term potentiation (Gutiérrez et al, J Cell Biol 2021) or synaptic removal and lysosomal degradation during long-term depression (Brachet et al, Cell Rep 2021). Additionally, we have also made important advances to understand how these processes are integrated within intracellular signaling pathways, both at the synaptic level (Draffin et al, EMBOJ 2021) and by controlling astrocyte-neuron communication (Navarrete et al, Nat Comm 2019). We have also addressed how genetic manipulations of these pathways (Sánchez-Castillo et al, Sci Adv 2022) or exogenous alterations by environmental contaminants (López-Merino et al, Cell Biol Toxicol 2022) lead to cognitive dysfunctions. Indeed, we have found that some signaling cascades controlling the trafficking machinery of neurotransmitter receptors are defective in Alzheimer's disease (Knafo et al, Nat Neurosci 2016) and some forms of autism (Knafo and Esteban, Trends Neurosci 2017). In fact, we aim at exploiting this molecular information, using mouse models and behavioral assays, to develop potential therapeutic avenues for cognitive enhancement (Knafo et al, PLoS Biol 2012). Overall, we are trying to understand how molecular and cellular mechanisms operating at the synapse contribute to brain function in health and disease.

These studies have received continuous funding from national and international agencies, from the NIH, NARSAD and the Alzheimer's Association (when the research group was located in the USA), and from the Spanish Ministry for Science, the Carlos III Health Institute, Ramón Areces Foundation and the European Union since our move to Spain.

Finally, our research group has an established record of training young investigators. Eleven PhD students have defended their thesis in the group. Of these, six are currently carrying out postdoctoral research, four are working at private biomedical research institutions, and one of them has a university teaching position. In addition, our research group has trained eleven postdoctoral investigators. Six of them currently direct their own laboratories as principal investigators in different institutions; two of them hold Research Associate positions at academic institutions, and two of them are Senior Scientists at private pharmaceutical companies.

SELECTED PUBLICATIONS

1. Sánchez-Castillo C, Cuartero MI, Fernández-Rodrigo A, Briz V, López-García S, Jiménez-Sánchez R, López JA, Graupera M, Esteban JA. Functional specialization of different PI3K isoforms for the control of neuronal architecture, synaptic plasticity and cognition. **Science Adv** 8:eabq8109, 2022. https://www.science.org/doi/10.1126/sciadv.abq8109
2. Brachet A, Lario A, Fernández-Rodrigo A, Heisler FF, Gutiérrez Y, Lobo C, Kneussel M, Esteban JA. A Kinesin 1-protrudin complex mediates AMPA receptor synaptic removal during long term depression. **Cell Rep** 36, 109499, 2021. https://www.cell.com/cell-reports/fulltext/S2211-1247(21)00927-X
3. Gutiérrez Y, López-García S, Lario A, Gutiérrez-Eisman S, Delevoye C, Esteban JA. KIF13A drives AMPA receptor synaptic delivery for long-term potentiation via endosomal remodeling. **J Cell Biol** 220:e202003183, 2021.

