

## **Research interests**

Combined, psychiatric disorders are the leading cause of disability worldwide. Perhaps because of their inherent social stigma, mental illnesses represent a particularly sensitive matter in modern societies. Our ongoing research aims to find the underlying molecular mechanisms involved in multiple human brain diseases. For example, all marketed drugs with proved antipsychotic activity are known to act at dopamine (DA) and/or serotonin (5-HT) receptors, all belonging to the G protein-coupled receptor (GPCR) family. Most of the current knowledge on GPCRs pharmacology assumes that these transmembrane proteins act as single molecules. We now know that GPCRs mainly work as heteromeric structures where two or more different GPCRs combine in the synaptic membrane to provide a physiological response. And yet the mechanisms underlying GPCR heteromerization and their impact on receptor pharmacology are poorly understood. Beyond receptors, the mechanisms ruling neurotransmitter release are also among our interests. Best known as SNARE complex, the neurosecretion machinery has an important role in psychiatric and neurological conditions. Misfolding and dysfunction of the proteins governing vesicle trafficking lead to cognitive and locomotor symptoms displayed by psychiatric patients. Our long-term goal is to find pharmacological tools that could ameliorate the suffering of people with severe mental illnesses

Our current research lines are:

- Molecular mechanisms of GPCR heteromerization and their role in schizophrenia.
- Presynaptic deficits in severe mental illnesses: focus on the SNARE complex
- Molecular underpinnings of brain connectivity associated with age-related cognitive decline and dementia.
- *In vivo* and *in silico* models of neuropathologic propagation in Alzheimer's disease.

## **Funding received**

1. RYC-2016-19282, Presynaptic mechanisms in psychiatric disorders: potential targets for novel drug development. 'Ramón y Cajal' Program, MINECO. June 2018 – June 2023.
2. MSFHR-5401, Screening and development of molecules targeting presynaptic SNARE protein-protein interactions as novel pharmacological strategy in schizophrenia and other mental illnesses. Research Trainee Competition for Post-Doctoral Fellowship Awards, Michael Smith Foundation for Health Research. September 2013 – December 2015.

## **Recent publications:**

**Ramos-Miguel A, Jones AA, Sawada K, Barr AM, Bayer TA, Falkai P, Leurgans SE, Schneider JA, Bennett DA, Honer WG (2018)** Frontotemporal dysregulation of the SNARE protein interactome is associated with faster cognitive decline in old age. *Neurobiol Dis* 114: 31–44. Impact factor (IF): 5.020

Beasley CL, Honer WG, **Ramos-Miguel A**, Vila-Rodriguez F, Barr AM (2018) Prefrontal fatty acid composition in schizophrenia and bipolar disorder: Association with reelin expression. *Schizophr Res* (in press) doi: 10.1016/j.schres.2017.05.033. IF: 4.453

White CC, Yang HS, Yu L, Chibnik LB, Dawe RJ, Yang J, Klein H-U, Felsky D, **Ramos-Miguel A**, Arfanakis K, Honer WG, Sperling RA, Schneider JA, Bennett DA, De Jager PL (2017) Identification of genes influencing the dissociation of cognitive performance and neuropathologic burden: Multistep analysis of genetic, epigenetic, and transcriptional data. *PLoS Med* 14: e1002287. IF: 13.585

**Ramos-Miguel A**, García-Sevilla JA, Barr AM, Bayer TA, Falkai P, Leurgans SE, Schneider JA, Bennett DA, Honer WG, García-Fuster MJ (2017) Decreased cortical FADD protein is associated with clinical dementia and cognitive decline in an elderly community sample. *Mol Neurodegener* 12: 26. IF: 6.560

**Ramos-Miguel A**, Sawada K, Jones AA, Thornton AE, Barr AM, Leurgans SE, Schneider JA, Bennett DA, Honer WG (2017) Presynaptic proteins complexin-I and complexin-II differentially influence cognitive function in early and late stages of Alzheimer's disease. *Acta Neuropathol* 133: 395-407. IF: 14.360

Yin J, Barr AM, **Ramos-Miguel A**, Procyshyn RM (2016) An evaluation of iatrogenic dopamine supersensitivity psychosis: A comprehensive review. *Curr Neuropharmacology* 15: 174-183. IF: 3.753

Wang CK, Aleksic A, Xu MS, Procyshyn RM, Ross CJ, Vila-Rodríguez F, **Ramos-Miguel A**, Honer WG, Barr AM (2016) A tetra-primer amplification refractory system technique for the cost-effective and novel genotyping of eight single-nucleotide polymorphisms of the catechol-O-methyltransferase gene. *Genet Test Mol Biomarkers* 20: 465-470. IF: 1.297

