BM1406-Newsletter

N° 1

May 2016

EUROPEAN COOPERATION IN SCIENCE AND TECHNOLOGY

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BM1406 Action is everybody's business!

Dr Florence Velge-Roussel, *Chair of the BM1406 Action, University François Rabelais, Tours, France*

Since the 31th March, we are building a scientific network in biophysics of immune cells in Europa and the surrounding countries. It's sometimes a little bit difficult because administrative tasks, or the way of going the project quite is very different from those we were used to. Probably, it will take a little time for us to understand how does COST work and how to manage the activities that it allows. The point is that BM1406 is a really great opportunity for all laboratories gathered into.

It is trite to say: together we will be stronger and more powerful. Numbers of the laboratories in the Action are well established and well known. I guess they could become even better with their partnership with the others. No matter the size of the lab, it's never possible to do all necessary experiments, to get all technical expertise, to master all appropriate skills. We always have to make choices in our project. If it's possible, thanks to collaboration between laboratories in the Action, to go further or deeper in a project, we all may gain in the quality of our research and in our publications. The BM1406 is like you have all the skills of your partners through a virtual European laboratory. Use it!

Our Action is promoting research in the biomedical field, especially trying to connect the ion channel to the immune cell skills in immune pathologies. We all need this trans-disciplinarily approach move forward in our projects. As COST recognizes a bottleneck in Europa concerning this question, our aim must be to give greater visibility to our thematic leading to a leadership position in the European research. The position will become evident if we show all other an efficient network leading to high-level research and new therapeutic strategies.

As lab manager, I know that we have never time enough dedicated to young people and women promotion. For those who are more advanced in their career, if we use our memories, achieving something new for us without any assistance or training was not always easy or comfortable. Thanks to the activities proposed in the Action, we have the opportunity to delegate responsibilities to our post-doc or young fellows. It's one way to encourage and train them having in-charge the scientific design of meeting sessions or management of a chair position in a meeting as an example.

One of the reasons we have get this Action was that we expressed the desire to build tomorrow's scientific network. Today, we must take time to gather all necessary conditions to make this Action dynamic, friendly and efficient. This future will be built also on the young fellows in our laboratories. We can now instil them good habits in terms of scientific cooperation for later. We must, if we can, now turn words and good intentions into concrete actions.

As regards on all opportunities that offer the Action, I have no doubt about your choice. I'm counting on you all to make the BM1406 Action, your project!

What is BM1406 all about?

The function of ion channels in immune cells is an emerging field of great basic science and clinical interest because they provide powerful molecular targets to modulate immune cell function. The Ionchan-Immunrespon network is a novel and exciting enterprise that involves internationally recognised scientists across 15 European countries.

The specific aims are i) to develop a strong European workforce to understand the role of ion channels in immune cells, and how deregulation of their function can cause disease, ii) to identify new targets for therapeutic immuno-interventions through modulation of ion channels. Our unique combination of biophysical approaches combined with molecular biology, cell biology and immunology provides a powerful approach for dissecting the functional cell biology of the immune system.

The Action therefore will strengthen academic research in Immunology within Europe and foster closer collaborations with drug and diagnostics development programs in industry..."

Action BM1406 is formed by three working groups

WG1: R. Murell-Lagnado : Identification and characterization of ion channels in immune cells
WG2: F. Di Virgilio : Role of ion channels in immune pathologies
WG3: F. Koch-Nolte: Ion channels as new targets in therapy and *dia*gnosis

First meeting in Warsaw, Poland, September 24th and 25th, 2015 at the International Institute of Molecular and Cell Biology in Warsaw.

