Plenary lecture

Highlights on common channel gating changes in Cav1.2 and Cav1.3 channelopathies associated with autism

Emilio Carbone (Torino, Italy)

Ion Channels as Therapeutic Targets in Motor Diseases

Riadh Gouider (Tunis, Tunisia)
Hilal Lashuel (Lausanne, Switzerland)
Eric Boué-Grabot (Bordeaux, France)

Hypoxia and ion channels

Bastien Masson (Paris, France)
Khilian Pascarel (Poitiers, France)
Luigi Catacuzzeno (Perugia, Italy)

Role of ion channels in stem/progenitor cells

Francesco Moccia (Pavia, Italy)
Lin-Hua Jiang (Xinxiang, China; Leeds, UK)
Loïc Lemonnier (Lille, France)

Ion channel and development

Lucile Miquerol (Marseille, France)
Adèle Faucherre (Montpellier, France)
Olga Andrini (Lyon, France)

Ionic channels in non excitable cells

Gilles Crambert (Paris, France)
Laurent Beck (Nantes, France)
Isabelle Callebaut (Paris, France)

Scientific fraud: a long history... with potentially disastrous consequences

Caroline Strube (Marseille, France)

Ion channels : global research trends, statistics, collaborations

Artem Kondratskyi (Lille, France)

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SCIENTIFIC COMMITTEE CANAUX IONIQUES

Lise RODAT-DESPOIX (Chair)
Laboratoire de Physiologie Cellulaire et Moléculaire, Université de Picardie
lise.despoix@u-picardie.fr

Pietro MESIRCA (co-Chair)
IGF-CNRS, CNRS UMR 5203, INSERM U1191, Université de Montpellier
pietro.mesirca@igf.cnrs.fr

Fabien BRETTE
PhyMedExp, Inserm U1046 - CNRS UMR 9214, Université de Montpellier
fabien.brette@inserm.fr

Anna Rita CANTELMO
Institut Pasteur de Lille, Inserm UMR1011, Université de Lille
anna-rita.cantelmo@univ-lille.fr

Valerie CORONAS
Laboratoire 4CS, CNRS UMR 6041, Université de Poitiers
valerie.coronas@univ-poitiers.fr

Marie DEMION
PhyMedExp, Inserm U1046 - CNRS UMR 9214, Université de Montpellier
Marie.demion@inserm.fr

Ines EL BINI
Institut Pasteur de Tunis, Laboratoire des Biomolécules, Venins et Applications Théranostiques
inesbini@yahoo.fr

Alban GIRAULT
Laboratoire de Physiologie Cellulaire et Moléculaire, Université de Picardie
alban.girault@u-picardie.fr

Cécile HILAIRE
INM INSERM U1298, Université de Montpellier
cecile.hilaire@umontpellier.fr

Perrine INQUIMBERT
INCI, CNRS UPR 3212, Université de Strasbourg
inquimbert@inci-cnrs.unistra.fr

Claire LEGENDRE
Laboratoire MitoVasc, UMR CNRS 6015 - INSERM U1083, Université d'Angers
claire.legendre@univ-angers.fr

Isabelle RUBERA
LP2M, UMR CNRS 7370, Université Côte d'Azur
isabelle.rubera@univ-cotedazur.fr

ASSOCIATION CANAUX IONIQUES

Arnaud MONTEIL (President)
Institut de Génomique Fonctionnelle, CNRS UMR 5203 - INSERM U1191
Université de Montpellier,
arnaud.monteil@igf.cnrs.fr

Caroline STRUBE (vice President)
Centre de Recherche en Neurobiologie et Neurophysiologie de Marseille, CNRS UMR 7286,
Université Aix Marseille,
caroline.strube@univ-amu.fr

Lise RODAT-DESPOIX (Treasurer)
Laboratoire de Physiologie Cellulaire et Moléculaire, Université de Picardie
lise.despoix@u-picardie.fr

Pietro MESIRCA (Secretary)
IGF-CNRS, CNRS UMR 5203, INSERM U1191, Université de Montpellier
pietro.mesirca@igf.cnrs.fr

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We thank them for their financial and material support.

FOREWORD / AVANT-PROPOS

Dear Colleagues,

We are delighted to meet again in Sète for the 32nd edition of the Ion Channels Meeting. For this new edition, we will have the chance to listen to talented researchers, senior and junior, present their exciting work on ion channels in fields as varied as autism, motor neuron diseases, hypoxia, stem cells, development or non-excitable cells.

The irreplaceable Jean Louis Bossu, master of the sudden death session, having no declared successor, we are offering this year, two conferences on burning scientific issues: ethics in research or the history of scientific fraud, as well as a bibliometric analysis of ion channels over the past 10 years.

Ion channels occupy a central role in current research and the French Ion Channel Association is proud of its 32 years of annual meetings and thankful to you for your participation, which reached 90 registrations this year.

This meeting wouldn't be possible without the support of our sponsors, as well as the resilience and hard work of all the members of the organizing committee, Fabien Brette, Anna-Rita Cantelmo, Valérie Coronas, Marie Demion, Ines El Bini, Alban Girault, Cécile Hilaire, Perrine Inquimbert, Claire Legendre, Pietro Mesirca, Isabelle Rubera; and of course Arnaud Monteil and Caroline Strube, the guardians of the soul of this congress.

I hope that our scientific exchanges will be even more fertile and that the Mediterranean environment of the Lazaret domain will be the perfect setting to strengthen and promote new collaborations within our network.

Enjoy the meeting!

Lise Despoix

President of the 32nd Ion Channels Meeting

PROGRAM

Sunday, September 17th 2023

16:00 – 19:00 Welcome of the meeting attendees

19:00 ***Welcome drink and Dinner***

21:00 **Plenary lecture**

Emilio Carbone (Torino, Italy)

Highlights on common gating changes in Cav1.2 and Cav1.3 channelopathies causing autism

Monday, September 18th 2023

08:30 Opening session

08:45 Symposium 1: "Ion channels as Therapeutic Targets in Motor Diseases"

*Organized by **Ines El Bini** (Tunis, Tunisia)*

Riadh Gouider (Tunis, Tunisia): Paramyotonia congenita: from bench to bedside

Hilal Lashuel (Lausanne, Switzerland): A spark of hope: targeting potassium channels in parkinson's disease

Eric Boué-Grabot (Bordeaux, France): Trafficking and function of ATP P2X4 receptors in Amyotrophic Lateral Sclerosis

Selected speaker: Ophélie Molton (Lausanne, Suisse): Determination of the Ca^{2+} binding sites of acid-sensing ion channel 1a (asic1a)

10:30 *Coffee break*

11:00 Oral communication session 1: "Opening the Ca^{2+} Floodgate"

*Organized by **Fabien Brette** (Montpellier, France)*

Caterina Azzoni (Montpellier, France): Control of the fight-or-flight response of heart rate and sino-atrial node automaticity by L-type Cav1.3 (α1D) channels

Lea Rethore (Angers, France): KB-R7943, a sodium/calcium exchanger (NCX) inhibitor, also targets voltage-gated sodium channels in GH3b6 cells

Federico Bertagna (Guildford, UK): Effects of pharmacological ryanodine receptor modulation on voltage-gated ionic currents in murine hippocampal cornu ammonis-1 pyramidal neurons

Mahira Kaabeche (Montpellier, France): Electrical properties and intracellular calcium signaling in cardiomyocytes from the honey bee heart

12:00 ***One-minute oral presentation for posters***

12:30 ***Lunch***

14:00 Poster session

15:45 ***Coffee break***

16:15 Sponsors presentation 1

16:30 Symposium 2: "Hypoxia and ion channels"

Organized by ***Alban Girault*** *(Amiens, France)*

Luigi Catacuzzeno (Perugia, Italy): Role of ion channels in the hypoxia-induced aggressiveness of glioblastoma

Khilian Pascarel (Poitiers, France): Impact of hypoxia on ion channels in the context of cystic fibrosis

Bastien Masson (Le Plessis-Robinson, France): Involvement of ORAI1 Ca^{2+} channel in the pathogenesis of pulmonary arterial hypertension

Selected speaker: Anaïs Saint-Martin Willer (Le Plessis-Robinson, France): Role of $CRACR_2A$ in the development of pulmonary arterial hypertension

18:15-18:30 Sponsors presentation 2

19:30 ***Apéritif dinatoire Sétois***

Tuesday, September 19th 2023

08:30 Symposium 3: "Role of ion channels in stem/progenitor cells"

*Organized by **Valérie Coronas** (Poitiers, France)*

Francesco Moccia (Pavia, Italy): Geneless optical stimulation generates pro-angiogenic Ca^{2+} signals in endothelial colony forming cells.

Lin-Hua Jiang (Xinxiang, China; Leeds, UK): Distinctive calcium channels integrate a signalling network to regulate mesenchymal stem cell function.

Loïc Lemonnier (Lille, France): Role of store-operated calcium channels in cancer stem cells.

Selected speaker: Arnaud Delafenetre (Poitiers, France): Functional characterization of muscle cells derived from healthy and DMD human induced pluripotent stem cells: focus on calcium regulation

10:15 *Coffee break*

10:45 Oral communication session 2: "ion channels and cancer"

*Organized by **Claire Legendre** (Angers, France)*

Romain Baudat (Gif-sur-yvette, France): Venom peptides: emergent biological tools for lung cancer imaging

Mélanie Laine (Amiens, France): Kv10.1 favors EMT and migration in breast cancer aggressiveness

Osbaldo Lopez-Charcas (Mexico, Mexico): The blocking mechanism of gossypol on t-type calcium channels and its impact on colon cancer cell growth

Dimitra Gkika (Lille, France): Non genomic regulation of trpm8: from thermosensation to cancer

11:45 Artem Kondratskyi (Lille, France): Ion channels: global research trends, statistics, collaborations

12:30 ***Lunch***

13:30 ***Appointment for Social event***

17:00 Sponsors presentation 3

17:15 Symposium 4: "Ion channel and development"

Organized by ***Marie Demion*** (Montpellier, France)

Lucile Miquerol (Marseille, France): Morphogenesis of the ventricular Purkinje network: linking architecture and function

Adèle Faucherre (Montpellier, France): Piezo1 in heart development and function

Olga Andrini (Lyon, France): TRK-1 sur *Caenorhabditis elegans* / mutations gain of function

Selected speaker: Eleonora Torre (Montpellier, France): Validation of differentiated sinoatrial-like hiPSCs as a model of native sinus node myocytes

19:00 Annual meeting of the Association

20:00 ***Dinner***

21:30 Evening Conference and Party

Caroline Strube (CNRS Research Integrity Office): Scientific fraud: a long history... with potentially disastrous consequences.

Wednesday, September 20th 2023

09:30 Symposium 5: "Ionic channels in non excitable cells"

*Organized by **Isabelle Rubera** (Nice, France)*

Gilles Crambert (Paris, France): $ASIC_2$ variant, a novel molecular entity involved in renal Na^+ retention during idiopathic nephrotic syndrome

Laurent Beck (Nantes, France): Uptake and efflux of phosphate in non-excitable cells: transporters, sensors and homeostatic regulation

Isabelle Callebaut (Paris, France): Molecular basis of function/dysfunction/modulation of the anion channel CFTR

Selected speaker: Mete Kayatekin (Nice, France): Activation of the LRRC8/VRAC anion channels in macrophages play a central role in micro-crystal-mediated il-1β release

11:15 *Coffee break*

11:40 Prizes and Meeting closure

12:00 *Lunch*

14:00 Airport shuttle departure

SYMPOSIA AND ORAL COMMUNICATIONS ABSTRACTS

Sunday, September 17th 2023

21:00 Plenary lecture

HIGHLIGHTS ON COMMON GATING CHANGES IN CAV1.2 AND CAV1.3 CHANNELOPATHIES CAUSING AUTISM.

Emilio CARBONE; Andrea MARCANTONI; Giuseppe CHIANTIA; Enis HIDISOGLU.
Dept. of Drug Science, Corso Raffaello 30, 10125 Torino (Italy)

L-type calcium channels are highly expressed in neurons, muscles, and neuroendocrine cells. They play key roles in long-term synaptic plasticity, sensory transduction, muscle contraction, and hormone release. Given their high rate of expression in neurons, de novo mutations in the gene encoding Cav1.2 (CACNA1C) and Cav1.3 (CACNA1D) α1 subunits cause various forms of syndromes including mental retardation and autism, which derive from specific gain-of-function alterations of channel gating (2, 3).
Using autistic mouse models (Cav1.2 TS2-neo and Cav1.3AG/WT), we found that point mutations on CACNA1C (1) and CACNA1D (4) produce common effects on channel activation and opposing effects on fast channel inactivation in chromaffin cells and hippocampal neurons. The Cav1.2 mutation (G406R on exon 8) reduces the rate of channel inactivation while the Cav1.3 mutation (A479G) increases the rate of channel inactivation. Both missense mutations, however, produce similar “leftward shift” of voltage-dependent activation and steady-state inactivation (1, 4). They are responsible of a robust increase of the “window calcium current” at rest that drives the basal activity of the cells.
How these common gating shifts alter cell firing and neurotransmitter release, and how they could possibly induce autism will be discussed.

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Monday, September 18th 2023

08:30 Opening session

08:45 Symposium 1: "Ion channels as Therapeutic Targets in Motor Diseases"

Organized by ***Ines El Bini*** *(Tunis, Tunisia)*

ARAMYOTONIA CONGENITA: FROM BENCH TO BEDSIDE.

Riadh GOUIDER; Youssef ABIDA.
Neurology Department, LR18SP03, Clinical Investigation Center Neurosciences and Mental Health - University Razi hospital – La Manouba, Tunis, Tunisia Faculty of Medicine of Tunis, University Tunis El Manar. Tunis, Tunisia

Paramyotonia congenita (PMC) is an autosomal dominant hereditary condition caused by a mutation in the alpha subunit of the Sodium ion channel gene (SCN4A). The prevalence ranges from 0.15 to 0.6 cases per 100,000 individuals, accounting for 21.4% to 55.5% of all muscular channelopathies. PMC is characterized by paradoxical myotonia with transient episodes of paralysis. Some patients experience symptoms triggered solely by exercise or exposure to cold, while others require the simultaneous presence of both factors (exercise in the cold) to elicit symptoms. Motor deficits secondary to myopathic changes may occur preferentially in proximal muscles but can also be distal. In our series, 20% of patients showed distal motor deficits. The pattern I of Fournier is characterized by an increasing reduction in compound muscle action potential (CMAP) amplitude at room temperature and the presence of repetitive myotonic discharges. Upon exposure to cold, Pattern I is observed in all patients with T1313M, R1448C, or R1448H mutations. At room temperature, 53.8% of our patients displayed a Pattern I phenotype, while 46.8% exhibited a Pattern III phenotype, resembling Sodium Channel Myotonia (SCM) phenotype. However, when exposed to cold, 96.5% of our patients displayed a Pattern I phenotype, a finding also observed in patients with the Q270K mutation. The responsible gene (SCN4A) is located on chromosome 17, at 17q13.1-q13.3. Several missense mutations have been identified, including T1313M, R1448C, R1448H, Q270K, and G1306V, with the most frequent and well-characterized being T1313M and R1448C. In our study including 30 members from a Tunisian family, we identified a double monoallelic mutation, comprising the T1313M mutation and a potentially deleterious variant, Asn1378Asp. T1313M, R1448C, and Q270K mutations have been studied for PMC, showing a decrease in fast and slow inactivation of ion channels, with an increase in slow inactivation upon exposure to cold. Drugs blocking sodium channels such as mexiletine, carbamazepine, lamotrigine, and flecainide along with non-pharmacological interventions have shown effectiveness in treating PMC. Current data highlights genetic and clinical variability in PMC. Consequently, further investigations which include mutation-driven therapy are warranted, subsequently improving the quality of life for PMC patients.

A SPARK OF HOPE: TARGETING POTASSIUM CHANNELS IN PARKINSON'S DISEASE.

Hilal LASHUEL.
Laboratory of Molecular and Chemical Biology of Neurodegeneration, Institute of Bioengineering, School of Life Sciences, École polytechnique fédérale de Lausanne (EPFL), SV LMNN Station 19, Lausanne, Switzerland CH-1015

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder with early prominent death of dopaminergic neurons in the substantia nigra pars compacta. Under pathological conditions, the presynaptic protein alpha-synuclein (α-Syn) misfolds, aggregates, and accumulates in the form of cytosolic inclusions known as the Lewy bodies and Lewy neurites, which are the defining hallmarks of PD. Mutations or duplications in the α-Syn gene cause familial PD. Together, these observations point to α-Syn as a central player in PD onset and explain why it has emerged as one of the primary targets for the development of diagnostics and therapies for PD. Previous studies have shown that extracellular α-syn aggregates are toxic and bind to cell surface receptors such as ion channels on neurons and/or microglia, leading to chronic neuroinflammation and neuronal damage. Accordingly, we hypothesize that specific ligands with known high affinity to integrins, metalloproteases, and ionic channels, such as active biomolecules from scorpion venom, could have a therapeutic effect on PD. To test this model, we employed a neuronal model that recapitulates the process of pathology formation (e.g., Lewy bodies, and Lewy neurite) and shows aSyn-aggregation linked neuronal dysfunction and degeneration. Using this model, we identified and validated venom-derived active biomolecules that exert marked inhibition of aSyn pathology formation and protect against aSyn-induced toxicity. Our findings suggest that targeting potassium ion channels offer new and exciting opportunities for treating Parkinson’s disease.

