Who we are

The Instituto Cajal is a neuroscience research center of the Spanish Research Council (CSIC). The Instituto Cajal is the oldest neurobiology research center in Spain. Along its more than 100 years of existence, renowned scientists and professionals have spread worldwide and contributed to the remarkable advancement of neurobiology. Today, the institute is prepared to confront the future challenges and to maintain the leading role in neurobiological research in Spain, always keeping in mind that the final destination of knowledge is the wellbeing of the society.

Contact Us

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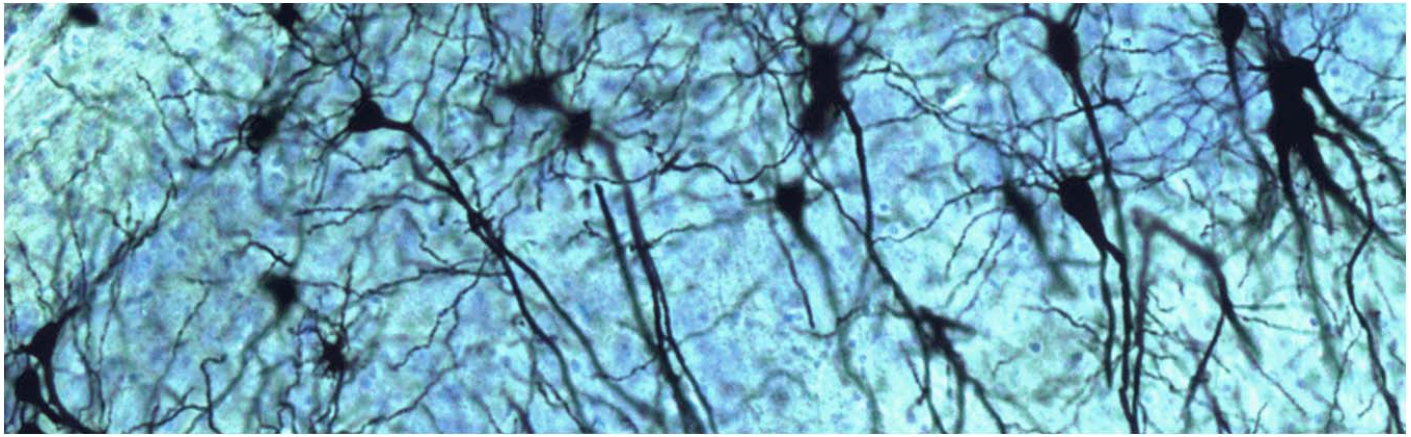
2015 CajalXmas Meeting

December 21st, 2015



INSTITUTO CAJAL CSIC

With the collaboration of PanLab-Harvard Apparatus, Leica Microsystems and Thermo Fisher Scientifc.

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INSTITUTO CAJAL CSIC

The 2015 CajalXmas

A Christmas meeting at the Cajal

The CajalXmas is a scientific and social meeting to bring together young and independent researchers from all over Spain and abroad to discuss and present their work in an informal environment during our traditional Christmas toast.

This one-day meeting is conceived to attract neuroscientists with potential interest in joining our institute or independent researchers with interest in scientific collaboration and discussion

Our focus

This year we bring the focus to some of the Instituto Cajal strategic lines, including

- Developmental neurobiology
- Traslational neuroscience
- Neuroimaging studies

Scientific Program

9.30-9.40 Welcome and presentation

09.40-10.10 Evgeny Shlevkov. Axonal Trafficking of Mitochondrial and Neurodegenerative Disorders

10.10-10.40 Jose A. Rodriguez Navarro. Autophagy, lipids and neurodegeneration

10.40-11.10 Elena Tortosa. Microtubule organization in the process of neuronal polarization

11.10-11.40 María José Galazo. Development of neuronal diversity in the cerebral cortex.

