UNIVERSITÀ DEGLI STUDI DI TORINO

I@UNITO – Visiting Scientists

Scientific area	Scientific responsible	Host Department	Type of activity	Start of mobility	Language
Physiology	Emilio Carbone	Dipartimento di Scienza e Tecnologia del Farmaco	Basic Research	April 2017	English
Type of fellowship	Senior (equal or more than 40 years old) 1 month				
Title of the research project	Altered excitation/inhibition balance in hippocampal neurons induced by mutations of L-type Ca^{2+} channels associated to forms of autism and mental retardation				
Description of the research project	Neuronal L-type calcium channels (Cav1.2 and Cav1.3) are largely expressed at the somatic and perisomatic levels of neurons in many brain areas, including the hippocampus [1]. Both channels activate at relatively low resting potentials (-50 to -40 mV) and thus allow Ca^{2+} to enter the neurons during basal and sustained neuronal activity. As cytosolic Ca^{2+} regulates a large number of intracellular modulatory pathways, both channels appear strategic to control neuronal survival and maturation. Both channels, indeed, are critical for regulating the outgrowth of neuritis and development of excitatory and inhibitory synapses (synaptogenesis). Cav1.2 and Cav1.3 channels are also critical for the control of somatic and perisomatic neuronal excitability. This derives from their high expression density and coupling to Ca^{2+}-dependent potassium channels: BK ("big K") and SK ("small K") channels. In this way, Cav1.2 and Cav1.3 regulate the waveform of action potentials (AP), the frequency of tonic firing, the timing of AP bursts and the onset of AP synchronisms in hippocampal microcircuits. Any pathological alteration of Cav1.2 and Cav1.3 "gating" properties induces profound changes to neuronal signaling and brain area functions. Among the neurodegenerative diseases associated to Cav1.2 and Cav1.3 channels, of particular interest are the point mutations that slow-down the "inactivation gate" of both channels. A reduced rate of inactivation causes increased Ca^{2+} entry in neurons with consequent altered degree of excitability, firing synchronism and excitation/inhibition balance. These mutations in humans are associated to two rare forms of the autistic spectrum disorder (ASD): the Timothy Syndrome (TS) [2] and the Primary Aldosteronism, Seizers and Neuronal Abnormalities (PASNA) [3]. Both are associated to a glycine to arginine mutation at position 406 (G406R) for Cav1.2 (TS) and at position 407 (G407R) for Cav1.3 (PASNA). Using intracellular patch-clamp recordings and extracellular microelectrode arrays (64 MEA) monitoring, in this project we will study the excitability properties of single neurons, the response of excitatory and inhibitory synapses and the synchronous versus asynchronous activity of hippocampal microcircuits in wild-type (WT) and knock-in (KI) mice with the mutation G406R Cav1.2 or G407R Cav1.3. Cultured hippocampal networks will be studied at different days *in vitro* (from day 11^{th} to 22^{nd}). The TS KI mice will be available from prof. Randy				

	Rasmusson (Buffalo, USA) while the PASNA KI mice will be available from prof. Joerg Striessnig (Innsbruck, Austria). Specifically, we will test how the Cav1.2 and Cav1.3 mutations alter the expression and the physiological properties of ion channels that control the AP firing at the somatic and perisomatic level (Cav, Nav, BK, SK and Kv) [4, 5]. We will also test how the two mutations causing autism affect the day at which the asynchronous activity of neurons switches to a synchronous burst activity of the developing hippocampal networks [6] and how they modify the synaptic plasticity of pyramidal excitatory neurons and inhibitory interneurons [7]. **References** 1. Marschallinger, J., et al., Cell Calcium, 2015. **58**(6): p. 606-16. 2. Splawski, I., et al., Cell, 2004. **119**(1): p. 19-31. 3. Scholl, U.I., et al., Nat Genet, 2013. **45**: p. 1050-4. 4. Marcantoni, A., et al., Journal of Neuroscience, 2010. **30**(2): p. 491-504. 5. Vandael, D.H.F., et al., Journal of Neuroscience, 2012. **32**(46): p. 16345-16359. 6. Gavello, D., et al., Plos One, 2012. **7**(7). 7. Baldelli, P., et al., Journal of Neuroscience, 2005. **25**(13): p. 3358-3368. 8. Crepel, V., et al., Neuron, 2007. **54**(1): p. 105-120. 9. Ben-Ari, Y., et al., Neuroscientist, 2012. **18**(5): p. 467-486.
Profile Description	Expert researcher on ion channels physiology, pharmacology and molecular biology. Technical experience on AP recordings from in vitro neurons with patch-clamp, MEAs and Ca^{2+} imaging
Research objectives	With the help of the senior researcher, we expect: 1) to determine how the two point mutations remodel the expression of the main ion channels regulating neuronal excitability (Cav, Nav, BK, SK and Kv). 2) to establish how the increased Ca^{2+} entry associated to the mutations could affect the activation of the Ca^{2+}-dependent BK and SK channels that condition somatic AP firing and burst rhythms that drive synaptic activity. 3) to highlight the origins of the neuronal network synchronism that occurs at the 14-18th day *in vitro*. We expect also to clarify if the synchronism is linked to Cav1.2 and Cav1.3 expression [8] and how much is conditioned by GABAergic interneurons maturation in culture [9].
Website and Contact	http://www.dstf.unito.it/do/gruppi.pl/Show?_id=q8tb http://orcid.org/0000-0003-2239-6280 emilio.carbone@unito.it