(IIMCB) 4 Trojdena Street, Warsaw (Ochota district)
http://www.iimcb.gov.pl/

Quorum:
2/3 of country representatives
23 countries in BM1406
2/3 = 15 countries
Today: 17/23 countries
32 participants (45,7%)

Adoption of agenda
The agenda has been approved by the Management Committee

Ion Channels and Immune Response (IONCHAN-IMMUNRESPON)
toward a global understanding of immune cell physiology and for new therapeutic approaches

In the Spotlight

Laboratory of Neurodegeneration: Prof Jacek Kuznicki

The group of Prof. Kuznicki is interested in the molecular mechanisms that are involved in neurodegeneration and psychiatric diseases, with a special emphasis on the role of calcium homeostasis and signaling and ß-catenin pathways. These processes are being studied at the genomic, proteomic, and cellular levels using zebrafish and mice as model organisms. Our major projects currently focus on the following:

1. Dysregulation of calcium homeostasis in neurodegenerative diseases

The vast majority of available animal models of AD are based on the ß-amyloid/tau hypothesis. These mice overexpress one or more mutated proteins that are known to be responsible for early-onset FAD. The FAD models, representing less than 5% of all human cases, appear to have little value for understanding the mechanisms of SAD (reviewed by Wojda and Kuznicki, J Alzheimers Dis, 2013). We generated transgenic mice that overexpress key proteins of store-operated calcium entry (SOCE) specifically in brain neurons (STIM1, STIM2, and Orai1 under the Thy1 promoter). Using RT-PCR and Western blot, we detected the presence and activity of all transgenes and analyzed their phenotypes. The lines that were obtained are currently being used to test the hypothesis that brain dysfunction during ageing is induced by changes in calcium homeostasis (work in progress).

FAD mutations in presenilins have been shown to alter both ER calcium signaling and SOCE, but the role of APP and APP FAD mutants in intracellular calcium homeostasis is controversial. We are addressing this issue using various cell models and both gain-of-function and loss-of-function approaches. Calcium dynamics are measured with cytosolic and ER-targeted calcium sensors and the quantitative co-localization of SOCE machinery components. Our results indicate that APP regulates intracellular calcium homeostasis, including ER calcium dynamics, but it is not directly involved in SOCE. Therefore, FAD-linked proteins appear to have both common and independent targets in the calcium signaling network (paper submitted).

To explore calcium homeostasis during the early stages of SAD and MCI, we investigated SOCE and inositol triphosphate receptor (IP3R)-mediated calcium release into the cytoplasm in unmodified B-lymphocytes from MCI subjects and SAD patients and compared them with non-demented subjects. We observed perturbed calcium homeostasis in peripheral cells from MCI and SAD patients, supporting the hypothesis that SAD is a systemic disease, and MCI is a risk factor for AD (Jaworska et al., BBA Mol Cell Res, 2013; reviewed by Majewski and Kuznicki, BBA Mol Cell Res, 2015).

We analyzed the expression of calcium-related genes in YAC128 transgenic mouse models of HD. We found that HAP1, CacyBP/SIP, and Calb2 were overexpressed in these mice (Czeredys & Kuznicki, Front Mol Neurosci, 2013). We have identified few compounds that rescue the increase in SOCE in cultures of YAC128 medium spiny neurons (MSNs) from the striatum of HD transgenic mice (paper submitted).

In collaboration with Prof. Oliver Bandmann (University of Sheffield), we used a pink1 mutant (pink-/-) zebrafish line with a premature stop mutation (Y431*) in the Pink1 kinase domain (Flinn et al., Ann Neurol, 2013). The knockdown of mcu rescued dopaminergic neurons in pink1 mutant zebrafish. To confirm the results from morpholino-based knockdown, we treated the experimental groups of zebrafish with ruthenium red (RR), a pharmacological inhibitor of Mcu, and performed WISH using a tyrosine hydroxylase riboprobe. We observed the rescue of dopamine neurons in RR-treated pink1-/- zebrafish.

This restoration of the number of dopaminergic neurons in pink1-/- zebrafish implies that the inhibition of mcu decreases mitochondrial calcium overload-based toxicity, leading to viable dopamine neurons. The knockdown of vdac1 did not rescue dopamine neurons in pink1 mutant zebrafish (paper submitted).