11.40-12.10 Coffee break

12.10-12.40 Christa Rhiner. New neurons for injured brain? The power of damage-responsive adult neural stem cells in *Drosophila*

12.40-13.10 Marcía Aranha. Identification of apterous brain neurons as circuit elements controlling female receptivity behavior

13.10-13.40 Silvia Corrochano. Muscle-specific mutation modifies systemic Hungtinton´s disease in mice

13.40-14.10 Manuel Valero. Determinants of different deep and superficial CA1 pyramidal cell dynamics during sharp-wave ripples

14.10-14.15 Concluding remarks

14.15-16.00 Christmas toast

16.00-18.00 Visits to laboratories and informal discussion

Evgeny Shlevkov

Boston Children´s Hospital Harvard Medical School. Boston. USA

Axonal Trafficking of Mitochondrial and Neurodegenerative Disorders

Neurons depend on mitochondrial trafficking for their survival. The urgency of proper mitochondrial transport in neurons arises from their exceptional morphology. Whereas most cells are measured in tens of microns, neurons extend their axons for millimeters, centimeters and, in the case of human peripheral nerves, up to a meter. Thus, the neuron poses an extreme case for mitochondrial distribution. Failures in mitochondrial trafficking are linked to several neurodegenerative disorders, and restoring mitochondrial trafficking is a rational therapeutic strategy. However, limited understanding of the pathways that mis-regulate mitochondrial transport in disease states, added to the limited number of known regulators of mitochondrial transport hamper the development of therapies. I will present a study of the functional interactions of Miro\RhoT1,2 a mitochondrial RhoGTPase and a key component of the motor/adaptor complex, with the PINK1/Parkin signaling pathway, a pathway implicated in Parkinson's disease. Our study shows unexpected ability of PINK1-phosphorylations of Miro to stimulate or suppress Parkin recruitment to mitochondria, depending on the site of Miro that is modified. In the second part of my talk I will present a high-content screening assay for regulators of mitochondrial trafficking in primary neurons. In summary, my talk will illustrate how we use a combination of classical bottom-up approaches with novel tools to learn the rules of mitochondrial traffic and look for therapeutics.

Shlevkov, **E** and Schwarz, TL. *For Parkin, it's not all or nothing*. (2014) The EMBO Journal 02; 33(4).

Shlevkov, E and Morata, G. *A dp53/JNK-dependant feedback amplification loop is essential for the apoptotic response to stress in Drosophila*. Cell Death and Differentiation (2011); 19(3):451-60.

Morata, G, **Shlevkov, E and** Pérez-Garijo, A: *Mitogenic signaling from apoptotic cells in Drosophila*. Development Growth and Differentiation (2011); 53(2):168-76.

Jose A. Rodriguez Navarro

Instituto Ramón y Cajal de Investigaciones Sanitarias. Madrid, Spain.

Autophagy, lipids and neurodegeneration

Autophagy dysfunction has been linked to a growing number of neurodegenerative disorders. Macroautophagy degrades organelles and proteins even after the formation of aggregates, whereas chaperone-mediated autophagy (CMA) is a type of autophagy selective for certain cytosolic proteins. We have conditionally knocked-out the lysosomal CMA receptor, Lysosomal Associated Membrane Protein 2A, in mouse dopaminergic neurons (Tyroxyne Hydroxylase-Cre) or in neurons in the cortex and the hippocampus (Calmoduline Kinase IIa-Cre). Phenotypic analysis of both mouse models revealed behavioral abnormalities and biochemical and histological signs of neurodegeneration. We have compared using iTRAQ proteomics the aggregates isolated from these mouse models and those isolated from the brain of mice defective for macroautophagy and using lipidomics we have studied the effect of lipids on CMA activity in vivo.

Tanase M, Zolla V, Clement CC, Borghi F, Urbanska AM, **Rodriguez-Navarro JA**, Roda B, Zattoni A, Reschiglian P, Cuervo AM, Santambrogio L. Hydrodynamic size-based separation and characterization of protein aggregates from total cell lysates. Nature Protocols. 2015. 10:134-148.

Yang DS, Stavrides P, Saito M[3], Kumar A, **Rodriguez-Navarro JA**, Pawlik M, Huo C, Walkley SU, Saito M, Cuervo AM, Nixon RA. Defective Macroautophagic Turnover of Brain Lipids in the TgCRND8 Alzheimer's Mouse Model: Prevention by Correcting Lysosomal Proteolytic Deficits. Brain. 2014. 137:3300-18.