TRAFFICKING AND FUNCTION OF ATP P2X4 RECEPTORS IN AMYOTROPHIC LATERAL SCLEROSIS.

Eric BOUE-GRABOT.
Institute for Neurodegenerative diseases (IMN), CNRS and university of Bordeaux

P2X receptors are ATP-gated cation channels widely expressed in the brain where they mediate action of extracellular ATP released by neurons and/or glia. P2X receptors has profound neuromodulatory effects on synaptic efficacy and plasticity at both the excitatory and inhibitory synapses. The surface trafficking of $P2X_4$ receptors is highly regulated and as a result, $P2X_4$ are mainly intracellular, limiting their putative implication in ATP signaling originating from either neuron or glia in normal conditions. This is likely to be important because an upregulation of surface $P2X_4$ receptors in neurons and/or glia was observed in various pathophysiological context such as chronic pain, epilepsy, multiple sclerosis or neurodegenerative diseases such as Amyotrophic Lateral Sclerosis (ALS). ALS is a fatal motoneuron disease characterized by protein misfolding and aggregation leading to cellular degeneration. I will present our results showing how misfolded proteins such as mutant SOD1 increase surface $P2X_4$ trafficking in the spinal cord of ALS SOD1G93A mice. Surface increase of $P2X_4$ was also observed in peripheral macrophages of SOD1 mice at presymptomatic stages, which may position $P2X_4$ as a putative early biomarker of ALS. We revealed also the complex role of $P2X_4$ in the ALS pathogenesis using double transgenic SOD_1 mice expressing internalization-defective P2X4mCherryIN knock-in gene ($P2X_4KI$) or invalidated for the $P2X_4$ ($P2X_4KO$). Preliminary data investigating the neuronal versus microglial roles of $P2X_4$ in ALS using novel triple transgenic SOD_1 mice expressing either $P2X_4KI$ or $P2X_4KO$ selectively in macrophage/microglia or neurons will be also presented.
This project is supported by grants from ARSLA, FRC and ANR.

DETERMINATION OF THE CA^{2+} BINDING SITES OF ACID-SENSING ION CHANNEL 1A (ASIC1A).

Ophélie MOLTON; Olivier BIGNUCOLO; Stephan KELLENBERGER.
Department of Biomedical Sciences, University of Lausanne, Switzerland

Acid-sensing ion channels (ASICs) are Na^+-permeable channels that are activated by extracellular acidification. Rapid acidification occurs in synapses during neuronal activity. ASICs are widely expressed in the nervous system and have many physiological and pathological functions, such as pain sensation and neurodegeneration after ischemia. $ASIC_{1a}$ is the most H^+-sensitive subunit expressed in the central nervous system. Free extracellular Ca^{2+} concentrations can change depending of neuronal activity and pathological conditions. Calcium appears to compete with protons for binding sites on $ASIC_{1a}$, thereby shifting the pH dependence. A recent study depicting the crystal structure of $ASIC_{1a}$ has shown approximate locations of calcium ions in two extracellular regions. Based on this structural information, Molecular Dynamics simulations have been carried out in our laboratory to refine the calcium coordination, identifying residues that may be part of the calcium binding sites. Site-directed mutagenesis of these amino acid residues to Alanine was done individually and in combination, and the pH dependence of ASIC1a WT and mutants expressed in Xenopus oocytes was measured by two-electrode voltage-clamp. Decreasing extracellular $[Ca^{2+}]$ shifted the pH_{50} of activation and steady-state desensitization to more alkaline values for $ASIC_{1a}$ WT. A significant reduction of this alkaline shift was observed for several mutants localized in two different extracellular regions of $ASIC_{1a}$, which have been shown to contain numerous proton binding sites. In conclusion, we identified several residues contributing to the Ca^{2+} binding sites on $ASIC_{1a}$. We also showed that the two residues that have been shown to block the pore of $ASIC_{1a}$ by coordinating Ca^{2+} seem to be involved in the modulation of the pH dependence by Ca^{2+}. Identification of divalent cations binding sites would improve the understanding of the activation mechanism, providing a further step towards the design of therapeutics targeting ASIC channels.

11:00 Oral communication session 1: "Opening the Ca^{2+} Floodgate"

*Organized by **Fabien Brette** (Montpellier, France)*

CONTROL OF THE FIGHT-OR-FLIGHT RESPONSE OF HEART RATE AND SINO-ATRIAL NODE AUTOMATICITY BY L-TYPE $CA_V1.3$ (α1D) CHANNELS.

Caterina AZZONI[1]; Eleonora TORRE[1]; Isabelle BIDAUD[1]; Mélanie FAURE[1]; Andrea SAPONARO[2]; Anna MORONI[2]; Steven O. MARX [3]; Dirk ISBRANDT[4]; Pietro MESIRCA[1]; Matteo e MANGONI[1].
1: Institut de Génomique Fonctionnelle, Université de Montpellier, CNRS, INSERM, LabEx Ion Channels Science and Therapeutics (ICST)
2: Department of Biosciences, University of Milan
3: Division of Cardiology, Department of Medicine, Columbia University, Vagelos College of Physicians and Surgeons
4: Experimental Neurophysiology, Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE)

The mechanisms underlying fight-or-flight response (FFR) of heart rate (HR), are incompletely understood. cAMP-dependent regulation of f-(HCN_4) channels and activation of the Na^+/Ca^{2+} exchanger (NCX_1) by ryanodine receptors (RyR_2) mediated Ca^{2+} release are considered as predominant mechanisms of HR FFR. However, it has been demonstrated that f-channels are not critical for sympathetic regulation of pacemaking and targeting of RyR_2 or NCX_1 does not abolish HR FFR either, suggesting other mechanism(s) are involved in HR FFR. L-type Cav1.3 calcium (Cav1.3) channels are required for β-adrenergic initiation of firing in dormant sino-atrial node (SAN) pacemaker cells.
The objective is to define the role of L-type Cav1.3 channels in the FFR of HR and SAN automaticity.
We crossed mice deficient in Cav1.3 channels (Cav1.3-/-) with mice lacking cAMP sensitivity of f-channels (CNBD). In vivo and in isolated hearts ECG recordings were performed. Automaticity and diastolic current of SAN cells were evaluated using patch-clamp technique.
Cav1.3-/- and CNBD mice displayed bradycardia at rest, but similar degrees of increase in HR after injection of isoproterenol (ISO) in comparison to control mice. However, Cav1.3-/-/CNBD mice did not show significant HR increase after injection of ISO or during physical exercise. ISO failed to increase the rate in isolated hearts and in the SAN cells from Cav1.3-/-/CNBD mice. Consistent with these data, mice in which L-type Cav1.2 channels have been rendered insensitive to dihydropyridines (Cav1.2DHP-/-) showed that concomitant selective pharmacologic inhibition of Cav1.3 and cAMP-dependent dependent regulation of f-HCN channels prevented the positive chronotropic response to ISO of SAN cells automaticity. Under the same conditions, ISO failed to increase diastolic current, explaining loss of SAN FFR. β-adrenergic activation of SAN automaticity, via L-type Cav1.3 channel, requires the phosphorylation of RAD protein by PKA.
Our study identifies Cav1.3 channels as key effectors of β-adrenergic regulation of FFR of heart rate.

KB-R7943, A SODIUM/CALCIUM EXCHANGER (NCX) INHIBITOR, ALSO TARGETS VOLTAGE-GATED SODIUM CHANNELS IN GH3B6 CELLS

Léa RETHORE[1]; Jérôme MONTNACH[2]; Stephan DE WAARD[2]; César MATTEI[1]; Daniel HENRION[1]; Michel DE WAARD[2]; Claire LEGENDRE[1]; Christian LEGROS[1];
1: Laboratoire MitoVasc
2: Institut du Thorax

The clonal pituitary GH3b6 cells represent a convenient cellular model to investigate the function and pharmacological properties of voltage-gated ion channels such as Nav and Cav channels. In a previous study, we have shown that the Nav channel activator, veratridine (VTD), induces indirectly the activation of L-type Cav channels (LTTC) and subsequent Ca^{2+} entry, as other Nav channel activators. This underlines a cross talk between Nav and Cav channels in these cells. Here, we investigated the effect of KB-R7943, a non-selective blocker of Na^{+}/Ca^{2+} ion exchanger (NCX), on Ca^{2+} responses, Na^{+} and Ca^{2+} currents in GH3b6 cells. Surprisingly, KB-R7943, efficiently prevented VTD-induced Ca^{2+} responses, which was fully abolished at concentration up to 50 µM, as nifedipine, the selective LTCC blocker. KB-R7943 reduced INa amplitudes in a non-voltage-dependent manner, and induced a negative shift of the voltage dependence of activation and inactivation. Altogether, our findings highlight that KB-R7943 inhibits VTD-induced Ca^{2+} responses in a concentration dependent manner and modifies electrophysiology properties of Nav channels, providing a non-specific action on NCX. To further characterize the pharmacological profile of KB-R7943, we are currently exploring its effects on Ca^{2+} currents and total currents with patch clamp experiments in GH3b6 cells.
Altogether, our data show that GH3b6 cells offer a convenient model for pharmacological assays using the Fura-2 Ca^{2+} probe to characterize Nav channel modulators thanks to Nav and Cav channels crosstalk. In addition, KB-R7943 should be used with precaution to investigate NCX function, since it also efficiently blocks Nav channels.

EFFECTS OF PHARMACOLOGICAL RYANODINE RECEPTOR MODULATION ON VOLTAGE-GATED IONIC CURRENTS IN MURINE HIPPOCAMPAL CORNU AMMONIS-1 PYRAMIDAL NEURONS.

Federico BERTAGNA[1]; Shiraz AHMAD[2]; Rebecca LEWIS[2]; S Ravi P SILVA[1]; Johnjoe MCFADDEN[1]; Christopher L.H HUANG[3]; Hugh R. MATTHEWS[3]; Kamalan JEEVARATNAM[1].
1: Leverhulme Quantum Biology Doctoral Training Centre, University of Surrey
2: School of Veterinary Medicine
3: Physiological Laboratory and the Department of Biochemistry, University of Cambridge

Recent reports in murine skeletal muscle (SkM) describe feedback effects inhibiting or enhancing Na^{+} channel (Nav) currents by caffeine-induced ryanodine receptor (RyR) mediated Ca^{2+} release activation or inactivation. Further effects of the RyR and Ca^{2+}-ATPase (SERCA) blockers dantrolene and cyclopiazonic acid (CPA) additionally implicated background tubular-sarcoplasmic Ca^{2+} domains in these actions. We here explore for parallel properties in similarly loose patch-clamped hippocampal cornu ammonis-1 (CA1) pyramidal neurons in murine hippocampal brain slices. CA1 pyramidal neurones similarly show RyR and SERCA-mediated intracellular store Ca^{2+} release and re-uptake following Nav-mediated action potential excitation, additional to a surface membrane Ca^{2+} influx. Depolarizing 15 ms duration steps to test voltages -40 to 120 mV positive to resting membrane potential demonstrated that 0.5 mM caffeine decreased inward current amplitudes agreeing with the previous SkM findings, and decreased transient but not prolonged outward, K^{+}, (Kv) current amplitudes. Contrastingly 2 mM caffeine affected neither inward nor transient outward while increasing prolonged outward currents. In contrast to SkM findings, both dantrolene (10 µM) and CPA (10 µM) pre-administration left inward and outward currents unchanged. Nevertheless, dantrolene pre-treatment abrogated effects of subsequent 0.5- and 2-mM caffeine challenge on both inward and outward currents. CPA abrogated effects of 0.5 mM caffeine on both inward and outward

currents; with 2 mM caffeine inward and transient outward currents were unchanged but prolonged outward currents increased. These respective similarities and contrasts to previous SkM findings suggest evoked but not background Ca^{2+}-store release influenced Nav and Kv excitation in murine CA1 pyramidal neurons.

ELECTRICAL PROPERTIES AND INTRACELLULAR CALCIUM SIGNALING IN CARDIOMYOCYTES FROM THE HONEY BEE HEART.

Mahira KAABECHE[1]; Mercédès CHARRETON[2]; Aklesso KADALA[2]; Mathieu ROUSSET[3]; Thierry CENS[3]; Michel VIGNES[3]; Patrick BOIS[4]; Pierre CHARNET[3]; Claude COLLET[2].
1: INRAE UR 406 Abeilles & Environnement, Avignon, France and CNRS UMR 5247 Institut des Biomolécules Max Mousseron Université de Montpellier 2, Montpellier, France
2: INRAE UR 406 Abeilles & Environnement, Avignon, France
3: CNRS UMR 5247 Institut des Biomolécules Max Mousseron Université de Montpellier 2, Montpellier, France
4: Laboratoire Signalisation et Transports Ioniques Membranaires CNRS Université de Poitiers, Poitiers, France

Although the genome of the economically important honey bee Apis mellifera is known for several years, roles and properties of ion channels in cellular excitability still remain to be extensively characterized in this model insect. Exploration of channels functions and sensitivity to insecticides is of primary importance in order to better evaluate the involvement of environmental pollution in the decline of insects abundance and species richness. We have recently shown that the toxicity of chlorantraniliprole (CHL), a member of a new family of insecticides targeting intracellular calcium release channels (ryanodine receptors, RyR), was more elevated when applied to the near-cardiac region of the bee body, suggesting a peculiar cardiotoxicity. In the present study, we show that CHL indeed interferes with the contractile function of the isolated cardiac tube. In order to characterize the modes of action of CHL in details, we have set-up the isolation of intact cardiomyocytes and studied single-cell intracellular calcium homeostasis and electrical excitability with calcium imaging and patch-clamp techniques. As expected from a RyR opener, CHL induces a cytoplasmic [Ca^{2+}] increase. Interestingly, cell exposure to CHL may also decrease low-voltage-activated and high-voltage activated calcium currents densities. CHL cardiotoxicity could thus be due to an action on multiple molecular targets. Further studies on honey bee intact cardiomyocytes will help to better understand the excitability of insect heart and cardiotoxicity of insecticides.

16:30 Symposium 2: "Hypoxia and ion channels"

*Organized by **Alban Girault** (Amiens, France)*

ROLE OF ION CHANNELS IN THE HYPOXIA-INDUCED AGGRESSIVENESS OF GLIOBLASTOMA

Luigi CATACUZZENO;
Dipartimento di chimica, biologia e biotecnologie bio/09 - fisiologia - universita degli studi di perugia

Malignancy of glioblastoma (GBM), the most common and aggressive form of human brain tumors, strongly correlates with the presence of hypoxic areas within the tumor mass. Oxygen levels have been shown to control several critical aspects of tumor aggressiveness, such as migration/invasion and cell death resistance, but the underlying mechanisms are still unclear. GBM cells express abundant amounts of K and Cl channels whose activity supports cell volume and membrane potential changes, critically important for cell proliferation, migration, or death. We found that the functional expression and/or activity of these channels are under the control of oxygen levels, and these regulations are involved in the hypoxia-induced GBM cell aggressiveness. More specifically, volume-regulated Cl channels (VRAC) were found to be acutely activated by a hypoxic stimulus, due to the cell volume change induced by this condition. Notably, the activation of Cl channels by the hypoxic insult, and the resulting activation of RVD, would prevent long-term cell swelling that would lead to necrotic cell death. Exposure to hypoxia was also found to upregulate the functional expression of large-conductance Ca^{2+}-activated K (BK) channels , and increase the migratory ability of GBM cells (wound healing and transwell migration assays). Hypoxia-induced migration of GBM cells was abolished in presence of BK channels inhibitors. The BK channel activity was also important for hypoxia-induced chemoresistance to cisplatin and de-differentiation of GBM cells (neither of these was observed when BK channels were blocked). Immunohistochemical analysis finally showed the increased expression of both BK and VRAC channels in hypoxic areas of human GBM tissues, suggesting that our findings may have physiopathological relevance in vivo. In conclusion, our data show that Cl and K channels concur in promoting several aspects of the aggressive potential of GBM cells induced by hypoxia, suggesting them as potential therapeutic targets in the treatment of GBM.