https://rupress.org/jcb/article/220/6/e202003183/212112/KIF13A-drives-AMPA-receptor-synaptic-delivery-for
4. Draffin JE, Sánchez-Castillo C, Fernández-Rodrigo A, Sánchez-Sáez X, Ávila J, Wagner FF, Esteban JA. GSK3α, not GSK3β, drives hippocampal NMDAR-dependent LTD via tau-mediated spine anchoring. **EMBOJ** 40:e105513, 2021. https://www.embopress.org/doi/full/10.15252/embj.2020105513
5. Navarrete M, Cuartero MI, Palenzuela R, Draffin JE, Konomi A, Serra I, Colié S, Castaño-Castaño S, Hasan MT, Nebreda AR, Esteban JA. Astrocytic p38α MAPK drives NMDA receptor-dependent long-term depression and modulates long-term memory. **Nat Commun** 10:2968, 2019. https://www.nature.com/articles/s41467-019-10830-9
6. Knafo S, Sánchez-Puelles C, Palomer E, Delgado I, Draffin JE, Mingo J, Wahle T, Kaleka K, Mou L, Pereda-Peréz I, Klosi E, Faber EB, Chapman HM, Lozano-Montes L, Ortega-Molina A, Ordóñez-Gutiérrez L, Wandosell F, Viña J, Dotti CG, Hall RA, Pulido R, Gerges NZ, Chan AM, Spaller MR, Serrano M, Venero C, Esteban JA. PTEN recruitment controls synaptic and cognitive function in Alzheimer's models. **Nat Neurosci** 19, 443-453, 2016. https://www.nature.com/articles/nn.4225
7. Brachet A, Norwood S, Brouwers JF, Palomer E, Helms JB, Dotti CG, Esteban JA. LTP-triggered cholesterol redistribution activates Cdc42 and drives AMPA receptor synaptic delivery. **J Cell Biol** 208, 791-806, 2015. https://rupress.org/jcb/article/208/6/791/38107/LTP-triggered-cholesterol-redistribution-activates
8. Benoist M, Palenzuela R, Rozas C, Rojas P, Tortosa E, Morales B, González-Billault C, Ávila J, Esteban JA. MAP1B-dependent Rac activation is required for AMPA receptor endocytosis during long-term depression. **EMBOJ** 32, 2287-2299, 2013. https://www.embopress.org/doi/full/10.1038/emboj.2013.166
9. Jurado S, Benoist M, Lario A, Knafo S, Petrok CN and Esteban JA. PTEN is recruited to the postsynaptic terminal for NMDA receptor-dependent long-term depression. **EMBOJ** 29:2827-2840, 2010. https://www.embopress.org/doi/full/10.1038/emboj.2010.160
10. Arendt KL, Royo M, Férnandez-Monreal M, Knafo S, Petrok CN, Martens JR and Esteban JA. PIP3 controls synaptic function by maintaining AMPA receptor clustering at the postsynaptic membrane. **Nat Neurosci** 13:36-44, 2010. https://www.nature.com/articles/nn.2462

RESEARCH PROJECTS (selection from last 10 years)

2024-2027	Ministerio de Ciencia, Innovación y Universidades, PID2023-149056OB-I00. "Metabolic regulation subserving synaptic plasticity".
2022-2024	Ministerio de Ciencia e Innovación/NextGenerationEU, PDC2021-120815-I00. "GSK3alpha, an unsuspected therapeutic target for Alzheimers disease".
2021-2024	Ministerio de Ciencia e Innovación, PID2020-117651RB. "Interplay between synaptic and metabolic plasticity. Relevance for mental disease".
2018-2020	Ministerio de Ciencia, Innovación y Universidades, SAF2017-86983-R. "Subcellular and molecular regulation of PI3K/PTEN signaling during synaptic plasticity. Strategies for Alzheimer's disease".
2017-2018	Ministerio de Economía y Competitividad, SAF2015-72988-EXP. "Optogenetic activation of neuronal circuits and synaptic communication using robotic micropositioning".
2016-2018	European Union HDHL Joint Action, "MiTyrAge: Targeting the mitochondria-tyr kinase axis to prevent age-associated neuronal decline".
2015-2017	Ministerio de Economía y Competitividad, SAF2014-57233-R. "PI3 Kinases. A link between synaptic plasticity, cognitive function and ageing".
2012-2014	Ministerio de Ciencia e Innovación, SAF2011-24730. "Molecular mechanisms of synaptic plasticity, cognitive function and age-dependent cognitive decline, controlled by the PI3K-PTEN pathway".
2011-2015	Ministerio de Ciencia e Innovación, CSD2010-00045. "BrainAge: Brain dysfunction during aging. Relevance for Alzheimer's disease".