Rodriguez-Navarro JA, Kaushik S, Koga H, Dall'Armi C, Shui G, Wenk MR, Di Paolo G, Cuervo AM. Inhibitory effect of dietary lipids on chaperone-mediated autophagy. Proc Natl Acad Sci U S A. 2012. 109. E705-14.

Elena Tortosa

Cell Biology Department, Faculty of Science Utrech Unversity.

Microtubule organization in the process of neuronal polarization

Neurons are cells with a very complex morphology that develop two different cytoplasmic extensions, one single axon and several dendrites. The maintenance of their polarity is essential for the correct function of neurons, and alterations in this polarity are associated with several human developmental and neurodegenerative diseases. Microtubule (MT) cytoskeleton is essential for the acquisition and maintenance of neuronal polarity. MTs are asymmetric structures, with two different ends: a very dynamic MT plus end and a more stable MT minus end. In cultured mammalian neurons, axon and dendrites have distinct MT properties and organization. However, how this organization is acquired is still little understood. We have systematically analysed by live-cell imaging MT plus-end orientations in polarize and unpolarised neurons. Interestingly, at early stages of neuronal development in non-polarized cells, newly formed neurites already contain MTs of opposite polarity, suggesting that the establishment of uniform plus-end out MTs occurs during axon formation. Proteins known as microtubule-associated proteins (MAPs) provide a mechanism to spatiotemporal control the architecture of the neuronal MT cytoskeleton during the different steps of development. Recent evidence suggests that MAPs also guide motor protein transport, interact with the actin cytoskeleton and act in various neuronal signalling networks. We have deepened in the role of some of these MAPs in the neuron and their importance in the process of neuronal polarization.

Yau KW, Schätzle P, **Tortosa E**, Pagès S, Holtmaat A, Kapitein L, Hoogenraad CC. Dendrites in vitro and in vivo contain microtubules of opposite polarity and axon formation correlates with uniform plus-end out microtubule orientation. J Neurosci. Under revision.

Sayas CL, **Tortosa E**, Bollati F, Ramírez-Ríos S, Arnal I, Avila J (2015). Tau regulates the localization and function of Endbinding proteins 1 and 3 in developing neuronal cells. J Neurochem. Jun;133(5):653-67.

Tortosa E, Galjart N, Avila J, Sayas L. (2013). MAP1B regulates microtubule dynamics by sequestering EB1/3 in the cytosol of developing neuronal cells. EMBO J. 32(9):1293-306.

María José Galazo

Harvard Department of Stem Cell and Regenerative Biology (HSCRB). Dept. Brain and Cognitive Sciences, MIT. Cambridge (USA)

Development of neuronal diversity in the cerebral cortex

The cerebral cortex is responsible for execution of higher-order brain functions. The remarkable computational power required for these tasks emerge from its sophisticated circuitry, which is built from a great diversity of neurons, generated and connected during development. The mechanisms that govern the emergence of this diversity of neuron types are only now beginning to be understood. Recently, progress has been made toward understanding controls over fate choice between subcerebral vs. corticocortical projection neuron subtypes. Here, we studied controls over development of Corticothalamic projection neurons (CThPN), which is the most abundant cortical output neuron subtype and critical for cortical function. We purified CThPN at important developmental stages, and compare their gene expression with other neocortical projection neuron subtypes. We identified a set of genes that both define CThPN, and control their differentiation, diversity, and function. Identifying controls regulating neuron subtype identity will contribute to understanding of cortical organization, diversity, function, and potentially contribute toward reprogramming-based strategies for neuronal directed differentiation for therapeutics.

Galazo MJ, Emsley G, Macklis JD. Identification of molecular controls over corticothalamic projection neuron development. In revision, *Neuron*.