IMPACT OF HYPOXIA ON ION CHANNELS IN THE CONTEXT OF CYSTIC FIBROSIS

Khilian PASCAREL, Clarisse VANDEBROUCK
Laboratoire PRéTI UR 24184 - Université de Poitiers - 1 Rue Georges Bonnet 86073 POITIERS France

The purpose of our respiratory system is to provide the body with the oxygen (O_2) it needs to ensure the aerobic metabolism of all the organs of the body, and to evacuate the carbon dioxide (CO_2) generated by this same metabolism in the peripheral tissues. Respiratory failure can therefore be defined as the inability of the lungs to supply the O_2 necessary for aerobic tissue metabolism (hypoxia). Chronic respiratory failure only appears at rest in advanced stages of obstructive diseases such as cystic fibrosis. More specifically, in the airways of patients with cystic fibrosis, mutations in the *CFTR* (Cystic Fibrosis Transmembrane Conductance Regulator) gene cause increased viscosity and mucus hypersecretion, affecting mucociliary clearance, which can lead to chronic hypoxia. Indeed, patients with cystic fibrosis suffer from anaemia and a state of proven chronic hypoxia. This is all the more so since the life expectancy of patients with cystic fibrosis is lengthening considerably (more than 40 years of life gained in 60 years) which makes this aspect of the pathology appear even more.

Our project aims to set up a hypoxic bronchial epithelial cell culture model on which we will be able to identify the ion channels whose activity is modulated as well as the signalling pathways associated with these modifications.
This information will give us new potential therapeutic targets to improve epithelial cell function in this hypoxic environment that will better reflect the natural environment of patient cells. Recently, innovative treatments have revolutionized the lives of patients with cystic fibrosis. These drugs aim to repair the CFTR protein, product of the mutated gene, by a combination of correctors associated with an activator of this protein. Thus, we will be able to test the effects of these current modulators of mutated CFTR on epithelial cells in hypoxia. This will allow us to better assess their effectiveness in this hypoxic context which will better reflect the pathophysiological situation of patients with cystic fibrosis.
All of these experiments should allow us to better understand the functioning of the ion channels of the cystic fibrosis epithelial cells of the airways in a context of hypoxia and to discover new therapeutic targets that will have to be tested in synergy with the current drugs of the pathology.

INVOLVEMENT OF ORAI1 CA^{2+} CHANNEL IN THE PATHOGENESIS OF PULMONARY ARTERIAL HYPERTENSION

Bastien MASSON, Fabrice ANTIGNY
INSERM U999, Hypertension Pulmonaire : Physiopathologie et Nouvelles Thérapies, Le Plessis Robinson (France)

Pulmonary arterial hypertension (PAH) is characterized by progressive distal pulmonary artery (PA) obstruction, leading to right ventricular hypertrophy and failure. Exacerbated intracellular calcium (Ca^{2+}) signaling contributes to abnormalities in PA smooth muscle cells (PASMCs), including aberrant proliferation, apoptosis resistance, exacerbated migration, and arterial contractility. Store-operated Ca^{2+} entry is involved in Ca^{2+} homeostasis in PASMCs, but its properties in PAH are unclear.
Using a combination of Ca^{2+} imaging, molecular biology, in vitro, ex vivo, and in vivo approaches, we investigated the roles of the Orai1 SOC channel in PA remodeling in PAH and determined the consequences of pharmacological Orai1 inhibition in vivo using experimental models of PAH.
Store-operated Ca^{2+} entry and Orai1 mRNA and protein were increased in human PASMCs (hPASMCs) from patients with PAH (PAH-hPASMCs). We found that MEK1/2 (mitogen-activated protein kinase kinase 1/2), NFAT (nuclear factor of activated T cells), and NFκB (nuclear factor-kappa B) contribute to the upregulation of Orai1 expression in PAH-hPASMCs. Using small interfering RNA (siRNA) and Orai1 inhibitors, we found that Orai1 inhibition reduced store-operated Ca^{2+} entry, mitochondrial Ca^{2+} uptake, aberrant proliferation, apoptosis resistance, migration, and excessive calcineurin activity in PAH-hPASMCs. Orai1 inhibitors reduced agonist-evoked constriction in human PAs. In three different experimental rat models of PAH administration of Orai1 inhibitors protected against PAH.
In human PAH and experimental PAH, Orai1 expression and activity are increased. Orai1 inhibition normalizes the PAH-hPASMCs phenotype and attenuates PAH in rat models. These results suggest that Orai1 should be considered as a relevant therapeutic target for PAH.

ROLE OF CRACR2A IN THE DEVELOPMENT OF PULMONARY ARTERIAL HYPERTENSION

Anaïs SAINT-MARTIN WILLER; Bastien MASSON; Mary DUTHEIL; Yann RUCHON; Marc HUMBERT; David MONTANI; Véronique CAPUANO; Fabrice ANTIGNY; INSERM UMR_S999 « Hypertension pulmonaire : Physiopathologie et Nouvelles Thérapies », Hôpital Marie Lannelongue, Le Plessis-Robinson, France

Pulmonary arterial hypertension (PAH) is a rare, progressive, and devastating disease resulting from the obstruction of distal pulmonary arteries. The pathobiology of PAH is multifactorial, involving all the cell spectrum of pulmonary circulation, including pulmonary arterial (PA) smooth muscle cells (PASMCs), endothelial cells (PECs), and PA adventitial fibroblasts (PAAFs). These cellular dysfunctions lead to a progressive narrowing of the small distal pulmonary arteries. The intracellular calcium (Ca^{2+}) signaling mishandling is crucial for all these cellular dysfunctions, including at least exacerbated proliferation and apoptosis resistance, aberrant migration, and excessive contraction. Recently, we demonstrated that the Store-Operated Calcium Entry (SOCE) is increased in PAH-hPASMCs in association with a two-fold increase of Orai1 protein expression and function. Orai1 requires STIM molecules to be functional and other proteins, such as CRACR2A, a regulatory protein of Orai1. Indeed, CRACR2A, a cytosolic Ca^{2+} sensor, plays a crucial role in SOCE by regulating the Orai1-STIM1 interaction. Moreover, a loss of function mutation in CRACR2A gene has been identified in an Italian PAH cohort. However, its role in PAH pathogenesis is unknown. Our goal was to study the role of CRACR2A in PAH pathogenesis. We used a siRNA strategy against CRACR2A in hPASMCs, hPECs, and hPAAF isolated from control and PAH patients. We then measured the consequences of the CRACR2A knockdown on SOCE by Ca^{2+} imaging measurement, on cell proliferation, migration capacity, apoptosis and in vitro angiogenesis. Finally, we measured the consequence on SOCE and Orai1 protein expression in PAH-hPASMCs overexpressing CRACR2A. We found that SOCE, migration, and proliferation were decreased in control-hPASMCs transfected with siCRACR2A. Surprisingly, in PAH-hPASMCs, the knockdown of CRACR2A increased SOCE, Orai1 expression, and cell proliferation. In contrast, CRACR2A overexpression in PAH-hPASMCs reduced SOCE. These results indicate that CRACR2A plays an essential role in pulmonary vascular cells from control and PAH patients by its involvement in SOCE, proliferation, and migration. The reduced CRACR2A expression in PAH-hPASMCs could partly explain why Orai1 expression/function is increased in PAH-hPASMCs. These results suggest that CRACR2A dysfunction is involved in PAH pathogenesis.

Tuesday, September 19th 2023

08:30 Symposium 3: "Role of ion channels in stem/progenitor cells"

Organized by ***Valérie Coronas*** *(Poitiers, France)*

GENELESS OPTICAL STIMULATION GENERATES PRO-ANGIOGENIC CA^{2+} SIGNALS IN ENDOTHELIAL COLONY FORMING CELLS

Francesco MOCCIA;
Laboratory of Ca^{2+} Signalling, Pavia, Italia

Therapeutic neovascularization represents a promising strategy to rescue the vascular network and restore organ function in cardiovascular disorders (CVDs), including acute myocardial infarction, heart failure, peripheral artery disease, and brain stroke. Endothelial colony forming cells (ECFCs), which are mobilized in circulation upon an ischemic insult, are commonly regarded as the most suitable cellular tool to achieve therapeutic neovascularization. ECFCs can be genetically or pharmacologically manipulated to enhance their vasoreparative potential by boosting specific pro-angiogenic signalling pathways. However, optical stimulation represents the most reliable approach to control cellular activity because of its high selectivity and unprecedented spatio-temporal resolution. Intracellular Ca^{2+} signals shaped by InsP3-dependent Ca^{2+} release from the endoplasmic reticulum, NAADP-evoked lysosomal Ca^{2+} release and store-operated Ca^{2+} entry (SOCE) regulate ECFCs' pro-angiogenic activity both in vitro and in vivo. Recent evidence revealed that intracellular Ca^{2+} oscillations could be exploited to stimulate ECFCs-dependent neovascularization for therapeutic purposes. Herein, we discuss a novel strategy to drive ECFC angiogenic activity in ischemic tissues by combining geneless optical excitation with photosensitive organic semiconductors. We describe how photoexcitation of the conducting polymer poly(3-hexylthiophene-2,5-diyl), also known as P3HT, stimulates extracellular Ca^{2+} entry through Transient Receptor Potential Vanilloid 1 (TRPV1) channels upon the production of hydrogen peroxide (H_2O_2) in the cleft between the nanomaterial and the cell membrane. H_2O_2-induced TRPV1-dependent Ca^{2+} entry stimulates ECFC proliferation and tube formation, thereby providing the proof-of-concept that photoexcitation of organic semiconductors may offer a reliable strategy to stimulate ECFCs-dependent neovascularization in cardiovascular disorders.

DISTINCTIVE CA^{2+} CHANNELS COORDINATE EXTRACELLULAR ATP-INDUCED CA^{2+} SIGNALLING AND FUNCTIONAL REGULATION IN MESENCHYMAL STEM CELLS

Lin-hua JIANG;
Department of Physiology and Pathophysiology, School of Basic Medical Science, Xinxiang Medical University, China, and 2.School of Biomedical Sciences, Faculty of Biological Sciences, University of Leeds, UK

Mesenchymal stem cells (MSC) are crucial in adult tissue morphogenesis and homeostasis and attract substantial attention as a cell source for tissue engineering and cell-based therapies. MSC release adenosine triphosphate (ATP), as documented in response to diverse mechanical stimuli, as an autocrine or paracrine signaling molecule that induces intracellular Ca^{2+} signals. Accumulating evidence supports that ATP-induced purinergic Ca^{2+} signalling plays an important role in the regulation of MSC functions. We examined the molecular mechanisms responsible for ATP-induced Ca^{2+} signalling and functional regulation in MSCs derived from human dental pulp tissues. Both the ionotropic P_2X and metabotropic P_2Y

receptors are expressed in MSC and participate in ATP-induced Ca^{2+} responses by mediating extracellular Ca^{2+} entry and stimulating the Gq/phospholipase C/inositol triphosphate receptor (IP_3R) signal pathway that leads to Ca^{2+} release from endoplasmic reticulum (ER), respectively. Following IP_3R-mediated Ca^{2+} release from ER, the store-operated Ca^{2+} or Ca^{2+} release-activated channels that are composed of Orai and ER calcium sensor STIM proteins are activated and mediate further extracellular Ca^{2+} entry. The expression of the mechanosensitive Piezo1 channel is detected in MSC and its activation prompts extracellular Ca^{2+} entry and ATP release. Finally, these Ca^{2+} channels are critical in ATP-induced regulation of MSC proliferation, migration and differentiation. In summary, MSC are equipped with distinctive Ca^{2+} channels as molecular mechanisms that coordinate extracellular ATP-induced Ca^{2+} signalling and regulation of MSC functions.

INVOLVEMENT OF ORAI1/SOCE IN CANCER STEM CELLS AND CHEMORESISTANCE

LEWUILLON Clara[1]; NOYER Lucile[2]; GUILLEMETTE Aurelie[1]; TITAH Sofia[3]; FLAMENCO Pilar[2]; QUESNEL Bruno[1]; PREVARSKAYA Natalia[2]; TOUIL Yasmine[1]; LEMONNIER Loïc[2];
1: UMR 9020
2: UMR 1003
3: UMR 1003/UMR 9020

Acute myeloid leukemia (AML) is a hematological malignancy with a high risk of relapse. This issue is associated with the development of mechanisms leading to drug resistance that are not yet fully understood. In this context, we previously showed the clinical significance of the ATP binding cassette subfamily B-member 1 (ABCB1) in AML patients, namely its association with stemness markers and an overall worth prognosis. Calcium signaling dysregulations affect numerous cellular functions and are associated with the development of the hallmarks of cancer. However, in AML, calcium-dependent signaling pathways remain poorly investigated. With this study, we show the involvement of the ORAI1 calcium channel in store-operated calcium entry (SOCE), the main calcium entry pathway in non-excitable cells, in two representative human AML cell lines (KG1 and U937) and in primary cells isolated from patients. Moreover, our data suggest that in these models, SOCE varies according to the differentiation status, ABCB1 activity level and leukemic stem cell (LSC) proportion. Finally, we present evidence that ORAI1 expression and SOCE amplitude are modulated during the establishment of an apoptosis resistance phenotype elicited by the chemotherapeutic drug Ara-C. Our results therefore suggest ORAI1/SOCE as potential markers of AML progression and drug resistance apparition.
Interestingly, we have obtained similar results in other cancer models (i.e., prostate cancer, melanoma), where chemoresistance is associated with the apparition of CSC (cancer stem cells)-like cells exhibiting a decrease in ORAI1/SOCE activity and expression. Taken together, our results point to the existence of a common resistance mechanism in cancer cells involving ORAI1.

FUNCTIONAL CHARACTERIZATION OF MUSCLE CELLS DERIVED FROM HEALTHY AND DMD HUMAN INDUCED PLURIPOTENT STEM CELLS: FOCUS ON CALCIUM REGULATION.

Arnaud DELAFENETRE[1]; Charles-Albert CHAPOTTE-BALDACCI[1]; Emmanuelle MASSOURIDES[2]; Aurélien CHATELIER[1]; Christian COGNARD[1]; Christian PINSET[2]; Stéphane SEBILLE[1].
1: PRéTI laboratory, University of Poitiers, France
2: INSERM UEVE UMR861, I-STEM AFM, Corbeil-Essonnes, France

Pluripotent stem cells offer great potential for the development of treatment for rare genetic diseases. Human induced pluripotent stem cells (hiPSCs) produced by genetic reprogramming of healthy donors or patients' cells are widely used to model pathologies. These cellular models are of great interest in the study of Duchenne Muscular Dystrophy (DMD), whose pathophysiology is still poorly understood and for which the actual treatments are not curative. The main objective is to functionally characterize muscle cells derived from hiPSCs (hiPSCs-MCs) generated from DMD patients and healthy individuals. We focused on both myoblast and myotube stages of hiPSCs-MCs, corresponding to crucial phases of differentiation and maturation of skeletal muscle cells. A first investigation on excitability status of cells was performed through the measurement of resting membrane potential using the microelectrode method. In myoblast stage, hiPSCs cells displayed membrane potential values of -9.0 ± 1.0 mV for healthy cells and -8.1 ± 0.6 mV for DMD cells, meaning that at this stage; cell membranes are weakly polarized. Polarization of membranes increased for both cell lines at myotube stage. Hence, hiPSC-MCs seemed to express the physiological machinery of various channel and pump proteins allowing to segregate ions across the lipid bilayer to establish the cellular resting potential. The calcium status of these cells, evaluated by quantitative measurement of calcium levels at rest, as well as calcium spontaneous activity, has also been evaluated. Results show that, as compared to healthy hiPSC-MCs, resting DMD hiPSC-MCs displayed specific spontaneous calcium signatures with high levels of intracellular calcium concentration. Furthermore, calcium increases through both electrical and acetylcholine stimulation have been compared between healthy and DMD cells. Electrical field stimulation and acetylcholine perfusion induced higher calcium responses in DMD hiPSC-MCs as compared to healthy cells. These results lead us to believe that muscle cells derived from DMD hiPSCs display a dysregulation of calcium homeostasis. Hence, hiPSC-MCs may model some aspects of functional dysregulation in DMD disease.

10:45 Oral communication session 2: "ion channels and cancer"

*Organized by **Claire Legendre** (Angers, France)*

VENOM PEPTIDES: EMERGENT BIOLOGICAL TOOLS FOR LUNG CANCER IMAGING.