**Ramos-Miguel A**, Hercher C, Beasley CL, Barr AM, Bayer TA, Falkai P, Leurgans SE, Schneider JA, Bennett DA, Honer WG (2015) Loss of Munc18-1 long splice variant in GABAergic terminals is associated with cognitive decline and increased risk of dementia in a community sample. *Mol Neurodegener* 10: 65. IF: 6.560

**Ramos-Miguel A**, Barr AM, Honer WG (2015) Spines, synapses and schizophrenia. *Biol Psychiatry* 78: 741-743. IF: 11.212

**Ramos-Miguel A**, Beasley CL, Dwork AJ, Mann JJ, Rosoklja G, Barr AM, Honer WG (2015) Increased SNARE protein-protein interactions in orbitofrontal and anterior cingulate cortices in schizophrenia. *Biol Psychiatry* 78: 361-373. IF: 11.212

**Ramos-Miguel A**, Honer WG, Boyda HN, Sawada K, Beasley CL, Procyshyn RM, Barr AM (2015) Exercise prevents downregulation of hippocampal presynaptic proteins following olanzapine-elicited metabolic dysregulation in rats: Distinct roles of inhibitory and excitatory terminals. *Neuroscience* 301: 298-311. IF: 3.357

Boyda HN, **Ramos-Miguel A**, Procyshyn RM, Töpfer E, Lant N, Choy HH, Wong R, Li L, Pang CC, Honer WG, Barr AM (2014) Routine exercise ameliorates the metabolic side-effects of treatment with the atypical antipsychotic drug olanzapine in rats. *Int J Neuropsychopharmacol* 17: 77-90. IF: 4.009

Velázquez-Sánchez C, Ferragud A, **Ramos-Miguel A**, García-Sevilla JA, Canales JJ (2013) Substituting a long-acting dopamine uptake inhibitor for cocaine prevents relapse to cocaine seeking. *Addict Biol* 18: 633-643. IF: 5.929

**Ramos-Miguel A**, Meana JJ, García-Sevilla JA (2013) Cyclin-dependent kinase-5 and p35/p25 activators in schizophrenia and major depression prefrontal cortex: basal contents and effects of psychotropic medications. *Int J Neuropsychopharmacol* 16: 683-689. IF: 4.009

**Ramos-Miguel A**, García-Sevilla JA (2012) Crosstalk between cdk5 and MEK-ERK signalling upon opioid receptor stimulation leads to upregulation of activator p25 and MEK1 inhibition in rat brain. *Neuroscience* 215: 17-30. IF: 3.357

Gil-Pisa I, Munarriz-Cuezva E, **Ramos-Miguel A**, Urigüen L, Meana JJ, García-Sevilla JA (2012) Regulation of munc18-1 and syntaxin-1A interactive partners in schizophrenia prefrontal cortex: downregulation of munc18-1a isoform and 75 kDa SNARE complex after antipsychotic treatment. *Int J Neuropsychopharmacol* 15: 573-588. IF: 4.009

**Ramos-Miguel A**, Álvaro-Bartolomé M, García-Fuster MJ, García-Sevilla JA (2012) Role of multifunctional FADD (Fas-Associated Death Domain) adaptor in drug addiction, in the book "Addictions - From Pathophysiology to Treatment" edited by David Belin, ISBN 978-953-51-0783-5, InTech, October 10, 2012. (Book Chapter)

**Ramos-Miguel A**, Miralles A, García-Sevilla JA (2011) Correlation of rat cortical FADD (Fas-associated death domain) protein phosphorylation with the severity of spontaneous morphine abstinence syndrome: Role of  $\alpha_2$ -adrenoceptors and extracellular signal-regulated kinases. *J Psychopharmacol* 25: 1691-1702. IF: 3.898

García-Sevilla JA, Alvaro-Bartolomé M, Díez-Alarcia R, **Ramos-Miguel A**, Puigdemont D, Pérez V, Alvarez E, Meana JJ (2010) Reduced platelet G protein-coupled receptor kinase 2 in major depressive disorder: antidepressant treatment-induced upregulation of GRK2 protein discriminates between responder and non-responder patients. *Eur Neuropsychopharmacol* 20: 721-730. IF: 4.409

**Ramos-Miguel A**, Esteban S, García-Sevilla JA (2010) The time course of unconditioned morphine-induced psychomotor sensitization mirrors the phosphorylation of FADD and MEK/ERK in rat striatum: Role of PEA-15 as a FADD-ERK binding partner in striatal plasticity. *Eur Neuropsychopharmacol* 20: 49-64. IF: 4.409