Litterman NK, Rodriguez--Muela N, Mull JL, Kim KJ, **Galazo MJ**, Makhortova NR, White A, Schein P, Lynes MM, Norabuena E, Chung WK, Davidow LS, Macklis JD, Rubin LL. Inhibition of SMN Protein Degradation Improves Survival of SMA and ALS Patient Motor Neurons. In revision, *Nature Medicine*.

Greig LC, Woodworth MB, **Galazo MJ**, Padmanaban H, Macklis JD. (2013) *Nature Rev Neurosci.* 14 (11): 755-69.

Christa Rhiner

Institute of Cell Biology. University of Bern. Switzerland.

New neurons for injured brain? The power of damage-responsive adult neural stem cells in *Drosophila.*

The majority of adult tissues harbor stem cells, which proliferate and produce differentiated daughter cells to compensate for tissue loss or damage. Certain tissues contain quiescent adult stem cells, which are activated upon injury to replace damaged cells. We could recently show that the adult brain of *Drosophila* contains damage-responsive adult neural stem cells, which trigger efficient regenerative neurogenesis upon traumatic brain injury. Based on our initial study, we identified that nuclear translocation of Deadpan, a neuroblast transcription factor, and upregulation of *Drosophila* Myc (dMyc) are important events to induce the division of quiescent neural stem cells. In our current work, we aim to unravel the genetic programs, which are activated upon brain injury and able to induce a robust neurogenic response. We use a combination of whole genome expression profiling (microarrays/RNAseq), functional RNAi assays and expression studies to identify novel regulators of neural stem cell activation and adult neurogenesis.

Moreno E, Fernandez-Marrero Y, Meyer P and **Rhiner C** (2015). Brain regeneration in *Drosophila* involves comparison of neuronal fitness. *Current Biology*, 25:1-9

Fernàndez-Hernàndez I**, Rhiner C** and Moreno E (2013). Adult Neurogenesis in *Drosophila*. *Cell Reports*, 3: 1857-65

Merino M, **Rhiner C**, Portela M and Moreno E (2013). "Fitness fingerprints" mediate physiological culling of unwanted neurons in *Drosophila. Current Biology*, 23:1300-9.

Márcia Aranha

Champalimaud Center for the Unknown. Lisbon, Portugal.

Identification of apterous brain neurons as circuit elements controlling female receptivity behavior

The mating behavior of the fruit fly *Drosophila melanogaster* is regulated by different internal and external factors. We aim to understand how sensory information coming from a courting male is processed by the female brain and how her mating status can affect her decision of mating or not. We use a combination of molecular, genetic, anatomical and behavioral approaches to study the female receptivity circuits. We have recently identified a new set of neurons in the female brain that are necessary for the female receptivity behavior. Manipulation of these neurons results in a reduction of the copulation success and in a unique behavioral response.

Aranha MM, Solá S, Santos DM, Low WC, Steer CJ, Rodrigues CMP. miR-34a regulates mouse neural stem cell differentiation. *PLoS One* 2011; 6 (8): e21396.

Solá S, Xavier JM, Santos DM, **Aranha MM**, Morgado AL, Jepsen K, Rodrigues CMP. p53 interaction with JMJD3 results in its nuclear distribution during mouse neural stem cell differentiation. *PLoS One* 2011; 6 (3): e18421.

Aranha MM, Santos DM, Xavier JM, Low WC, Steer CJ, Solá S, Rodrigues CMP. Apoptosis-associated microRNAs are modulated in mouse, rat and human neural differentiation. *BMC Genomics* 2010, 11:514.

Silvia Corrochano

MRC Mammalian Genetics Unit, Harwell, Oxfordshire, UK.