Romain BAUDAT; Evelyne BENOIT; Mathilde KECK; Pascal KESSLER; Denis SERVENT.
Université Paris-Saclay, CEA, Institut des sciences du vivant Frédéric Joliot, Département Médicaments et Technologies pour la Santé (DMTS), Service d'Ingénierie Moléculaire pour la Santé (SIMoS)

Many cancers, and the non-small cell lung cancer in particular, are associated with a disturbance of the mechanisms controlling ion homeostasis due, especially, to dysfunction and/or overexpression of many ion channels such as certain subtypes of sodium ($NaV_{1.7}$), potassium ($KCa_{3.1}$) channels, pH-sensitive channels (ASICs for acid sensing ion channels) or nicotinic acetylcholine receptors ($nAChr_{\alpha7}$, $nAChr_{\alpha9/\alpha10}$). In particular, the activation of these ion channels plays an important role in cancer cell aggressiveness and tumor invasion, their overexpression seeming to be correlated with the appearance of metastases. Although imaging approaches (radiography, CT-scan for computed tomography scanning, PET-scan or positron emission tomography) are commonly used in the anatomical characterization of lung cancer, some of their limitations require the development of new imaging probes more specific of overexpressed molecular targets in lung adenocarcinomas. Peptide toxins, which have unique pharmacological properties, are well known to act selectively and with high affinity on certain overexpressed ion channels in cancer cells. Therefore, a promising solution towards the development of new lung cancer biomarkers appears to be the chemical synthesis of these toxins allowing them to be marked by "click" chemistry using various fluorescent or radioactive probes.

KV10.1 FAVORS EMT AND MIGRATION IN BREAST CANCER AGGRESSIVENESS

Mélanie LAINE; Frédéric HAGUE; Halima OUADID AHIDOUCH; Alban GIRAULT;
Laboratoire de Physiologie Cellulaire et Moléculaire - UR UPJV 4667, UFR Sciences, Université de Picardie Jules Verne (UPJV), 80039, Amiens, France.

Breast cancer (BC) is the most common cancer diagnosed in women and remains the leading cause of cancer-related death. This high mortality is correlated with metastases development. BC aggressiveness is often correlated with Epithelial-mesenchymal transition (EMT) and migration (1). Hypoxia, characteristic of tumors, is responsible for the activation of Hypoxia Inducible Factor 1 alpha (HIF-1α). Moreover, severe hypoxia (1% oxygen) is responsible for the expression of genes involved in carcinogenesis (2). Kv10.1, a voltage-dependent potassium channel, is involved in various BC tumorigenesis processes (3). It has been demonstrated that Kv10.1 regulates HIF-1α expression in CHO cells (4), but, the role of Kv10.1 in BC tumor progression under hypoxic conditions is still poorly understood. Here, we reported the contribution of Kv10.1 in BC metastasis by promoting EMT and migration under severe hypoxia.
We found that Kv10.1 expression was increased in severe hypoxia (1% O_2, 18h) and that HIF-1α expression was decreased when Kv10.1 was silenced. Protein analysis showed that Kv10.1 channel silencing also decreased a mesenchymal marker N-cadherin expression by 50% (+/- 10%) in a basal triple negative cell line (MDA-MB-231). In addition, in MCF-7 cells, a luminal epithelial cell line, transfected with siKv10.1, E-cadherin expression (an epithelial marker) increased by 30% (+/- 8%) and N-cadherin expression decreased by 50% (+/-15%). These results suggest that Kv10.1 favors the mesenchymal phenotype. We also investigated the role of this channel in migration under hypoxia. Hypoxia increased migration that was significantly reduced in Kv10.1-silenced cells. This effect is associated with a morphological change

resulting in cell rounding. We then investigated the Kv10.1 silencing's impact on the expression of two migration actors: β1-integrin and Focal Adhesion Kinase (FAK). Kv10.1 silencing decreased the expression of β1-integrin and the FAK phosphorylation (or activation). Furthermore, we showed, by immunofluorescence, in normoxia that Kv10.1 is co-expressed with β1-integrin and with pFAK (or FAK), and this effect was promoted under severe hypoxia. In conclusion, Kv10.1 is increased by hypoxia in a basal breast cancer cell and appears to be a pro-mesenchymal and a pro-migratory modulator in response to hypoxia.

(1) Yeeravalli et al., 2021 ; (2) Vaupel et al., 2004 ; (3) Ouadid-Ahidouch et al., 2016 ; (4) Downie et al., 2008

THE BLOCKING MECHANISM OF GOSSYPOL ON T-TYPE CALCIUM CHANNELS AND ITS IMPACT ON COLON CANCER CELL GROWTH.

Osbaldo LOPEZ-CHARCAS[1]; Oumnia BENOUNA[2]; Roxane LEMOINE[2]; Margarita ROSENDO-PINEDA[1]; Tonantzin ANGUHEVEN-LEDEZMA[1]; Fabio FERRO[2]; Pierre BESSON[2]; Lin-hua JIANG[3]; Sébastien ROGER[2]; Juan carlos GOMORA[1].

1: Departamento de Neuropatología Molecular, División de Neurociencias, Instituto de Fisiología Celular, Universidad Nacional Autónoma de México, 04510 Ciudad de México, México.

2: EA4245, Transplantation, Immunologie et Inflammation, Faculté de Médecine, Université de Tours, 37032 Tours, France.

3: School of Biomedical Sciences, Faculty of Biological Sciences, University of Leeds, Leeds, United Kingdom. Department of Physiology and Pathophysiology Xinxiang Medical University, China.

The Cav3 calcium channels subfamily, also known as T-type calcium channels, comprises Cav3.1, Cav3.2, and Cav3.3 subunits, which are overexpressed in gastrointestinal tract tumors. Cav3 channels have been proposed in colon cancer to regulate cellular growth and apoptosis. Gossypol has antitumoral properties and inhibits Cav3 currents. In this work, we investigated how gossypol blocks each member of the Cav3 subfamily and its antitumor effects in human colon cancer cells expressing different basal levels of the Cav3 isoforms. Transcripts encoding for Cav3 and the corresponding proteins were studied in gastrointestinal tract cancers using public database repositories and the human colon cancer cell lines HCT116, SW480, and SW620. Through heterologous expression systems, patch-clamp experiments, and biophysical analyses, we described the gossypol-blocking mechanism on Cav3 channels. Cell viability experiments, flow cytometry, and cell-cycle profiling addressed the antitumoral properties of gossypol. Our results indicated that high levels of transcripts encoding for Cav3 channels represent a poor prognosis in gastrointestinal cancers. The Cav3.2 subunit was the most sensitive to gossypol. We demonstrated that gossypol accesses more easily from the extracellular side to exert its inhibitory effect on Cav3 channels. Gossypol showed a use-dependent blocking component, and it also blocked the closed state of Cav3.3 channels. Furthermore, gossypol inhibited colon cancer cell proliferation by arresting cell cycle at the G0/G1 phase. We found that gossypol differentially blocks Cav3 subunits, and its antitumor activity was positively correlated with high levels of the Cav3.1 subunit expression in colon cancer cells. Our findings suggest that T-type calcium channels could serve as molecular targets for cancer therapy.

NON GENOMIC REGULATION OF TRPM8: FROM THERMOSENSATION TO CANCER.

Dimitra GKIKA.
CANTHER Lab, UMR9020 CNRS - UMR-1277 Inserm, University of Lille, France

TRPM8, a predominant detector of cold temperatures in vivo, is also expressed in sensory fibers innervating visceral organs and in epithelia such as prostate, bladder, testis and skin. In epithelia TRPM8 was involved in carcinogenesis and seems to be one of the most promising clinical targets for prostate cancer due to the variation in its expression. In an effort to characterize physiological factors other than cold playing a putative role in TRPM8 activation/modulation, several hormones were tested in our laboratory. In this context we have recently shown that testosterone regulates directly TRPM8 activity in both prostate carcinogenesis and cold thermosensation. In this presentation, I will provide a mechanistic insight in the hormonal non genomic regulation of TRPM8 channel in two processes modulated during ageing, cold thermosensation and malignant transformation.

17:15 Symposium 4: "Ion channel and development"

Organized by ***Marie Demion*** (Montpellier, France)

MORPHOGENESIS OF THE VENTRICULAR PURKINJE NETWORK: LINKING ARCHITECTURE AND FUNCTION

Lucile MIQUEROL
IBDM CNRS UMR7288, Marseille, France

The rapid propagation of electrical activity through the ventricular conduction system (VCS) controls spatiotemporal contraction of the ventricles. Cardiac conduction defects or arrhythmias in man are often associated with mutations in key cardiac transcription factors that have been shown to play important roles in VCS morphogenesis in mice. Understanding of the mechanisms of VCS development is thus crucial to decipher the etiology of conduction disturbances in adults. During embryogenesis, the VCS, consisting of the His bundle, bundle branches and the distal Purkinje network, originates from two independent progenitor populations in the primary ring and the ventricular trabeculae. Differentiation into fast-conducting cardiomyocytes occurs progressively as ventricles develop to form a unique electrical pathway at late fetal stages. The objectives of this talk are to highlight the structure-function relationship between VCS morphogenesis and conduction defects and to discuss recent data on the origin and development of the VCS with a focus on the distal Purkinje fiber network

PIEZO1 IN HEART DEVELOPMENT AND FUNCTION

Adèle FAUCHERRE
Institut de Génomique Fonctionnelle, Montpellier, France

The PIEZO family of stretch activated ion channels are a class of mechanosensitive proteins which allow cells to respond to a variety of physical stimuli and may therefore have a role in detecting the forces associated with circulatory blood flow. Our lab has identified 3 piezo homologs in zebrafish namely piezo1a, piezo1b and piezo2. We have shown that piezo1a plays a role in erythrocyte homeostasis and that piezo2 regulates vertebrate light touch. Lastly, we have found that piezo1b regulates vertebrate cardiogenesis. Our results show that the zebrafish piezo1b homolog is expressed in the endothelial cells lining the heart and vasculature with a particularly strong expression in the outflow tract (OFT). Consequently, disrupting Piezo1 signalling leads to defective outflow tract and aortic valve development and indicates this gene may be involved in the etiology of congenital heart diseases. Based on these findings, we analysed genomic data generated from patients who suffer from bicuspid aortic valve (BAV) and identified probands who each harboured potentially pathogenic variants in PIEZO1. Subsequent in vitro and in vivo assays indicates that these variants behave as dominant negatives leading to an inhibition of normal PIEZO1 mechanosensory activity. Mechanosensitive ion channels are also thought to be the main proponents of mechanoelectric feedback as they provide a rapid response to mechanical stimulation and can directly affect cardiac electrical activity. We demonstrated that Piezo1 is expressed in zebrafish cardiomyocytes. Furthermore, chemically prolonging Piezo1 activation in zebrafish results in cardiac arrhythmias, indicating that this ion channel plays an important role in mechanoelectric feedback. This also raises the possibility that PIEZO1 gain of function mutations could be linked to heritable cardiac arrhythmias in humans.

MOLECULAR BASIS OF THE UNCONVENTIONAL SELECTIVITY OF THE C.ELEGANS K2P CHANNEL UNC-58

Olga ANDRINI[1]; Ismail BEN SOUSSIA [1]; Philippe TARDY[1]; Denise WALKER [2]; David RAMIREZ [3]; Wendy GONZALEZ[4]; Marie GENDREL [1]; William SCHAFER [2]; Maelle JOSPIN[1]; Thomas BOULIN [1];
1 Univ Lyon, Université Claude Bernard Lyon 1, MeLiS, CNRS UMR 5284, INSERM U1314, Institut NeuroMyoGène, Lyon 69008, France
2 Neurobiology Division, MRC Laboratory of Molecular Biology, Francis Crick Avenue, Cambridge, UK
3 Departamento de Farmacología, Facultad de Ciencias Biológicas, Universidad de Concepción, Chile
4 Center for Bioinformatics, Simulation and Modelling (CBSM) University of Talca, Chile

In most excitable tissues, the establishment and maintenance of a negative membrane potential is essential to ensure normal cellular excitability. Despite the crucial role of two-pore domain potassium (K2P) channels in maintaining the resting membrane potential at hyperpolarized values, recent studies have revealed the peculiar properties of some K2P channels, which result in a reduced K+ selectivity and non-selective ion conduction. With 47 subunit-coding genes, K2Ps are the largest ion channel class in C. elegans. This remarkable expansion has been accompanied by the evolution of channel genes with atypical sequence features, such as selectivity filter sequences that diverge from canonical G(Y/F)G triplets. We focused our study on UNC-58, a K2P channel that is expressed in muscles and neurons. Surprisingly, UNC-58 gain-of-function lead to hyper-excitability of touch neurons (ALM) and striated muscle cells. Indeed, these physiological responses are not consistent with the expected hyperpolarizing effect of a hyperactive K^+ channel. By investigating its ion selectivity, we demonstrate that UNC-58 is in fact permeable to sodium. Close examination of the the selectivity filter (SF) sequences revealed an unusual amino acid signature. Unique among all nematode K2P channels – and in fact all known K^+ channel genes in any organism – UNC-58 harbors a cysteine residue in SF1 selectivity filter. MD simulations indicated a collapse in the S2 selectivity filter site caused by a loss of coordination between Cys266 and the K^+ ion. Using electrophysiological and calcium imaging approaches, we show that this single amino acid change caused UNC-58 to become a constitutively non-selective K2P channel that therefore increases cellular excitability.

VALIDATION OF DIFFERENTIATED SINOATRIAL-LIKE HIPSCS AS A MODEL OF NATIVE SINUS NODE MYOCYTES

Eleonora TORRE[1]; Yvonne SLEIMAN [2]; Azzouz CHARRABI[2]; Leïla TALSSI[1]; Haikel DRIDI[3]; Jean-luc PASQUIE[2]; Alain LACAMPAGNE[2]; Matteo e MANGONI[1]; Pietro MESIRCA[1]; Albano c MELI[2];
1 Institut de Génomique Fonctionnelle, Université de Montpellier, CNRS, INSERM, LabEx Ion Channels Science and Therapeutics (ICST)
2 PhyMedExp, University of Montpellier, INSERM, CNRS, Montpellier, France
3 Department of Physiology and Cellular Biophysics, Columbia University Vagelos College of Physicians and Surgeons, New York, NY, USA

Human induced pluripotent stem cell derived cardiomyocytes (hiPSC-CMs) constitute an attractive approach for both basic research and pharmacologic screening of new molecules of clinical interest. The majority of the cardiac differentiation protocols using hiPSC have been focused on ventricular-like cardiomyocytes (ventricular-like hiPSC-CMs). However, only a few protocols are available to obtain patient-derived sinoatrial node-like pacemaker myocytes (PM-hiPSC-CMs). Here we aim to validate differentiated PM-hiPSC-CMs to obtain a mature model of native sinoatrial node (SAN) myocytes to study SAN dysfunction (SND). We generated PM-hiPSC-CMs through a 2D matrix-sandwich method which promotes epithelial-to-mesenchymal

transition and small molecule-based temporal modulation of Wnt signaling pathway. Moreover, we treated our cells with triiodothyronine, dexamethasone and intracellular cyclic AMP (DTA) 'cocktail' to improve the key properties of the hiPSC-CMs by ameliorating, in particular, the intracellular calcium handling machinery. Using proteomic analyses, we observed that obtained DTA-treated PM-hiPSC-CMs express key SAN proteins. The amelioration of the intracellular Ca^{2+} dynamic in differentiated DTA-treated PM-hiPSC-CMs, as reported by both, protein expression and functional data, was observed. DTA-treated PM-hiPSC-CMs displayed action potentials and ionic currents typical of native SAN. In addition, pacemaker activity responded to both β-adrenergic and muscarinic stimulation. Altogether, our data indicate that the differentiation protocol effectively generates PM-hiPSC-CMs with typical native SAN features. This protocol may serve as a potential approach to generate PM-hiPSC-CMs from patients with a history of SND carrying different mutations in ion channels underlying pacemaking. These in vitro models of SND could be used for testing long-term vector-based gene therapeutic strategy to handle bradycardia.

21:30 Evening Conference and Party

SCIENTIFIC FRAUD: A LONG HISTORY... WITH POTENTIALLY DISASTROUS CONSEQUENCES.

Caroline STRUBE
CNRS Research Integrity Office

Honest and responsible research is a prerequisite for the credibility of science and the trust of society. Yet there are deviations, and widely publicized cases of scientific fraud contribute to suspicion towards science and scientists. We could think that these abuses are simply the consequence of the pressure put on researchers in a world of intense competition. But scientific fraud has always existed. The history of science is full of more or less conscious errors, proven frauds and impostures. Some of the oldest, committed by illustrious scientists, have led to major and indisputable scientific advances; but others, more recent, have disturbed public decisions, spread false ideas, and even led to avoidable deaths.

