BM1406-Newsletter

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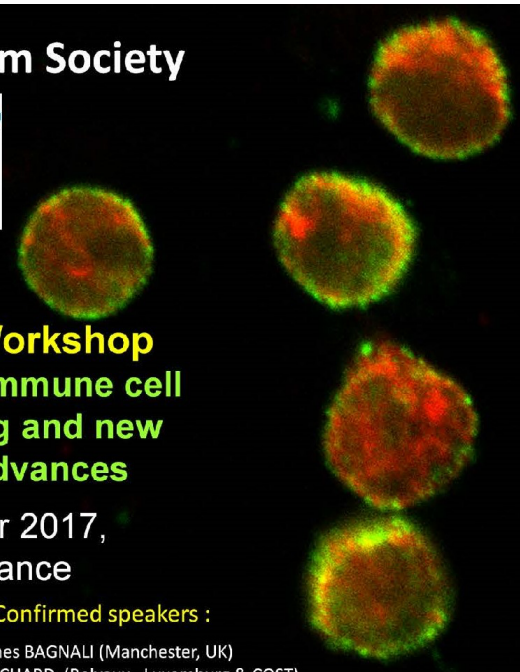
EUROPEAN COOPERATION IN SCIENCE AND TECHNOLOGY

European Calcium Society



International Workshop
Breakthrough in immune cell calcium signaling and new therapeutics advances

16-18th October 2017,
Toulouse, France

Confirmed speakers :

James BAGNALI (Manchester, UK)
Sabrina BRÉCHARD (Belvaux , Luxemburg & COST)
Peter N. COCKERILL (Cambridge, UK)
Nicolas DEMAUREX (Geneva, Switzerland & COST
Oliver GRIESBECK (Martinsried, Germany)
Andreas GUSE (Hamburg, Germany & COST)
Renaud LESOURNE (Toulouse, France)
Cédric LOUVET (Nantes, France & COST)
Thomas MANGEAT (Toulouse, France)
Olivier MIGNEN (Brest, France & COST)
Jose R. NARANJO (Madrid, Spain & COST)
Barbara NIEMEYER (Homburg, Germany & COST)
Martin OHEIM (Paris, France)
Gyorgy PANYI (Devrecen, Hungary & COST)
Mathieu ROUSSET (Montpellier, France)
Romain RONCAGALLI (Marseille, France)
Magali SAVIGNAC (Toulouse, France & COST)
Salvatore VALITUTTI (Toulouse, France)

Plenary Lecture : Patrick Hogan (La Jolla, USA)

Organizing committee

Lucette Pelletier, Marc Moreau, Catherine Leclerc, Magali Savignac,
Jacques Haiech, Mathieu Rousset, Olivier Mignen

Information : http:// ecs2017.univ-tlse3.fr

This workshop is supported by cost EUROPEAN COOPERATION IN SCIENCE AND TECHNOLOGY

toward a global understanding of immune cell physiology and for new therapeutic approaches

In this fall of 2017, the 7th European Calcium Society workshop took place in the Pink City of Toulouse (France) from the 16th to the 18th of October, with the support of COST Action BM1406 “Ion channels and immune cells”. It was hosted by the Natural History Museum of Toulouse and organised by Lucette Pelletier and Magali Savignac from the Center of Pathophysiology Toulouse-Purpan, Marc Moreau and Catherine Leclerc from the Center for Developmental Biology (Toulouse), as well as Jacques Haiech (Strasbourg), Mathieu Rousset (Montpellier) and Olivier Mignen (Brest). Around 80 participants from all around the world (Switzerland, Germany, Luxembourg, Qatar, USA, Spain, UK, Austria, Australia…) gathered to share their knowledge and experiences around this year's subject "*breakthrough in immune cell calcium signalling and new therapeutics advances*". This workshop was divided into 7 sessions with specific themes, 2 round tables, some selected short communications and a plenary lecture by Patrick Hogan.