Muscle-specific mutation modifies systemic HD disease in mice

Huntington's disease (HD) is a dominant, progressive, fatal, neurodegenerative disorder caused by an expanded polyglutamine tract (PolyQ) in exon 1 of the Huntington's gene. Up to 70% of the variance in severity and age of onset is accounted for by the number of glutamine repeats. The rest of the variance is accounted for by environmental and genetic factors (modifiers). We identified the gene responsible for one of the HD enhancer lines: a novel mutation in the mouse skeletal muscle specific voltage-gated sodium channel transgene N171-82Q (HD; *Scn4a*$^{Dgn/+}$) enhance the overall HD disease phenotype. In the brain the HD transgene is strongly expressed but there is no expression of the *Scn4a* gene. In the skeletal muscle, however, both mutations, *Scn4a*^{Dgn} and mutant huntingtin, are expressed. In the muscle we found cell autonomous effects of the combination of both mutations, such us atrophy, fibber-type changing and calcium deregulation. The worsening of HD muscle pathology leads to whole body metabolic changes and systemic effects. We found a dramatic reduction in survival and metabolic changes associated to weight loss in the double mutants (HD; *Scn4a*$^{Dgn/+}$) when compared to HD littermate controls (HD; *Scn4a*$^{+/+}$). Importantly, HD patients also suffer from muscle atrophy, weight loss and metabolic disturbances. These systemic metabolic alterations can ultimately affect the brain, as evidenced by differential expression of many genes, including immediate early genes (IEG) such as *Fos* and *Arc* in double mutant HD; *Scn4a*$^{Dgn/+}$ mice. Thus, we provide novel insights into the systemic nature of HD pathogenesis, showing how pathological changes in the periphery can in turn affect the overall HD disease phenotype.

Corrochano, S et al. Novel mutations in human and mouse SCN4A implicate AMPK in myotonia and periodic paralysis. (2014). *Brain*. 137:3171-85.

Corrochano S et al. Alpha-synuclein levels modulate Huntington's disease in mice. (2012). *Human Molecular Genetics*. Feb 1; 21 (3):485-94.

Silvia Corrochano, Mauricio Renna, Sarah Carter, Michelle Stewart, Steve DM Brown, David C. Rubinsztein and Abraham Acevedo-Arozena. *Reducing Igf-1r levels leads to paradoxical and sexually dimorphic effects in HD mice* (2014). Plos One. DOI: 10.1371/journal.pone.0105595.

Manuel Valero

Instituto Cajal. Consejo Superior de Investigaciones Científicas. Madrid, Spain.

Determinants of different deep and superficial CA1 pyramidal cell dynamics during sharp-wave ripples.

Sharp-wave ripples represent the most synchronous population activity in the mammalian brain, with key function in memory consolidation. A plethora of hippocampal GABAergic interneuronal types exhibit specific phase-locked firing or even silence during sharp-wave ripples, but the mechanism of pyramidal cell participation are unknown. Using sharp and multi-site recordings in combination with neurochemical profiling we found opposite membrane polarization of deep (closer to stratum oriens) and superficial (closer to stratum radiatum) rat CA1 PCs during sharp-wave ripples. Biased contribution of perisomatic GABAergic inputs, together with suppression of CA2 PCs, may explain the selection of CA1 PCs during sharp-wave ripples. We also showed that in freely moving animals, the deep-superficial gradient interacted with behavioral and spatial effects to determine cell participation. Thus, the firing dynamics of hippocampal PCs are exquisitely controlled at subcellular, microcircuit and sublayer levels. The collateral and original idea of two sublayers get back to early work by Schaffer in 1892. Our current research is focused on the behavior of the two CA1 pyramidal cell sublayers during theta oscillations, and CA1 deep-superficial axis disturbances in the epileptic hippocampus.

Valero M, Cid E, Averkin RG, Aguilar J, Sanchez-Aguilera A, Viney TJ, Gomez-Dominguez D, Bellistri E, Menendez de la Prida L. Determinants of different deep and superficial CA1 pyramidal cell dynamics during sharp-wave ripples. Nature Neurosci 18, 1281–1290 (2015).

Laurent F, Brotons-Mas JR, Cid E, Lopez-Pigozzi D, **Valero M**, Gal B, Menendez de la Prida L. Proximodistal structure of theta coordination in the dorsal hippocampus of epileptic rats. J Neurosci. 35(11): 4760-4775 (2015).

Aivar P, **Valero M**, Bellistri E, Menendez de la Prida L. Extracellular calcium controls the expression of two different forms of ripple-like hippocampal oscillations. J Neurosci. 34(8): 2989-3004 (2014).