Wednesday, September 20th 2023

09:30 Symposium 5: "Ion channels in non excitable cells"

*Organized by **Isabelle Rubera** (Nice, France)*

ASIC2 VARIANT, A NOVEL MOLECULAR ENTITY INVOLVED IN RENAL NA RETENTION DURING IDIOPATHIC NEPHROTIC SYNDROME

Marc FILA[1]; Ali SASSI[2]; Gaelle BRIDEAU[3]; Lydie CHEVAL[3]; Luciana MORLA[3]; Pascal HOUILLIER[3]; Gabrielle PLANELLES[3]; Naziha BAKOUH[3]; Alain DOUCET[3]; Gilles CRAMBERT[3];
1: CHU Montpellier
2: Université de Genève
3: Centre de Recherche des Cordeliers

Idiopathic nephrotic syndrome (INS) is characterized by proteinuria and renal Na retention leading to oedema. This Na retention is usually attributed to the overexpression and activity of the epithelial sodium channel (ENaC) following plasma aldosterone increase. However, most nephrotic patients show normal aldosterone levels. We therefore developed a model of INS that does not exhibit any increase of plasma aldosterone using a corticosteroid-clamped rat model (CC-PAN). We showed that the observed electrogenic and amiloride-sensitive Na retention could not be attributed to ENaC because this activity exhibits different properties that are not attributable to ENaC. This electrogenic and amiloride-sensitive Na activity is not sensitive to Zn or low pH which is characteristic of ENaC. We, then, identified a truncated variant of acid sensing ion channel 2b (ASIC2b) that induced sustained acid-stimulated sodium currents when co-expressed with ASIC2a. Interestingly, CC-PAN nephrotic ASIC2b-null rats did not develop sodium retention. We finally showed that expression of the truncated ASIC2b in kidney was dependent on the presence of albumin in the tubule lumen and activation of ERK in renal cells. Finally, the presence of ASIC2 mRNA was also detected in kidney biopsies from patients with INS but not in any of the patients with other renal diseases. We have, therefore, identified a novel variant of ASIC2b responsible for the renal Na retention in the pathological context of INS.

UPTAKE AND EFFLUX OF PHOSPHATE IN NON-EXCITABLE CELLS: TRANSPORTERS, SENSORS AND HOMEOSTATIC REGULATION

Sarah BECK-CORMIER[1]; Nathan CHATE[1]; Marie GUICHETEAU[1]; Nina BON[2]; Laurent BECK[1];
1 L'institut du thorax, Inserm UMR1087/CNRS6291, Nantes
2 RMeS Inserm UMR1229, Nantes

Phosphate (Pi) is involved in countless biological processes that require its extracellular and intracellular concentrations to be finely controlled, and these regulations to be coordinated. At the interface of extra- and intra-cellular volumes, Pi transporters expressed at the plasma membrane play a key role in this process. In mammals, the Pi transporters are divided into 2 families involved in Pi uptake into the cell, and one family involved in Pi export out of the cell. The SLC34 family comprises the SLC34A1 (Npt2a), SLC34A2 (Npt2b) and SLC34a3 (Npt2c) transporters allowing the sodium-coupled uptake of Pi at the plasma membrane. This family differs from the other two in its tissue-specific expression (mainly kidney and intestine). The hormonal regulation of their plasma membrane expression by FGF23 and PTH is a key mechanism in the body's phosphate balance. The SLC20 family, which also function as a high-

affinity sodium-coupled transporter of Pi, includes SLC20A1 (PiT1) and SLC20A2 (PiT2), which are expressed in all tissues. In addition to their transport function, these proteins are now described as multi-functional proteins involved in numerous cellular processes independent of their transport function, such as their role in the sensing of extracellular Pi. The third family, SLC53, comprises only one member, XPR1, whose functions, expression and location are still poorly understood. Unlike the other two families, XPR1 is described both as a Pi exporter at the plasma membrane and a key player in the regulation of intracellular Pi homeostasis. The aim of this talk will be to provide an overview of the functions, mechanisms of action and physiological importance of these different transporters, and to offer a more detailed insight into their involvement in physiological mineralisation and pathophysiological calcification.

STRUCTURE, FUNCTION AND MODULATION OF CFTR, AN ANION CHANNEL EVOLVED FROM AN ABC TRANSPORTER

Isabelle CALLEBAUT;
Sorbonne Université, Muséum National d'Histoire Naturelle, UMR CNRS 7590, Institut de Minéralogie, de Physique des Matériaux et de Cosmochimie, IMPMC, 75005 Paris, France

The Cystic Fibrosis Transmembrane conductance Regulator (CFTR) protein is a member of the ATP-Binding Cassette (ABC) transporter superfamily which functions as an ATP-gated anion channel in many epithelia-lining tissues. As a member of the ABC superfamily, CFTR forms a pseudo-dimeric architecture made of two subunits, each comprising a six-spanning transmembrane domain (TMD) and a nucleotide-binding domain (NBD). The two subunits are linked by a large cytosolic regulatory (R) region, which is largely disordered. This R region contains multiple sites for PKA-dependent phosphorylation, which are required for CFTR function as an ATP-gated ion channel. Loss of function of the CFTR protein leads to cystic fibrosis (CF), the most common life-shortening disease in the Caucasian population. Outstanding progress has been made in recent years in the treatment of CF, through the development of combinatorial therapies to correct different and often multiple defects associated with the disease-causing mutations. This has been made possible by the high-throughput screening of small molecules, as well as by the development of assays allowing the testing of patients' responsiveness to drugs. Here I wish to highlight how structural information (both experimental and computational) can help to explain the specific evolution of this member of the ABC transporter superfamily towards a channel function. This structural information can also be considered to elucidate the molecular basis of the impact of mutations on protein folding and function, as well as of the mechanism of action of modulators. Work in our lab has been supported by the French Association Vaincre La Mucoviscidose.

ACTIVATION OF THE LRRC8/VRAC ANION CHANNELS IN MACROPHAGES PLAY A CENTRAL ROLE IN MICRO-CRYSTAL-MEDIATED IL-1β RELEASE

Mete KAYATEKIN[1]; Twinu Wilson CHIRAYATH[2]; Matthias OLLIVIER[3]; Francois RASSENDREN[3]; Vincent COMPAN[3]; Hang korng EA[2]; Isabelle RUBERA[1]; Christophe DURANTON[1];

1 Université Côte d'Azur, CNRS UMR-7370, Laboratoire de Physiomédecine Moléculaire, Labex ICST, Nice, France.

2 Bioscar, INSERM UMR1132, Hôpital Lariboisière, AP-HP, Paris, France

3 IGF, INSERM, CNRS, Labex ICST, Univ Montpellier, Montpellier, France

Monosodium urate (MSU) and calcium pyrophosphate (CPP) crystals depositions are responsible for interleukin (IL-1β) mediated human inflammatory joint diseases (gout and pseudogout, respectively). In macrophages, MSU or CPP induce the release of IL-1β through the activation of the NLRP3 inflammasome. Interestingly, a decrease of extracellular osmolarity also cause NLRP3 inflammasome activation. Lowering extracellular osmolarity induces a compensatory mechanism (RVD) allowing loss of ions and osmotically obliged water through the activation of K^+ channels and volume-regulated anion channels (VRACs). The ubiquitously expressed LRRC8 anion channel family has been identified as the main molecular component of the VRAC. These channels are composed by a mandatory subunit LRRC8A and at least one other member of the LRRC8 family (A to E) to create functional channel. In this work, we investigated the link between the LRRC8/VRAC channels and the crystals-mediated NLRP3 inflammasome activation. MSU or CPP exposure (200µg/ml, 3h) on primed THP-1 cells (human monocytic cell line, 500nM PMA) triggered NLRP3 activation and IL-1β release. This release was reduced by (i) increasing osmolarity of the cell culture medium, (ii) blocking LRRC8/VRAC channels with DCPIB (a selective VRAC inhibitor, 20µM) or (iii) silencing the mandatory subunit (LRRC8A KD). We next investigated cell volume change under crystals exposure (2h) by calcein fluorescence quenching technique. Addition of MSU or CPP crystals induced a rapid cell swelling followed by a cell volume decrease in WT THP-1 cells. Cells treated with DCPIB or LRRC8A KD THP-1 cells showed an absence of RVD mechanism after crystal exposure. Interestingly, crystals exposure (2h) induced an increase of extracellular ATP concentration that was impaired in the presence of DCPIB or in LRRC8A KD cells. With patch-clamp technique, we showed that LRRC8 exhibited an ATP conductance under a hypo-osmotic challenge that is blunted by DCPIB or in LRRC8A KD cells. We also confirmed the contribution of P2Y receptors in IL-1b secretion mediated by MSU or CPP crystals. In conclusion, our results suggest that LRRC8/VRAC channels play a crucial role in crystal-mediated inflammasome activation through its ability to trigger ATP release and the activation of purinergic pathways.

POSTER ABSTRACTS

P1- EXPERIMENTAL AND COMPUTATIONAL INVESTIGATION OF ION SELECTIVITY IN ASIC1

Cedric VALLEE[1]; Max WINOKAN[1]; Sylvie DIOCHOT[2]; Marco SACCHI[3]; Brendan j HOWLIN[3]; Rebecca LEWIS[4];
1: Leverhulme Quantum Biology Doctoral Training Centre, University of Surrey, Guildford GU2 5XH, UK
2: CNRS UMR 7275, Institut de Pharmacologie Moléculaire et Cellulaire, LabEx ICST, FHU InovPain, Université Côte d'Azur, 660 Route des Lucioles, Sophia-Antipolis, 06560 Nice, France.
3: Department of Chemistry, Faculty of Engineering and Physical Sciences, University of Surrey, Guildford GU2 7XH, UK
4: Department of Comparative Biomedical Sciences, Faculty of Health and Medical Sciences, University of Surrey, Guildford GU2 7AL, UK

Acid Sensing Ion Channels (ASICs) are proton-gated ion channels selective to cations with a higher selectivity towards sodium (Na^+) compared to the other cations. They are involved in several important physiological roles [1-2]. The ASIC1 subunit can function as a homotrimeric channel, and its structure is currently the most established of the whole Epithelial Sodium Channel/Degenerin (ENaC/DEG) superfamily; hence ASICs are one of the most studied channels of this family [2-5]. By computing the single ion free energy profile on different ASIC1 structures, we recently showed that the channel is indeed cation-selective and that the histidine of the conserved 'HG' motif from the re-entrant loop plays an important role for binding Na+ in a partially hydrated state [6]. Based on these results, we investigated ion selectivity experimentally and computationally for different cations (Na^+, K^+, and Li^+) as well as different solvents (water and heavy water) using electrophysiology techniques, classical and quantum free energy calculations as well as multivariance correlation analysis. Our experimental results suggest that ASIC1 is more selective to Na^+ and Li^+ compared to K^+ and that heavy water affects ion selectivity. The computational results show further differences between the different cations and solvents with a stronger correlation between ion selectivity and hydration/binding energies. Therefore, this study suggests that ionic selectivity in ASIC1 would be mainly driven by the hydration and dehydration reactions experienced by the cation during permeation through the selectivity filter.

References

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P2- IDENTIFICATION AND CHARACTERIZATION OF A MITOCHONDRIAL ISOFORM OF TRPV1

Florian BEIGNON; Mattei CESAR; Lenaers GUY;
MitoVasc (UMR INSERM 1083 CNRS 6015)

During evolution, mitochondrial energy metabolism has been associated with heat production in endothermic species. This heat production is caused by the uncoupling of different biochemical reactions of transformation, storage and use of energy. Subsequently, homeotherms acquired the ability to regulate this heat production in order to maintain a constant body temperature.
The systemic physiological mechanisms involved in thermoregulation have been extensively studied. However, at the cellular and molecular scale, there are still many uncertainties regarding the regulation our body temperature. The mitochondria is particularly known to be the center of energy metabolism and cellular thermogenesis. Estimates of the temperature of active mitochondria suggest that it is closer to 45°C to 50°C than 37°C. This new data, which overturns our current knowledge, requires rethinking the regulation of thermogenesis at the cellular level.
In this context, we have identified a mitochondrial variant of the TRPV1 channel, presenting a mitochondrial addressing sequence. The TRPV1 channel is a cation channel sensitive to high temperatures (>43°C) sometimes located in the mitochondria of different cell types. Thus, its potential involvement in mitochondrial calcium homeostasis associated with its thermosensitivity would allow the regulation of mitochondrial thermogenesis. In addition, 4 variants of TRPV1 have recently been associated with malignant hyperthermia per anesthetic and exercise heat stroke, syndromes related to dysregulation of body thermoregulation. The identification and characterization of this mitochondrial isoform of TRPV1 open new perspectives on the metabolic dynamics of mitochondria and its dysfunctions in relation to the hyperthermia associated with it.

P3- POLYUNSATURATED FATTY ACIDS ALLOW THE RECRUITMENT OF "SILENT" TREK-1 CHANNELS THROUGH A DIRECT INTERACTION

Emilie BECHARD-DRIMARACCI; Xavier BUSSY; Jean-yves LE GUENNEC; Marie DEMION;
PhyMedExp, INSERM U1046, Montpellier

Among the K2P channels family, TREK-1 channel is a background potassium channel. TREK-1 belongs to the TREK subfamily of mechanosensitive channels and it is expressed in excitable cells as neurons and cardiomyocytes. Its polymodulation by a wide range of chemical and physical stimuli (pressure, pH modifications and polyunsaturated fatty acids (PUFAs)) makes it a good target in the pathophysiology of pain, depression and arrythmias. The mechanism of activation of the TREK mechanosensitive channels by PUFAs is thought to involve membrane tension increase by PUFAs insertion in the membrane.
In whole-cell and inside-out configurations of the patch-clamp technique we tested the effects of 9 PUFAs at 10 µM having different carbon chain length in a HEK hTREK-1 cell line.
First, we found that TREK-1 activation by PUFAs does not involve changes in membrane tension. At 10 µM of PUFAs, PUFAs do not induce membrane fluidification, but at 100 µM. The amplitude of TREK-1 activation is not correlated with the acyl chain length or their ability to insert within the membrane. By comparing the activation and reversibility kinetics of PUFAs and ML402, a direct activator of TREK-1, we show that PUFAs behave like the direct activator of TREK-1. The inside-out and whole-cell experiments suggest that the binding site of PUFAs on TREK-1 is accessible from the inner and/or the outer leaflet of the membrane as for ML402.
In inside-out configuration, the open probability of TREK-1 is very low in basal conditions, but the perfusion of PUFAs 5 µM reveals a large number of "silent" channels. In whole-cell configuration, there is a negative relationship between Imax/I0-PUFA and I0 (Imax/I0-PUFA=f(I0)) explaining that amplitude of the activation depends of the initial fraction of "silent"

TREK-1 channels. Finally, the gain-of-function G171D mutated TREK-1 channel (increased open probability) is activated by PUFAs but this activation is smaller than the transfected WT TREK-1 (Imax/I0-WT = 16,58±4,28; Imax/I0-G171D = 2,67±0,14).
Altogether, these results suggest that PUFAs activation of TREK-1 is (1) due to a direct interaction PUFAs/TREK-1 and (2) that PUFAs allows the recruitment of “silent” TREK-1 channels.

P4- ROLE OF L-TYPE CAV1.3 (α1D) CA^{2+} CHANNELS IN HEART FAILURE-RELATED VENTRICULAR ARRHYTHMIAS.

Mélanie FAURE[1]; Isabelle BIDAUD[1]; Sami AL OTHMAN[2]; Alicia D'SOUZA[2]; Pietro MESIRCA[1]; Stéphanie BARRERE-LEMAIRE[1]; Matteo MANGONI[1];
1: Institut de Génomique Fonctionnelle, Université de Montpellier
2: Division of Cardiovascular Sciences, University of Manchester

Heart failure (HF) is a major public healthcare concern. Although ventricular arrhythmias are a primary cause of sudden death in patients with HF, the underlying electrophysiological and molecular mechanisms are incompletely understood precluding the development of targeted therapies. L-type Cav1.3 channels underlie automaticity in the sinoatrial node (SAN) and are not expressed in the adult ventricle under physiological conditions. Recent studies in literature and by our collaborators have demonstrated an increased Cav1.3 protein expression in human failing hearts with EF<35% vs normal hearts. Consistently, interrogation of publicly-available cardiac single-nucleus RNAseq datasets by our group indicated an increase in Cav1.3 gene expression in ventricular myocytes from failing mouse and human hearts. We have previously demonstrated that Cav1.3 channels initiate automaticity in silent SAN cells in response to catecholaminergic activation and that Cav1.3 is a key effector in the b-adrenergic response of heart rate.
Expression data in failing ventricles, coupled with our previous observations on the functional role of Cav1.3 have prompted the hypothesis that activation of Cav1.3 channels in the failing ventricle creates ectopic catecholaminergic automaticity, triggering ventricular arrhythmias.
To validate this hypothesis, we subjected mice in which Cav1.2 channels have been rendered insensitive to dihydropyridines (DHP) by a knock-in DHP binding site (Cav1.2DHP-/- mouse) to chronic angiotensin (Ang)II infusion by osmotic minipumps for 3 weeks to model HF secondary to hypertension. In these mice, cardiac effects of DHP can be attributed to selective blockade of Cav1.3. AngII treatment (vs. vehicle) resulted in canonical features of HF including significant hypertrophy and drop in EF (64,93% vs 47,04%). Hearts were then studied using the Langendorff system under baseline conditions (n=6) or under catecholaminegic stimulation (n=6), and tested for inducible ventricular tachycardia (VT) by extrastimulus ventricular pacing. Extrasystoles (n=3/6), transient (n=1/6) or sustained (n=2/6) VT occurred in failing hearts whereas none of control hearts became arrhythmic. Perfusion of nifedipine prevented ventricular arrhythmias in Cav1.2DHP-/- hearts from AngII treated mice (n=6/6), suggesting blockade of newly expressed Cav1.3 channels was preventing ventricular arrhythmias.
In conclusion, these preliminary data indicate a new role for Cav1.3 in generating DHP-sensitive VT in failing ventricles.