2. Role of STIM proteins in store-operated calcium entry in neurons

We previously showed that STIM1 is involved in thapsigargin-induced SOCE, whereas STIM2 is mostly active after the ethylene glycol tetraacetic acid (EGTA)-driven depletion of extracellular calcium (*PLoS One*, 2011; *J Neurochem*, 2013). We are looking for new partners of STIM proteins other than ORAI channels.

3. ß-catenin in mature neurons

By combining bioinformatics and experimental approaches, we identified genes that are involved in neuronal excitability as a ß-catenin target (Wisniewska et al., *BMC Genomics*, 2012), suggesting that ß-catenin might contribute to electrical signal propagation in thalamic neurons. We analyzed LEF1/TCF protein localization in the adult mouse brain and the expression profile of their isoforms in cortical, thalamic, and midbrain regions (Nagalski et al. *Brain Struct Funct*, 2013; 2015). As a continuation of these projects, we focused on the role of lithium in ß-catenin stabilization in neurons of the adult brain. We demonstrate that therapeutically relevant doses of lithium selectively activate Wnt/ß-catenin signaling in thalamic neurons (paper submitted). This project was initiated in our laboratory and currently is a collaborative effort together with the Laboratory of Molecular Neurobiology at CeNT, University of Warsaw, headed by a former lab member, Dr. Marta B. Wisniewska. Moreover, in collaboration with Prof. Shernaz Bamji from the Brain Research Center, University of British Columbia, Vancouver, Canada, we participated in a paper on the effects of ß-catenin stabilization *in vivo* on cognitive flexibility and long-term synaptic depression (Mills et al., Proc *Natl Acad Sci USA*, 2014).
We also study the consequences of impairments in the polysialylation of neuronal cell adhesion molecule (NCAM), the cytoplasmic domain of which is bound under certain conditions to the protein complex that consists of GSK3 and ß-catenin. We found that myelin content was decreased and axons showed some features of degeneration in the brains of mice that are deficient in ST8SIA2, but not ST8SIA4 (two polysialyltransferases) (paper submitted).

Updates & announcements

Update from the Action Chair

Welcome to the two new participating countries **LATVIA**: Zaiga NORA-KRUKLE & Martin KALIS and **TURKEY**: Ozlen KONU & Nuray ERIN

Update from the Grant Holder

Grant Agreement has been signed
65 % of the total amount has been paid

STSM new applications

1-Alba Clara Sarti from the Department of Morphology, Surgery and Experimental Medicine University of Ferrara
Host institute: Institute for Research in Biomedicine
Bellinzona (Switzerland) Prof. **Fabio Grassi** group leader. **Date of stay**: January 1st to March 31st 2016

2-Chiara Parisi from the IBCN-CNR Via del Fosso di Fiorano Rome, Italy
Host institute: IMIB-Arrixaca El Palmar, Murcia, Spain Dr. Pablo Pelegrin Dates of stay: 01/03/2016 to 31/05/2016

3-Iva Hafner Bratkovič from the National Institute of Chemistry Ljubljana Slovenia
Host institute: Clinical University Hospital Virgen de la Arrixaca El Palmar, Murcia, Spain Dr. Pablo Pelegrin **Dates of stay**: 16th January 2016- 16th April 2016

Update from the COST Association

New dissemination guidelines (August 2015)
Science Officer: Dr Inga Dadeshidze
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Creation of a new website and Social media account

- Official website: http://costbm1406-univ-tours.fr
- Social media: Facebook account for Cost Action BM1406

BM1406 Action members taking action in the IIMCB Warsaw

Location and date of next meeting:

Faculty of Pharmacy, University of Lisbon, Av. Prof. Gama Pinto 1649-003 Lisbon, Portugal, Wednesday march 9th to friday march 11th, 2016.
Focus on WG3.