Session I: *Calcium and innate immunity*

Nicolas Demaurex (Geneva, Switzerland) started the meeting with his lecture about the role of STIM1 in phagocytic white blood cells. He showed that in neutrophils, the endoplasmic reticulum (ER) Ca^{2+}-sensing protein STIM1 mediates a local periphagosomal Ca^{2+} signal that promote phagocytosis. Besides in dendritic cells, STIM1 acts on both local and global Ca^{2+} signal to enhance phago-endosome fusion and proteolysis necessary to the antigen cross-presentation. Then *Barbara Niemeyer* (Hamburg, Germany) intervened about the store-operated calcium entry (SOCE) tuning cytotoxicity. Indeed, the target lysis by cytotoxic T lymphocytes has a calcium optimum required for a maximal lytic granule release. Pr. Niemeyer also showed that H_2O_2 inhibits Orai1, which is sensitive to oxydation contrary to Orai3. Thus the Orai3/Orai1 ratio regulates redox sensitivity of monocyte SOCE. Closing this first session, *Sabrina Brechard* (Luxembourg) talked about the calcium-dependant regulation of pro-inflammatory functions of human neutrophils. Indeed, SOCE is a key regulator of NADPH oxidase activity and cytokine secretion in these cells.

Round Table with Pharmas

The first round table of the workshop was animated by *Jacques Haiech* (Strasbourg) and *Ronald Rooke* (Paris). It led to a very interesting debate with the two points of vue from the academic world and from the pharmaceutical industry. Collaboration between these two, particularly early in the research process, would be necessary to discover new efficient drugs. Pr. Haiech also talked about the System Biology approach corresponding to a global view, taking into account the temporal-spatial regulation and interactions of the calcium signal components for example. This would allow to design a pharmacological toolkit against several integrator’s and/or ligands to abandon the reductionnist view of aiming only one validated target.

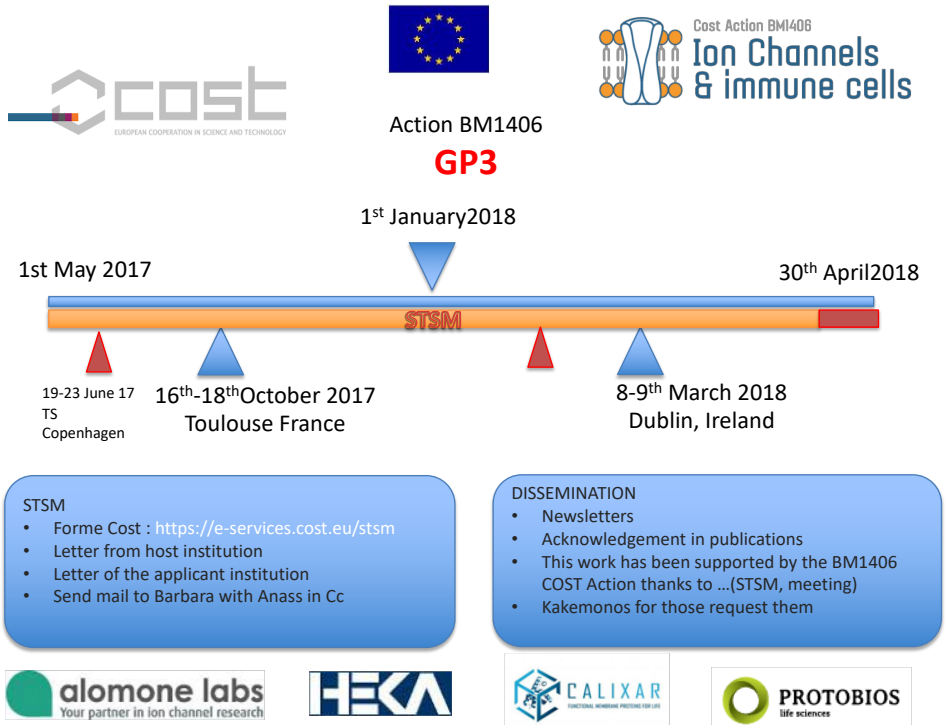
Session II: *Calcium signalling in lymphocytes*