P5- DECIPHERING THE PHARMACOLOGY AND BIOPHYSICAL PROPERTIES OF THE ABCC6 TRANSPORTER

Laetitia CLOTAIRE[1; 2]; Georges LEFTHERIOTIS[1; 3]; Saïd BENDAHHOU[1]; Isabelle RUBERA[1]; Christophe DURANTON [1];
1: Université Côte d'Azur, LP2M, CNRS-UMR 7370, Labex ICST, Faculté de Médecine, 28 Av. Valombrose, Tour Pasteur, 06000 Nice
2: ProNutri company, 5ème avenue, 17ème Rue, 06510 Carros
3: Centre Hospitalier Universitaire de Nice, Service de Médecine et d'Explorations Vasculaires, Hôpital Pasteur 1, Pavillon I, 30 Voie Romaine, 06108 Nice

Pseudoxanthoma elasticum (PXE, OMIM 26480) is a rare inherited multisystemic disease characterized by progressive ectopic calcification, most prominently affecting ocular, cardiovascular, dermal and kidney tissues. PXE is caused by mutations of ABCC6 gene, encoding for the hepatic ABCC6 membrane protein, a member of the ATP-binding cassette (ABC) transporter superfamily. PXE disease is characterized by a low plasma level of pyrophosphate (PPi), a key inhibitor of soft tissue calcification. Since the evidence of ABCC6 involvement in PXE, its molecular function has been described as a mediator of nucleotide efflux. However, the endogenous substrates of ABCC6 are still unknow. We used HEK-293 cells overexpressing ABCC6 protein to explore the contribution of this transporter in the modulation of nucleotides release and to characterize its biophysical properties. Cells overexpressing ABCC6 exhibited a significantly higher concentrations of adenosine triphosphate (ATP) and PPi in the extracellular medium as compared to cells not expressing the ABCC6 protein. Using pharmacological approach, we screened 30 compounds known to target various nucleotide-mediated pathways. Interestingly, we identified unreported molecules that markedly affect in vitro the ABCC6-mediated PPi/ATP extracellular release. Furthermore, to characterize the biophysical properties of ABCC6 transporter, we designed a modified ABCC6 protein expressing extracellular hemagglutinin tag (HA-tag) that allows its purification. By using magnetic beads, we isolated the modified protein and monitored single ion-channel PPi and ATP-evoked currents using a horizontal planar lipid bilayer system (orbitmini, Nanion). As preliminary results, we were able to measure electrogenic activity after incorporation of the ABCC6-HA purified protein into artificial lipid bilayers. Finally, these experiments supported that ABCC6 can contribute to the electrogenic transport of nucleotides. Further experiments are required, with mutated ABCC6, to confirm these results.

P6- DEVELOPMENT OF A PREDICTIVE ASSAY FOR TORSADOGENIC EFFECTS OF DRUGS USING NEURO-CARDIAC ORGAN-ON-CHIP

Elisa BOUNASRI[1]; Lamia GOUAL[2]; Jean-Luc PASQUIE[2]; Philippe LORY[3]; Jérôme THIREAU[2]; Alain LACAMPAGNE[2]; Albano c. MELI[2];
1: PhyMedExp, University of Montpellier, Inserm, CNRS, Montpellier, France / MicroBrain Biotech S.A.S., Marly Le-Roi, France
2: PhyMedExp, University of Montpellier, Inserm, CNRS, Montpellier, France
3: Institut de Génomique Fonctionnelle, University of Montpellier, CNRS, INSERM, Montpellier, France

Long QT syndrome (LQT) is a primary arrhythmia syndrome with high risk of sudden cardiac death (SCD) with genetic or iatrogenic etiology. For the drugs known to induce LQT, the consequence is the blocking of the rapid component of the delayed rectifier potassium current (IKr), encoded by the human ether-a-go-go-related gene (hERG), inducing an abnormal lengthening of ventricular repolarization (VR) and finally Torsades de Pointes (TdPs). Thus, regulatory tests on hERG channel blocking effects are required for safety evaluation of new drugs. However, a prolonged VR is just a surrogate marker with an imperfect predictive value for TdPs, recent literature showed that hERG blockers also have to affect the activity of

autonomic nervous system to trigger TdPs. However, current regulatory tests do not consider possible autonomic effects of drugs that might interfere with the cardiac responses.
The main aim is to develop a new predictive assay through detection of torsadogenic effects of drugs, based on neuro-cardiac organ-on-chip composed of patient-derived autonomic neurons innervating cardiomyocytes using human induced pluripotent stem cells (hiPSC) and microfluidic technologies.
To achieve this, we differentiated hiPSC-derived cardiomyocytes and sympathetic neurons. Each cell type was characterized, respectively, by the expression of sarcomeric cardiac markers (α-actinin, cardiac-troponin-I) and neuronal structure markers (β3-tubulin, tyrosine-hydroxylase, dopamine-beta-hydroxylase). In addition, we monitored the expression of hERG channel.
We investigated the cellular functional properties, with a particular focus on the intracellular Ca^{2+} cycling and contractile properties. Our preliminary data suggest that cardiomyocytes respond to adrenergic stimulation, by modulating intracellular Ca^{2+} transient properties, including Ca^{2+} release and contraction frequency. Effects of hERG channel blockers were assessed, inducing aberrant intracellular Ca^{2+}.
Next objective is to combined hiPSC-derived cardiomyocytes and sympathetic neurons on microfluidic device to decipher the neurocardiac dysfunctions at the origin of TdPs, to determine the conditions for TdP genesis by hERG blocking compounds. We aim to investigate the neurocardiac dysfunctions associated with TdPs and develop a patient-specific testing platform to enhance the evaluation of new pharmacological compounds for safety and efficacy.

P7- TWIK1: SHOULD WE FOCUS ON TARGETING A POTASSIUM CHANNEL OR A SODIUM CHANNEL?

Franck CHATELAIN[1]; Nicolas GILBERT[2]; Delphine BICHET[1]; Annaïse JAUCH[3]; Florian LESAGE[1]; Olivier BIGNUCOLO[4];
1: IPMC
2: Universite de Nice
3: Departtment Biomedivine, Basel
4: Swiss Institute Bioinformatics

TWIK1, a member of the two-pore-domain potassium channel family, presents a remarkable characteristic as the first known ion channel capable of transitioning from an inhibitory to an excitatory state under normal physiological conditions. Initially, at neutral pH, it functions as a highly potassium-selective channel. However, when exposed to acidic conditions within recycling endosomes, it undergoes a rapid change, becoming permeable to sodium. This transformation occurs within minutes and is fully reversible.
Our study delves into the intriguing process behind this unique dynamic ion selectivity, employing an integrated approach that combines pKa calculations of titratable residues, molecular dynamics simulations, mutagenesis experiments, and electrophysiology measurements. Through these techniques, we have identified a network of specific residues responsible for conferring this remarkable property.
Incorporating the latest cryo-EM structures, our investigations captured crucial features such as the conformation of the key proton sensor His122 and the elongation of the entire structure upon acidification. Additionally, molecular simulations revealed a complex arrangement of salt bridges and other interactions formed at neutral pH. However, this intricate pattern transforms into a much simpler set of strong interactions at low pH, leading to the unique ion selectivity shift.
Furthermore, this mechanism affects an aromatic residue that forms stacking interactions with His122, thereby stabilizing the selectivity filter in its highly potassium-selective state at neutral pH. At low pH, these interactions cease, causing the aromatic residue to dissociate from the network and resulting in a change in ion selectivity.

Beyond uncovering this fascinating molecular mechanism, our study exemplifies the power of collaborative efforts involving experts with complementary skills and knowledge. Together, we have illuminated the intricate workings of TWIK1 and expanded our understanding of ion channel behavior under varying physiological conditions.

P8- CADMIUM EXPOSURE ENHANCES CONSTITUTIVE CATION ENTRY AND TRANSFORMS HUMAN PANCREATIC STELLATE CELLS INTO A MYOFIBROBLASTIC PHENOTYPE

Mathilde FOURGEAUD[1]; Sara AGRANE[1]; Océane DUSAILLY[2]; Julie AUWERCX[1]; Frédéric HAGUE[1]; Sylvie BRASSART-PASCO[2]; Nicolas JONCKHEERE[3]; Bertrand BRASSART[2]; Mathieu GAUTIER[1];
1: Université de Picardie Jules Verne, UFR des Sciences, UR-UPJV 4667, F-80000 Amiens, France
2: Université de Reims Champagne-Ardenne, CNRS, UMR7369—MEDyC—Matrice Extracellulaire et Dynamique Cellulaire, F-51000 Reims, France
3: Univ. Lille, CNRS, Inserm, CHU Lille, UMR9020-U1277—CANTHER—Cancer Heterogeneity Plasticity and Resistance to Therapies, F-59000 Lille, France

Introduction: Pancreatic stellate cells (PSCs) represent almost 4-7% of the whole pancreas. They are quiescent in the healthy pancreas but they can be activated by alcohol or fatty acids. Activated PSCs triggered stroma remodelling by secreting matrix metalloproteases (MMPs) and extracellular matrix (ECM) leading to desmoplasia which is a key feature of pancreatitis and pancreatic ductal adenocarcinoma (PDAC). The incidence of these exocrine pancreatic diseases is dramatically increasing worldwide. Indeed, there is an urgent need to better understand the mechanisms of activation of PSCs. Cadmium (Cd) is a metal pollutant present in contaminated soils and possibly in food and water. Some epidemiologic studies suggest a link between Cd exposure and several cancers like PDAC. The aim of our study is to characterize the effects of Cd exposure on human PSC activation.
Methods: PS-1 cells were chronically exposed to 1µM $CdCl_2$ during 30 weeks. Expression of activated PSC marker GFAP (Glial Fibrillary Acidic Protein) was assessed by western-blot. Lipid droplets and α-SMA (α-Smooth Muscle Actin) were detected by immunofluorescence. The constitutive cation entry was recorded by using the Mn2+ quenching assay. Cell viability was studied by MTT assays, and cell migration was studied in Boyden chambers and by wound healing. ECM protein secretion was studied by zymography. Finally, the effect of Cd on pancreas remodelling was studied in vivo in a model of C57BL/6J mice treated by Cd (1 mg/kg CdCl2, intraperitoneal).
Results: An increase of GFAP expression was detected in Cd-treated cells. This was accompanied by the loss of lipid droplets and the remodelling of α-SMA which forms organized stress fibres. Cell viability was not altered following Cd exposure but cell migration was significantly enhanced. We also noticed an increase of constitutive cation entries in Cd-treated cells. Interestingly, Cd-treated cells secreted more ECM proteins such as MMP-2 and uPA (Urokinase-type plasminogen activator). Taken together, these results strongly suggest that Cd exposure has induced the activation of PSCs into a myofibroblastic phenotype. Finally, the pancreas was bigger in mice treated with Cd confirming the role of Cd in pancreatic remodelling.
Conclusion: In this study, we showed that Cd exposure activates PSCs and induces a myofibroblastic phenotype. This effect is at least partly due to enhanced constitutive cation entries. Further experiments are required to understand the molecular mechanism involved in Cd-induced PSC activation.

P9- MECHANOSENSITIVE CALCIUM CHANNELS TRIGGER ENDOTHELIAL DEFECTS IN CEREBRAL CAVERNOUS MALFORMATIONS

Candice PASQUIER[1]; Janne DE JONG[2]; Remi SELORON[1]; Thomas MANICOM-RAMSAMY[1]; Sabrina LEVERRIER-PENNA[3]; Edwige HIRIART-BRYANT[1]; Olivier DESTAING[1]; Aubin PENNA[3]; Hans VAN OOSTERWYCK[2]; Eva FAUROBERT[1];
1: Institute for Advanced Biosciences, team DYSAD, Grenoble, France
2: KU Leuven, team Mechanobiology and Tissue Engineering, Leuven, Belgium
3: Université de Poitiers, STIM, team 4CS, Poitiers, France

P10- MODELLING THE NEUROCARDIAC JUNCTION IN LONG QT SYNDROME TYPE 2

Lamia GOUAL[1]; Elisa BOUNASRI[2]; Sophie NICOLE[3]; Philippe LORY[3]; Alain LACAMPAGNE[1]; Albano c MELI[1]; Jérôme THIREAU[1];
1: PhyMedExp, University of Montpellier, INSERM, CNRS, Montpellier, France
2: PhyMedExp, University of Montpellier, INSERM, CNRS, Montpellier, France / MicroBrain Biotech S.A.S., Marly Le-Roi, France
3: Institut de Génomique Fonctionnelle, University of Montpellier, INSERM, CNRS, Montpellier, France

Long QT syndrome (LQT, 1:2000 of live birth) is a potentially life-threatening cardiac arrhythmia characterized by delayed myocardial repolarization that produces QT prolongation and increased risk of Torsades de Pointes (TdP). This syndrome triggers syncopes, seizures, and sudden cardiac death in an otherwise healthy young individual with a structurally normal heart. Type 2 LQT (LQT2) is a rare condition (30-40% of LQTS), caused by pathogenic variants in the KCNH2 gene. KCNH2 encodes the α-subunit of the human ether-a-gogo (hERG) channel, thus affecting the rapid component of the delayed rectifier K^+ current (IKr) of the action potential. Associations between HERG/KCNH2, LQT2 and SUDEP (Sudden Unexpected Death in Epilepsy) suggest that HERG/KCNH2 mutations confer a susceptibility to primary neuronal excitability defects.

The main aim of our work is to model the neurocardiac axis through a human-derived neuro-cardiac junction from healthy and LQT2 patients to decipher the plausible involvement of neurocardiac defects in LQT2.

Using a 2D sandwich-based protocol, we differentiated hiPSC-derived ventricular cardiomyocytes and sympathetic neurons. We investigated the sympathetic neuronal markers (β3-tubulin and tyrosine hydroxylase) and sarcomeric markers (α-actinin and cardiac troponin I). We confirmed the expression of the hERG channel and investigated the functional

properties of cardiomyocytes in monoculture, focusing on the intracellular Ca^{2+} handling and contractile properties.
Our preliminary data suggest that both cell lines respond to β-adrenergic stimulation by modulating intracellular Ca^{2+} transient properties. The LQT2 hiPSC-cardiomyocytes exhibit a high incidence of aberrant Ca^{2+} transients. The intracellular Ca^{2+} cycling was also assessed on neurons with or without nicotinic stimulation. We observed that our hiPSC-sympathetic neurons respond to nicotinic stimulation. Finally, we attempted to develop the organ-on-chip of these two hiPSC lines in microfluidic chambers, enabling the axons to project towards cardiomyocytes.
These technological developments should enable us to decipher the neurocardiac dysfunctions at the origin of the LQT2 syndrome.

ATTENDEES: CONTACT INFO

ANDRINI Olga
Institut NeuroMyoGène
Faculté de Médecine - 3ème étage, aile D
8 avenue Rockefeller
69008 Lyon - France
Tel: +33 4 26 68 82 82
olga.andrini@univ-lyon1.fr

AZZONI Caterina
IGF-cnrs Montpellier
141, rue de la Cardonille
34000 montpellier - france
Tel: +39 3484724843
caterina.azzoni@igf.cnrs.fr

ØSTERDAL-SANDOVAL Henrik
Sophion Bioscience
Baltorpvej 154
2750 Ballerup - Denmark
Tel: +45 20660612
hsa@sophion.com

BALCON Mélaine
Université de Strasbourg
Faculté de Pharmacie,
74 Rte du Rhin
67400 Illkirch-Graffenstaden - France
Tel: 0645837090
melaine.balcon@etu.unistra.fr

BARA Anissa
Sophion Bioscience
Baltorpvej 154
2750 Ballerup - Denmark
Tel: 20843990
aba@sophion.com

BAUDAT Romain
CEA
Bat 152 SIMoS
Route de Saclay
91140 gif-sur-yvette - France
Tel: 0616271765
romain.baudat23160@gmail.com

BECHARD Emilie
PhyMedExp
371 av du doyen G Giroud
34295 Montpellier Cedex 5 - France
Tel: 0646776450
emilie.bechard@inserm.fr

BECK Laurent
Inserm UMR 1087/CNRS UMR 6291
institut du thorax IRS-UN
8 quai Moncousu
BP 70721
44007 Nantes - France
Tel: 00 33 2 28 08 01 26
laurent.beck@inserm.fr

BEIGNON Florian
Laboratoire Mitovasc
(UMR INSERM 1083 -CNRS 6015)
3 Rue Roger Amsler
49100 Angers - France
Tel: 06 37 37 25 46
flo.beignon@gmail.com

BENDAHHOU Said
UMR7370 CNRS-LP2M
28 Avenue de Valombrose
06107 NICE CEDEX 2 - France
Tel: 0489153550
said.bendahhou@univ-cotedazur.fr

BENOIT Evelyne
CEA/CNRS
SIMoS, CEA de Saclay, bât. 152
91191 Gif-sur-Yvette - France
Tel: 33663751939
evelyne.benoit@cea.fr

BERROU Mikael
World Precision Instruments
Pfingstweide 16
61169 Friedberg - Germany
Tel: 0970449000
mberrou@wpi-europe.com

BERTAGNA Federico
University of Surrey
Stag Hill, University Campus, Guildford GU2 7XH
GU2 7XH Guildford - United Kingdom
Tel: +393316152993
fb00397@surrey.ac.uk

BIGNUCOLO Olivier
Miri DynaMics
Lothringerstr. 6
4056 Basel - Switzerland
Tel: 0636906321
olivier.bignucolo@gmail.com

BINI Ines
Pasteur Institute
Labratory of Biomolecules, Venoms and Theranostic Applications
1002 Tunis - Tunisia
Tel: 0021652188717
inesbini@yahoo.fr

BOUE-GRABOT Eric
CNRS-Bordeaux, France
Signalisation purinergique, inflammation et troubles neurologiques
Université de Bordeaux - CNRS
33076 Bordeaux - France
Tel: +33 5 33 51 47 95
eric.boue-grabot@u-bordeaux.fr

BOUHAOUALA-ZAHAR Balkiss
Institut pasteur tunis
13 Place Pasteur BP74,
1002 Tunis - Tunisia
Tel: 0021655345262
Balkiss.bouhaouala@pasteur.utm.tn

BOUNASRI Elisa
INSERM U1046
371 Avenue du Doyen G. Giraud,
CHU Arnaud de Villeneuve,
Bâtiment Crastes de Paulet
34295 Montpellier - France
Tel: 04 67 41 52 40
elisa.bounasri@inserm.fr

BRETTE Fabien
INSERM
Inserm U1046 - CNRS UMR9214 – Université de Montpellier Physiologie et Médecine Expérimentale du Coeur et des Muscles
CHU Arnaud de Villeneuve
Batiment Crastes de Paulet
371 Avenue du doyen Gaston Giraud
34295 MONTPELLIER - France
Tel: 06 27 77 72 42
fabien.brette@inserm.fr

CALLEBAUT Isabelle
UMR 7590 - Sorbonne Université/CNRS/MNHN/IRD
Institut de minéalogie, de physique des matériaux et de cosmochimie
4, place Jussieu
75005 Paris - France
Tel: 00 33 1 44 27 45 87
isabelle.callebaut@upmc.fr

CANTELMO Anna rita
Inserm, Institut Pasteur de Lille
1 rue du Professeur Calmette
59000 Lille - France
Tel: +33 320 87 71 48
anna-rita.cantelmo@univ-lille.fr

CARBONE Emilio
University of Torino
Corso Raffaello 30
10125 Torino - Italy
Tel: +39.348.739.8305
emilio.carbone@unito.it

CATACUZZENO Luigi
DIPARTIMENTO DI CHIMICA, BIOLOGIA E BIOTECNOLOGIE BIO/09 - FISIOLOGIA
University of Perugia
06121 Perugia - Italy
Tel: +390755855758
luigi.catacuzzeno@unipg.it

CLOTAIRE Laetitia
LP2M - UMR7370-UCA
28 Avenue de Valombrose
06516 NICE CEDEX 2 - France
Tel: 0767687860
laetitia.clotaire@etu.univ-cotedazur.fr

CHARNET Pierre
CNRS
IBMM, UMR 5247 1919 Route de Mende
34293 Montpellier cedex 5 - France
Tel: 0448792066 - Fax:
pierre.charnet@cnrs.fr

CONSTANTIN Bruno
Laboratory 4CS
UMR 6041 CNRS-Université de Poitiers
Pôle Biologie Santé, Bâtiment B36,
1 Rue Georges Bonnet - TSA 51106 - Cedex 9
86073 POITIERS - France
Tel: 0549453527
bruno.constantin@univ-poitiers.fr

CORONAS Valerie
Laboratoire 4CS
Université de Poitiers-CNRS UMR 6041
Pole Biologie Santé (B36)
1 rue Georges Bonnet
86073 Poitiers - France
Tel: 05 49 45 36 55
valerie.coronas@univ-poitiers.fr

CRAMBERT Gilles
INSERM/Sorbonne Université/Université de Paris - U1138 -Centre de Recherche des Cordeliers
INSERM/Sorbonne Université/Université de Paris - U1138 - Equipe Physiologie Rénale et Tubulopathies
15 rue de l'Ecole de Médecine
75270 Paris - France
Tel: 00 33 (0)1 44 27 50
gilles.crambert@crc.jussieu.fr

DAVAKAN Amaël
Institut de Génomique Fonctionnelle
141 Rue Cardonille
34094 Montpellier - France
Tel: 04 34 35 92 51
amael.davakan@igf.cnrs.fr

DELAFENETRE Arnaud
University of Poitiers
Pôle Biologie Santé Bât B36/B37 Université de Poitiers
1 rue Georges Bonnet
86000 Poitiers - France
Tel: 0643753291
arnaud.delafenetre@univ-poitiers.fr

DEMION Marie
PhyMedExp
371 av du doyen G. Giroud
34295 Montpellier cedex 5 - FRANCE
Tel: 0660266532
Marie.demion@inserm.fr

DUFOR Tom
Multi Channel Systems MCS GmbH
Aspenhaustrasse 21
72770 Reutlingen - Deutschland
Tel: 071219092546
seif@multichannelsystems.com

DURANTON Christophe
LP2M, CNRS UMR 7370, UCA
28 AV. valombrose, Faculté de médecine
06107 NICE - FR
Tel: 06 24 49 32 85
duranton@unice.Fr

FAUCHERRE Adèle
IGF
141 Rue de la Cardonille,
34000 Montpellier - France
Tel: 0675506620
Adele.Faucherre@igf.cnrs.fr

FAURE Mélanie
IGF Montpellier
2 bis rue Marguerite
34000 Montpellier - France
Tel: 0618802261
melanie.faure@igf.cnrs.fr

FOURGEAUD Mathilde
LPCM UR UPJV 4667
UFR des Sciences 33 rue Saint Leu
80000 Amiens - France
Tel: 0661376296
mathilde.fourgeaud@etud.u-picardie.fr

GAUTIER Mathieu
LPCM UR-UPJV 4667,
Université de Picardie Jules Verne, UFR des Sciences
33, rue Saint-Leu
80039 Amiens - France
Tel: 03.22..82.76.42
mathieu.gautier@u-picardie.fr

GIRAULT Alban
Université de Picardie Jules Verne
LPCM UR UPJV4667
Bâtiment des minimes,
33 Rue St Leu
80039 Amiens - France
Tel: 0322827641
alban.girault@u-picardie.fr

GKIKA Dimitra
Univerity of Lille / Inserm
Bât. ONCOLille
Bd du Professeur Jules Leclerc
59000 Lille cedex - Γαλλία
Tel: 0320436838
dimitra.gkika@univ-lille.fr

GOUAL Lamia
INSERM U1046
371 Avenue du Doyen G. Giraud,
CHU Arnaud de Villeneuve,
Bâtiment Crastes de Paulet
34295 Montpellier - France
Tel: +33 4 67 41 52 40
lamia.goual@inserm.fr

GOUIDER Riadh
Neurology department of Razi University Hospital and Clinical Investigation Center Neurosciences and Mental Health
2011 Manouba - Tunisia
Tel: 0021671600339
riadh.gouider@gnet.tn

GUERINEAU Nathalie
Institut de Génomique Fonctionnelle (IGF)
141 rue de la Cardonille
34094 Montpellier - FRANCE
Tel: 33-4-34-35-92-50
nathalie.guerineau@igf.cnrs.fr

HILAIRE Cecile
INM, INSERM 1298 Hôpital saint Eloi,
80 rue Augustin Fliche BP 74103
34091 Montpellier - France
Tel: 04 11 75 94 79 - Fax:
cecile.hilaire@umontpellier.fr

HILAL Lashual
Ecole polytechnique fédérale de Lausanne, Switzerland
Laboratory of Molecular and Chemical Biology of Neurodegeneration, Institute of Bioengineering, School of Life Sciences,
1015 Lausanne - Switzerland
Tel: +41 21 693 96 91
hilal.lashuel@epfl.ch

INQUIMBERT Perrine
INCI CNRS UPR3212/ Université de Strasbourg
8 allée du Général Rouvillois
67000 Strasbourg - France
Tel: 0388456662
inquimbert@unistra.fr

JIANG Lin-hua
Xinxiang Medical University
Department of Physiology and Pathophysiology, School of Basic Medical Science
453003 Xinxiang - China
Tel: 008615937353761
L.H.Jiang@leeds.ac.uk

KAABECHE Mahira
IBMM / CNRS
1919 Rte de Mende,
34000 Montpellier - France
Tel: 0762999213
mahirakaabeche@gmail.com

KAYATEKIN Mete
LP2M - UMR 7370 CNRS
28 Avenue de Valombrose
06107 Nice - France
Tel: 0782913987
mete.kayatekin@etu.univ-cotedazur.fr

KELLENBERGER Stephan
University of Lausanne
Department of biomedical Sciences
Rue du Bugnon 27
1011 Lausanne - Switzerland
Tel: +41216925422
stephan.kellenberger@unil.ch

KONDRATSKYI Artem
Nanion
59650 Villeneuve d'Ascq - France
Tel: +33762415503
Artem.Kondratskyi@nanion.de

LAINE Mélanie
LPCM UR-UPJV 4667
UFR des Sciences
33, rue Saint Leu
80000 Amiens - France
Tel: 0678762708
melanie.laine@etud.u-picardie.fr

LE GUENNEC Jean-yves
PhyMedExp
371 av du doyen G Giroud
34295 Montpellier Cedex 5 - France
Tel: 0650670595
jean-yves.le-guennec@umontpellier.fr

LEGENDRE Claire
UMR CNRS 6015 - INSERM U1083 - Laboratoire MitoVasc
3 rue Roger Amsler
49100 ANGERS - FRANCES
Tel: 0244688286
claire.legendre@univ-angers.fr

LEGROS Christian
University of Angers
Lab. MITOVASC UMR CNRS6015, Inserm U1083 3 Rue Roger Amsler
49000 ANGERS - France
Tel: 0244688273
christian.legros@univ-angers.fr

LEMONNIER Loïc
Inserm UMR 1003, Laboratoire de Physiologie Cellulaire
Bâtiment SN3, Campus Sciences et Technologies, Université de Lille
59655 Villeneuve d'Ascq - France
Tel: 33 320 33 62 07
loic.lemonnier@inserm.fr

LIND Christof
Harvard Bioscience
Multi Channel Systems MCS GmbH
Aspenhaustraße 21
72770 Reutlingen - Deutschland
Tel: +49712190925646
clind@multichannelsystems.com

LOPEZ-CHARCAS Osbaldo
Intituto de Fisiologia Celular, UNAM.
Circuito Exterior SN, Ciudad Universitaria,
Coyoacan.
04510 Mexico City - Mexico
Tel: 52 55 56 22 57 52
olopez@comunidad.unam.mx

LORY Philippe
IGF Montpellier
141 rue de la Cardonille
34094 Montpellier - France
Tel: 0434359250
philippe.lory@igf.cnrs.fr

MALECOT Lionel
MICRO MECANIQUE
101 RUE PEREIRE BÂT EH PARC PEREIRE
78100 Saint-Germain-en-Laye - France
Tel: 0672364541
malecot.l@micromecanique.fr

MANICOM RAMSAMY Thomas
Institute for Advanced Biosciences INSEM 1209
CNRS 5309
Site Santé, Allée des Alpes
38700 La Tronche - France
Tel: 0618081708
thomas.manicom-ramsamy@univ-grenoble-alpes.fr

MASSON Bastien
INSERM U999, Hypertension Pulmonaire :
Physiopathologie et Nouvelles Thérapies
Hôpital Marie Lannelongue
133, Avenue de la Résistance
92350 Le Plessis Robinson
Tel: +331 40 94 22 99
bastien.masson@universite-paris-saclay.fr

MÉRY Pierre-françois
Institut de Génomique Fonctionnelle
Dynamique des canaux calciques et nociception
Inserm U1191 - Cnrs 5203 - Université de Montpellier.
141 rue de la Cardonille
34094 Montpellier - France
Tel: 0781885678
pierre-francois.mery@igf.cnrs.fr

MESIRCA Pietro
Institut de Génomique Fonctionnelle UMR5203
141, rue de la Cardonille
34094 Montpellier - France
Tel: 04 34359246
pietro.mesirca@igf.cnrs.fr

MIQUEROL Lucile
IBDM
Parc Scientifique de,
Av. de Luminy
13288 Marseille Cedex 9 - France
Tel: 04 91 26 97 35
lucile.miquerol@univ-amu.fr

MOCCIA Francesco
University of Pava
Department of Biology and Biotechnology “L. Spallanzani” , University of Pavia, Via Forlanini 6
27100 Pavia - Italy
Tel: 39 339 3304531
francesco.moccia@unipv.it

MOLTON Ophélie
Département des Sciences Biomédicales - Université de Lausanne
Rue du Bugnon 27
1011 Lausanne - Switzerland
Tel: +33(0)675136534
ophelie.molton@unil.ch

MONTEIL Arnaud
Institute for Functional Genomics
141 rue de la Cardonille
34094 Montpellier Cedex 5 - France
Tel: +33 (0) 4 3435 9250
arnaud.monteil@igf.cnrs.fr

MORLA Luciana
CNRS,
Laboratoire de Métabolisme et physiologie rénales,
Centre de Recherche des Cordeliers,
15 rue de l'école de médecine,
75006 Paris - France
Tel: 0681228466
luciana.morla@crc.jussieu.fr

PASCAREL Khilian
Laboratoire PRéTI Pôle Biologie Santé Bât B36/B37
Université de Poitiers
1 rue Georges Bonnet TSA 51106
86073 POITIERS CEDEX 9 FRANCE
Tel: +33 6 08 42 41 94
khilian.pascarel@univ-poitiers.fr

PASQUIER Candice
INOVOTION / Institute for Advanced Biosciences
Site Santé, Allée des Alpes
38700 La Tronche - France
Tel: 0629910496
candice.pasquier@univ-grenoble-alpes.fr

PORRO Alessandro
Elements srl
viale Europa 596
47521 Cesena - Italia
Tel: +393473845105
aporro@elements-ic.com

QUIGNARD Jean-francois
CRCTB U1045
PTIB, Hopital X. Arnozan
Av Haut Leveque
33600 Pessac - France
Tel: 0557102864
jean-francois.quignard@u-bordeaux.fr

RAMAY Elise
CNRS - IPMC
660 route des lucioles
06560 Valbonne - France
Tel: 04 93 95 77 32
ramaye@ipmc.cnrs.fr

RAPETTI-MAUSS Raphael
Institut de Biologie Valrose (iBV)
UMR CNRS 7277- UMR INSERM 1091 Université Côte d'Azur
Parc Valrose Bâtiment de sciences naturelles
06108 Nice - France
Tel: 0489150813
raphael.rapetti-mauss@univ-cotedazur.fr

RÉTHORÉ Léa
Laboratoire MitoVasc
Laboratoire MitoVasc - équipe CarMe
Bâtiment IRIS 2
3 Rue Roger Amsler
49100 ANGERS - FRANCE
Tel: 0640066079
rethorelea22@gmail.com

RODAT-DESPOIX Lise
Université de Picardie Jules Verne UR-UPJV 4667 - Laboratoire de Physiologie Cellulaire et Moléculaire - UFR des Sciences
33 rue saint leu
80039 Amiens - France
Tel: 0322827647
lise.despoix@u-picardie.fr