Olivier Mignen (Brest) opened the second session with his talk during which he characterised Ca^{2+}-signalling defects in B cells from patients suffering from Chronic lymphocytic leukemia (CLL) and Systemic Lupus Erythematosus (SLE). He highlighted the importance of STIM1 to regulate a new BCR-independent constitutive Ca^{2+} entry in B lymphocytes and thus proposed an anti-STIM1 antibody for CLL and SLE treatment. As described during the round table, *Romain Roncagalli* (Marseille) presented an approach of system biology in T cells. He used knock-in mice to add StrepTag on his proteins of interest and performed affinity purification followed by mass spectrometry to identify interactomes in primary T cells. This allowed a better understanding of the organisation of complex molecular networks. To conclude, *Renaud Lesourne* (Toulouse) talked about THEMIS, a T-lineage specific protein required during thymocyte positive selection. Using mass spectrometry to identify THEMIS-binding partners, Dr Lesourne showed that THEMIS enhances TCR signalling in thymocytes by blocking the inhibitory phosphatase SHP-1 and by stabilising the adaptor protein Grb2, enabling thymocytes to reach the threshold for positive selection.

Session III: ***Targeting calcium signalling in diseases. What's in the air?***

In this third session, *Philippe Lory* (Montpellier) presented his works of functional modelling of human channelopathies. These latter are defined as diseases caused by a dysfunction of a ionic channel. He described Ca_v3 (T-type) mutants linked with several diseases such as ataxia and primary aldosteronism and studied the consequences of such mutations on the electrophysiological properties of the channels. Then, *Khaled Machaca* (Doha, Qatar) introduced us to the phenomenon of Ca^{2+} tunneling/teleporting which allows a selective activation of Ca^{2+}-dependent effectors downstream of SOCE. Indeed, SOCE-dependent Ca^{2+} signalling can extend spatial spread by using ER tunnels and then activate distant effectors leading to

(in T lymphocytes) and Cav1.3-deficient mice, which display decreased characteristics of asthma in several experimental models. Finally, *Salvatore Valitutti* (Toulouse) spoke about the lytic synapses formed by human cytotoxic T lymphocytes (CTL) when interacting with target cells, especially against tumors. It was found that melanoma cells resist to CTL attacks and Dr Valitutti showed that altering Ca^{2+} pathway increases melanoma cells sensitivity to CTL attack. So melanoma cells employ an ancestral Ca^{2+}-dependent membrane reparation mechanism to "speak back" to CTL at the lytic synapse.



Session V: ***Specific features of calcium signalling***

Jose R. Naranjo (Madrid, Spain) started the fifth session with a lecture about the multifunctional neuronal calcium sensor DREAM. The nuclear form is Ca^{2+}-free, binds DNA and acts as a transcriptional repressor, repressing cytokine production and regulating proliferation of T lymphocytes. In the plasma membrane, DREAM acts as an auxiliary protein, regulating channels such as the Ca_v ones in a Ca^{2+}-dependent manner. Calcium binding to its EF-hands triggers conformational change that prevents binding to DNA and modifies its affinity for some interacting proteins. These conformational changes can also be induced by the binding of small molecules and surface plasmon resonance assay was used to identify such molecules. Then, *Cédric Louvet* (Nantes) introduced us to the RUSH system. He is interested in intracellular ion channels and he developed a method to track down the their trafficking of channels from the endoplasmic reticulum (ER) to post-Golgi vesicles. This system allows retention of the channels using selective hooks that are streptavidine-fused proteins staying in the ER. The reporter protein of interest is fused to streptavidine-binding protein and biotin addition causes the release from the hook. Finally, *Sarah Bevington* (Birmingham, UK) held her presentation about T cell memory. Indeed, previously activated T cells exhibit immunological memory responding to re-stimulation much faster than naive T cells. She proposed a model where such memory is first established in a calcium/NFAT- and AP-1-dependent manner by TCR signalling, but is then maintained through IL-2 and IL-7 signaling pathways upstream of