RUBERA Isabelle
LP2M UMR CNRS 7370
Faculté de médecine
28 avenue de Valombrose
06108 Nice - France
Tel: 0033686558970
isabelle.rubera@univ-cotedazur.fr

SAINT-MARTIN WILLER Anaïs
INSERM U999
133 Avenue de la Resistance
92350 Le Plessis-Robinson - France
Tel: 0634098611
anais.saint-martin@universite-paris-saclay.fr

SEBILLE Stéphane
Laboratoire PRéTI UR 24184 - Université de Poitiers - UFR SFA Pôle Biologie Santé Bâtiment B36/B37
1 Rue Georges Bonnet
TSA 51106
86073 POITIERS Cedex 9
Tel: 33(0) 549 453 767
stephane.sebille@univ-poitiers.fr

SEUTIN Vincent
Liège University
Laboratoire de Neurophysiologie, GIGA Neurosciences CHU de Liège , tour 4 (B36)
Av. Hippocrate 15
4000 Liège - Belgium
Tel: +32491113705
V.Seutin@uliege.be

STRUBE Caroline
CNRS
Déléguée Scientifique à la Mission à l'Intégrité Scientifique (MIS) du CNRS Chargée de mission pour la cellule RIRe - Recherche Intègre et Responsable Laboratoire de Neurosciences Cognitives - UMR 7291 Bat 9 - Campus St Charles - 3 place Victor Hugo
13003 Marseille - France
Tel: 04 13 55 10 25
caroline.strube@univ-amu.fr

THIREAU Jerome
INSERM U1046
371 Avenue du Doyen Gaston Giraud,
CHU Arnaud de Villeneuve,
Batiment Crastes de Paulet,
34295 Montpellier Cedex 5 - France
Tel: 0681506971
jerome.thireau@inserm.fr

THONGSEPEE Nattaya
Institute for Functional Genomics
141 rue de la Cardonille
34094 Montpellier - France
Tel: 0749547268
nattaya.thongsepee@igf.cnrs.fr

TITAH Sofia
Université de Lille - Laboratoires CANTHER / PHYCELL
6 rue du Maréchal Foch
59120 LOOS - FRANCE
Tel: 07 50 26 61 01
sofia.titah@inserm.fr

TORRE Eleonora
IGF-CNRS Montpellier
141, rue de la cardonille
34000 Montpellier - France
Tel: 0619127133
eleonora.torre@igf.cnrs.fr

VALLEE Cedric
University of Surrey
Stag Hill, University Campus
GU2 7XH Guildford - United Kingdom
Tel: +44 1483 300800
c.vallee@surrey.ac.uk

WEIDEL Petra
6, rue des Pruniers
86300 Chauvigny - France
Tel: 0780256098 - Fax:
Petraweidel@t-online.de

USEFUL INFORMATION

The attendees are expected on Sunday, between 4PM and 7PM. During this period, they would have the time to proceed to their check-in and meet each other before a welcome drink and the diner. The congress will begin on sunday evening with the plenary lecture and finish on Wednesday after lunch.

The conference will take place at Centre de vacances du Lazaret, a leisure center at Sète on the Mediterranean coast of France, close to the city of Montpellier.

A forum has been setup if you want to share a taxi or a car (personal or rental one).

Directions to "Le Lazaret"

Le Lazaret
La Corniche
223 Rue Pasteur Benoît
34200 Sète

Tel: +33 (0)4 67 53 22 47
Fax: +33 (0)4 67 53 36 13

Web: www.lazaret-sete.com

Mail: le-lazaret@capfrance.com

GPS coordinates:
43°23'40.01 N
003°40'26.60 E

Arriving

By Air:

Montpellier Méditerranée Airport is the closest airport. At you arrival you will find taxi. We strongly encourage you to share a taxi using the forum.

If you want to book a taxi in advance you can use

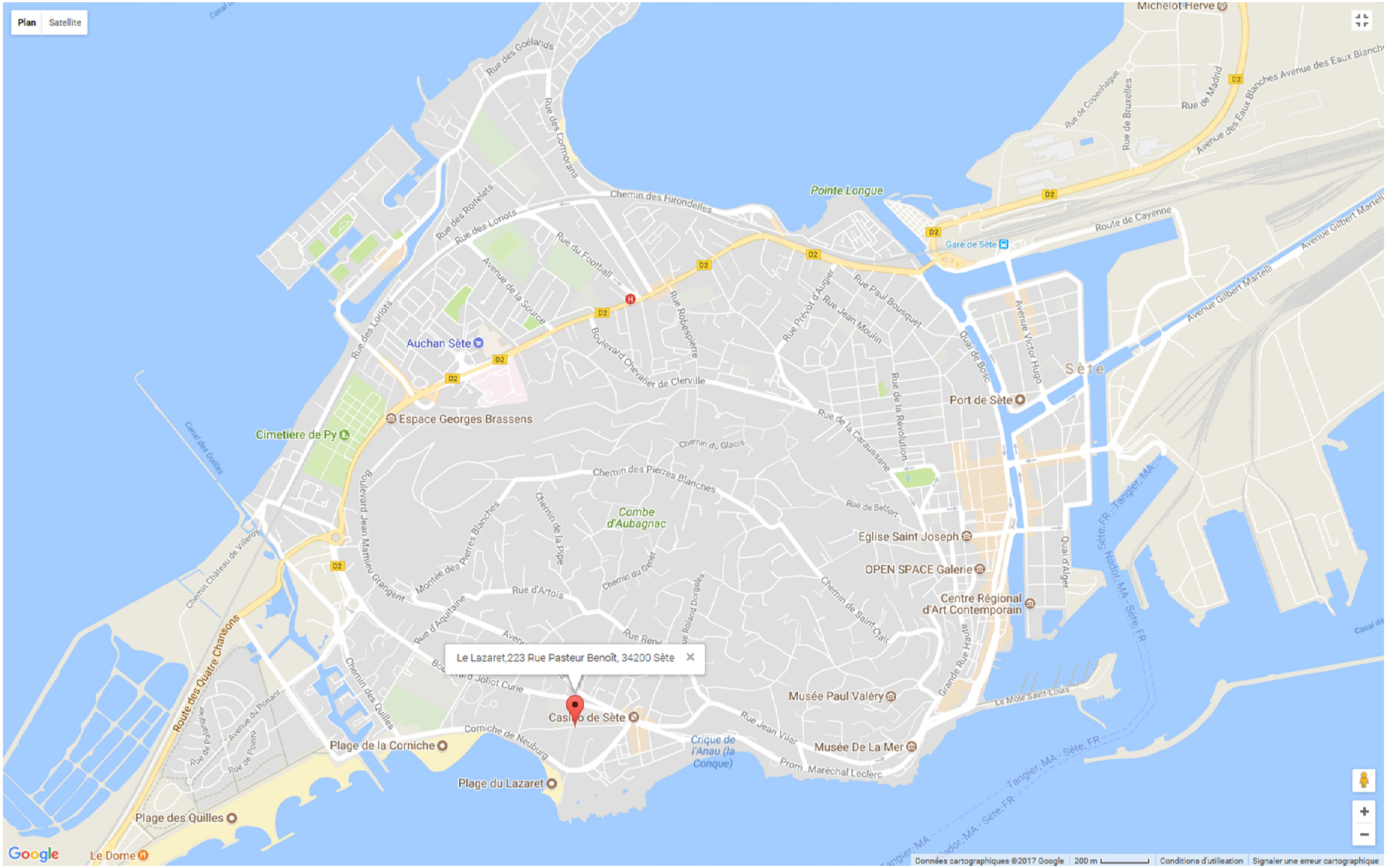
Taxi Valenti, +33 611 57 18 05, taxi.valenti@sfr.fr

By train:

In Sète, there is a SNCF railway station, which is covered by TGV. At your arrival you can find taxis and public transportation. For city bus you can take a bus of the n°23 line operating to the Centre Malraux and stop at the halt "Plan de la Corniche". Alternatively, you can take a bus of the n°9 line operating to Marseillan Plage and stop at the halt "Le Lazaret". You can check for timetables, directions and prices at the following web address: http://www.thau-agglo.fr

By Car :

Free parking are available at the center of "le Lazaret".


Plan
Satellite
Le Lazaret,223 Rue Pasteur Benoît, 34200 Sète
Pointe Longue
Auchan Sète
Espace Georges Brassens
Cimetière de Py
Combe d'Aubagnac
Port de Sète
Sète
Gare de Sète
Eglise Saint Joseph
OPEN SPACE Galerie
Centre Régional d'Art Contemporain
Musée Paul Valéry
Musée De La Mer
Casino de Sète
Plage de la Corniche
Plage du Lazaret
Plage des Quilles
Crique de l'Anau (la Conque)
Le Dome
Route des Quatre Chansons
Rue des Goélands
Rue des Cormorans
Chemin des Hirondelles
Rue des Rotelets
Rue des Lorlots
Rue du Football
Avenue de la Source
Rue Robespierre
Boulevard Chevalier de Clerville
Rue Prévot d'Augier
Rue Jean Moulin
Rue Paul Bousquet
Quai de Bosc
Avenue Victor Hugo
Rue de la Révolution
Rue de la Caraussane
Chemin du Glacis
Chemin des Pierres Blanches
Rue de Belfort
Chemin de la Pipe
Chemin du Genet
Rue d'Artois
Rue d'Aquitaine
Montée des Pierres Blanches
Boulevard Jean Mathieu Grangent
Chemin Château de Villeroy
Chemin de Saint Clair
Grande Rue Haute
Quai d'Alger
Le Môle Saint-Louis
Rue Jean Vilar
Corniche de Neuburg
Prom. Maréchal Leclerc
Chemin des Quilles
Avenue du Ponant
Rue de Copenhague
Rue de Bruxelles
Rue de Madrid
Avenue des Eaux Blanches
Avenue Gilbert Martelli
Route de Cayenne
Michelot Herve
Canal des Quilles
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Nador,MA - Sète,FR
Tangier,MA - Sète,FR
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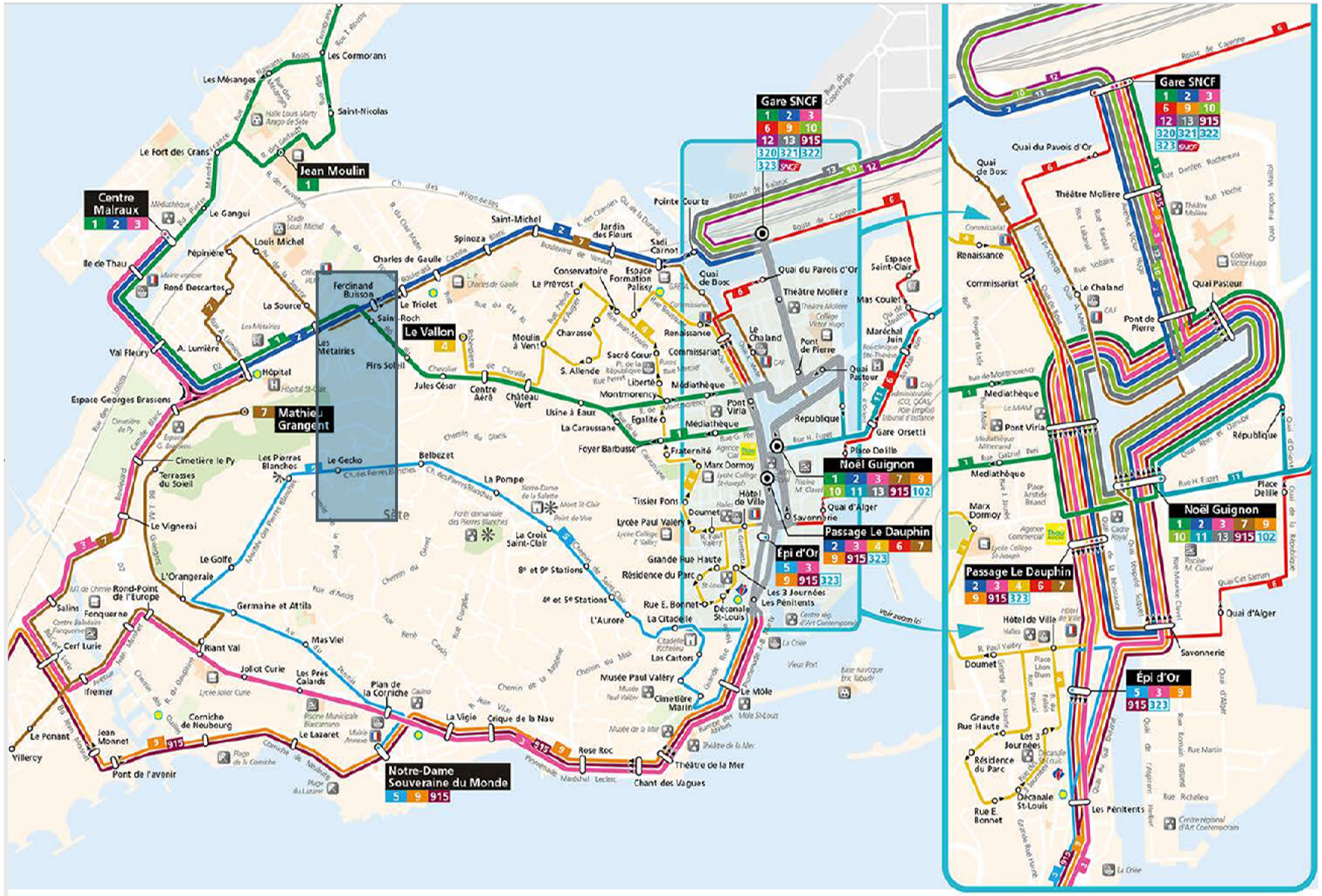
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1 2 3
Jean Moulin
1
Le Vallon
4
Mathieu Grangent
7
Notre-Dame Souveraine du Monde
5 9 915
Gare SNCF
1 2 3 6 9 10 12 13 915 320 321 322 323 SNCF
Noël Guignon
1 2 3 7 9 10 11 13 915 102
Passage Le Dauphin
2 3 4 6 7 9 915 323
Épi d'Or
5 3 9 915 323
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Le Fort des Crans
Les Cormorans
Les Mésanges
Saint-Nicolas
Le Gangui
Pépinière
Ile de Thau
Rond Descartes
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La Source
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Terrasses du Soleil
Le Vignerai
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L'Orangeraie
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Mas Viel
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La Vigie
Crique de la Nau
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Espace Formation Palissy
Moulin à Vent
Chavasse
Sacré Cœur
S. Allende
Renaissance
Commissariat
Quai de Bosc
Quai du Pavois d'Or
Théâtre Molière
Le Chaland
Pont de Pierre
Espace Saint-Clair
Mas Coulet
Maréchal Juin
Quai Pasteur
République
Gare Orsetti
Place Delille
Marx Dormoy
Hôtel de Ville
Quai d'Alger
Savonnerie
Tissier Pons
Doumet
Lycée Paul Valéry
La Croix Saint-Clair
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4e et 5e Stations
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Résidence du Parc
Rue E. Bonnet
L'Aurore
La Citadelle
Les Cattons
Déconale St-Louis
Les 3 Journées
Les Pénitents
Musée Paul Valéry
Cimetière Marin
Le Môle
Musée de la Mer
Théâtre de la Mer
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Centre régional d'Art Contemporain
La Criée

MISCELLANEOUS

Lazaret Holiday Village
www.lazaretsete.com
Rue du Pasteur Lucien Benoît, 34200 Sète Téléphone : 04 67 53 22 47

Tourist office
www.tourisme-sete.com/
60, Grande Rue Mario Roustan, 34200 Sète, 04 99 04 71 71

Public bus
http://mobilite.thau-agglo.fr/eng, 04 67 53 01 01
The direct bus line between the Sète SNCF railway station and the Lazaret are the line 3 and 9

Espace Georges Brassens
http://www.espace-brassens.fr/
67 Boulevard Camille Blanc, 34200 Sète, France 04 99 04 76 26

Musée Paul Valéry
http://www.museepaulvalery-sete.fr/
Rue François Desnoyer, 34200 Sète, France 04 99 04 76 16
Fermé le lundi

MIAM (Musée international des arts modestes)
https://miam.org/
23 quai Maréchal de Lattre de Tassiny, 34200 Sète, France 04 99 04 76 44
Fermé le Lundi

CRAC (Centre régional d'art contemporain)
https://crac.laregion.fr/
26 quai Aspirant Herber 34200 Sète, France 0467749437
Fermé le Mardi

Others activities
https://www.tripadvisor.fr/Attractions-g660465-Activities-Sete_Herault_Occitanie.html#ATTRACTION_LIST

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