Round Table Future of Ca^{2+} signalling

The second round table was a discussion between *Jacques Haiech* (Strasbourg), *Mathieu Rousset* (Montpellier), *Marc Moreau* (Toulouse), *Lucette Pelletier* (Toulouse) and all the audience, around the perspectives of the Ca^{2+} signalling going further than studying one by one the element of the calcium toolkit and studying the whole properties of the dynamic Ca^{2+} network. Modelisation would be a new tool to predict how the network operates but it has to integrate a lot of variable. Modern technology allow new tools to study it and combined expertises could be used in multidisciplinary teams. The European Calcium Society is a solution, with shared knowledge between the participants as mutual assistance should not be mutually exclusive with career and publishing. The development of new database and bioinformatic is a key to diffuse such knowledge. Then, they talked about calcium imaging, with new techniques such as total internal reflection fluorescence microscopy (TIRFM) allowing to reveal brief events of Ca^{2+} pulses through channels. It raised the problem of the Ca^{2+} probes that can displace equilibrium, changing biochemical behaviour or localisation of elements.

Session VI: *Novel in vivo technics for calcium imaging*

Following these questions about probes, *Oliver Griesbeck* (Martinsried, Germany) introduced us to optimized ratiometric fluorescent calcium biosensors based on FRET that have minimised calcium-binding domain so less binding sites per sensor. He presented these calcium biosensors called "Twitch" explaining their characterisation, screening and then showed examples such as *in vivo* calcium imaging of T lymphocytes in mouse lymph nodes. Then, *James Bagnall* (Manchester, UK) talked about quantitative single-cell analyses of immune-cell activation. Lentiviral gene transfer allow to obtain quantitative dynamic imaging using Fluorescence Calibrated Spectroscopy (FCS) time-lapse microscopy to analyse of a set of inflammation-related signalling networks. Single-cell RNA seq and smFISH were also used to study gene expression and allowed to measure dynamic and heterogeneous responses during immune-cell activation.

Session VII: Novel microscopy for calcium imaging

Still on the topic of calcium imaging, the last day of the workshop started with a presentation by *Martin Oheim* (Paris) explaining how to reduce photodamage during two-photon imaging of microdomain calcium transients. Indeed, direct near-infrared absorption caused by two-photo excitation fluorescence results in the spatial and temporal accumulation of a damage-promoting factor modifying Ca^{2+} homeostasis in cortical astrocytes and such photo-damages can be reduced but not abolished using shorter, higher-energy pulses and lower average power. Then *Thomas Mangeat* (Toulouse) presented the super-resolved speckle microscopy, his latest Structure Illumination Microscopy (SIM) strategy. Classical SIM is a widefield super-resolution technique using harmonic illumination patterns. Combination of new fast structured illumination allows considerably less complexity and toxicity with similar or better results. Such technology can be used to study fast biological events.

Selected short communications

Besides, short communications gave the opportunity to young researchers to present the works about diverse subjects including SOCE (*Olivier Dellis*, *Rainer Schindl*), TRPM3 on NK cells (*Hélène Cabanas*), ER structure (*Christopher Henry*), oligomers that enhances Ca^{2+} responses and neurone cell death (*Lucia Nuñez*), and the effects of Ca^{2+} via microdomain formation in T cells (*Björn-Philipp Diercks*), or on membrane repair (*René Köffel*) or on ERK1/2 pathway (*Souleymane Abdoul-Azize*).

To conclude, the joint association of the COST Action BM1406 and ECS favoured interconnection and future cooperation between the members of these two organisations. It also allowed the success of this workshop, with a good organisation within the Natural History Museum and with restaurants doing honour to the gastronomy of the South West France.

Done by Dr Nicolas Giang, supervised Dr L. Pelletier et Dr F. Velge-Roussel.

Dissemination

Dr Ruth Murell-Lagnado, invited in Tours, Juin 2017

Update from the COST Association

New vademecum guidelines (2017)

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Creation of a website and Social media account

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

University of Dublin, Irlande

8-9th March 2018

ION CHANNELS IN CANCER

Moreover, ion channels have been demonstrated to become activated during the stress response of tumor cells and to confer therapy resistance. In combination with their tumor-associated expression, ion channels, therefore, seem to be ideal targets to sensitize tumor cells to anti-tumor therapy. As a matter of fact, many approved drugs modify on purpose or as side effect ion channels suggesting that the clinical translation of pharmacological ion channel targeting is feasible.

We will happy to welcome talks in immunology, cancer physiology and clinicians